Requests to Add a Debilitating Medical Condition or Treatment

ADHS will begin to accept requests to add a debilitating medical condition to the list of debilitating medical conditions for the Medical Marijuana Program. Requests will be accepted from **January 23rd to January 27th, 2012 at close of business.** Requests received as indicated by its postmark prior to or after these dates will not be accepted. ADHS will also receive requests during the month of July 2012 (specific dates TBD).

Upon submittal, ADHS will notify the requester within 30 days that the request was received. An initial review will be conducted to determine if the information provided in the request provides evidence that:

- The specified medical condition or treatment of the medical condition impairs the ability of the individual to accomplish activities of daily living, and
- Marijuana usage provides a therapeutic or palliative benefit to an individual suffering from the medical condition or treatment of the medical condition.

If the information provided meets the requirements above, ADHS will schedule a public hearing to discuss the request and provide a date for the hearing. If the information provided does not meet the requirements above, ADHS will notify the requester with reasons and provide for a process for requesting judicial review.

During the review process, ADHS will partner with the University of Arizona, Colleges of Public Health and Medicines (University) to review the requests. The University will be able to provide ADHS valuable support, including further research of each condition or treatment and summary reports with recommendations by accessing its extensive public health and medical expertise.

Within 180 days after the original request submission, ADHS will either add the medical condition to the list of debilitating medical conditions or provide written notice to the requester of ADHS' decision to deny the request. The written notice will include specific reasons for the denial and the process for requesting judicial review.

ADHS will accept the request via U.S. mail only. Each request **must** include the following components:

- The completed submittal cover sheet that includes:
  - The entity's name, mailing address, name of contact individual, telephone number, and email address
  - The name of the medical condition the entity is requesting be added
- A description of the symptoms and other physiological effects experienced by an individual suffering from the medical condition or a treatment of the medical condition that may impair the ability of the individual to accomplish activities of daily living
- The availability of conventional medical treatments to provide therapeutic or palliative benefit for the medical condition or a treatment of the medical condition
- A summary of the evidence that the use of marijuana will provide therapeutic or palliative benefit for the medical condition or a treatment of the medical condition; and
- Articles, published in peer-reviewed, scientific journals, reporting the results of research on the effects of marijuana on the medical condition or a treatment of the medical condition supporting why the medical condition should be added. *The full article must be submitted (no abstracts).*

Submit requests via U.S. mail to:
ADHS
P.O. Box 19000
Phoenix, AZ 85005

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Depression (major depression)

By Mayo Clinic staff

Original Article: http://www.mayoclinic.com/health/depression/DS00175

Definition

Depression is a medical illness that causes a persistent feeling of sadness and loss of interest. Depression can cause physical symptoms, too.

Also called major depression, major depressive disorder and clinical depression, it affects how you feel, think and behave. Depression can lead to a variety of emotional and physical problems. You may have trouble doing normal day-to-day activities, and depression may make you feel as if life isn't worth living.

More than just a bout of the blues, depression isn't a weakness, nor is it something that you can simply "snap out" of. Depression is a chronic illness that usually requires long-term treatment, like diabetes or high blood pressure. But don't get discouraged. Most people with depression feel better with medication, psychological counseling or other treatment.

Symptoms

Depression symptoms include:

- Feelings of sadness or unhappiness
- Irritability or frustration, even over small matters
- Loss of interest or pleasure in normal activities

- Reduced sex drive
- Insomnia or excessive sleeping
- Changes in appetite — depression often causes decreased appetite and weight loss, but in some people it causes increased cravings for food and weight gain
- Agitation or restlessness — for example, pacing, hand-wringing or an inability to sit still
- Irritability or angry outbursts
- Slowed thinking, speaking or body movements
- Indecisiveness, distractibility and decreased concentration
- Fatigue, tiredness and loss of energy — even small tasks may seem to require a lot of effort
- Feelings of worthlessness or guilt, fixating on past failures or blaming yourself when things aren't going right
- Trouble thinking, concentrating, making decisions and remembering things
- Frequent thoughts of death, dying or suicide
- Crying spells for no apparent reason
- Unexplained physical problems, such as back pain or headaches

For some people, depression symptoms are so severe that it's obvious something isn't right. Other people feel generally miserable or unhappy without really knowing why.

Depression affects each person in different ways, so symptoms caused by depression vary from person to person. Inherited traits, age, gender and cultural background all play a role in how depression may affect you.

Depression symptoms in children and teens
Common symptoms of depression can be a little different in children and teens than they are in adults.

- In younger children, symptoms of depression may include sadness, irritability, hopelessness and worry.
- Symptoms in adolescents and teens may include anxiety, anger and avoidance of social interaction.

- Changes in thinking and sleep are common signs of depression in adolescents and adults but are not as common in younger children.
- In children and teens, depression often occurs along with behavior problems and other mental health conditions, such as anxiety or attention-deficit/hyperactivity disorder (ADHD).
- Schoolwork may suffer in children who are depressed.

Depression symptoms in older adults
Depression is not a normal part of growing older, and most seniors feel satisfied with their lives. However, depression can and does occur in older adults. Unfortunately, it often goes undiagnosed and untreated. Many adults with depression feel reluctant to seek help when they're feeling down.

- In older adults, depression may go undiagnosed because symptoms — for example, fatigue, loss of appetite, sleep problems or loss of interest in sex — may seem to be caused by other illnesses.
- Older adults with depression may have less obvious symptoms. They may feel dissatisfied with life in general, bored, helpless or worthless. They may always want to stay at home, rather than going out to socialize or doing new things.
- Suicidal thinking or feelings in older adults is a sign of serious depression that should never be taken lightly, especially in men. Of all people with depression, older adult men are at the highest risk of suicide.

When to see a doctor
If you feel depressed, make an appointment to see your doctor as soon as you can. Depression symptoms may not get better on their own — and depression may get worse if it isn't treated. Untreated depression can lead to other mental and physical health problems or problems in other areas of your life. Feelings of depression can also lead to suicide.

If you're reluctant to seek treatment, talk to a friend or loved one, a health care professional, a faith leader, or someone else you trust.

If you have suicidal thoughts
If you or someone you know is having suicidal thoughts, get help right away. Here are some steps you can take:

- Contact a family member or friend.
- Seek help from your doctor, a mental health provider or other health care professional.

- Call a suicide hot line number — in the United States, you can reach the toll-free, 24-hour hot line of the National Suicide Prevention Lifeline at 800-273-8255 to talk to a trained counselor.
- Contact a minister, spiritual leader or someone in your faith community.

When to get emergency help
If you think you may hurt yourself or attempt suicide, call 911 or your local emergency number immediately. If you have a loved one who has harmed himself or herself, or is seriously considering doing so, make sure someone stays with that person. Take him or her to the hospital or call for emergency help.

Causes

It's not known exactly what causes depression. As with many mental illnesses, it appears a variety of factors may be involved. These include:

- **Biological differences.** People with depression appear to have physical changes in their brains. The significance of these changes is still uncertain, but may eventually help pinpoint causes.
- **Neurotransmitters.** These naturally occurring brain chemicals linked to mood are thought to play a direct role in depression.
- **Hormones.** Changes in the body's balance of hormones may be involved in causing or triggering depression. Hormone changes can result from thyroid problems, menopause or a number of other conditions.
- **Inherited traits.** Depression is more common in people whose biological family members also have this condition. Researchers are trying to find genes that may be involved in causing depression.
- **Life events.** Certain events, such as the death or loss of a loved one, financial problems, and high stress, can trigger depression in some people.
- **Early childhood trauma.** Traumatic events during childhood, such as abuse or loss of a parent, may cause permanent changes in the brain that make you more susceptible to depression.

Risk factors

Depression often begins in the teens, 20s or 30s, but it can happen at any age. Twice as many women are diagnosed with depression as men, but this may be due in part because women are more likely to seek treatment for depression.

Although the precise cause of depression isn't known, researchers have identified certain factors that seem to increase the risk of developing or triggering depression, including:

- Having biological relatives with depression
- Being a woman
- Having traumatic experiences as a child
- Having family members or friends who have been depressed
- Experiencing stressful life events, such as the death of a loved one
- Having few friends or other personal relationships
- Recently having given birth (postpartum depression)
- Having been depressed previously
- Having a serious illness, such as cancer, diabetes, heart disease, Alzheimer's or HIV/AIDS
- Having certain personality traits, such as having low self-esteem and being overly dependent, self-critical or pessimistic
- Abusing alcohol, nicotine or illicit drugs
- Taking certain high blood pressure medications, sleeping pills or certain other medications (Talk to your doctor before stopping any medication you think could be affecting your mood.)

Complications

Depression is a serious illness that can take a terrible toll on individuals and families. Untreated depression can result in emotional, behavioral and health problems that affect every area of your life. Complications associated with depression can include:

- Alcohol abuse
- Substance abuse
- Anxiety
- Work or school problems
- Family conflicts

- Relationship difficulties
- Social isolation
- Suicide
- Self-mutilation, such as cutting
- Premature death from other medical conditions

Preparing for your appointment

You're likely to start by seeing your primary care doctor. However, in some cases when you call to set up an appointment, you may be referred directly to a health provider who specializes in diagnosing and treating mental health conditions (psychologist or psychiatrist).

Because appointments can be brief, and because there's often a lot of ground to cover, it's a good idea to be well prepared for your appointment. Here's some information to help you get ready for your appointment, and know what to expect from your health provider.

What you can do

- **Write down any symptoms you've had,** including any that may seem unrelated to the reason for which you scheduled the appointment.
- **Write down key personal information,** including any major stresses or recent life changes.
- **Make a list of all medications,** vitamins or supplements that you're taking.
- **Take a family member or friend along,** if possible. Sometimes it can be difficult to remember all of the information provided to you during an appointment. Someone who accompanies you may remember something that you missed or forgot.
- **Write down questions to ask** your health provider.

Your time with your health provider is limited, so preparing a list of questions ahead of time will help you make the most of your time together. List your questions from most important to least important in case time runs out. For problems related to depression, some basic questions to ask your health provider include:

- Is depression the most likely cause of my symptoms?

- Other than the most likely cause, what are other possible causes for my symptoms or condition?
- What kinds of tests will I need?
- What treatment is likely to work best for me?
- What are the alternatives to the primary approach that you're suggesting?
- I have these other health conditions. How can I best manage them together?
- Are there any restrictions that I need to follow?
- Should I see a psychiatrist or other mental health provider?
- Are there any possible side effects or other issues I should be aware of with

the medications you're recommending?

- Is there a generic alternative to the medicine you're prescribing?
- Are there any brochures or other printed material that I can take home with me? What websites do you recommend visiting?

In addition to the questions that you've prepared to ask your health provider, don't hesitate to ask any additional questions that may occur to you during your appointment.

What to expect from your health provider
Your health provider is likely to ask you a number of questions. Being ready to answer them may reserve time to go over any points you want to spend more time on. Your health provider may ask:

- When did you or your loved ones first notice your symptoms of depression?
- How long have you felt depressed? Do you generally always feel down, or does your mood fluctuate?
- Does your mood ever swing from feeling down to feeling euphoric and full of energy?
- Do you ever have suicidal thoughts when you're feeling down?
- How severe are your symptoms? Do they interfere with your daily life or relationships?
- Do you have any biological relatives with depression or another mood disorder?

- What other mental or physical health conditions do you have?
- Do you drink alcohol or use illegal drugs?
- How much do you sleep at night? Does it change over time?
- What, if anything, seems to improve your symptoms?
- What, if anything, appears to worsen your symptoms?

Tests and diagnosis

Because depression is common and often goes undiagnosed, some doctors and health care providers may ask questions about your mood and thoughts during routine medical visits. They may even ask you to fill out a brief questionnaire to help check for depression symptoms.

When doctors suspect someone has depression, they generally ask a number of questions and may do medical and psychological tests. These can help rule out other problems that could be causing your symptoms, pinpoint a diagnosis and also check for any related complications. These exams and tests generally include:

- **Physical exam.** This may include measuring your height and weight; checking your vital signs, such as heart rate, blood pressure and temperature; listening to your heart and lungs; and examining your abdomen.
- **Laboratory tests.** For example, your doctor may do a blood test called a complete blood count (CBC) or test your thyroid to make sure it's functioning properly.
- **Psychological evaluation.** To check for signs of depression, your doctor or mental health provider will talk to you about your thoughts, feelings and behavior patterns. He or she will ask about your symptoms, and whether you've had similar episodes in the past. You'll also discuss any thoughts you may have of suicide or self-harm. Your doctor may have you fill out a written questionnaire to help answer these questions.

Diagnostic criteria for depression

To be diagnosed with major depression, you must meet the symptom criteria spelled out in the Diagnostic and Statistical Manual of Mental Disorders (DSM). This manual is published by the American Psychiatric Association and is used by mental health providers to diagnose mental conditions and by insurance companies to reimburse for treatment.

To be diagnosed with major depression, you must have five or more of the following symptoms over a two-week period. At least one of the symptoms must be either a

depressed mood or a loss of interest or pleasure. Symptoms can be based on your own feelings or may be based on the observations of someone else. They include:

- Depressed mood most of the day, nearly every day, such as feeling sad, empty or tearful (in children and adolescents, depressed mood can appear as constant irritability)
- Diminished interest or feeling no pleasure in all — or almost all — activities most of the day, nearly every day
- Significant weight loss when not dieting, weight gain, or decrease or increase in appetite nearly every day (in children, failure to gain weight as expected can be a sign of depression)
- Insomnia or increased desire to sleep nearly every day
- Either restlessness or slowed behavior that can be observed by others
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness, or excessive or inappropriate guilt nearly every day
- Trouble making decisions, or trouble thinking or concentrating nearly every day
- Recurrent thoughts of death or suicide, or a suicide attempt

To be considered major depression:

- Your symptoms aren't due to a mixed episode — simultaneous mania and depression that can occur in bipolar disorder
- Symptoms must be severe enough to cause noticeable problems in day-to-day activities, such as work, school, social activities or relationships with others
- Symptoms are not due to the direct effects of something else, such as drug abuse, taking a medication or having a medical condition such as hypothyroidism
- Symptoms are not caused by grieving, such as temporary sadness after the loss of a loved one

Other conditions that cause depression symptoms
There are several other conditions with symptoms that can include depression. It's important to get an accurate diagnosis so you can get the appropriate treatment for your particular condition. Your doctor or mental health provider's evaluation will help

determine if your symptoms of depression are caused by one of the following conditions:

- **Adjustment disorder.** An adjustment disorder is a severe emotional reaction to a difficult event in your life. It's a type of stress-related mental illness that may affect your feelings, thoughts and behavior.
- **Bipolar disorder.** This type of depression is characterized by mood swings that range from highs to lows. It's sometimes difficult to distinguish between bipolar disorder and depression, but it's important to get an accurate diagnosis so that you can get the proper treatment and medications.
- **Cyclothymia.** Cyclothymia (si-klo-THI-me-uh), also called cyclothymic disorder, is a milder form of bipolar disorder.
- **Dysthymia.** Dysthymia (dis-THI-me-uh) is a less severe but more chronic form of depression. While it's usually not disabling, dysthymia can prevent you from functioning normally in your daily routine and from living life to its fullest.
- **Postpartum depression.** This is a common type of depression that occurs in new mothers. It often occurs between two weeks and six months after delivery.
- **Psychotic depression.** This is severe depression accompanied by psychotic symptoms, such as delusions or hallucinations.
- **Seasonal affective disorder.** This type of depression is related to changes in seasons and diminished exposure to sunlight.

Make sure you understand what type of depression you have so that you can learn more about your specific situation and its treatments.

Treatments and drugs

Numerous depression treatments are available. Medications and psychological counseling (psychotherapy) are very effective for most people.

In some cases, a primary care doctor can prescribe medications to relieve depression symptoms. However, many people need to see a doctor who specializes in diagnosing and treating mental health conditions (psychiatrist). Many people with depression also benefit from seeing a psychologist or other mental health counselor. Usually the most effective treatment for depression is a combination of medication and psychotherapy.

If you have severe depression, a doctor, loved one or guardian may need to guide your care until you're well enough to participate in decision making. You may need

a hospital stay, or you may need to participate in an outpatient treatment program until your symptoms improve.

Here's a closer look at your depression treatment options.

Medications
A number of antidepressant medications are available to treat depression. There are several different types of antidepressants. Antidepressants are generally categorized by how they affect the naturally occurring chemicals in your brain to change your mood.

Types of antidepressants include:

- **Selective serotonin reuptake inhibitors (SSRIs).** Many doctors start depression treatment by prescribing an SSRI. These medications are safer and generally cause fewer bothersome side effects than do other types of antidepressants. SSRIs include fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro). The most common side effects include decreased sexual desire and delayed orgasm. Other side effects may go away as your body adjusts to the medication. They can include digestive problems, jitteriness, restlessness, headache and insomnia.
- **Serotonin and norepinephrine reuptake inhibitors (SNRIs).** These medications include duloxetine (Cymbalta), venlafaxine (Effexor XR) and desvenlafaxine (Pristiq). Side effects are similar to those caused by SSRIs. These medications can cause increased sweating, dry mouth, fast heart rate and constipation.
- **Norepinephrine and dopamine reuptake inhibitors (NDRIs).** Bupropion (Wellbutrin) falls into this category. It's one of the few antidepressants that doesn't cause sexual side effects. At high doses, bupropion may increase your risk of having seizures.
- **Atypical antidepressants.** These medications are called atypical because they don't fit neatly into another antidepressant category. They include trazodone (Oleptro) and mirtazapine (Remeron). Both of these antidepressants are sedating and are usually taken in the evening. In some cases, one of these medications is added to other antidepressants to help with sleep. The newest medication in this class of drugs is vilazodone (Viibryd). Vilazodone has a low risk of sexual side effects. The most common side

effects associated with vilazodone are diarrhea, nausea, vomiting and insomnia.

- **Tricyclic antidepressants.** These antidepressants have been used for years and are generally as effective as newer medications. But because they tend to have more numerous and more-severe side effects, a tricyclic antidepressant generally isn't prescribed unless you've tried an SSRI first without an improvement in your depression. Side effects can include dry mouth, blurred vision, constipation, urinary retention, fast heartbeat and confusion. Tricyclic antidepressants are also known to cause weight gain.
- **Monoamine oxidase inhibitors (MAOIs)**. MAOIs — such as tranylcypromine (Parnate) and phenelzine (Nardil) — are usually prescribed as a last resort, when other medications haven't worked. That's because MAOIs can have serious harmful side effects. They require a strict diet because of dangerous (or even deadly) interactions with foods, such as certain cheeses, pickles and wines, and some medications including decongestants. Selegiline (Emsam) is a newer MAOI that you stick on your skin as a patch rather than swallowing. It may cause fewer side effects than other MAOIs. These medications can't be combined with SSRIs.
- **Other medication strategies.** Your doctor may suggest other medications to treat your depression. These may include stimulants, mood-stabilizing medications, anti-anxiety medications or antipsychotic medications. In some cases, your doctor may recommend combining two or more antidepressants or other medications for better effect. This strategy is known as augmentation.

Finding the right medication

Everyone's different, so finding the right medication or medications for you will likely take some trial and error. This requires patience, as some medications need eight weeks or longer to take full effect and for side effects to ease as your body adjusts. If you have bothersome side effects, don't stop taking an antidepressant without talking to your doctor first. Some antidepressants can cause withdrawal symptoms unless you slowly taper off your dose, and quitting suddenly may cause a sudden worsening of depression. Don't give up until you find an antidepressant or medication that's suitable for you — you're likely to find one that works and that doesn't have intolerable side effects.

If antidepressant treatment doesn't seem to be working, your doctor may recommend a blood test to check for specific genes that affect how your body uses antidepressants. The cytochrome P450 (CYP450) genotyping test is one example of this type of exam. Genetic testing of this kind can help predict how well your body can or can't process (metabolize) a medication. This may help identify which

antidepressant might be a good choice for you. These genetic tests may not be widely available, so they're an option only for people who have access to a clinic that offers them.

Antidepressants and pregnancy
If you're pregnant or breast-feeding, some antidepressants may pose an increased health risk to your unborn child or nursing child. Talk to your doctor if you become pregnant or are planning on becoming pregnant.

Antidepressants and increased suicide risk
Although most antidepressants are generally safe, be careful when taking them. The Food and Drug Administration (FDA) now requires that all antidepressant medications carry black box warnings. These are the strictest warnings that the FDA can issue for prescription medications.

The antidepressant warnings note that in some cases, children, adolescents and young adults under 25 may have an increase in suicidal thoughts or behavior when taking antidepressants, especially in the first few weeks after starting an antidepressant or when the dose is changed. Because of this risk, people in these age groups must be closely monitored by loved ones, caregivers and health care providers while taking antidepressants. If you — or someone you know — have suicidal thoughts when taking an antidepressant, immediately contact your doctor or get emergency help.

Again, make sure you understand the risks of the various antidepressants. Working together, you and your doctor can explore options to get your depression symptoms under control.

Psychotherapy
Psychological counseling is another key depression treatment. Psychotherapy is a general term for a way of treating depression by talking about your condition and related issues with a mental health provider. Psychotherapy is also known as therapy, talk therapy, counseling or psychosocial therapy.

Through these talk sessions, you learn about the causes of depression so that you can better understand it. You also learn how to identify and make changes in unhealthy behavior or thoughts, explore relationships and experiences, find better ways to cope and solve problems, and set realistic goals for your life. Psychotherapy can help you regain a sense of happiness and control in your life and help ease depression symptoms such as hopelessness and anger. It may also help you adjust to a crisis or other current difficulty.

There are several types of psychotherapy that are effective for depression. Cognitive behavioral therapy is one of the most commonly used therapies. This type of therapy helps you identify negative beliefs and behaviors and replace them with healthy, positive ones. It's based on the idea that your own thoughts — not other people or situations — determine how you feel or behave. Even if an unwanted situation doesn't change, you can change the way you think and behave in a

positive way. Interpersonal therapy and psychodynamic psychotherapy are other types of counseling commonly used to treat depression.

Electroconvulsive therapy (ECT)
In ECT, electrical currents are passed through the brain. This procedure is thought to affect levels of neurotransmitters in your brain. Although many people are leery of ECT and its side effects, it typically offers immediate relief of even severe depression when other treatments don't work. It's unclear how this therapy relieves the signs and symptoms of depression. The most common side effect is confusion, which can last from a few minutes to several hours. Some people also have memory loss, which is usually temporary.

ECT is usually used for people who don't get better with medications and for those at high risk of suicide. ECT may be an option if you have severe depression when you're pregnant and can't take your regular medications. It can also be an effective treatment for older adults who have severe depression and can't take antidepressants for health reasons.

Hospitalization and residential treatment programs
In some people, depression is so severe that a hospital stay is needed. Inpatient hospitalization may be necessary if you aren't able to care for yourself properly or when you're in immediate danger of harming yourself or someone else. Getting psychiatric treatment at a hospital can help keep you calm and safe until your mood improves. Partial hospitalization or day treatment programs also are helpful for some people. These programs provide the support and counseling you need while you get symptoms under control.

Other treatments for depression
If standard depression treatment hasn't been effective, your psychiatrist may consider whether you might benefit from a less commonly used procedure, such as:

- **Vagus nerve stimulation.** This treatment uses electrical impulses with a surgically implanted pulse generator to affect mood centers of the brain. This may be an option if you have chronic, treatment-resistant depression.
- **Transcranial magnetic stimulation.** These treatments use powerful magnetic fields to alter brain activity. A large electromagnetic coil is held against your scalp near your forehead to produce an electrical current in your brain. Transcranial magnetic stimulation may be an option for those who haven't responded to antidepressants.

Lifestyle and home remedies

Depression generally isn't an illness that you can treat on your own. But you can do some things for yourself that will help. In addition to professional treatment, follow these self-care steps:

- **Stick to your treatment plan.** Don't skip psychotherapy sessions or appointments, even if you don't feel like going. Even if you're feeling well, resist any temptation to skip your medications. If you stop, depression symptoms may come back, and you could also experience withdrawal-like symptoms.
- **Learn about depression.** Education about your condition can empower you and motivate you to stick to your treatment plan.
- **Pay attention to warning signs.** Work with your doctor or therapist to learn what might trigger your depression symptoms. Make a plan so that you know what to do if your symptoms get worse. Contact your doctor or therapist if you notice any changes in symptoms or how you feel. Ask family members or friends to help watch for warning signs.
- **Get exercise.** Physical activity reduces depression symptoms. Consider walking, jogging, swimming, gardening or taking up another activity you enjoy.
- **Avoid alcohol and illegal drugs.** It may seem like alcohol or drugs lessen depression symptoms, but in the long run they generally worsen symptoms and make depression harder to treat. Talk with your doctor or therapist if you need help with alcohol or substance abuse.
- **Get plenty of sleep.** Sleeping well is important for both your physical and mental well-being. If you're having trouble sleeping, talk to your doctor about what you can do.

Alternative medicine

You may be interested in trying to relieve depression symptoms with complementary or alternative medicine strategies. These include supplements and mind-body techniques. Make certain you understand risks as well as possible benefits before pursuing alternative therapy. Don't forgo conventional medical treatment or psychotherapy for alternative medicine. When it comes to depression, alternative treatments aren't a substitute for medical care.

Here are some common alternative treatments that are used for depression.

Herbal remedies and supplements
A number of herbal remedies and supplements have been used for depression. A few common ones include:

- **St. John's wort.** Known scientifically as Hypericum perforatum, this is an herb that's been used for centuries to treat a variety of ills, including depression. It's

not approved by the FDA to treat depression in the United States. Rather, it's classified as a dietary supplement. However, it's a popular treatment in Europe for mild or moderate depression. But, it can interfere with other depression medicines, as well as some drugs used to treat people with heart disease, seizures, cancer and organ transplant.

- **SAMe.** Pronounced "sammy," this is a synthetic form of a chemical that occurs naturally in the body. The name is short for S-adenosylmethionine. It's not approved by the FDA to treat depression in the United States. Rather, it's classified as a dietary supplement. Side effects are usually minimal, but SAMe can trigger mania in people with bipolar disorder.
- **Omega-3 fatty acids.** Eating a diet rich in omega-3s or taking omega-3 supplements may help ease depression, especially when used in addition to standard depression treatments. These healthy fats are found in cold-water fish, flaxseed, flax oil, walnuts and some other foods.
- **Folate.** Low levels of folate, a B vitamin, may cause a slowed response to some antidepressants. Taking folate supplements (folic acid) may be helpful when used in addition to antidepressants. Ask your doctor what amount is right for you.

Keep in mind that nutritional and dietary products aren't monitored by the FDA the same way medications are. You can't always be certain of what you're getting and if it's safe. Also, be aware that some herbal and dietary supplements can interfere with prescription medications or cause dangerous interactions. To be safe, talk to your doctors and other health care providers before taking any herbal or dietary supplements.

Mind-body connections
The connection between mind and body has been studied for centuries. Complementary and alternative medicine practitioners believe the mind and body must be in harmony for you to stay healthy.

Mind-body techniques that may be tried to ease depression symptoms include:

- Acupuncture
- Yoga
- Meditation
- Guided imagery
- Massage therapy

As with dietary supplements, take care in using these techniques. Although they may pose less of a risk, relying solely on these therapies is not enough to treat depression.

Coping and support

Coping with depression can be challenging. Talk to your doctor or therapist about improving your coping skills, and try these tips:

- **Simplify your life.** Cut back on obligations when possible, and set reasonable goals for yourself. Give yourself permission to do less when you feel down.
- **Consider writing in a journal.** Journaling can improve mood by allowing you to express pain, anger, fear or other emotions.
- **Read reputable self-help books and websites.** Your doctor or therapist may be able to recommend books to read.
- **Join a support group.** Connecting with others facing similar challenges can help you cope. Local support groups for depression are available in many communities, and support groups for depression are also offered online.
- **Don't become isolated.** Try to participate in social activities, and get together with family or friends regularly.
- **Take care of yourself.** Eat a healthy diet, exercise regularly and get plenty of sleep.
- **Learn ways to relax and manage your stress.** Examples include meditation, yoga and tai chi.
- **Structure your time.** Plan your day and activities. You may find it helpful to make a list of daily tasks, use sticky notes as reminders or use a planner to stay organized.
- **Don't make important decisions when you're down.** Avoid decision making when you're feeling very depressed, since you may not be thinking clearly.

Prevention

There's no sure way to prevent depression. However, taking steps to control stress, to increase your resilience and to boost low self-esteem may help. Friendship and social support, especially in times of crisis, can help you weather rough spells. In addition, treatment at the earliest sign of a problem can help prevent depression from worsening. Long-term maintenance treatment also may help prevent a relapse of depression symptoms.

References

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WebMD

Article Link: http://www.webmd.com/depression/guide/depression-treatment-options?page=3

Symptoms | Doctors | Health Insurance

Depression Health Center

Listen

Depression Treatment Options

Once you have a depression diagnosis, your doctor will discuss various depression treatment options with you.

The kind of depression treatment that's best for you depends on the type of depression you have. For example, some patients with clinical depression are treated with psychotherapy, and some are prescribed antidepressants. Others are prescribed antidepressants and psychotherapy. Still others who don't respond to standard depression treatments may opt to try brain stimulation techniques such as electroconvulsive therapy (ECT), also called electroshock therapy, transcranial magnetic stimulation (TMS), or vagus nerve stimulation (VNS).

In people with bipolar depression, traditional antidepressants are not always effective and sometimes can make mood swings worse; doctors therefore often prescribe other types of medicines to treat bipolar depression, including mood stabilizers (such as Depakote, lithium or Lamictal) or some atypical antipsychotics (such as Seroquel or Symbyax) that are proven remedies for bipolar depression.

Whatever depression treatment your doctor prescribes, it's important to understand that there are no "instant" solutions. You may have to try different antidepressants to find the most effective drug for you. In addition, you'll have to take the antidepressant for several weeks to see if it benefits you at all. Being patient is important. Trust your doctor to know your personal history. With that, he or she can find the best depression treatment options that help improve your mood.

Recommended
Related to Depression

3 Food Traps to Avoid When You're Depressed

When you're struggling with depression, your eating habits often suffer. Some people overeat and gain weight, turning to food to lift their mood. Others find they're too exhausted to prepare balanced meals or that they've lost their appetite. "Whether you're overeating or not eating enough, you may be using food to feel better or to cope with difficult feelings," says Susan Albers, PsyD, a clinical psychologist at the Cleveland Clinic in Wooster, Ohio and author of 50 Ways to Soothe Yourself Without...

Read the 3 Food Traps to Avoid When You're Depressed article > >

What Are Depression Drugs?

Depression drugs can help lift your mood and ease the sadness and hopelessness you feel. You'll need to work with your doctor to find the depression medicine that is most effective with the fewest side effects.

For in-depth information, see WebMD's Depression Medicines.

How Do Antidepressants Work?

Many chemicals are involved in the brain circuits that regulate mood. Three known important chemicals are norepinephrine, serotonin, and dopamine, which are neurotransmitters. Neurotransmitters transmit electrical signals between brain cells.

Researchers have found a link between a chemical imbalance in these brain chemicals and depression. Antidepressant medications increase the availability of neurotransmitters or by changing the sensitivity of the receptors for these chemical messengers. It is believed that modifying these brain chemicals can help improve mood, although the exact way they work is still unclear.

What Are the Types of Antidepressants?

There are several types of antidepressants that improve of depression. The major types of antidepressants include:

Selective serotonin reuptake inhibitors (SSRIs). SSRIs work by altering the amount of a chemical in the brain called serotonin.

Serotonin and norepinephrine reuptake inhibitors (SNRIs). SNRIs are another form of antidepressant medicine that treat depression by increasing availability of the brain chemicals serotonin and norepinephrine.

Tricyclic antidepressants (TCAs). TCAs primarily affect the levels of two chemical messengers in the brain, norepinephrine and serotonin. Although these drugs are effective in treating depression, they can have more side effects than other drugs. So, they typically aren't the first drugs prescribed.

Monoamine oxidase inhibitors (MAOIs). MAOIs are most effective in people with depression who do not respond to other treatments. They are also effective for treating other mental illnesses. Substances in certain foods like cheese and aged meats, and certain medications (like decongestants or some

cough syrups) can interact dangerously with an MAOI. So people taking this drug must adhere to strict dietary restrictions. For this reason these antidepressants also aren't usually the first drugs prescribed.

There are other antidepressants that are not members of these classes.

Why Are Stimulants Prescribed for Depression?

Doctors sometimes prescribe other medications such as stimulants and anti-anxiety drugs to use in conjunction with an antidepressant. This is especially likely if the patient has a co-existing mental or physical disorder. However, neither anti-anxiety medications nor stimulants are effective against depression when taken alone.

Talk to your doctor about this type of treatment. Ask if it might boost the effect of your antidepressant.

What Is Psychotherapy's Role in Depression Treatment?

The role of psychotherapy in treating depression is to help the person develop appropriate and workable coping strategies, as well as to "restructure" attitudes and outlooks that are influenced by depression. These strategies help deal with everyday stressors and increase medication adherence. There are different types of psychotherapy, including individual, family, and group therapy. Your doctor will help you find the best type of psychotherapy for you.

For in-depth information, see WebMD's Psychotherapy for Depression.

When Is Electroconvulsive Therapy (ECT) Recommended for Depression?

Electroconvulsive therapy (ECT), also known as electroshock therapy, is typically used to treat severe depression. During ECT, a skilled doctor applies a brief electric current through the scalp to the brain while the patient is sedated. This current induces a seizure. ECT is very effective at treating depression.

ECT is generally used when severe depression is unresponsive to other forms of therapy. Or it might be used when patients pose a severe threat to themselves or others and it is dangerous to wait until medications take effect.

For in-depth information, see WebMD's Electroconvulsive Therapy (ECT) for Depression.

What Is the Transcranial Magnetic Stimulation (TMS) Device for Treating Depression?

In 2008, the FDA approved a transcranial magnetic stimulation device for treating major depression in adults for whom one antidepressant has failed to work. It is the least invasive of the brain stimulation techniques used in drug-resistant depression.

While electroconvulsive therapy (ECT or electroshock therapy) uses an electric current to induce seizure, TMS creates a magnetic field to induce a much smaller electric current in a specific part of the brain without causing seizure or loss of consciousness. The TMS device, an electromagnetic coil, is placed against the scalp near the forehead, sending pulses that stimulate nerve cells in the prefrontal cortex region of the brain, which controls mood.

Also unlike ECT, sedation of the patient isn't required. The procedure is done on an outpatient basis four or five times each week for up to six weeks. TMS is considered safe, and studies have shown it can be effective, although it has not been shown to be as effective as ECT.

For in-depth information, see WebMD's video on Brain Stimulation for Depression, and WebMD's High-Tech Treatments for Depression and Therapies for Treatment-Resistant Depression.

What Is Vagus Nerve Stimulation (VNS) for Depression?

Vagus nerve stimulation (VNS) is an invasive brain stimulation technique that is also used to treat those with treatment-resistant depression.

The way it works: A pacemaker-like device the size of a pocket watch is implanted in the chest, its wires leading to the left vagus nerve in your neck. The device sends regular electrical impulses to this nerve, which relays information to and from the brain.

For in-depth information, see WebMD's Vagus Nerve Stimulation for Depression.

Further Reading:

Slideshow: 11 Warning Signs of a Depression Relapse
Electroconvulsive Therapy (ECT) and Mental Illness
Depression: Why Aren't You Getting Treatment?
The Difference Between Depression and the Blues
Electroconvulsive Therapy (ECT) for Depression
Electroconvulsive Therapy and Other Depression Treatments
An Overview of Depression
See All Electroconvulsive Therapy (ECT) Topics

WebMD Medical Reference
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Depression Guide

1 Overview & Facts
2 Symptoms & Types
3 Diagnosis & Tests
4 Treatment & Care
5 Home Remedies
6 Finding Help for Depression

My Notes:

Comments about adding depression as a debilitating condition

I have long numerous of medicine allergies and could not have anti depression RX from DR (MD) anything they have to offer, I actually am allergy to all RX as they make me headache or migraine also cause me throw up and nausea feeling very ill, some water retention, gain over 60 lbs. I have been smoking marijuana since teenager and I'm now in 50's. It has kept me sane whole time. Best to smoke marijuana and talk things out instead pop pills and being zombie with mind being fogged!

You will still cry.. Rather cry to get out of chest than bottle up with anti depression rx and end up like zombie. anti depression pills never make me laugh, or being real me.. marijuana makes me laugh, being so me.. Very natural rather than chemical.

Cannabis is my choice for a "happy"pill. It treats me alot better than meds and the super abusive UPC (hospital)

I have been seeking help for my major depression for over six years and I believe that if I were able to come home after work and use marijuana I could stop taking so many prescription pills.

I have suffered depression throughout my military career and have never received benefits from the prescription drugs like I have with cannabis. The pills only made my symptoms worse and messed up my digestive tract where I couldn't even make it to a bathroom. Cannabis has given me freedoms I couldn't enjoy while foggy and cloudy minded on anti-depressants and anti-anxiety pills.

Juicing is a safe and healthy alternative and this woman and her testimony is proof that it works:

http://www.youtube.com/watch?v=S-iU9QN0fEM

Personally, I have suffered from depression for 15 years. I have tried two medications: Paxil and Zoloft with bad side effects from both. Zoloft has given me headaches and a sharp pain at the top of my brain. When I stopped taking Zoloft, I was at the highest dose that you can prescribe. To wean myself off, I used cannabis. I have been a daily user of cannabis and it has worked wonders for me, my mental health and my physical health. I am a mother of four children, one of which is handicapped. The stress is a lot most days. Cannabis helps me eat, calms my heart and blood pressure and helps me cope with general day to day life.

Being able to escape is what people that are caught in a vicious cycle seek. To be able to forget your psychic and probably accompanying physical pain for a period of time daily would be a relief to the affected party as well as ER's and community counseling sites. The public system takes the major psychiatric and emotional tasks of managing this difficult population. Instant relief relaxation and forgetting one's own pain and get some sleep is what Marijuana can do in this situation.

States that have authorized medical marijuana have seen a reduction in suicides. Some of those authorized patients use cannabis for depression and I strongly urge you to add depression to the list of authorized medical cannabis ailments.

http://ideas.repec.org/p/iza/izadps/dp6280.html

"Using state-level data for the period 1990 through 2007, we estimate the effect of legalizing medical marijuana on suicide rates. Our results suggest that the passage of a medical marijuana law is associated with an almost 5 percent reduction in the total suicide rate, an 11 percent reduction in the suicide rate of 20- through 29-year-old males, and a 9 percent reduction in the suicide rate of 30- through 39-year-old males. Estimates of the relationship between legalization and female suicides are less precise and are sensitive to functional form."

Frank Lucido, MD, a private practice physician, stated in his article "Implementation of the Compassionate Use Act in a Family Medical Practice: Seven Years Clinical Experience," available on his website

(accessed June 2, 2006):

"With appropriate use of medical cannabis, many of these patients have been able to reduce or eliminate the use of opiates and other pain pills, ritalin, tranquilizers, sleeping pills, anti-depressants and other psychiatric medicines.."

Lester Grinspoon, MD, Professor of Psychiatry at the Harvard Medical School stated in his 1997 book Marihuana: The Forbidden Medicine:

"Thirty to forty percent of patients with bipolar disorder are not consistently helped by conventional treatment. For some of them cannabis may be useful in ameliorating the symptoms, reducing side effects of lithium, or both."

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none

While using marijuana to treat chronic pain, I discovered a positive side-effect. The marijuana also managed my PTSD symptoms, which include depression. I have taken the prescriptions drugs my doctors have recommended over the years, but they were not effective. I did not feel normal and did not take them for very long. Marijuana has helped me with PTSD, depression, and anxiety while managing my chronic pain. And I am able to use my medicine with absolutely no side effects or toxicity by using edibles and tinctures. This medicine is natural and I can say from experience, it helps me manage the depression I have had my whole life, likely caused by childhood trauma. Therefore, I do not see why it would not help with depression in general. Concerning depression, Buder et al. (2006) reports common mental health symptoms include "major depressive disorder, anxiety disorders, and substance abuse" (p. 125). Buder et al. report "adults who had PTSD in childhood are 2 to 12 times more likely to smoke, abuse alcohol or drugs, develop depression, or attempt suicide" (p. 125).

Because Arizona would be the first state to add depression to the list of qualifying conditions, it will likely be difficult to obtain peer reviewed research regarding the benefits of marijuana on depression. As more people learn the positive qualities and many uses of marijuana, and see the benefit in themselves and their loved ones, we will be able to obtain more peer reviewed research so people can use marijuana to treat different medical conditions. By adding depression to the list of qualifying conditions, people will be able to have a healthier option to treat depression and live a healthier and more productive life. And there will be more opportunity for peer reviewed research. More importantly, people suffering with depression will be able to choose a healthier option than those drugs that may make them feel abnormal and cause more problems due to side effects. Thank you for taking the time to read this.

Sources:

Buder, K., Falcone, T. & Franco, K. (2006). Diagnosing and managing posttraumatic stress disorder, Cleveland Clinic Journal of Medicine, 73(2), 121-129.

I can only tell you, IT DOES help depression. Depression seems to lock one into recurring negative thoughts and possible suicide, Marijuana helps to alleviate those thoughts. That type of negative thought becomes only fleeting.

Cannabis has potentially powerful calming properties. It can make the less important worries go away as they should, while helping the person focus on what is truly important. Personally, my anger over how horrible people can be leads to episodes of depression, but with cannabis, I am able to cope with the mean people we all must live with less painfully. Then, I can stop dwelling on the bad and get to work fixing up the good things in my life.

I suffer from this condition and have for many years. Marijuana is and has been my ali for many decades and I am so greatful that I am able to see the great progress we have made in our country. The FED'S need to get on board and get the stick out of their desk drawers.

I do not know of any specific studies, but I know what works for me. I have suffered from depression and anxiety since I was a teenager, for over 15 years. Where all other medications have failed, marijuana has succeeded in my personal case.
I would be concerned with adding this generalized condition as just about everyone has something to be depressed about. There may be certain specific patients who may have severe depression from dealing with something extremely traumatic for a long period of time who may certainly benefit from using Medical Marijuana. In most cases of depression of this magnitude would probably fall under PTSD or some other Anxiety Disorder so I would be leary of adding a generalized depression condition to the list of approved conditions.
Being treated for depression/Anxiety helps, however, the medication doesn't always help with all of the debilitating symptoms. Marijuana helps to calm down the anxiety & balances out the depression concerns.
Many veterans and residences in Arizona are suffering from Depression. They are searching for another way to help their symptoms. Getting the people in need certified for medical marijuana would not only give patients another answer for therapy, but also an economical boost for the state of Arizona. Adding all four conditions benefits both the economy and citizens in our community.
No doubt I was a dpressed Teen. It is hard not to be these days. Once I started smoking cannabis, I often questioned if it was really worth getting "fucked up" all of the time. It took much experience but at the same time only a little to realize that cannabis does not "fuck you up". It actually does quite the opposite. So much , that through using it, I now do not get trashed drinking alcohol anymore. I no longer have a desire to drink what so ever. I have not smoked for months now due to some legal issues, but I still have no desire to use spice or alcohol. Cannabis not only bettered me, it cured me of depression and betted the life I have ahead of me. So proud to know that people are focused on spreading its many medical uses.
Just like with my PTSD, out of all the medications prescribed to me from the Veterans Administration nothing has come close to the relief medical marijuana provides for my depression. I also have no adverse side effects from medical marijuana which I cannot say the same about the prescription medications.
Depression can be mild or serious. smoking a little marijuana not only relieves anxiety but also calms the nervous system so that a person can feel better about themselves.
I think adding DEPRESSION would be of great benefit.I have suffered from it my whole life, and taking medical marijuana for my bad knee has also helped my DEPRESSION .Also it helps with the many side affects of the DEPRESSION pills that I take. Thank you
It takes my sadness away Op
I have found Cannabis far superior in treating my depression than any regimen of anti-depressants which made me suicidal.
I am bipolar with devastating depression episodes. I think that medical marijuana would go far to help curb some of my depression.
This comment is to address the concerns of the doctor who testified at the hearing against medical marijuana for the treatment of depression. The doctor pointed out that people who don't find releif with anti-depresssants should try other anti-depressants. I tried four different medicines before I found one that worked reasonably well and had side effects that I could tolerate. Even this medicine was inneffective against my worst depressive episodes. The doctor also stated that he did not beleive mmj would be of use for depression in the long term. I don't beleive he has empirical evidence to support that statement. Medicines afffect different people differently, as the doctor pointed out. And, even if it is not a long-term cure for depression, even the doctor admits that it does help people suffering from depression in the short term. That in itself will save lives. It takes weeks and sometimes months for patients to find the right antidepressant. Anything that provids releif for symptoms of severe depression,even if it is only short-term

releif, will save lives. Because of the stigma associated with mental illness many people wait to seek treatment until they are suicidal. Mmj could provide those patients with immediate releif, and save their lives and improve the quality of their lives. Let people use this while they wait for their other drugs to take effect. Medical marijuana is not perfect, but what medicine is? There is no legitmate reason to keep this from patients who do find relief with it.
it should be added
I for one and very enthusiastic about this. Depression is at least partially a chemical process, but it is made so much worse by mental factors, the greatest of which is a distortion of perception. Depression makes one myopic and self-centered, while at the same time creating a sense of hopelessness. Marijuana can assist many people in achieving an objective perspective on their lives and situations. This view of the "big picture" has the effect of diminishing the perception of immediate problems and seeing them for what they are, temporary speedbumps. In addition, many people are able to see, from outside, their own thinking patterns, which allows them to identify and correct those that do not serve them. This treatment strikes the root, rather than masking symptoms. In the long term, it is a far, far better way to approach the problem.
Adding depression would help a lot of people out there that suffer from depression that don't want to take pills. Mental illness can be just as difficult to live with as physical illness.
As an individual who has suffered from episodes of extreme, suicidal depression, I believe cannabis has been more effective than any other drug I have used to ameliorate depression and suicidal thoughts. I have tried Prozac, Paxil, Wellbutrin, Lithium, Dexedrine, Ritalin and Concerta. I have also tried 5-htp, ginseng, tea, coffee, vitamins, minerals, and various supplements, No other substance has effectively halted a depressive episode as effectively as cannabis. It allowed me to feel again and stopped me from killing myself in very desperate times. Aside from its antidepressant potential, cannabis encouraged me to eat and sleep regularly, which conventional antidepressants do not encourage. This allowed me some stability and rational thoughts in a time when I needed them.
As a patient in California, as well as a resident in Arizona, I feel it is important that depression gets added to the list of conditions for medical marijuana use. With California allowing depression as a condition I have been able to get off of Cymbalta, Zyprexa, and Xanax for the last year and a half. I feel that now, not only can I drive without feeling nauseous because of the medication I was on, but I feel like my old self just by being able to medicate in the morning and evening. That's not smoking all day, just enough to take the edge off a few times per day. As well as the panic and anxiety attacks that I used to get frequently.
Pills can help make you happy. Drinking alcohol can cause people to be happy or mean and aggressive. Both can have devastating effects on the body. Marijuana makes people happy and hungry, with very little side effects. I think of the declining susicide rates in the states who passed Mmj years ago! That should speak for itself!
I believe it should be added
Depression is the lack of hope due to crushing social and economic factors. This is probably the best case scenario for these people who feel downtrodden all the time. Marijuana lifts the spirit and allows the individual to have a chance to gain a better perspective.
Hi. I have a medical history going back 27 years with a disease named 'Multifocal Motor Neuropathy/MMN'... through this I have been hospitalized on several occasions with PTSD, Depression & GAD indirectly from dealing with this ailment. Every single time I used cannabis to control these issues, I have found comfort and a pathway to recovery. Please feel free to contact me for medical records and/or Doctor names for verification of this testimony. Thank You in Advance,
Add it. Cannabis helps this.

The prescribe medical MJ for depression in the Netherlands. I went there with another patient to see a doctor there about 15 years ago. He was prescribed marijuana for the depression and he was back able to work after many years of being totally shut in because of the depression. I really saw the difference it made in his life.
This simply makes sense. Depression stems from low serotonin levels, and marijuana temporarily increases serotonin production, and marijuana is safer than many current pharmacutical treatments, which also tend to work for a certain stretch of time, them begin to lose their functionaily.
When I was severely depressed and suicidal, cannabis was the only natural substance that when under it's influence would mitigate my negative thoughts, allow me to breathe,and allow me to take a step back to look at my situation and what I can do about it in a positively induced state of mind. It would allow me to perceive quite clearer. Infinite help. Self study. As legitimate as any.
This is a fantastic proposal. As a long time sufferer of both Depression and Anxiety disorder I can easily say that Marijuana worked great for me. I am originally from New York where it was decriminalized. When I moved to Arizona I had to give it up and I had to replace Marijuana with four different prescription drugs that took the place of the marijuana - and not only costed a great deal more financially - they also had several problematic side effects. Approving Medical Marijuana for patients suffering from these proposed conditions would not only help a great many people medically - it would also ease the financial burden on many people.
I have suffered from depression in the past related to P.T.S.D., and I have used medical cannabis since the passing of SB420 in California. It's replaced the need for other medications approximately 96% of the time. It's a much safer alternative to prescription medications offered for the same type of treatment. My doctors, both psychological and orthopedic, have recommended the use of marijuana for treatment in lieu of prescription medications.
I was diagnosed with major depression in 1996 and I've been taking anti-depressants as prescribed by a psychiatrist since that time. In 2002 I was diagnosed with Post Traumatic Stress Disorder by a Masters-level therapist. The trauma is related to several years of child abuse. I also experience anxiety and insomnia. The medicine I currently take, sertraline, is insufficient and has side effects I find unpleasant and debilitating in their own right. For example, in 2009 I suffered a loss that left me extremely depressed for months. I experienced suicidal thoughts at least once every day for over 100 days in a row, and often several times per day. This happened while I was taking the maximum dose of sertraline. The side effects I experience with sertraline include dry mouth, weight gain, personality changes which cause relationship difficulties, and insomnia. These side effects have almost as much negative impact on my life as the depression. When I tried a supplemental prescription I suffered these side effects even more, as well as confusion and memory problems that I found intolerable. Using marijuana elevates my mood and helps me fall asleep and stay asleep all night. It helps me relax, focus my thoughts and remain calm when I'm experiencing stress. I've used marijuana in the past to self-medicate for depression and anxiety. The withdrawal experience for marijuana was less of a problem than a common cold. And I quit smoking tobacco and kicked addictions to meth and cocaine, so I know what withdrawal feels like. I don't consider marijuana addictive. I think it is the least harmful, most beneficial alternative for my health condition. I should be allowed to choose the medicine that works best for me.
The pills that are prescribed for depression are UN-healthy, damaging to your system and addicting. Cannabis is a much safer choice.
Many people in California who suffer from this disorder have benefited from the use of MMJ.
Having severe pain and not being able to afford the operation to correct the problem
I know many patients who were certified through cancer or chronic pain, but also are now relieved from

depression through using cannabis. I also know many patients waiting to be certified once Depression is passed as a qualifying medical condition. they are tired of the side effects of their anti-depressants
Without the illegal use of marijuana to calm me down when I reach lows, I would have taken my own life years ago. Please allow this to qualify so that I don't have to choose between being a criminal or being dead.
Myself and several members of my family suffer from depression, cannabis is extremly helpful and does not have the side effects of the pills i take for it. I recently found out that my liver is having problems due to the pills. Please add depresion to the list of acceptable conditions. Thank you
I am a registerd patient in Vermont and find that medicinal cannabis relieves depression. I have been using cannabis for over a year.
My psychiatrist actually suggested this for off label use as he was aware I was trying to get it for chronic pain issues related to my back. At the time I was taking depakote, celexa, trazadone and xanax. After smoking regularly for a couple of weeks I was able to eliminate my insomnia (caused by the anxiety and depression) and therefore my trazadone use. I was able to stop the celexa and depakote almost immediately that was directly for the depression by replacing the morning pills with cannabis. I still take the xanax, but only because I work somewhere that has doesn't allow for possession on the property and some days are still worse than others, but we are hoping as this law progresses that will change and I will be able to eliminate all pharmaceuticals in my body.
I am currently being treated for depression at the Yavapai Guidance Clinic in Prescott. I KNOW for a fact that the medicinal benefits of marijuana would far outweigh anything I have been prescribed at the clinic. I have never asked or spoken to the psychiatrist in this regard for fear of repercussion. Paranoia is not something I needed to add to the list of what I have been diagnosed with.
As a sufferer of Major Depressive Disorder I found marijuana to be very helpful. It does not have the horrible side effects as of the common depression medication. And there is no two weeks to a month wait to find out if the medication will even work. And I never got suicidal from using marijuana to treat my depression. In a controlled manner I believe marijuana could be a great help for alot of fellow sufferers of depression.
PTSD can and often does lead to depression. Depression can result in a state like AZ to any average people who have lost jobs late in life and are losing their homes as well. AZ is one of the worst hit states for a depression. SCottsdale used to have an upmarket reputation and now it is consignment stores who rip off the people and GOODWILL warehouses opening everywhere. SCottsdale is NOT what it used to be and that is depressing if you live there and have watched the decline.
My wife suffers from clinical depression and is schizo-effective, she uses medical cannabis and it helps her feel so much better, it's like night and day. Please just legalize it as it's not only harmless but has many uses even beyond medical uses.
I personally have used marijuana to treat manic deppression for the past 20 years. IT works and has less side affects than antideppressants.
I am presently a covered patient under HCV; however prior to using Med Mar I suffered from moderate depression and anxiety and this is no longer the case. I attribute this to the medicine.
very good decision, i know it will help, ty
I think people who suffer from depression could also benefit from medical marijuana.
Cannabis is one medicine that doesn't give me depression as side effect

Certainly, a substance which makes one feel good, would seem like a great treatment for depression. It's hard to be depressed when you're high!
I feel that if a doctor deems marijuana use a proper medicine to give patients who suffer depression . It should be ok.
Marijuana cured my depression in so many ways..
Anyone who has ever experienced chronic depression can attest that it is a debilitating condition. As with the other mental health conditions proposed depression is all too often treated with drugs whose side affects are themselves debilitating. Medical marijuana with the direction of knowledgeable physicians, growers, and or dispensaries can become an important aspect of the treatment of depression. I believe that in cordination with therapy strains of marijuana can be beneficial in the treatment of this debilitating condition.
Citations: The Therapeutic Potential of the Endocannabinoid System for the Development of a Novel Class of Antidepressants. Trends in Pharmacological Sciences, Volume 30, Issue 9, September 2009, Pages 484-493. Matthew N. Hill, Cecilia J. Hillard, Francis R. Bambico, Sachin Patel, Boris B. Gorzalka, Gabriella Gobbi. The endocannabinoid system and the treatment of mood and anxiety disorders. Hill MN, Gorzalka BB. Laboratory of Neuroendocrinology, The Rockefeller University, New York, NY, USA. J Pharmacol Exp Ther. 2006 Jul;318(1):304-11. Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: further evidence for an anxiolytic role for endogenous cannabinoid signaling. Patel S, Hillard CJ. Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, WI 53226, USA. J Pharmacol Exp Ther. 2006 Jul;318(1):304-11.
I am a father who happens to have two hidden disabilities. I couldn't agree more with George McMahon author and medical marijuana patient of the U.S. Federal Drug Administrations Investigational New Drug Program as he states in his 2003 book Prescription Pot: People who have never struggled with a life threatening or disabling illness often do not comprehend how debilating the resulting depression can be. Long days spent struggling with sickness can wear patients down, suppress their appetites and slowly destroy their will to live. Lastly Mr.McMahon states that the elevated mood associated with cannabis definitely affected his health in a positive way more engaged with life. The same as it has done for me. Thank You.
Depression should be added to the list of debilitating conditions. It could help people get off of much more dangerous Rx medicines that have a high overdose/death potential
I am certified as a medical marijuana patient. I am also diagnosed with PTSD. In using my medicine to help me control my physical pain, it has also lessened my PTSD symtoms as well. I am certified as a medical marijuana patient. I am also diagnosed with Bi Polar disorder. In using my medicine to help me control my physical pain, it has also lessened my Bi Polar symtoms as well.
Depression would only get worse if you didnt smoke or take it all day
I have also experienced evidence that medical marijuana aids in eliminating depression systems.

This is very obvious, Marijuana is a depressing drug, sedative, nonmotivated thought process and certainly does nothing but make the depression worse. Where is the documented research that is truly a validated reason to resolve a biochemical imbalance in the brain. My patients do not function on Marijuana they are addicted and do not function, use while pregnant and are very depressed and anxious due to withdrawal when they try to get off the drug. They are less alert, cognitive impairment and overall decreased qualtiy of life.

People who are depressed have enough issues to deal with, without adding addiction to their woes

Marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision. The drug is listed in Schedule I of the Controlled Substances Act (CSA), which is the most restrictive schedule. The Drug Enforcement Administration, which administers the CSA, continues to support that placement. The FDA concurred because marijuana met the three criteria I stated above for placement in Schedule I under 21 U.S.C. 812(b)(1)

Depression, as it is presently understood, is an effect of a full brain condition that has influences both psychosomatic and physiologic. The most commonly prescribed medications for depression are SSRIs or selective serotonin re-uptake inhibitors. These drugs allow for the neurotransmitter serotonin to remain present for a longer duration within the interstitial spaces of neurons, allowing for a longer time of action. Unfortunately, many SSRIs have a litany of unintended side effects, ranging from serotonin syndrome, sexual dysfunction to prolonged nausea, vomiting, and diarrhea. Medical marijuana can allow for patients with depression, ranging from mild to severe, to treat themselves with a substance that allows for increased production of serotonin, which can act in small doses without the side effects commonly seen with SSRIs. This treatment also allows patients who would otherwise choose to forgo treatment with synthetic drugs, an option to utilize medical marijuana in a way that is not otherwise deleterious to their health (ie: consuming edible foods containing THC or tinctures rather than smoking or vaporizing the substance). The THC in the cannabis acts directly on the cannabanoid receptors CB1 and CB2 in the brain and periphery CNS, both of which are known to suffer from reduced signaling in patients with diagnosed depression. The CB1 receptors in the prefrontal cortex and hippocampus exhibit increased serotenergic neurotransmission as well as noradrenergic neurotransmission and increased nuerogenesis in regions of the hippocampus. I know from personal knowledge that those individuals diagnosed with depression gain a vast improvement in quality of life from the use of marijuana in limited amounts. I very strongly support and encourage the addition of depression and depressive disorders to the list of conditions that qualify for medical marijuana use. I cite the following articles:

- Denson, T.F.; Earleywine, M. Decreased depression in marijuana users. Addict. Behav., 2006, 31, 738-742.;
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- Bambico, F.R.; Katz, N.; Debonnel, G.; Gobbi, G. Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. J. Neurosci., 2007, 27, 11700-11711.;
- Adamczyk, P.; Golda, A.; McCreary, A.C.; Filip, M.; Przegalinski, E. Activation of endocannabinoid transmission induces antidepressant-like effects in rats. J. Physiol. Pharmacol., 2008, 59, 217-228.;
- Jiang, W.; Zhang, Y.; Xiao, L.; Van Cleemput, J.; Ji, S.P.; Bai, G.; Zhang, X. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J. Clin. Invest., 2005, 115, 3104-3116.;
- Morrish, A.C.; Hill, M.N.; Riebe, C.J.; Gorzalka, B.B. Protracted cannabinoid administration elicits antidepressant behavioral responses in rats: role of gender and noradrenergic transmission. Physiol. Behav., 2009, 98(1-2), 118-124.;
- McLaughlin, R.J.; Hill, M.N.; Morrish, A.C.; Gorzalka, B.B. Local enhancement of cannabinoid CB1 receptor signalling in the dorsal hippocampus elicits an antidepressant-like effect. Behav. Pharmacol., 2007, 18, 431-438.;
- Hill, M.N.; Karacabeyli, E.S.; Gorzalka, B.B. Local enhancementof cannabinoid CB1 receptor signalling in the dorsal hippocampus elicits an antidepressant-like effect. Psychoneuroendocrinology, 2007, 32, 350-357.

There is no research that constructively shows that MJ will aid someone with depression. MJ can have the opposite effects and cause a further and deeper depression.
How do you define depression and this is one of self-reporting or do you have to have a diagnosis of clinical depression? What about postpartum depression where the life of the child is in danger because of the deteriorating mental state of a new mother? What about the effects of breast feeding on new babies if the mother is on medical marijuana? Will children be taken away from their mothers if a positive test for cannabis is given and the mother is a medical marijuana patient? What protections will you offer to the patients if this condition is added? Also what test is available to show depression other than anecdotal? Most people suffering from depression self-medicate (alcohol being the number #1 mendicant) and how is now medicating with another substance (cannabis) going to interact with other medications (both OTC, legal and illegal) going to benefit someone with depression. How will this work in older patients who living in nursing homes where depression is a given especially with the lack of outdoor sunshine resulting in "Sundowners Syndrome." Will the AzDHS make all efforts to help patients that are confined in nursing homes and have so little say in their treatment plan an option of medical marijuana with the skilled nursing staff?
Why would we resort to an illegal drug when there are proven therapies that include behavioral and medical treatments to correct this illness?
Who gets to decide which emotionaly disabled students need to smoke marijuana and at what age they should be entitled to do so? This is not something that should be considered with all of the medications currently in stock and approved for the treatment of depression. Counseling is more reliable and useful that drugs for depression. Human companionship, and compassion not drugs.
As someone who suffers from depression from chronic pain, it is not advisable to throw another drug in the mix to lift the mood temporarily when it could lead some to continual substance abuse.
A number of studies have shown an association between chronic marijuana use and increased rates of anxiety, depression, and schizophrenia. Some of these studies have shown age at first use to be an important risk factor, where early use is a marker of increased vulnerability to later problems. However, at this time, it is not clear whether marijuana use causes mental problems, exacerbates them, or reflects an attempt to self-medicate symptoms already in existence. - NIDA
Now a days almost everyone suffers from depression. I have many clients who effectively treat there depression with medication and I personally feel that the use of marijuana is unnessasary. Working at a substance abuse treatment center and working with psychiatrists daily I feel that this motion is ridiculous.
Again, I work with individuals with depression, I have not seen anyone that uses marijuana get better with it, in fact it just leads to other things.
There are current medications for this illness that work
as above
It is not appropriate for the Arizona Department of Health Services to add marijuana as a treatment for mental or physical conditions - knowing that marijuana remains an illegal substance under Federal Law.
There are better treatments for depression such as SamE and less debilitating therapeutic methods. Using marijuana for depression would further exacerbate the amotivational aspects of depression which occur as a result of the depressive disorder in the first place.
Enough is know about brain chemistry to fairly well determine which of the three classes of antidepressants would be the best medical treatment for depression. Is there a real reason to add marijuan to the mix, other than simply making it legal?
It is not appropriate for the Arizona Department of Health Services to add marijuana as a treatment for

mental or physical conditions because marijuana is an illegal substance under Federal Law.

There is a huge correlation between the increase of 'medical' marijuana and increasing use of marijuana among teens. The data is very alarming as early use of marijuana greatly increases the risk for abusing other drugs and addiction.

Expansion of 'medical' marijuana for use in other conditions, although allowed under the Initiative Prop 203, should only be considered in extreme situations because of the Federal illegality, increasing substance abuse risks, health and safety risks it places upon youth and other Arizona citizens.

Further, the AZ Department of Health Services is not in the business of approving untested medication for treatment.

It is not appropriate for the Arizona Department of Health Services to add marijuana as a treatment for mental or physical conditions - knowing that marijuana remains an illegal substance under Federal Law.

Marijuana DOES NOT CURE an illness, rather it relieves symptoms, but so would a massage. This is ludicrous.

It is not appropriate for the Arizona Department of Health Services to add marijuana as a treatment for mental or physical conditions - knowing that marijuana remains an illegal substance under Federal Law.

Medical marijuana helps with lots of the symptoms of depression and you don"t have to worry about the possible side effect of thoughts of suicide as well as many other harmful things the pills prescribed to treat this. Any time you see a commercial on tv to advertise depression treatment over half of the commercial is devoted to warning you of the side effects, which some of are worse than the illness itself.

Pharmacology and effects of cannabis: a brief review†

1. C. HEATHER ASHTON, FRCP, Emeritus Professor of Clinical Psychopharmacology

The British Journal of Psychiatry (2001) 178: 101-106 doi: 10.1192/bjp.178.2.101

ACTIONS OF CANNABIS IN HUMANS

Cannabis affects almost every body system. It combines many of the properties of alcohol, tranquillisers, opiates and hallucinogens; it is anxiolytic, sedative, analgesic, psychedelic; it stimulates appetite and has many systemic effects. In addition, its acute toxicity is extremely low: no deaths directly due to acute cannabis use have ever been reported. Only a selection of cannabis effects are described in this review; other actions are reviewed by Paton & Pertwee (1973), Pertwee (1995), Adams & Martin (1996) and many others.

Psychological effects

Effect on mood

The main feature of the recreational use of cannabis is that it produces a euphoriant effect or 'high'. The high can be induced with doses of THC as low as 2.5 mg in a herbal cigarette and includes a feeling of intoxication, with decreased anxiety, alertness, depression and tension and increased sociability (if taken in friendly surroundings). The high comes on within minutes of smoking and then reaches a plateau lasting 2 hours or more, depending on dose. It is not surprising that the overwhelming reason for taking cannabis given by recreational users is simply 'pleasure' (Webb et al, 1996, 1998). However, cannabis can also produce dysphoric reactions, including severe anxiety and panic, paranoia and psychosis. These reactions are dose-related and more common in naïve users, anxious subjects and psychologically vulnerable individuals. (Psychiatric reactions including aggravation or precipitation of schizophrenia are described by Johns, 2001, this issue).

Effects on perception

Accompanying the high, and often contributing to it, cannabis produces perceptual changes. Colours may seem brighter, music more vivid, emotions more poignant and meaningful. Spatial perception is distorted and time perception is impaired so that perceived time goes faster than clock time. Hallucinations may occur with high doses.

Effects on cognition and psychomotor performance

Not surprisingly, cannabis impairs cognitive and psychomotor performance. The effects are similar to those of alcohol and benzodiazepines and include slowing of reaction time, motor incoordination, specific defects in short-term memory, difficulty in concentration and particular impairment in complex tasks which require divided attention. The effects are dose-related but can be demonstrated after relatively small doses (5-10 mg THC in a joint), even in experienced cannabis users, and have been shown in many studies across a wide range of neurocognitive and psychomotor tests. These effects are additive with those of other central nervous system depressants.

Driving and piloting skills

These effects combine to affect skills related to driving a vehicle or flying an aeroplane. Numerous studies have shown that cannabis impairs road-driving performance and have linked cannabis use with increased incidence of road traffic accidents. In the UK, USA, Australia, New Zealand and many European countries, cannabis is the most common drug, apart from alcohol, to be detected in drivers involved in fatal accidents or stopped for impaired driving. A large proportion of such drivers have not taken alcohol or have concentrations below the legal limit. For example, in two studies from the UK Department of Transport (Everest et al, 1989; Department of Environment, Transport and the Regions, 1998), no alcohol was detected post-mortem in 70% and 80%, respectively, in road traffic accident fatalities testing positive for cannabis. In Australia (Road Safety Committee, 1995) only half of surviving drivers of vehicle collisions involving death or life-threatening injuries who tested positive for cannabis had also taken alcohol. In Norway, 56% of a sample of drug-impaired drivers negative for alcohol gave positive blood samples for THC (Gjerde & Kinn, 1991). From the USA, McBay (1986) had earlier found that 75% of a sample of drivers with cannabinoids in their blood were also intoxicated with alcohol. The World Health Organization (1997, p. 15) concluded:

"There is sufficient consistency and coherence from experimental studies and studies of cannabinoid levels among accident victims...to conclude that there is an increased risk of motor vehicle accidents among persons who drive when intoxicated with cannabis....The risk is magnified when cannabis is combined with intoxicating doses of alcohol".

Piloting an aeroplane is an even more complex task than driving a car and cannabis has been shown in several investigations seriously to impair aircraft piloting skills. The results of one placebo-controlled study are shown in Fig. 4 (Leirer et al, 1991). The subjects were nine licensed pilots, highly trained in a flight simulator task, who were current cannabis users. They received a cannabis cigarette containing 20 mg THC (a moderate dose by present-day standards). This dose caused a significant decrement in performance compared with placebo and the impairment lasted over 24 hours after this single dose. Furthermore, most of the pilots were unaware that their performance was still impaired at 24 hours. Several pilots reported that they had actually flown while high on cannabis, and the authors noted that in at least one aeroplane crash the pilot was known to have taken cannabis some hours before flying and to have made a similar landing misjudgement (poor alignment on the runway) as was noted in experimental studies.

Fig. 4

Effect of smoking a cannabis cigarette containing 20 mg tetrahydrocannabinol (THC) on pilot performance in a flight simulator landing task (Leirer et al, 1991). - - ▪ - -, 20 mg THC; –[UNK]–, placebo.

There is evidence that similar longlasting impairments apply to motor cyclists, train drivers, signal

operators, air traffic controllers and operators of heavy machinery. However, a problem is that because of the very slow elimination of cannabinoids, there is no accurate way of relating blood, urine, saliva or sweat concentrations to the degree of intoxication of the driver or pilot at the time of an accident, no way of telling exactly when the last dose was taken and no proof that cannabis was actually the cause of an accident.

Long-term effects of chronic use

There is considerable evidence, reviewed by Hall et al (1994), that performance in heavy, chronic cannabis users remains impaired even when they are not actually intoxicated. These impairments, especially of attention, memory and ability to process complex information, can last for many weeks, months or even years after cessation of cannabis use (Solowij, 1998). Whether or not there is permanent cognitive impairment in heavy long-term users is not clear.

Tolerance, dependence, withdrawal effects

Tolerance has been shown to develop to many effects of cannabis including the high and many systemic effects, and a cannabis withdrawal syndrome has been clearly demonstrated in controlled studies in both animals and man (Jones, 1983; Kouri et al, 1999). The withdrawal syndrome has similarities to alcohol, opiate and benzodiazepine withdrawal states and includes restlessness, insomnia, anxiety, increased aggression, anorexia, muscle tremor and autonomic effects. A daily oral dose of 180 mg of THC (one or two modern, good-quality joints) for 11-21 days is sufficient to produce a well-defined withdrawal syndrome (Jones, 1983). The development of tolerance leads some cannabis users to escalate dosage, and the presence of withdrawal syndrome encourages continued drug use. Thus, chronic cannabis use can lead to drug dependence, and reports from the USA, UK and New Zealand (Roffman & Barnhart, 1987; Stephens et al, 1993) indicate that many cannabis users are now seeking treatment for cannabis dependence.

J Addict Med. 2011 Mar;5(1):1-8.

An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions.

Crean RD, Crane NA, Mason BJ.

Source

Committee on the Neurobiology of Addictive Disorders; The Scripps Research Institute; La Jolla, CA 92037, USA.

Abstract

Cannabis use has been shown to impair cognitive functions on a number of levels-from basic motor coordination to more complex executive function tasks, such as the ability to plan, organize, solve problems, make decisions, remember, and control emotions and behavior. These deficits differ in severity depending on the quantity, recency, age of onset and duration of marijuana use. Understanding how cannabis use impairs executive function is important. Individuals with cannabis-related impairment in executive functions have been found to have trouble learning and applying the skills required for successful recovery, putting them at increased risk for relapse to cannabis use. Here we review the research on the acute, residual, and long-term effects of cannabis use on executive functions, and discuss the implications for treatment.

Please don't add. It is so difficult raising children now, a 20 year old young man told me the other day he was going to get a medical marijuana card because he can't eat or sleep without smoking pot. That is called addiction, not depression.

Depression is a debilitating condition based on the fact that the joy one gets from life is taken away, and

no matter what one thinks, serotonin levels in the brain prevent that joy. Depression patients have a high risk of suicide. Cannabis is an effective alternative to antidepressants, because it has been shown to have antidepressant-like effects without the risk of dependency or addiction that is associated with actual antidepressants. Antidepressants carry a strong warning that patients just starting the drug may have an increased risk of suicide and therefore must be monitored closely. This is a legal drug, and it may cause a person to kill him/herself. Antidepressants can also reduce hunger, which is not healthy. Cannabis increases hunger and allows depressed patients to eat more. Another issue with antidepressants relates to sexual side effects. Antidepressants can cause impotence and lack of sexual desire. This type of side effect only compounds the original condition for which treatment was sought. Medical marijuana should be permitted for those with severe depression.
Marijuana is the safest anti-depressent known.
Needs to be added. Most effective non narcotic alternative.
I know that medical marijuana does help with depression, if only to allow an escape. There is the concern about depression being easily diagnosed, thus allowing it to be an easy pathway to getting illegitimate medicine, but this should NOT get in the way of people who actually want to treat their depression with medical marijuana. That problem should be handled in a way that does not obstruct the patients' pursuit of health.
Marijuana also lifts depression with out having to wait for weeks as with Prozac and similar medicines. It works very well. Why not use it? This illness also needs to be included in the schedule of diseases with the the State of Arizona.
I will put my concern under depression since depression is a common youth condition. My high school children now think that smoking marijuana is not harmful because of this law. It is now common for high school age students to purchase marijuana from someone with a medical marijuana card for rec use. If additional conditions are added that pertain to youth then the youth in their under-developed logic think marijuana is not harmful to them and they will continue to buy from someone with a card. Please do not add more conditions to this harmful law. I respect the truly ill and their desire for relief however, the risk to youth and their safety is a greater concern of mine in the overall picture. Unfortunately, many abuse the law and it is not easily enforceable.
Since becoming a licensed medical marijuana user I have noticed the beneficial effects with my depression diagnosis, I feel better than I have felt in 11 years since my cancer diagnosis. Depression is gone, happier, healthier, livelier and more self confident knowing I can medicate and be legal. Thank you Mr. Humble. Definitely add depression to the list of debilitating conditions.
I'm pro for adding depression. My mother has suffered from depression and suffers more almost from the side effects of prescribed medications. Following is an excerpt backing my pro opinion. "I think cannabis has a lot of potential in the treatment of mental illness," says Lester Grinspoon, emeritus professor of psychiatry at the Harvard School of Medicine. He says that it can be an effective treatment for bipolar disorder and depression. Like any medicine, he cautions, " it will not work for everyone. " Grinspoon has, over the last three decades, been one of the few psychiatrists willing to speak publicly on " mental marijuana." Two weeks ago, the Israeli army said it would provide, on an experimental basis, medical marijuana to troops suffering from post-traumatic stress disorder, another mental illness. Good enough for an army, good enough for me.
Marijuana will increase amotivation which is a major symptom of depression.
It works for depression when I have felt sad or depressed a little bit will make me feel back to my old self quite quickly

There is an incredibly strong correlation with marijuana use and depression--marijuana very often causes loss of motivation, which exacerbates and can even cause depression. It would interfere with treatment, and in fact long-term marijuana use can make a person treatment resistant. Again, users would be self-medicating for the rest of their lives--it is just an excuse to continue using marijuana, despite the side effects it causes, including depressive symptoms over time.

Please add.

Woefully low documentation

yes add it.

As a psychologist, I am concerned that people with depression would cover up their symptoms with marijuana rather then change a situation that may be the result of their depression. Treating their symtoms and eliminating the source of their depression with known interventions that are recognized as the best practice for this disorder should be the goal of any wellness program. Providing someone with an addictive drug is not good interventions for this very common problem. Intervention approaches such as Eye Movement Desensitization and Reprocessing (EMDR) and other cogntive behavorial interventions are effective treatment methods that do not interfer with healthy brain functioning like marijuanna does. I support medical marijuane for medical conditions such as pain, which may have no symptom relief with any other intervention. If marijuana use for this diagnosis is approved, I would hope that one requirement prior to resorting to marijuana would be that all other forms of recognized effective mental health treatment and psychotropic medications would have been tried and had failed.

I'm sure you are getting a lot of comments about adding depression and GAD to the current medical marijuana law, so I appreciate you taking the time to read my comments and concerns.

As a 35 y.o. living with Bipolar II, I do believe that there will be a lot of people who will fake both depression, GAD, or anxiety as a symptom to simply get a medical marijuana card. Knowing that, however, is also extremely frustrating to those of us who suffer from these conditions each and every day. My daily/nightly ritual has revolved around taking a mix of alprazolam 1MG 3x/day, Lyrica 100MG 2x/day, Viibryd 40MG 1x/day at night, trazadone 100MG 1/day before bed, and now switching to lithium from lamotrigine 200mg/2x a day due to side effects. While they have helped a small bit in my anxiety/depression, they have also had the effect of numbing me more to life and losing any true feelings. While I'm not saying they don't work to a degree, they still have not stopped the bouts of insomnia; irrational anxiety about how I'm going to pay my bills (I have $40K in a savings account because I refuse to move it in case I may lose my job; run in to a stop light and be denied insurance, be subject to a lawsuit etc). They haven't fully stopped the the depression that keeps me in bed some days, nor other symptoms from returning at a moments notice. For instance, I missed an 8 a.m. meeting with our largest corporate sponsor two weeks ago because I couldn't sleep for 36 hrs. straight the nights prior and then, when I finally did sleep, slept right through the three alarm clocks I must keep in my room for those days when I finally crash. How do you tell a client/sponsor "I'm sorry, but my crazy meds are acting up again."? Thankfully, I work for a non-profit health agency that is well suited to understand these issues, but what if I didn't?

I would like your panel to remember that everything can be used inappropriately. Kitty Dukakis herself admitted to drinking rubbing alcohol as a substitute; people use spray paint to get high from the fumes; Benadryl is now behind counters because of its use in Meth production. These are all legal substances that, in the wrong hands, can be harmful. So I understand that your decision will likely face those dilemmas.

However, I'd also like for you to keep in mind those of us who may benefit from marijuana. The only time I've ever used marijuana was when I was in my young 20's and visiting Amsterdam. I remember that it was the first time I truly laughed and felt at ease. And by 'truly laughed', I meant the laughter wasn't the fake 'this is where I'm supposed to laugh in a social situation' but a truly, heart felt laugh. It was amazing to feel so normal. To have my committee (as I like to call the numerous voices in my head telling me I need to be worried about X,Y, and Z) finally be silent and my own mind saying 'it's OK. Just relax." Was

an eye opening experience. Since that has been many, many years ago, I don't know if marijuana would work for me now but I feel I should at least be given the option to try. I read about how the military is using MDMA to help treat PTSD patients and I ask; why are we still so hung up on allowing marijuana to be used as a medication.

Will medical marijuana truly change our culture? If I wanted, I could sell the alprazolam and Lyrica I get each month from Walgreens to individuals who could use it to get high. Allowing the addition of marijuana as a treatment for these conditions will certainly lead to those who abuse the system, but these people already likely abuse the system by buying marijuana illegally so I do not believe there would be any societal change in usage. However, denying the addition would only harm those of us who follow the law and are allowed to physically and mentally suffer because of our conditions.

In summary, it is a damned if you do, damned if you don't decision and I don't envy the ultimate decision you will have to make. However, I sincerely hope you will choose to recognize that our current legal structure will only ensure that those who want marijuana for recreational purposes will continue to get it, while those of us who want it for medicinal purposes won't.

Thank you for taking the time to read my comments. I am more than happy to expand on the above information if you should so need it.
Best regards

My Doctor Perscribed Zanex then Zolof, that lit me up and ended up in the ER, I stopped taking the meds, These affect a person in diffrent ways, might as well try Marijuana and be a subject of the side affects. Use to smoke before moving to AZ but the the strict laws stopped using Marijuana, would like to go back without breaking the law.

Certain Sativa strains have eased my depression. Only certain ones though. Thinking about this, I realize how not having a dispensary with specific strains not avilable harms patients. Many depression patients already use cannabis. Most are at lower economic levels, and have not had their college paid for, etc. This is the primary thing already use to cure their depression with - along with alcohol unfortunately. I do not drink. This should absolutely be added to the list. The reduced fear of law enforcement alone will assist with curing their depression. No one can argue this point.

Recent studies show marijuana CAUSES depression. Adding depression as a condition will create more people suffering from depression, not alleviate it. Recent studies also confirm that marijuana makes people lazy, destroys brain cells and robs them of ambition. It is a bad idea to spread its use under the label "medical."

This should be added as there are plenty of studies that were done that show Medical Marijuana can be used to help people who suffer from depression and lower suicide rates.

I am currently suffering from depression. It has really crippled me for the past 6 months. I have had to drop out of school, Im seeing a therapist, and i am on anti-depressants. These things all help to make my life a little better, but the depression just isnt going away. I have read peer review articles online and in journals that say that medical marijuana can truely help some people. I feel like it's worth taking a chance on medical marijuana if it truely could help people like me suffering from major depression.

Depression is such a broad medical term that this could cause a flood of people getting medical marijuana cards. it does not take alot to get diagnosed with depression and people know it. To add this to the list would creat wide spread social and economic problems. Plus marijuana is a depressant and to help some one with depression you do not give them something that will just make them more depressed.

Last year, I became a registered patient of the Arizona Medical Marijuana Program. It has helped tremendously with my chronic back pain. At about the same time, I was undergoing therapy for bipolar depression, under cooperation between my medical doctor and my psychological therapist. Subsequently, I was put on Seroquel XR 300mg daily. This helped to even out the peaks of mania and valleys of depression, but does not eliminate them. It provided a measure of control where none existed before, but

it is not a cure by any means. I became aware of how the seroquel helped manage my condition. Quite by coincidence, I also became aware of how the medical marijuana not only helped manage my back pain, but I was surprised to note that it had a similar palliative benefit on my depression as did seroquel. Further, I noticed that of the two major strains, Sativa and Indica, it was the more Sativa-dominant strains that helped the most with depression, while the more Indica-dominant strains helped the most with pain. I encourage the Arizona Department of Health Services to add depression to the list of debilitating conditions.

Article taken from Science News:
Not just a high Scientists test medicinal marijuana against MS, inflammation and cancer
By Nathan Seppa

June 19th, 2010; Vol.177 #13 (p. 16)

NOT JUST A HIGH

Cannabis compounds show their stuff against a host of medical problems, relieving symptoms far beyond pain and nausea.

KatsgraphicsLV/iStockphoto

In science's struggle to keep up with life on the streets, smoking cannabis for medical purposes stands as Exhibit A.

Medical use of cannabis has taken on momentum of its own, surging ahead of scientists' ability to measure the drug's benefits. The pace has been a little too quick for some, who see medicinal joints as a punch line, a ruse to free up access to a recreational drug.

But while the medical marijuana movement has been generating political news, some researchers have been quietly moving in new directions -- testing cannabis and its derivatives against a host of diseases. The scientific literature now brims with potential uses for cannabis that extend beyond its well-known abilities to fend off nausea and block pain in people with cancer and AIDS. Cannabis derivatives may combat multiple sclerosis, Crohn's disease and other inflammatory conditions, the new research finds. Cannabis may even kill cancerous tumors.

Many in the scientific community are now keen to see if this potential will be fulfilled, but they haven't always been. Pharmacologist Roger Pertwee of the University of Aberdeen in Scotland recalls attending scientific conferences 30 years ago, eager to present his latest findings on the therapeutic effects of cannabis. It was a hard sell.

"Our talks would be scheduled at the end of the day, and our posters would be stuck in the corner somewhere," he says. "That's all changed."

Underlying biology

The long march to credibility for cannabis research has been built on molecular biology. Smoking or otherwise consuming marijuana – Latin name Cannabis sativa – has a medical history that dates back thousands of years. But the euphoria-inducing component of cannabis, delta-9-tetrahydrocannabinol, or THC, wasn't isolated until 1964, by biochemist Raphael Mechoulam, then of the Weizmann Institute of Science in Rehovot, Israel, and his colleagues. Within two decades, other researchers had developed synthetic THC to use in pill form.

The secrets of how THC worked in the body lay hidden until the late 1980s, when researchers working with rats found that the compound binds to a protein that pops up on the surface of nerve cells. Further tests showed that THC also hooks up with another protein found elsewhere in the body. These receptor proteins were dubbed CB1 and CB2.

A bigger revelation came in 1992: Mammals make their own compound that binds to, and switches on, the CB1 receptor. Scientists named the compound anandamide. Researchers soon found its counterpart that binds mainly to the CB2 receptor, calling that one 2AG, for 2-arachidonyl glycerol. The body routinely makes these compounds, called endocannabinoids, and sends them into action as needed.

"At that point, this became a very, very respectable field," says Mechoulam, now at Hebrew University of Jerusalem, who along with Pertwee and others reported the anandamide discovery in Science. "THC just mimics the effects of these compounds in our bodies," Mechoulam says. Although the receptors are abundant, anandamide and 2AG are short-acting compounds, so their effects are fleeting.

In contrast, when a person consumes cannabis, a flood of THC molecules bind to thousands of CB1 and CB2 receptors, with longer-lasting effects. The binding triggers so many internal changes that, decades after the receptors' discovery, scientists are still sorting out the effects. From a biological standpoint, smoking pot to get high is like starting up a semitruck just to listen to the radio. There's a lot more going on.

SANCTIONED SMOKING

View larger image | Though smoked cannabis has not been approved by the Food and Drug Administration, its use for medical purposes has been sanctioned by law in 14 states (shown in green, year given). Different states apply their own restrictions, some of which are highlighted.

kelly ann mccann; source: D.E. hoffmann and E. weber/nejm 2010

Though the psychoactive effect of THC has slowed approval for cannabis-based drugs, the high might also have brought on a serendipitous discovery, says neurologist Ethan Russo, senior medical adviser for GW Pharmaceuticals, which is based in Porton Down, England. "How much longer would it have taken us to figure out the endocannabinoid system if cannabis didn't happen to have these unusual effects on human physiology?"

Beyond the pain

Today smoked cannabis is a sanctioned self-treatment for verifiable medical conditions in 14 U.S. states, Canada, the Netherlands and Israel, among other places. It usually requires a doctor's recommendation and some paperwork.

People smoke the drug to alleviate pain, sleep easier and deal with nausea, lack of appetite and mood disorders such as anxiety, stress and depression. Patients not wanting to smoke cannabis can seek out prescriptions for FDA-approved capsules containing cannabis compounds for treatment of some of these same problems.

Research now suggests that multiple sclerosis could join the growing list of cannabis-treated ailments. More than a dozen medical trials in the past decade have shown that treatments containing THC (and some that combine THC with another derivative called cannabidiol, or CBD) not only ease pain in MS patients but also alleviate other problems associated with the disease. MS results from damage to the fatty sheaths that insulate nerves in the brain and spinal cord.

"MS patients get burning pain in the legs and muscle stiffness and spasms that keep them awake at night," says John Zajicek, a neurologist at the Peninsula College of Medicine and Dentistry in Plymouth, England. Patients can take potent steroids and other anti-inflammatory drugs, but the effects of these medications can be inconsistent.

Pertwee has analyzed 17 trials in which MS patients received some form of cannabis or its derivatives. Reports from the patients themselves, who didn't know if they were getting real cannabinoids or a placebo in most of the trials, show improvements in muscle spasticity, sleep quality, shakiness, sense of well-being and mobility. Pertwee, who is also a consultant for GW Pharmaceuticals – which makes a cannabinoid drug that is delivered in spray form, called Sativex – reviewed the findings in Molecular

Neurobiology in 2007.

Sativex was approved in Canada for MS in 2005 after studies (some included in Pertwee's analysis) showed its success in relieving symptoms of the disease. GW Pharmaceuticals expects clearance for MS treatment in the United Kingdom and Spain this year. Later, the company plans to seek U.S. approval of Sativex for cancer pain.

Zajicek's team has also compared MS patients who received a placebo with patients receiving either a capsule containing THC or one with THC and CBD. Both of the cannabis-based drugs outperformed a placebo, and the researchers are now working on a multiyear MS trial.

Calming symptoms such as muscle spasticity and pain is useful, Zajicek says, but the true value of cannabinoids may exceed that. "To me, the really exciting stuff is whether these drugs have a much more fundamental role in changing the course of MS over the longer term," he says. "We've got nothing that actually slows progression of the disease."

Fighting inflammation

TUMOR SUPPRESSION

View larger image | In patients with aggressive brain tumors, THC seems to knock down MMP-2 (green in images above left), an enzyme that facilitates cancer's spread by breaking down tissues. Cannabinoids also affect other cancer cells in rodents and in lab-dish experiments (see table).

c. Blázquez

CBD, the same cannabis component that proved beneficial alongside THC for MS, may also work on other hard-to-treat diseases. Tests on cell cultures and lab animals have revealed that CBD fights inflammation and mitigates the psychoactive effects of THC.

Crohn's disease, which can lead to chronic pain, diarrhea and ulcerations, could be a fitting target for CBD. In Crohn's disease, inflammatory proteins damage the intestinal lining, causing leaks that allow bacteria in the gut to spread where they shouldn't. This spread leads to a vicious cycle that can trigger more inflammation.

Karen Wright, a pharmacologist at Lancaster University in England, and her colleagues have found that CBD inhibits this inflammation and can reverse the microscopic intestinal leakiness in lab tests of human cells. Adding

THC doesn't seem to boost the benefit, Wright reported in December 2009 in London at a meeting of the British Pharmacological Society. The results bolster earlier findings by Wright's team showing that cannabinoids could improve wound healing in intestinal cells.

CBD's anti-inflammatory effect may work, at least in some cases, through its antioxidant properties – the ability to soak up highly reactive molecules called free radicals, which cause cell damage.

In the brain and eye, CBD slows the action of microglia, immune cells that can foster harmful inflammation when hyperactivated by free radicals. Working with rats whose retinas were induced to have inflammation, biochemist Gregory Liou of the Medical College of Georgia in Augusta and his team found that CBD neutralized free radicals, preventing eye damage. This finding could have implications for people with diabetes who develop vision loss.

Apart from being an anti-inflammatory and antioxidant, CBD tones down the psychoactive effect of THC without eliminating its medical properties. CBD also mutes the occasional anxiety and even paranoia that THC can induce. This has been welcome news to scientists, who consider the "buzz" of cannabis little more than psychoactive baggage.

But CBD has paid a price for this anti-upper effect. "CBD has essentially been bred out of North American black market drug strains," Russo says. People growing cannabis for its recreational qualities have preferred plants high in THC, so people lighting up for medical purposes, whether to boost appetite in AIDS patients or alleviate cancer pain, may be missing a valuable cannabis component.

Cannabis versus cancer

With or without CBD, cannabis may someday do more for cancer patients than relieve pain and nausea. New research suggests THC may be lethal to tumors themselves. Biochemists Guillermo Velasco and Manuel Guzmán of Complutense University in Madrid have spent more than a decade establishing in lab-dish and animal tests that THC can kill cancer of the brain, skin and pancreas.

THC ignites programmed suicide in some cancerous cells, the researchers reported in 2009 in the Journal of Clinical Investigation. The team's previous work showed that THC sabotages the process by which a tumor hastily forms a netting of blood vessels to nourish itself, and also keeps cancer cells from moving around.

THC achieves this wizardry by binding to protein receptors on a cancerous cell's surface. Once attached, the THC induces the cell to make a fatty substance called ceramide, which prompts the cell to start devouring itself. "We see programmed cell death," Velasco says. What's more, noncancerous cells don't make ceramide when they come into contact with THC. The healthy cells don't die.

Many compounds kill cancer in a test tube and even in animals, but most prove useless because they cause side effects or just don't work in people. The Madrid team is now seeking funding to test whether cannabis derivatives can kill tumors in cancer patients. In an early trial of nine brain cancer patients whose disease had worsened despite standard therapy, the scientists found that THC injections into tumors were safe to give.

Early reports from other research groups suggest that THC also fights breast cancer and leukemia. "I think the cancer research is extremely promising," Russo says. "Heretofore, the model for cancer was to use an agent that's extremely toxic to kill the cancer before it kills you. With cannabinoids, we have an opportunity to use agents that are selectively toxic to cancer cells."

Looking ahead

Testing of cannabis and its derivatives has also begun on type 1 diabetes, rheumatoid arthritis, stroke, Tourette syndrome, epilepsy, depression, bipolar disorder and schizophrenia. Pertwee is particularly optimistic that cannabis will help people with post-traumatic stress disorder. Experiments in rats show that THC "speeds up the rate at which the animals forget unpleasant experiences," he says. And a recent study in people with PTSD showed that THC capsules improved sleep and stopped nightmares.

Despite these heady beginnings, medical cannabis still faces an uphill climb. Although some states have sanctioned its use, no smoked substance has ever been formally approved as a medicine by U.S. regulatory agencies. Smoking cannabis can lead to chronic coughing and bronchitis, and smoking renders a drug off-limits for children, Mechoulam notes.

THC pills don't have these downsides, but the drugs have received only lukewarm acceptance. Despite smoking's drawbacks, "it is seen as better because you can regulate the amount of THC you're getting by not puffing as much," says pharmacologist Daniele Piomelli of the University of California, Irvine. Capsules can cause dizziness and make it hard to focus. "Patients suffering from neuropathic pain or depression don't want to be stoned – they want relief," he says.

Controlled, randomized trials that seek to clarify whether smoked cannabis delivers on its medical promise – with acceptable side effects – have been hard to come by. But scientists in California have recently concluded several studies in which patients with severe pain received actual cannabis cigarettes or cannabis cigarettes with the cannabinoids removed.

In one trial, researchers randomly assigned 27 HIV patients to get the real thing and 28 to get fake joints. All the patients had neuropathic pain, in which neurons can overreact to even mild stimuli. About half of the people getting real cannabis experienced a pain reduction of 30 percent or greater, a standard benchmark in pain measurement. Only one-quarter of volunteers getting the placebo reported such a reduction.

"That's about as good [a reduction] as other drugs provide," says Igor Grant, a neuropsychiatrist at the University of California, San Diego, who is among the scientists overseeing the trials.

While such studies provide evidence that smoked marijuana has medical benefits, future trials are more likely to explore the benefits of cannabis derivatives that don't carry the baggage that smoking does.

Ultimately, the fate of medical cannabis and its derivatives will rest on the same make-or-break requirements that every experimental medicine faces – whether it cures a disease or alleviates its symptoms, and whether it's tolerable.

"We have to be careful that marijuana isn't seen as a panacea that will help everybody," Grant says. "It probably has a niche.... We can't ignore the fact that cannabis is a substance of abuse in some people."

Getting cannabis in

When most people think of medicinal cannabis, smoking comes to mind. Though smoking works quickly and allows users to regulate their intake, it's hardly a scientific approach: Cannabis quality is often unknown, and inhaling burned materials is bad for the lungs. These and other drawbacks have spawned new ways to consume medical marijuana.

Some people inhale cannabis by using a device that heats the plant without igniting it. This vaporization unleashes many of the same cannabinoid compounds as smoking does, without the combustion by-products, researchers say. Anecdotally, patients report that the effect is prompt, on a par with smoking.

Because cannabis derivatives can pass through the lining of the mouth and throat, a company called GW Pharmaceuticals has devised a spray product called Sativex. This drug contains roughly equal amounts of two key cannabinoids – THC and CBD – plus other cannabis components in an alcohol solution. A dose of Sativex is sprayed under the tongue; no smoking required.

In the face of these options, the "pot pill" seems almost passé. But capsules of synthetic THC exist. One called Marinol has been approved in the United States since 1985, and another called Cesamet was cleared more recently. Doctors can prescribe the drugs for nausea, vomiting, loss of appetite and weight loss. Though sales of capsules have increased recently, many users complain of psychoactive side effects and slow action.

Taken from:

http://www.sciencenews.org/view/feature/id/59872/title/Not_just_a_high

I think medicinal marijuana would help get people off the "crazy pills" in a safe and natural way.

http://www.cannabismd.net/depression/

This DEFINATELY should have been on the original list. Anti-depressants are dangerous! I've used both medical marijuana and prescribed anti-depressants, and the medical marijuana has always worked, but I've had issues with prescriptions, some even making things worse.

I could not believe that depression wasn't part of the initial recognized medical conditions. It's a MUST.

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ADDICTIVE BEHAVIORS

Short communication

Decreased depression in marijuana users

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Abstract

Over 4400 adult internet users completed The Center for Epidemiologic Studies Depression scale and measures of marijuana use. We employed an internet survey in an effort to recruit the most depressed and marijuana-involved participants, including those who might prove unwilling to travel to the laboratory or discuss drug use on the phone or in person. We compared those who consumed marijuana daily, once a week or less, or never in their lives. Despite comparable ranges of scores on all depression subscales, those who used once per week or less had less depressed mood, more positive affect, and fewer somatic complaints than non-users. Daily users reported less depressed mood and more positive affect than non-users. The three groups did not differ on interpersonal symptoms. Separate analyses for medical vs. recreational users demonstrated that medical users reported more depressed mood and more somatic complaints than recreational users, suggesting that medical conditions clearly contribute to depression scores and should be considered in studies of marijuana and depression. These data suggest that adults apparently do not increase their risk for depression by using marijuana.
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Keywords: Marijuana; Depression; Interpersonal symptoms; Somatic and retarded activity; Deppressed affect; Positive affect; Medical marijuana

The media continues to report links between marijuana and depression. In a recent review, Degenhardt, Hall, and Lynskey (2003) identified a modest relationship only among problematic users. Many studies show no link between cannabis and depression despite appropriate statistical power, measurement, and design (Fergusson & Horwood, 1997; Fergusson, Lynskey, & Horwood, 1996; Green & Ritter, 2000; Kouri, Pope, Yurgelun-Todd, & Gruber, 1995; McGee, Williams, Poulton, & Moffitt, 2000; Musty & Kaback, 1995; Rowe, Fleming, Barry, Manwell, & Kropp, 1995). One neglected source

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of depression among marijuana users may stem from medical use. Those who use the plant to battle symptoms of illness may be depressed because of illness, not marijuana. With over 4400 participants, our study is the largest investigation of marijuana and depression to date. We use robust statistical methods specifically designed to maximize power with non-normal data, as drug use and depression are rarely normally distributed. Our study also contains a control group of both males and females who reported never using marijuana, which some other studies lack. We also assessed medical use, which other studies have not done.

1. Method

1.1. Participants

Approximately 9000 people replied to an email request sent to drug policy organizations, in an effort to target a range of cannabis users. The 4494 people who used daily, once a week or less, or never (2834 men (63%), 1660 women (37%), mean age = 32.19, SD = 12.92 years) had a median education of some college without a degree, and a median income of $20,000 to $40,000 per year. Respondents were primarily Caucasian (87%), but included African Americans (1%), Native Americans (3%), Asians (3%), Latinos (4%), and people of mixed race (2%). Those who used cannabis began at a mean age of 16.8 (SD = 4.3).

1.2. Procedure

1.2.1. Cannabis use

The daily users (DU) reported using 7 days/week (n = 3323). Those who reported using less than or equal to 1 day/week but had used within the last 30 days comprised the group who used once per week or less (WU; n = 861). Only those who had never used in their lifetimes were included in the group who had never used (NU; n = 310).

1.2.2. Medical use

Medical users identified themselves and listed their ailments. The most common conditions were nausea, vomiting, cancer, attention deficit, and poor appetite.

1.2.3. Depression

The Center for Epidemiologic Studies Depression scale (CES-D) contains 4 factors: depressed affect, positive affect, somatic and retarded activity, and interpersonal symptoms, each with good to excellent psychometric properties (Radloff, 1977).

2. Results

2.1. Comparing user groups by gender

Internal consistency (α) was 0.90 for the Total Score (TS), but ranged for subscales: Depressed Affect (DA; 0.84), Positive Affect (PA; 0.78), Somatic and Retarded Activity (SR; 0.61) and

Interpersonal Symptoms (IS; 0.63). Two (gender) × 3 (user group) ANOVAs were conducted, with subsequent post hoc bootstrap linear contrasts on the 20% trimmed means. This approach allows for maximum power given these deviant distributions (Wilcox, 2003). TS revealed a significant main effect for user group, $F_t=8.83$, $p<0.05$. NUs had higher levels of depression than WUs, $\psi=4.39$, $p<0.001$, and DUs, $\psi=3.90$, $p<0.001$, who did not differ from each other, $\psi=-1.51$, $p=0.13$. A robust effect size estimate (Wilcox, 2003) revealed that user group accounted for 16% of the winsorized variance in TS.

DA revealed a main effect for sex, $F_t=10.38$, $p<0.01$ [women ($M_t=2.16$) reported more depressed mood than men ($M_t=1.64$)], and user group, $F_t=5.20$, $p<0.01$. NUs reported more depression than WUs, $\psi=3.20$, $p=0.003$, and DUs, $\psi=2.91$, $p<0.003$, who did not differ $\psi=-0.99$, $p=0.33$. User group accounted for 11% of the winsorized variance. PA showed a main effect for user group $F_t=15.85$, $p<0.001$. NUs reported less positive affect than WUs, $\psi=4.58$, p=0.001, and DUs, $\psi=5.56$, $p<0.001$, who did not differ $\psi=1.29$, $p=0.19$. User group accounted for 25% of the winsorized variance. SR reports showed a main effect for sex, $F_t=18.22$, $p<0.001$ [women ($M_t=3.12$) had more complaints than men ($M_t=2.57$)] and user group $F_t=6.95$, $p<0.05$. NUs had higher levels of somatic symptoms than WUs, $\psi=2.34$, $p=0.03$, but not DUs, $\psi=0.17$, $p=0.88$. DUs reported more somatic complaints than WUs, $\psi=-3.66$, $p=0.01$. User group accounted for 5% of the winsorized variance. IS did not vary with use or gender. See Table 1.

2.2. Medical marijuana use and depression

A 3 (type of use: never used, medical use, recreational use) × 2 (gender: male, female) ANOVA on 20% trimmed means with follow-up bootstrap linear contrasts tested the role of medical use. TS revealed a main effect for group ($F_t=26.62$, $p<0.0001$). Medical users reported more depression than recreational users, $\psi=5.18$, $p<0.01$. NUs also had more depression than recreational users, $\psi=5.04$, $p<0.01$. DA revealed a main effect for group ($F_t=14.80$, $p=0.001$). Medical users scored higher than recreational users, $\psi=4.34$, $p<0.01$, as did NUs, $\psi=3.79$, $p<0.01$. PA revealed a main effect ($F_t=18.31$, $p<0.0001$), with both medical, $\psi=4.54$, $p<0.001$, and recreational users, $\psi=5.75$, $p<0.001$, reporting more positive affect than NUs. SR revealed main effects for group ($F_t=21.20$, $p<0.0001$) and gender ($F_t=23.25$, $p<0.0001$) indicating that women reported more somatic complaints than men. These main effects were qualified by an interaction, $F_t=6.26$, $p<0.05$. Among men, medical users reported more somatic complaints than recreational users, $\psi=4.37$, $p<0.001$. Among women,

Table 1
Trimmed mean CES-D scores and range (in parentheses) as a function of frequency of marijuana use and gender

CES-D subscale	Never used		Weekly or less		Daily use	
	Men	Women	Men	Women	Men	Women
Total	10.15 (0–49)[a]	11.49 (0–48)[a]	7.72 (0–42)[b]	8.44 (0–54)[b]	8.35 (0–55)[a,b]	8.83 (0–52)[b]
Depressed affect	2.08 (0–14)[a]	2.62 (0–15)[a]	1.34 (0–14)[b]	1.89 (0–15)[a]	1.50 (0–15)[a,b]	1.97 (0–15)[a]
Positive affect	2.09 (0–12)[a]	2.10 (0–12)[a]	1.99 (0–11)[b]	1.10 (0–12)[b]	1.14 (0–12)[b]	0.91 (0–12)[b]
Somatic activity	2.52 (0–15)[a,b]	3.47 (0–15)[a]	2.42 (0–13)[b,c]	2.73 (0–14)[b]	2.77 (0–15)[a]	3.17 (0–15)[a]
Interpersonal	0.38 (0–6)[a]	0.43 (0–6)[a]	0.36 (0–5)[a]	0.31 (0–6)[a]	0.45 (0–6)[a]	0.41 (0–6)[a]

Within rows and within gender, means with different superscripts are significantly ($\alpha=0.05$) different from each other. Familywise error rate was controlled with Rom's (1990) method.

Table 2
Trimmed mean CES-D scores and range (in parentheses) as a function of gender and type of marijuana use

CES-D subscale	Never used		Medical		Recreational	
	Men	Women	Men	Women	Men	Women
Total	10.28 (0–49)[a]	11.38 (0–48)[a]	9.14 (0–55)[a]	10.25 (0–52)[a]	7.86 (0–51)[b]	8.14 (0–54)[b]
Depressed affect	2.11 (0–14)[a]	2.58 (0–15)[a]	1.74 (0–15)[a]	2.38 (0–15)[a]	1.32 (0–15)[b]	1.78 (0–15)[b]
Positive affect	2.13 (0–12)[a]	2.08 (0–12)[a]	1.23 (0–12)[b]	1.14 (0–12)[b]	1.12 (0–12)[b]	0.88 (0–12)[b]
Somatic activity	2.54 (0–15)[a,b]	3.44 (0–15)[a]	3.09 (0–15)[b]	3.74 (0–14)[a]	2.54 (0–15)[a]	2.78 (0–15)[b]
Interpersonal	0.40 (0–6)[a]	0.43 (0–6)[a]	0.46 (0–6)[a]	0.43 (0–6)[a]	0.42 (0–6)[a]	0.37 (0–6)[a]

Within rows and within gender, means with different superscripts are significantly ($\alpha = 0.05$) different from each other. Familywise error rate was controlled with Rom's (1990) method.

both NUs, $\psi = 2.93$, $p < 0.01$, and medical users, $\psi = 5.14$, $p < 0.001$, reported more complaints than recreational users. There were no significant effects on the IS. Data appear in Table 2.

3. Discussion

Those who consume marijuana occasionally or even daily have lower levels of depressive symptoms than those who have never tried marijuana. Specifically, weekly users had less depressed mood, more positive affect, and fewer somatic complaints than non-users. Daily users reported less depressed mood and more positive affect than non-users. The groups did not differ on interpersonal symptoms. Our results add to the growing body of literature on depression and marijuana and are generally consistent with a number of studies that have failed to confirm a relationship between the two after controlling for relevant variables.

This study was also the first to our knowledge to separately investigate depression in medical marijuana users relative to recreational users. Medical users reported more depressed mood and more somatic complaints than recreational users, but reported less negative affect and fewer somatic complaints (among women) than those who had never used marijuana. These latter results suggest that our findings should be even more robust among individuals without medical conditions. They also suggest that medical users may contribute to studies that find positive associations between marijuana use and depression. Further investigations on this topic will benefit by assessing medical conditions in addition to marijuana use and depressive symptoms. The potential for medical conditions to contribute to spurious links between marijuana and greater depression requires further investigation.

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Cannabinoids Elicit Antidepressant-Like Behavior and Activate Serotonergic Neurons through the Medial Prefrontal Cortex

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Abstract

Preclinical and clinical studies show that cannabis modulates mood and possesses antidepressant-like properties, mediated by the agonistic activity of cannabinoids on central CB_1 receptors (CB_1Rs). The action of CB_1R agonists on the serotonin (5-HT) system, the major transmitter system involved in mood control and implicated in the mechanism of action of antidepressants, remains however poorly understood. In this study, we demonstrated that, at low doses, the CB_1R agonist WIN55,212-2 [*R*(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl) methanone mesylate] exerts potent antidepressant-like properties in the rat forced-swim test (FST). This effect is CB_1R dependent because it was blocked by the CB_1R antagonist rimonabant and is 5-HT mediated because it was abolished by pretreatment with the 5-HT-depleting agent parachlorophenylalanine. Then, using *in vivo* electrophysiology, we showed that low doses of WIN55,212-2 dose dependently enhanced dorsal raphe nucleus 5-HT neuronal activity through a CB_1R-dependent mechanism. Conversely, high doses of WIN55,212-2 were ineffective in the

FST and decreased 5-HT neuronal activity through a CB_1R-independent mechanism. The CB_1R agonist-induced enhancement of 5-HT neuronal activity was abolished by total or medial prefrontocortical, but not by lateral prefrontocortical, transection. Furthermore, 5-HT neuronal activity was enhanced by the local microinjection of WIN55,212-2 into the ventromedial prefrontal cortex (mPFCv) but not by the local microinjection of WIN55,212-2 into the lateral prefrontal cortex. Similarly, the microinjection of WIN55,212-2 into the mPFCv produced a CB_1R-dependent antidepressant-like effect in the FST. These results demonstrate that CB_1R agonists possess antidepressant-like properties and modulate 5-HT neuronal activity via the mPFCv.

Introduction

Cannabis is the most widely used illicit drug (World Health Organization, 2006). Its major psychoactive constituent, Δ^9-tetrahydrocannabinol, and other cannabinoids exhibit high affinity to brain CB_1 receptors (CB_1Rs). CB_1R activation modulates physiological, affective, cognitive, and psychomotor functions. Cannabis intoxication for instance engenders enhanced sociability, mood, and well-being, a condition described as "fatuous euphoria" (Iversen, 2003) whose physiological and subjective components are selectively blocked by the CB_1R antagonist rimonabant (RIM) (Huestis et al., 2001).

Increased attention has been directed toward understanding the role of the endocannabinoid system in mood regulation. Clinical studies have reported benefits of cannabis on mood disorders (Ashton et al., 2005; Ware et al., 2005). Genetic (Haller et al., 2002, 2004; Martin et al., 2002) or pharmacological (Navarro et al., 1997; Deroche-Gamonet et al., 2001) CB_1R blockade in murine models yields enhanced expression of depression/anxiety-like behaviors. There are conflicting reports on the mood-related effects of CB_1R agonists and antagonists/inverse agonists with regards to direction and potency of effects. Shearman et al. (2003) for example reported instead an antidepressant-like activity of the CB_1R inverse agonist AM251 [*N*-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-1-piperidinyl-1*H*-pyrazole-3-carboxamide]. This apparent complexity has been attributed to dose-dependent bidirectional modulation, sensitivity of cannabimimetic responses to contextual conditions, and the kind of animal model and strain used (for review, see Viveros et al., 2005). Also, the possibility of interaction among receptor subtypes including a putative CB_3R and vanilloid receptors, which has likewise been demonstrated operating in a plethora of cannabimimetic responses, may underlie ambivalent effects on mood modulation.

Despite evidence for the impact of CB_1R activity on mood regulation, information on direct effects of cannabinoids on serotonergic neurotransmission remain meager. Serotonin (5-HT) is the major neurotransmitter implicated in mood pathophysiology and in the mechanism of antidepresssant action (Blier and de Montigny, 1999). Several studies have nevertheless provided indications of functional cannabinoid–5-HT interaction. First, the dorsal raphe (DR), the principal source of forebrain 5-HT, expresses the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) (Egertova et al., 1998, 2003), the CB_1R in rats (Moldrich and Wenger, 2000), and CB_1R mRNA in mice (Häring et al., 2007). Second, CB_1Rs are abundantly expressed in the prefrontal cortex (PFC) (Marsicano and Lutz, 1999; Moldrich and Wenger, 2000), which sends excitatory afferents to the DR, coursing from the medial PFC (mPFC) (Jankowski and

Sesack, 2004). Furthermore, upregulation in PFC CB_1R density, likely a compensatory feedback, was observed in suicidal depressives (Hungund et al., 2004). Imaging studies revealed that cannabis alters PFC regional cerebral blood flow and metabolic activity. The degree was correlated with subjective effects, and the pattern was consistent with CB_1R localization (Volkow et al., 1991; Matthew et al., 2002). Third, CB_1R agonism alters 5-HT_{1A} and $5HT_{2A}$ receptor-mediated behavioral responses (Hill et al., 2006) and inhibits 5-HT reuptake *in vitro* (Banerjee et al., 1975; Johnson et al., 1976). In this study, we therefore aimed at determining whether the CB_1R agonist WIN55,212-2 (WIN) [*R*(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl) methanone mesylate] exhibits antidepressant-like effects in the forced swim test (FST), modulates 5-HT activity through a CB_1R-mediated mechanism, and effects dose-dependent bidirectional modulations. Furthermore, using local microinfusions, we aimed to demonstrate that the mPFC is strongly involved in mediating these effects.

Materials and Methods

Animals

Adult male Sprague Dawley rats (Charles River; Saint-Constant, Quebec, Canada) weighing 280–350 g at the time of experiments were housed in pairs in standard polycarbonate cages. They were kept under standard laboratory conditions (12 h light/dark cycle, lights on at 7:30 A.M.; temperature at 20 ± 2°C; 50–60% relative humidity). All rats had *ad libitum* access to food and water. One week before the start of experiments, rats were exposed to the testing environment and allowed to habituate to testing conditions. For rats that have undergone intracerebral cannulation, weights were monitored after surgery, and at least 4 d of postoperative recovery period was observed before additional tests were conducted. Drug administrations and electrophysiological and behavioral experiments were conducted between 2:00 P.M. and 10:00 P.M. All procedures were approved by the local institutional animal care and use committee and were in accordance to the ethical guidelines set by the Canadian Institutes of Health Research and the Society for Neuroscience.

Drugs

The CB_1R agonist WIN55,212-2 (Sigma, Oakville, Ontario, Canada) was emulsified in Tween 80 (polyoxyethylene-sorbitan mono-oleate; Sigma) and further dissolved in saline with 5% Tween 80 and 5% poly(ethylene) glycol (Sigma). The WIN55,212-2 solution used for intracerebral microinfusions was dissolved in dimethylsulfoxide (DMSO) (Sigma) and vehicle (VEH) (1:2) because of the hydrophobic property of WIN55–212-2. The CB_1R antagonist SR141716A/rimonabant [*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazolecarboxamide] (a kind gift from Dr. D. Piomelli, University of California, Irvine, CA) and the transient receptor potential vanilloid type 1 (TRPV1)/vanilloid receptor antagonist capsazepine (CPZ) (Tocris Bioscience, Ballwin, MO) were initially dissolved in DMSO and further diluted (1:20) with saline containing 5% Tween 80 and 5% poly(ethylene) glycol. Desipramine hydrochloride (DMI), parachlorophenylalanine (pCPA) (Sigma), and citalopram hydrobromide (CIT) (kindly provided by Lundbeck, Copenhagen, Denmark), were dissolved in

0.9% physiological saline. The pH of vehicles and solutions used in the experiments was adjusted to 7.2.

Experiment 1: forced swim test

The FST examines the dynamics of transition from an active (swimming and climbing) to a passive (immobility) mode of coping in an inescapable cylindrical water pool (20 cm diameter, 50 cm high; 30 cm water depth, 25–27°C water temperature). During the course of the 5 min test swim session, an enhanced transition from activity to immobility resulting from a 15 min preexposure to the pool (preswim 24 h previously) has often been equated to learned behavioral despair (Porsolt et al., 1978). This enhancement of immobility is prevented by antidepressant treatment. Here, rats received 0.05, 0.2, 1.0, or 2.0 mg/kg intraperitoneal injections of the potent CB_1R agonist WIN55,212-2 23, 5, and 0.75 h before the test swim, modified after the protocol previously described by Page et al. (1999). A second cohort of rats was used to assess the effect of coadministering rimonabant with the dose of WIN55,212-2 that elicited the maximal antidepressant-like effect. A third cohort of rats was used to verify the role of 5-HT in mediating the effects of WIN55,212-2. Vehicle or pCPA (350 mg/kg, i.p., once daily), a selective inhibitor of the 5-HT synthesis precursory enzyme tryptophan hydroxylase that therefore depletes endogenous 5-HT, was administered 72 and 48 h before the swim test. WIN55,212-2 (0.2 mg/kg, i.p.) or vehicle were administered 23, 5, and 0.75 h before the swim test (modified after Page et al., 1999). Behavioral endpoints were analyzed by an automated tracking system equipped with infrared-sensitive cameras (Videotrack; Viewpoint Life Science, Montreal, Quebec, Canada). The predominant behaviors assessed were subsumed to one of three categories: immobility, in which the rat was making minimal movements to keep its head above water; swimming, in which the rat was engaged in average movements that cause it to move (usually horizontally) within the cylinder; and climbing (burst activity), in which forceful thrashing limb movements against the walls of the cylinder were observed. It has been shown that antidepressants with 5-HT-specific action selectively increase the duration of swimming, whereas those with a predominantly noradrenergic-specific activity increase those of climbing (Page et al., 1999). In all sessions, each animal was held on the neck and back, gently immersed in the pool hindlimbs first. They were removed from the pool using a plastic grid, then dried with a towel, and caged near a heat source. The FST is both sensitive and selective for clinically effective antidepressants, has been repeatedly validated, and is currently the most popular model for detecting antidepressant activity attributable to its simplicity, reliability, and high predictive validity (Lucki, 1997; Cryan et al., 2005). To control for false positives (increased activity in the FST of non-antidepressants), as has been consistently observed with psychostimulants (for review, see Cryan et al., 2005), a test for locomotor activity (5 min) in an open field (80 × 80 cm), was also conducted, in which locomotor activity was operationalized as movement velocity (distance traveled in centimeters per minute).

Experiment 2: electrophysiology

In vivo extracellular single-unit recordings of presumed DR 5-HT neurons were performed to determine whether the antidepressant-like properties of WIN55,212-2 in the FST corresponded to a capacity to enhance 5-HT neurotransmission. Recordings were conducted after repeated intraperitoneal administration following the FST protocol as well as after intravenous

administration. All stereotaxic coordinates used in the succeeding experiments were based on the stereotaxic atlas of Paxinos and Watson (1986).

Preparation for electrophysiological experiments.

Rats were anesthetized with chloral hydrate (400 mg/kg, i.p.) and mounted in a stereotaxic frame (David Kopf Instruments, Tujunga, CA) with the skull positioned horizontally (incisor bar at −3.3). To maintain a full anesthetic state characterized by the absence of a nociceptive reaction to a paw/tail pinch and eyeblink response to pressure, chloral hydrate was continuously administered intraperitoneally at a dose of 50–70 $mg \cdot kg^{-1} \cdot h^{-1}$ using an infusion pump (Braintree Scientific, Braintree, MA). Body temperature was maintained at 37 ± 0.5°C throughout the experiment using a rectal probe and a heating pad (Seabrook International, Seabrook, NH). Before electrophysiological recordings, a catheter was inserted into the lateral tail vein to facilitate systemic administration of drugs. Extracellular single-unit recordings were performed using single-barreled glass micropipettes pulled from 2 mm Stoelting (Wood Dale, IL) capillary glass on a Narashige (Tokyo, Japan) PE-21 pipette puller and preloaded with fiberglass strands to promote capillary filling with 2% Pontamine Sky Blue dye in sodium acetate (0.5 m, pH 7.5). The micropipette tips were broken down to diameters of 1–3 μm. Electrode impedances ranged from 2 to 4 MΩ. At the end of each experiment, the recording site was marked by iontophoretic ejection (5–10 μA, negative current for 10 min) of Pontamine Sky Blue for histological verification.

Single-unit extracellular recordings of DR 5-HT neurons.

The dose–response of putative 5-HT neurons was assessed after single intravenous (0.05–0.8 mg/kg) and repeated intraperitoneal (0.05–2 mg/kg) administrations of WIN55,212-2. A burr hole was drilled on the midline, 1.2 mm anterior to interaural zero. Using a hydraulic micropositioner (model 650; David Kopf Instruments), the electrode was lowered into the DR. Putative 5-HT neurons were encountered immediately below the ventral border of the Sylvian aqueduct and abound between 5.0 and 6.5 mm ventral to the dura mater. These neurons under normal conditions were identified according to the following criteria: a slow (0.1–4 Hz) and prominently regular firing rate (coefficient of variation ranges from 0.12 to 0.87) and a broad positive action potential (0.8–3.5 ms; 1.4 ms first positive and negative deflections) (Baraban and Aghajanian, 1980; Allers and Sharp, 2003). An inhibitory response to the $GABA_B$ agonist baclofen after intravenous drug administrations also confirmed that neurons were 5-HT because $GABA_B$ receptors are almost exclusively limited to 5-HT neurons in the DR (Wirtshafter and Sheppard, 2001).

5-HT burst activity.

Burst activity pattern was analyzed based on the criteria of Gobbi et al. (2005), such that a train of at least two spikes with an onset defined by a maximum initial interspike interval of 20 ms within a regular low-frequency firing pattern was categorized as a burst. The longest interspike interval allowed within a burst was 40 ms. In intraperitoneal experiments, two to four electrode descents were made to obtain a maximal sample of neurons across the rostrocaudal medial extent of the DR presumed richest in 5-HT neurons (Descarries et al., 1982). Recordings were also performed after coadministration of rimonabant (1 mg/kg) injected intraperitoneally 10 min

before the last WIN55,212-2 injection. Single-unit activity was recorded as discriminated action potentials amplified by a Tennelec (Oakridge, TN) TB3 MDA3 amplifier, postamplified and filtered by a Realistic 10 band frequency equalizer, digitalized by a CED1401 interface system (Cambridge Electronic Design, Cambridge, UK), processed on-line, and analyzed off-line by Spike2 software version 5.05 for Windows PC (Microsoft, Seattle, WA). Changes in neuronal firing pattern resulting from drug administrations were continuously monitored; the first 30 s immediately after drug injections were not considered to eliminate injection artifacts. Neurons were considered nonresponding if percentage change from baseline firing activity after drug administrations was <10%.

Experiment 3: PFC transections

To determine whether cannabinoid-induced modulation of DR 5-HT neurons originate in the PFC and are relayed via the descending corticoraphe fibers, systematic transections of the PFC–DR pathway were performed on anesthetized rats before electrophysiological recordings. For a total bilateral PFC transection (tPFC), a fine needle (0.35 mm diameter) was initially positioned at 1 mm anterior to bregma and 0.8 mm left of the midline. It was lowered 6.8 mm from the dura mater, slowly slid leftward 5 mm from the midline (0.5 mm/min), and then slowly retracted vertically using a micropositioner (10 μm/min). To avoid damaging the sinus, the needle was positioned 1.2 mm from the midline on the right hemisphere, lowered 6.8 mm at a 20° angle, and then moved 5 mm rightward (modified after Diaz-Mataix et al., 2005). Selective transection of PFC subregions were performed by positioning the needle 2.5 mm anterior to bregma, lowered 6.8 mm from the dura mater, and moved 1.5 mm (on both sides) from the midline for an mPFC transection (areas transected included the dorsal peduncular, infralimbic, prelimbic Cg3, and cingulate Cg1 cortices) or from 1.5 to 5 mm for a transection of the lateral aspect of the prefrontal cortex (latPFC): mainly the lateral prefrontal/agranular insular, but also the frontal Fr2, Fr1, and Fr3; the ventrolateral and lateral orbital cortices; and some parts of parietal area 1 (modified after Hajos et al., 1999). 5-HT single-unit recordings were conducted 1.5–2 h after transection.

Experiment 4: combined intracerebral microinfusion and electrophysiology

Experiment 4A: intracerebral microinfusion into the dorsal raphe nucleus.

Anesthetized rats were implanted with a single guide cannula (22 gauge; Plastics One, Roanoke, VA) for intra-DR microinfusion of WIN55,212-2. The guide cannula was angled at 25° from the vertical axis and aimed 1 mm above the DR to allow termination of the injector tip within the nucleus (+1.2 mm from interaural zero, ±1.4 from midline, and −6.0 mm from the dura mater). The cannula was fixed to the skull with the use of skull screws and dental acrylic. A 1.5–2 h postoperative interim period was allowed before the start of electrophysiological recordings (as described above in experiment 2). Once a stably firing 5-HT neuron was found and 1–3 min of baseline activity was established, microinfusion of either vehicle (0.5 μl) or WIN55,212-2 (5 μg/0.5 μl) was initiated and continuously delivered for 3 min. Substances were infused into the DR via a 28 gauge stainless steel injector attached by polyethylene tubing to a 1 ml syringe driven by a CMA 400 microdialysis syringe pump (CMA Microdialysis, Solma, Sweden). Changes in neuronal discharge pattern were continually monitored for up to 45 min after the cessation of microinfusion. The probability that results were confounded by random diffusion of

solutions to neighboring structures was remote because, aside from the strictly controlled injection volume, the vehicle used was relatively viscous and lipophilic compared with conventional solvents. To mark the site of injection at the end of each experiment, a small volume (50 nl/cannula) of Pontamine Sky Blue was infused via the same injector that was used for drug injections or was iontophoretically ejected from the recording pipette (see Fig. 5*C*).

Experiment 4B: intracerebral microinfusion into the prefrontal cortex, intra-mPFCv.

Simultaneous bilateral microinfusion of WIN55,212-2 (5 μg/0.5 μl) into the ventromedial subregions of the mPFC (mPFCv) (prelimbic–infralimbic cortices; +2.2 mm from bregma, ±0.5 from midline, −3.5 mm from the dura mater) was performed using a bilateral guide cannula (22 gauge, 1 mm center-to-center distance; Plastics One). The rest of the procedure was as described in the intra-DR microinfusion experiment (see above, experiment 4A).

Experiment 4C: intracerebral microinfusion into the prefrontal cortex, intra-latPFC.

Simultaneous bilateral microinfusion of WIN55,212-2 (5 μg/0.5 μl) into the latPFC (agranular insular cortex; +3.2 mm from bregma, ±4.2 from midline, and −4.2 mm from the dura mater) was performed with two single guide cannulas (22 gauge; Plastics One). The rest of the procedure was as described in the intra-DR microinfusion experiment (see above, experiment 4A).

Experiment 4D: intracerebral microinfusion into the prefrontal cortex, intra-mPFCv with PFC transection.

To confirm whether the integrity of the mPFC–DR pathway is required for the modulatory effect of WIN55,212-2 on DR 5-HT neurons, a final negative control procedure was performed by combined microinfusion and electrophysiological techniques on PFC-transected rats. Anesthetized rats first underwent transection of the PFC (1 mm anterior to bregma; see above, experiment 3) and immediately implanted with a bilateral cannula into the mPFCv, as described previously (2.2 mm anterior to bregma; see above, experiment 4B) anterior to the transection lesion. Then, following the procedure used in experiment 4B, WIN55,212-2 was infused while performing single-unit recording on a DR 5-HT neuron.

Experiment 5: intracerebral mPFCv microinfusion and FST

Under Equithesin anesthesia (3 ml/kg) (1.96 g of sodium pentobarbital, 8.5 g of chloral hydrate, 4.25 g of $MgSO_4$ hexahydrate, 60 ml of propylene glycol, 20 ml of ethanol, and 58 ml of distilled water, adjusted to 200 ml with distilled water), rats were mounted in a stereotaxic frame as described previously. Cannulation procedure was the same as in experiment 4B. After surgery, the incisions were stitched and applied with antiseptics. The cannulas were occluded with stainless steel wire stylets (Plastics One) to maintain patency. A postoperative recovery period of 8 d was allowed. Thereafter, cannulated rats were submitted to the FST (see above, experiment 1). A 15 min preswim test was conducted. The next day, rats were allowed to habituate to the testing room for 2 h before microinfusion. Then, WIN55,212-2 (1 or 5 μg in 0.5 μl of vehicle) or vehicle (0.5 μl) was continuously delivered for 3 min. In some cases, infusion of rimonabant [1 μg (Caillé and Parsons, 2006) in 0.25 μl of vehicle for 1.5 min] was performed 1 min before infusion of WIN55,212-2 (1 μg in 0.25 μl of vehicle for 1.5 min). In all groups, total infusion

volume was 0.5 μl. The microinfusion connector assembly was left in place 4 more min to allow the drug solution to diffuse into the target structure (mPFCv). The rats were then placed in the cylindrical pool and subjected to the FST (5 min test swim recording).

Histology

Histological verification of the extent and selectivity of lesions imprinted by transections and cannula/microinjector trajectories were performed at the end of each experiment. The rats were deeply anesthetized (400 mg/kg chloral hydrate, i.p.) and then perfused according to standard procedures (fixative, 4% paraformaldehyde with 0.1% glutaraldehyde). The brains were harvested and postfixed in 4% paraformaldehyde overnight and incubated in 30% sucrose for 2 d. Adjacent series of 20–50 μA brain slices within the vicinity of lesions were cut using a freezing microtome and stained with thionin acetate (Sigma) for light microscopic verification or stored in a cryoprotectant solution at −20% until inspection.

Statistical analyses

SPSS (version 13; SPSS, Chicago, IL) was used to organize and statistically analyze data. All data were expressed as mean ± SEM and were submitted to parametric tests (one-way or two-way ANOVA), followed by Student's *t* test/Dunnett's test for *post hoc* comparisons. When assumptions of normality and variance homogeneity were not satisfied, nonparametric tests (Kruskal–Wallis or Friedman's tests for ANOVA, Mann–Whitney *U* test for *post hoc* comparisons) were performed. Dunnett's *post hoc* test was used for comparing with baseline drug-induced changes in neuronal activity. Nonlinear curve fitting and the calculation of ED_{50} were performed using Microcal Software (Northampton, MA) Origin (version 7). Fisher's exact test was used to assess the differential response to CB_1R blockade versus TRPV1 blockade after intravenous administrations of rimonabant and capsazepine. Statistical values reaching $p \leq 0.05$ were considered significant.

Results

Effect of subchronic low and high doses of WIN55,212-2 in the FST

To examine the possible dose-dependent effect of CB_1R agonists on stress-coping behavior, we tested low and high doses of WIN55,212-2 in the FST. A low dose of WIN55,212-2 (0.2 mg/kg, i.p.) compared with vehicle elicited a significant decrease in total time spent in immobility (WIN at 0.2 mg/kg, 54.05 ± 11.11; VEH, 159.9 ± 10.94; −66.2%, $p < 0.01$) (Fig. 1*A*) and a significant increase in total swimming duration (WIN at 0.2 mg/kg, 220.08 ± 10.39; VEH, 128.86 ± 10.72; +70.79%, $p < 0.01$) (Fig. 1*A*) but did not affect total climbing duration [WIN at 0.2 mg/kg, 24.73 ± 4.79; VEH, 11.21 ± 15; no significant difference (NS)] (Fig. 1*A*). These effects were comparable with those produced by the clinically used selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram (5 mg/kg, i.p.; immobility, 47.8 ± 15.25, −72.84%, $p < 0.01$ vs VEH; swimming, 218.83 ± 25.4, +119.8%, $p < 0.01$ vs VEH; climbing, 33.33 ± 13.78, +36.37%, NS vs VEH) (Fig. 1*A*). Conversely, the selective norepinephrine reuptake inhibitor DMI (10 mg/kg, i.p.) elicited a decrease in total immobility duration (30 ± 6.57, −82.95%, $p < 0.01$ vs VEH) and an increase in total climbing duration (142.01 ± 19.6, +481.06%, $p < 0.01$ vs VEH)

but not an increase in total swimming duration (127.99 ± 14.88, +28.56%, NS vs VEH), confirming its primary action on noradrenergic transmission (Fig. 1*A*). The effects of the low dose of WIN55,212-2 on immobility and swimming behaviors were prevented by the coadministration of the CB_1R antagonist RIM (1 mg/kg, i.p.) (WIN at 0.2 mg/kg plus RIM at 1 mg/kg, i.p.; immobility, 122.52 ± 26.49, −23.38%, NS vs VEH; swimming, 154.16 ± 25.39, +19.63%, NS vs VEH) (Fig. 1*A*). A high dose of WIN55,212-2 (2 mg/kg, i.p.) did not shorten total immobility duration (174.91 ± 36.57, −0.91%, NS vs VEH) and prolonged neither total swim duration (106.42 ± 32.1, +6.89%, NS vs VEH) nor total climbing duration (17.16 ± 6.5, −29.79%, NS vs VEH) (Fig. 1*A*). This inert activity of the high dose of WIN55,212-2 was not changed during coapplication with RIM (WIN at 2.0 mg/kg plus RIM at 1 mg/kg, i.p; immobility, 122.52 ± 26.49; swimming, 154.16 ± 25.39; or climbing, 23.4 ± 2.0 vs VEH, NS) (Fig. 1*A*). RIM (1 mg/kg, i.p.) did not induce any significant change in behavior (immobility, 128.32 ± 23.26; swimming, 159.34 ± 22.48; or climbing, 12.46 ± 2.0 vs VEH, NS) (Fig. 1*A*). The locomotor activity (movement velocity) of all drug-treated groups were not significantly different from that of the vehicle-treated group (CIT at 5 mg/kg, 433.24 ± 19.52; DMI at 10 mg/kg, 423.97 ± 22.44; WIN at 0.05 mg/kg, 423.21 ± 30.12; WIN at 0.10 mg/kg, 445.65 ± 29.45; WIN at 0.2 mg/kg, 434.71 ± 26.31; WIN at 2.0 mg/kg, 371.26 ± 33.16; WIN at 0.2 mg/kg plus RIM at 1 mg/kg, 476.82 ± 21.46; WIN at 2.0 mg/kg plus RIM at 1 mg/kg, 382.12 ± 37.26; or RIM at 1 mg/kg, 399.92 ± 22.50, NS vs VEH, 433.23 ± 24.21).

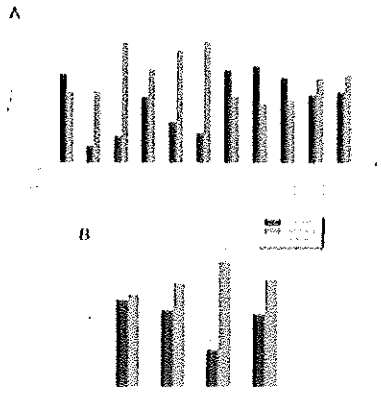

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Figure 1.

Antidepressant-like activity of WIN in the rat FST. ***A***, Behavioral effects of intraperitoneally administered vehicle, CIT (5 mg/kg, i.p.), DMI (10 mg/kg, i.p.), and WIN (0.05, 0.1, 0.2, 1.0, and 2.0 mg/kg, i.p.). Single injection of RIM (1 mg/kg, i.p.) 10 min before administration of a low dose of WIN (0.2 mg/kg, i.p.) blocked the antidepressant-like effect. Single injection of RIM (1 mg/kg, i.p.) 10 min before administration of a high dose of WIN (2 mg/kg, i.p.) did not modify the inert effect of WIN. Note that RIM by itself did not have any significant effect. ***B***, The antidepressant-like effect of WIN (0.2 mg/kg, i.p.) was abrogated by pretreatment with pCPA (150 mg/kg, i.p.) 72 and 48 h before pretest. Pretreatment of pCPA by itself did not have any significant effect. All treatments were administered 23, 5, and 0.75 h before test swim according to the method of Page et al. (1999). $n = 8–15$ per treatment group. Bars represent mean ± SEM total time of behaviors indicated. $*p < 0.05$ or $**p < 0.01$ versus vehicle.

Effect of pCPA pretreatment on WIN55,212-2 antidepressant-like activity in the FST

Because the activity of the low dose of WIN55,212-2 in the FST was similar to that of the SSRI citalopram, we tested whether this antidepressant-like activity was via a main action on 5-HT transmission as observed with SSRIs (Page et al., 1999). When injected with the low dose of WIN55,212-2, rats pretreated with the 5-HT-depleting agent pCPA expressed neither increased swimming behavior (pCPA plus WIN at 0.2 mg/kg, i.p., 166.35 ± 15.06 vs VEH plus VEH, 142.54 ± 17.2, NS) (Fig. 1*B*) nor decreased immobility (pCPA plus WIN at 0.2 mg/kg, i.p., 112.54 ± 15.35 vs VEH plus VEH, 134.34 ± 18.3, NS) (Fig. 1*B*). Pretreatment of pCPA alone did not induce any effect significantly different from vehicle pretreatment (pCPA plus VEH; immobility, 118.57 ± 9.72; swimming, 160.6 ± 9.65; or climbing, 20.93 ± 2.24 vs VEH plus VEH, NS) (Fig. 1*B*).

Effect of subchronic intraperitoneal doses of WIN55,212-2 on 5-HT single-unit activity

To test whether antidepressant-like behavioral effects of WIN55,212-2 in the FST were paralleled by enhanced 5-HT neuronal firing activity, we performed *in vivo* extracellular recordings of presumed 5-HT neurons following the same treatment schedule as in the FST. WIN55,212-2 was administered 23, 5, and 0.75 h before electrophysiological recordings. In some animals, RIM was injected intraperitoneally 10 min before the third administration of 0.2 mg/kg WIN55,212-2. Mean spontaneous firing rate of 5-HT neurons showed a biphasic response profile after incremental doses of WIN55,212-2. One-way ANOVA revealed a dose-dependent increase with lower doses of WIN55,212-2 (VEH, 1.14 ± 0.04; WIN at 0.05 mg/kg, 1.35 ± 0.11; WIN at 0.1 mg/kg, 1.88 ± 0.15; WIN at 0.2 mg/kg, 2.58 ± 0.25; $F_{(3,203)} = 10.97$; $p < 0.01$) (Fig. 2*A*), and the coadministration of RIM prevented this increase. A dose of 0.2 mg/kg WIN55,212-2 yielded a maximal 126.32% increase in neuronal activity. Conversely, a high dose of WIN55,212-2 (2.0 mg/kg) yielded a significant decrease compared with vehicle (WIN at 2.0 mg/kg, 0.41 ± 0.11, −64%, $p < 0.01$ vs VEH) (Fig. 2*A*). We also calculated the mean number of neurons per electrode descent, which served as an indirect measure of spontaneously active neurons (Gobbi et al., 2007). Compared with vehicle injections (VEH, 3.75 ± 0.16), there were 28% more spontaneously active 5-HT neurons after treatment with 0.1 mg/kg WIN55,212-2 (4.8 ± 0.39, $p < 0.05$) and 33.33% more active neurons with 0.2 mg/kg WIN55,212-2 (5.0 ± 0.46, $p < 0.01$), whereas a high dose of WIN55,212-2 had fewer active neurons than the control (WIN at 2.0 mg/kg, 1.92 ± 0.39, −48.8%, $p < 0.01$). The number of spontaneously active neurons in rats treated with a low dose of WIN55,212-2 (0.2 mg/kg) coapplied with RIM (1.0 mg/kg) did not significantly differ from those treated with the vehicle (Fig. 2*B*).

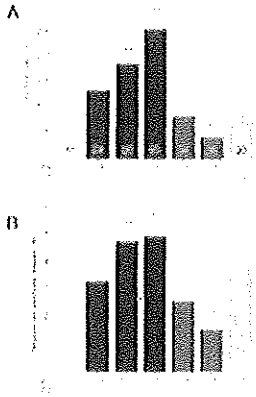

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Figure 2.

Effect of intraperitoneal administration of WIN on DR 5-HT neurons. ***A***, Effect of WIN on 5-HT neuronal firing activity. WIN (0.05–2.0 mg/kg, i.p.) was administered 23, 5, and 0.75 h before electrophysiological recordings. Coapplication of RIM (1 mg/kg, i.p.) 10 min before WIN (0.2 mg/kg, i.p.) blocked the increase in spontaneous 5-HT single-unit firing activity. ***B***, Effect of WIN on the number of spontaneously active 5-HT neurons. The number of spontaneously active neurons was calculated as the number of recorded 5-HT neurons per electrode descent in each treatment group. Values at the base of each column in *A* denote the number of 5-HT neurons recorded. Bars represent mean ± SEM values. $^{**}p < 0.01$ versus vehicle.

Effects of a single intravenous administration of low doses of WIN55,212-2 on 5-HT firing activity

To appraise whether the CB_1R agonist WIN55,212-2 rapidly influences 5-HT neurotransmission, we measured the spontaneous single-unit firing activity of DR 5-HT neurons after cumulative intravenous administration of WIN55,212-2. Incremental doses of WIN55,212-2 (0.05–0.2 mg/kg) evoked a dose-dependent increase in 5-HT unit firing activity ($F_{(3,62)} = 4.64$, $p < 0.01$, one-way ANOVA; VEH, 1.04 ± 0.10 Hz; WIN at 0.05 mg/kg, 1.17 ± 0.28 Hz; WIN at 0.1 mg/kg, 1.61 ± 0.37; WIN at 0.2 mg/kg, 2.04 ± 0.27) (Fig. 3*E*), which was half-maximal (ED_{50}) at a dose of 0.1 mg/kg and was not blocked by capsazepine (20 μg/kg, i.v.) but was blocked by RIM (1 mg/kg, i.v.) in 100% of neurons tested ($n = 4$; Fisher's test, $p = 0.01$) (Fig. 3*A*). WIN55,212-2 treatment also increased burst activity, a pattern of neural activity that is associated with enhanced 5-HT release in postsynaptic regions (Gartside et al., 2000), as well as antidepressant-like activity (Gobbi et al., 2005). The maximal increase in burst frequency from baseline (percentage recorded spikes contained in bursts) was recorded at 0.2 mg/kg (VEH, 3.71 ± 1.16%; WIN at 0.05 mg/kg, 8.85 ± 3.59%; WIN at 0.1 mg/kg, 9.61 ± 3.15%; WIN at 0.2 mg/kg, 12.51 ± 4.07; $\chi^2_{(3)} = 12.56$; $p < 0.01$, Kruskal–Wallis test) (Fig. 3*F*, top). The maximal

increase in the mean number of spikes in a burst was 324% occurring at 0.2 mg/kg (VEH, 0.63 ± 0.13; WIN at 0.05 mg/kg, 1.23 ± 0.42; WIN at 0.1 mg/kg, 1.28 ± 0.32; WIN at 0.2 mg/kg, 2.67 ± 1.3; $\chi^2_{(3)} = 10.01$; $p < 0.01$, Kruskal–Wallis test) (data not shown). Mean burst length was 82.25, 235.35, and 175.83% greater than baseline (vehicle) after incremental doses of 0.05, 0.1, and 0.2 mg/kg WIN55,212-2, respectively (VEH, 13.24 ± 3.75 ms; WIN at 0.05 mg/kg, 24.13 ± 10.79 ms; WIN at 0.1 mg/kg, 44.4 ± 18.1 ms; WIN at 0.2 mg/kg, 36.52 ± 14.64 ms; $\chi^2_{(3)} = 9.03$; $p < 0.05$, Kruskal–Wallis test) (Fig. 3*F*, bottom). Among all neurons recorded, 66.67% ($n = 16$) of 5-HT neurons responded to increasing dose injections of WIN55,212-2, whereas 33.33% ($n = 8$) of neurons were nonresponding. All responding and nonresponding neurons showed the same electrophysiological characteristics, were inhibited by baclofen, and were localized in the DR.

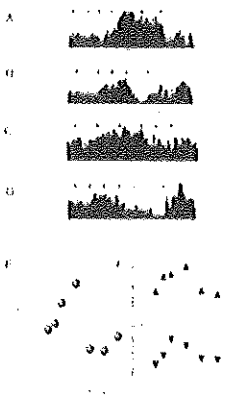

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Figure 3.

Effect of intravenous administration of cumulative doses of WIN on DR 5-HT neurons. ***A–D***, Integrated firing rate histograms of 5-HT neurons illustrating that low doses of WIN (0.1–0.2 mg/kg, i.v.) rapidly increased single-unit firing activity. ***A***, This effect was reversed by RIM (1.0 mg/kg, i.v.; $n = 4$) but not by CPZ (0.02 mg/kg, i.v.; $n = 4$). ***B–D***, High dose of WIN (0.30–0.50 mg/kg, i.v.) rapidly decreased single-unit firing activity. This effect was reversed by CPZ (0.02 mg/kg, i.v.) in two of three neurons (***D***) and partially reversed (***B***) or unreversed (***C***) by RIM (1 mg/kg, i.v.) in one and three neurons, respectively. 5-HT neuronal firing rate in each histogram is plotted as spikes per 10 s. Calibration bar on right side of each histogram, 1 min. The vertical lines depicted below each histogram represent the frequency of neuronal burst activity such that each tick corresponds to a burst discharge event. ***E***, WIN (0.05–0.5 mg/kg, i.v.) produced a biphasic response profile in 5-HT single-unit activity. ***F***, Line graphs showing that cumulative doses of WIN modulated 5-HT neuronal burst activity measured as percentage of spikes within bursts (top) and mean burst length (bottom). $^*p < 0.05$ or $^{**}p < 0.01$ vs baseline (vehicle).

Effects of a single intravenous administration of high doses of WIN55,212-2 on 5-HT firing activity

Remarkably, cumulative doses higher than 0.2 mg/kg WIN55,212-2 injected intravenously generally produced a decline in neuronal excitation significant at both 0.3 and 0.4 mg/kg and achieved a maximal level 45% below baseline (vehicle) after 0.4 mg/kg WIN55,212-2 (VEH, 1.04 ± 0.10 Hz; WIN at 0.04 mg/kg, 0.59 ± 0.08 Hz; $F_{(1,45)} = 6.7$; $p < 0.01$) (Fig. 3*E*). A waning of stimulatory effects was also observed with burst activity: burst frequency (percentage of total number of recorded spikes; WIN at 0.3 mg/kg, 3.9 ± 2.85%; WIN at 0.4 mg/kg, 2.67 ± 1.82; WIN at 0.5 mg/kg, 10.51 ± 6.21%) (Fig. 3*F*, top), mean number of spikes in a burst (WIN at 0.3 mg/kg, 0.64 ± 0.34; WIN at 0.4 mg/kg, 1.83 ± 1.11; WIN at 0.5 mg/kg, 1.5 ± 0.5) (data not shown), mean burst length (WIN at 0.3 mg/kg, 20.73 ± 15.94 ms; WIN at 0.4 mg/kg, 19.54 ± 9.59 ms; WIN at 0.5 mg/kg, 15.53 ± 7.75 ms) (Fig. 3*F*, bottom). The CB_1R antagonist RIM (1 mg/kg, i.v.) partially reversed this decline only in one of four neurons (Fig. 3*B*). Three neurons were nonresponsive (Fig. 3*C*). In two of three neurons tested, capsazepine reversed the decrease induced by high doses of WIN55,212-2 (Fig. 3*D*). This complex response pattern suggests that the CB_1R may not be involved in the 5-HT effects induced by high doses of WIN55,212-2 (Fisher's test, $p = 0.57$, NS). Neither RIM (RIM at 1 mg/kg, i.v.) alone nor capsazepine (CPZ at 20 μg/kg, i.v.) alone had a significant effect on 5-HT single-unit firing activity (VEH, 1.3 ± 0.33; CPZ, 1.2 ± 0.57, $n = 5$; RIM, 1.48 ± 0.52, $n = 7$).

5-HT single-unit activity after PFC transections

DR 5-HT neurons receive important excitatory inputs from pyramidal (glutamatergic) cells of the PFC (Jankowski and Sesack, 2004). To verify whether cortical CB_1Rs in the PFC or its subregions are essential in the control of DR 5-HT neurons by cannabinoids, rats were subjected to a tPFC, latPFC, or mPFC deafferentation by mechanical transection before 5-HT single-unit recordings. After tPFC transection, we observed that WIN55,212-2 failed to increase 5-HT single-unit firing activity at otherwise stimulatory doses in intact brains (tPFC transection: baseline, 1.46 ± 0.39 Hz, $n = 7$; WIN at 0.05 mg/kg, 0.78 ± 0.17 Hz, $n = 6$; WIN at 0.1 mg/kg, 0.91 ± 0.25 Hz, $n = 5$; WIN at 0.2 mg/kg, 0.97 ± 0.29 Hz, $n = 5$; WIN at 0.3 mg/kg, 1.04 ± 0.18 Hz, $n = 4$; WIN at 0.4 mg/kg, 0.97 ± 0.17 Hz, $n = 4$; WIN at 0.5 mg/kg, 1.10 ± 0.15 Hz, $n = 4$; WIN at 0.6 mg/kg, 1.31 ± 0.40 Hz, $n = 3$; $p < 0.01$) (Fig. 4*A*). We noted that, at doses higher than 0.6 mg/kg intravenously, a moderate increase of firing activity can be elicited but was not sensitive to RIM (non-CB_1R-selective), which may indicate unspecific binding (data not shown). To pinpoint the specific subregion of the PFC that is critical in mediating the modulation of 5-HT single-unit activity, we compared transection of the mPFC with that of the latPFC. The response of 5-HT single units to the latPFC did not significantly differ from the control (baseline, 1.40 ± 0.12 Hz, $n = 4$; WIN at 0.05 mg/kg, 1.97 ± 0.57 Hz, $n = 4$; WIN at 0.1 mg/kg, 2.18 ± 0.59 Hz, $n = 4$; WIN at 0.2 mg/kg, 0.96 ± 0.02 Hz, $n = 4$; NS vs control, between-groups ANOVA) (Fig. 4*A*). On the contrary, mPFC transection produced an effect similar to tPFC transection and was significantly different from the control (baseline, 0.79 ± 0.22 Hz, $n = 4$; WIN at 0.05 mg/kg, 0.79 ± 0.20 Hz, $n = 4$; WIN at 0.1 mg/kg, 0.81 ± 0.23 Hz, $n = 4$; WIN at 0.2 mg/kg, 0.69 ± 0.26 Hz, $n = 4$; WIN at 0.3 mg/kg, −0.62 ± 0.30 Hz, $n = 4$; WIN at 0.4 mg/kg, 0.71 ± 0.21 Hz, $n = 4$; WIN at 0.6 mg/kg, 1.03 ± 0.33 Hz, $n = 4$; WIN at 0.7 mg/kg, 0.87 ± 0.06, $n = 4$; $p < 0.05$ vs control, between-groups ANOVA) (Fig. 4*A*), thus indicating that the medial, but not lateral, parts

are responsible for the 5-HT firing activity enhancement by CB_1R agonism. The transection procedure did not significantly modify the basal discharge rate of DR 5-HT neurons as was also observed by Hajos et al. (1999).

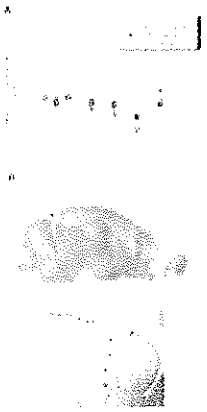

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Figure 4.

Effect of PFC transections on the modulation of DR 5-HT neuronal activity by intravenous administration of WIN. ***A***, Line graph showing the modulatory effect of cumulative doses of WIN (0–0.5 mg/kg) on 5-HT single-unit firing activity after tPFC (shaded inverted triangles), ablation of mPFC (shaded squares), or latPFC (shaded upright triangles) subregions compared with sham-exposed controls (open circles). tPFC and mPFC transections abrogated the excitatory response to low doses of WIN (0.05–0.2 mg/kg, i.v.), whereas latPFC transection did not significantly reduce the excitatory response to low doses of WIN (0.05–0.2 mg/kg, i.v.). $n = 3–7$ animals per group. Values are expressed as mean ± SEM of increase in 5-HT unit firing rate (percentage of baseline). $^{**}p < 0.01$ mPFC transection versus control; $^{++}p < 0.01$ tPFC transection versus control. ***B***, Histological verification of the lesion left by a tPFC transection. Gray rectangle encompasses the anteroposterior range of all transections, and arrows point to an example of a cortical lesion trace on a midsagittal brain section (~0.4 mm lateral to midline according to Paxinos and Watson, 1986). Shown is an illustrative depiction of the electrode placement and a typical action potential waveform of a putative 5-HT neuron (top) and a closer inspection of the lesion trace (bottom).

Microinfusion of WIN55,212-2 into the mPFCv and DR: electrophysiology on 5-HT neurons

To further localize the action of cannabinoids on 5-HT neurons, local microinfusion experiments were performed. Because the CB_1R (Moldrich and Wenger, 2000) and CB_1R mRNA (Häring et al., 2007) are present in the DR, it appeared reasonable to begin our attempt to localize the action

of WIN55,212-2 within this nucleus, with the hypothesis that cannabinoid-induced 5-HT neuronal modulation occurs through local DR circuits. The microinfusion of WIN55,212-2 into the DR elicited a rapid increase (63.64%) and decrease (30%) in single-unit firing activity in one positive responder and one negative responder, respectively. The other two of four neurons recorded were nonresponders (Fig. 5*A*,*B*).

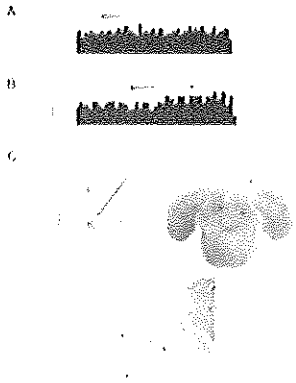

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Figure 5.

Effect of WIN microinfused into the DR. ***A***, Integrated firing rate histogram of a 5-HT neuron before and after intra-DR microinfusion of vehicle (0.5 μl) ($n = 3$ neurons). ***B***, Integrated firing rate histogram of a 5-HT neuron before and after intra-DR microinfusion of WIN (5 μg in 0.5 μl of vehicle) showing a slight increase in single-unit firing activity immediately after infusion observed in one of four neurons. Among the other three neurons, one showed a decrease whereas the other two did not respond at all. On each histogram, 5-HT neuronal firing rate is plotted as spikes per 10 s. Horizontal bar on top represents the time course of infusion, and vertical lines at the bottom represent the frequency of neuronal burst activity such that each tick corresponds to a burst event. ***C***, Left, An illustrative depiction of the electrode descent into the DR (shaded gray area) and the trajectory of the microcannula based on the stereotaxic atlas of Paxinos and Watson (1986). Right, Histological verification of lesions imprinted by the electrode descent (left arrow) and of the microcannula (right arrow) on a coronal brain section (~1.2 anterior to interaural zero) showing the DR (shaded gray area). Bottom, Closer inspection of lesion traces.

The mPFCv is functionally associated with stress and coping mechanisms through the regulation of the DR (Amat et al., 2005). Therefore, we further assessed the impact of CB_1R activation in the ventral prelimbic–infralimbic cortex (mPFCv) on 5-HT single-unit activity. To strengthen results obtained from the selective mPFC transection, we locally microinfused WIN55,212-2 into the mPFCv of both cortical hemispheres. Corroborating the results from the transections (experiment 3), a gradual increase in 5-HT single-unit firing activity was elicited in four of five

(80%) neurons recorded. This increase plateaued after 10–20 min and was rapidly nullified by the injection of RIM (1 mg/kg, i.v.) (Fig. 6*A*). Furthermore, microinfusion of WIN55,212-2 into the same site in mPFC-transected brains ($n = 2$) (Fig. 6*C*) as well as into the latPFC ($n = 2$) (Fig. 6*D*) did not elicit an increase in 5-HT single-unit activity in support of the necessity of the mPFC in cannabinoid-induced modulation of DR 5-HT neurons.

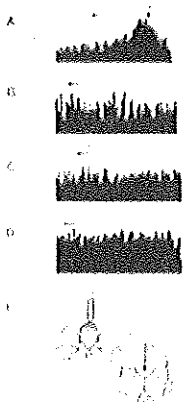

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Figure 6.

Effect of bilateral microinfusion of WIN into the mPFCv and latPFC on DR 5-HT neuronal activity. ***A***, Integrated firing rate histogram of a 5-HT neuron showing a robust but slow-onset increase in single-unit activity after intra-mPFCv infusion of WIN (5 μg in 0.5 μl of vehicle) in four of five neurons. This effect was abrogated by RIM (1.0 mg/kg, i.v.). ***B***, Integrated firing rate histogram of a 5-HT neuron before and after intra-mPFCv infusion of WIN (5 μg in 0.5 μl of vehicle) showing an abolition of increased single-unit activity resulting from total prefrontocortical transection ($n = 2$ neurons). The microinfusion site was anterior to the transection lesion. ***C***, Integrated firing rate histogram of a 5-HT neuron before and after intra-mPFCv infusion of vehicle (0.5 μl), showing no apparent effect on neuronal activity ($n = 4$ neurons). ***D***, Integrated firing rate histogram showing that intra-latPFC infusion of WIN (5 μg in 0.5 μl of vehicle) did not produce an increase in 5-HT single-unit activity ($n = 2$ neurons). On each histogram, 5-HT neuronal firing rate is plotted as spikes per 10 s. Horizontal bar represents the time course of infusion, and vertical lines at the bottom represent the frequency of neuronal burst discharge such that each tick corresponds to a burst event. ***E***, Illustrative depiction of the placement of cannulas directed into the mPFCv (shaded region area, bregma +2.2) and the electrode descent into the dorsal raphe nucleus (interaural 0 + 1.2), based on the stereotaxic atlas of Paxinos and Watson (1986).

Microinfusion of WIN55,212-2 into the mPFCv: behavior in the FST

Because the results obtained from intracerebral WIN55,212-2 microinfusions with electrophysiology seemed to point to the mPFCv as a structure that plays an important role in cannabinoid-induced activation of DR 5-HT neurons, we therefore examined whether local bilateral microinfusion of WIN55,212-2 into the mPFCv is sufficient to alter stress-coping behaviors in the FST. Both microdoses of WIN55,212-2 used (1 and 5 μg in 0.5 μl of vehicle), compared with vehicle, produced a reduction of 47.43 and 36.24%, respectively, in total immobility time (VEH, 142.92 ± 14.29 s; WIN at 1 μg, 75.13 ± 15.74 s; WIN at 5 μg, 90.12 ± 20.93 s; $p < 0.01$ vs VEH) (Fig. 7) and an enhancement of 38.78 and 32.31%, respectively, in total swimming time (VEH, 141.09 ± 12.97 s; WIN at 1 μg, 195.81 ± 15.49 s; WIN at 5 μg, 186.68 ± 18.84 s; $p < 0.01$ vs VEH) (Fig. 7). There were no significant changes observed in climbing behavior (VEH, 16.07 ± 3.23 s; WIN at 1 μg, 29.2 ± 5.22 s; WIN at 5 μg, 21.50 ± 7.43 s; NS vs VEH) (Fig. 7), implying that enhancement in noradrenergic transmission may not be as important as enhancement in serotonergic transmission in mediating the antidepressant-like effects of WIN55,212-2 in the FST. A microdose of RIM (1 μg) that by itself did not induce any significant effect in the FST (immobility, 05.0 ± 40; swimming, 170.5 ± 20.2; or climbing, 23.5 ± 10 vs VEH, NS) blocked the effect of 1 μg of WIN55,212-2 when microinfused 1 min before WIN55,212-2. In the open-field test, neither WIN55,212-2, RIM, nor RIM plus WIN55,212-2 induced a change in locomotor activity with the microdoses used, eliminating the possibility of a false positive in the FST (VEH, 422.93 ± 41.38; WIN at 1 μg, 400.31 ± 50.86; WIN at 5 μg, 397.89 ± 64.02; RIM at 1 μg plus WIN at 1 μg, 431.43 ± 42.12; or RIM at 1 μg, 455.26 ± 31.9).

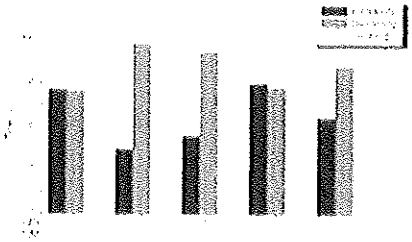

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Figure 7.

Behavioral effects of bilateral microinfusion of WIN and RIM into the mPFCv in the rat FST. WIN (1 or 5 μg in 0.5 μl of vehicle infused for 3 min) administered 7–10 min before the FST increased total time spent swimming and decreased total time spent immobile. Bilateral microinfusion of RIM (1 μg in 0.25 μl of vehicle for 1.5 min) 1 min before microinfusion of WIN (1 μg in 0.25 μl for 1.5 min) abrogated antidepressant-like effect. RIM (1 μg in 0.5 μl of vehicle for 3 min) did not have any significant effect. $n = 7–11$ animals per treatment group. $^{**}p < 0.01$ versus vehicle.

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Discussion

These results establish that low doses of a CB_1R agonist elicit potent antidepressant-like behavior and enhance 5-HT neurotransmission, mediated by CB_1R activation in the mPFCv. Conversely, high doses nullify antidepressant-like behavior and markedly attenuate 5-HT neurotransmission, an effect that appears to be instigated by a non-CB_1R mechanism.

Similar to antidepressants selectively blocking 5-HT reuptake (SSRIs), the CB_1R agonist WIN55,212-2 potently decreased immobility and increased swim behavior in the FST. This was attributed to direct CB_1R activation that modulates 5-HT because it was blocked by the CB_1R antagonist rimonabant and the 5-HT-depleting agent pCPA. Highlighting the role of CB_1R in mood regulation, preclinical studies have indeed shown that its genetic and pharmacological blockade rendered animals more emotionally reactive and anxious (Haller et al., 2002, 2004; Martin et al., 2002), susceptible to chronic stress-induced anhedonia (Martin et al., 2002), and liable to impairments in hypothalamic–pituitary–adrenal regulation (Barna et al., 2004) reminiscent of neuroendocrine dysfunction observed in depression. Interestingly, CB_1R knock-out mice presented impaired extinction of aversive memories (Marsicano et al., 2002), invoking the pathological hallmark of posttraumatic stress disorder, a condition possessing overlapping symptomatology and high rate of comorbidity with major depression (Vieweg et al., 2006). Antidepressant-like effects in the FST have also been reported previously with the endocannabinoid reuptake inhibitor AM404 [*N*-(4-hydroxyphenyl)-arachidonamide] (Hill and Gorzalka, 2005) and the direct CB_1R agonist HU-210 [3-(1,1-dimethylheptyl)-(−)-11-hydroxy-Δ^8-tetrahydro-cannabinol] (Hill and Gorzalka, 2005; Jiang et al., 2005). Chronic HU-210 treatment was also found to drive hippocampal cell proliferation (Jiang et al., 2005), believed to be a downstream sequela of antidepressant treatment (Malberg et al., 2000). We recently demonstrated that the selective FAAH inhibitor URB597 cyclohexylcarbamic acid 3′-carbamoylbiphenyl-3yl ester possesses antidepressant-like properties in the FST, tail suspension test (Gobbi et al., 2005), and chronic mild stress paradigm (Bortolato et al., 2007), in support of the concept that the endocannabinoid system may serve as target for depression therapy without the unwanted psychotropic effects of direct CB_1R agonists. Moreover, perturbations in endocannabinoid signaling may very well be implicated in depression etiology, supported by the following. First, chronic unpredictable stress, used to model anhedonia, a core depression symptom, is associated with decreased endocannabinoid 2-arachidonoylglycerol in the rat hippocampus (Hill et al., 2005). Second, in humans, upregulation of PFC CB_1R in suicidal depressives may indicate an adaptive response to decreased endocannabinoids (Hungund et al., 2004). Third, randomized trials of the CB_1R antagonist rimonabant for obesity management increased adverse effects of depression and anxiety (Bronander and Bloch, 2007).

We demonstrated that WIN55,212-2 dose dependently enhances the number, firing, and burst activity of spontaneously active DR 5-HT neurons, corroborating microdialysis experiments that found increased synaptic 5-HT release in subcortical target regions (Fadda et al., 2006). We reported that elevating intrinsic anandamide through URB597 similarly elicited increased 5-HT activity (Gobbi et al., 2005). Both URB597 and WIN55,212-2 effects were CB_1R mediated because these were blocked by rimonabant. Noteworthy, the effects here observed with WIN55,212-2 were markedly different from those exerted by URB597 in at least two features. First, WIN55,212-2 elicited a rapid response as opposed to the 2 h delay with URB597; this

difference might be ascribed to the kinetics of FAAH inhibition preceding anandamide-induced CB_1R activation. Second, higher URB597 doses produced an enduring (plateau effect) excitation (Gobbi et al., 2005), whereas higher doses of WIN55,212-2 resulted in a rapid decline in excitation; this difference could be attributable to the fact that direct CB_1R agonists activate whole-brain CB_1Rs, whereas FAAH inhibitors indirectly activate a subpopulation of these receptors colocalized with FAAH.

We identified that a CB_1R subpopulation mediating 5-HT excitatory response to WIN55,212-2 is localized in the mPFC, the main source of cortical afferents to the DR (Hajos et al., 1999; Jankowski and Sesack, 2004). Convergent with results shown here, limbic 5-HT was enhanced after electrical stimulation of the mPFC but not of the latPFC (Juckel et al., 1999). Indeed, transecting mPFC efferents to the DR abolished the response of all recorded DR 5-HT neurons to the excitatory dose of WIN55,212-2. This was not observed after latPFC transection because of the absence of DR afferents from this area (Peyron et al., 1998). We surmise that the mPFCv particularly contained this receptor subpopulation because WIN55,212-2 bilaterally infused into this subregion markedly decreased FST immobility and increased basal discharge activity of DR 5-HT neurons. These effects were blocked by rimonabant.

The action of WIN55,212-2 may be explained by an enhanced feedforward excitatory input along mPFC–DR monosynaptic projections to 5-HT neurons possibly driven by disinhibiting pyramidal neurons (Fortin et al., 2004). Disinhibition was likely engaged by CB_1R inhibitory control of cortical interneurons (Trettel and Levine, 2002), in agreement with the $G_{i/o}$-protein-linked transduction mechanism known to be associated with it and the resultant inhibition of voltage-sensitive calcium channels (Piomelli, 2003). This view is strengthened by the abundant perisomatic expression of CB_1Rs in neocortical and PFC interneurons (Tsou et al., 1998; Marsicano and Lutz, 1999). Also, cannabinoids have been shown to increase cortical excitatory transmission and net spiking probability of pyramidal neurons *in vivo* (Pistis et al., 2001; Fortin et al., 2004), consistent with a concurrent increment of basal glutamate levels and decrement of basal GABA levels in prefrontocortical microdialysis experiments observed in anesthetized (Pistis et al., 2002) and awake (Ferraro et al., 2001) rats, as well as in prefrontocortical *in vitro* culture (Ferraro et al., 2001; Tomasini et al., 2002).

The degree of controllability over stressors is processed by the mPFCv, which in turn influences brainstem monoaminergic activity, particularly the DR (Amat et al., 2005, 2006; Maier et al., 2006). As such, it can be posited that the integrity of DR function in normosensitive states in relation to stress-coping and mood-related behaviors relies on the efficiency of mPFCv pyramidal activity. The therapeutic relevance of increasing pyramidal transmission becomes explicit on consideration that simply brief exposures to uncontrollable stress already can inflict significant dendritic retraction of infralimbic pyramidal neurons and impair stress-coping and fear extinction in murines (Izquierdo et al., 2006). Incidentally, hyperactivating anandamide through FAAH knock-out, thereby enhancing intrinsic CB_1R activity, has been observed to modulate PFC plasticity, significantly increasing dendritic spine density (Patel et al., 2007). This neuroplastic change is as well akin to an antidepressant-like effect on the mPFC observed after chronic antidepressant treatment (Sairanen et al., 2007).

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Medical Marijuana for the Treatment of Depression:

An Evidence Review

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Introduction

Purpose of the Evidence Review

This review evaluates evidence on cannabis use in adults for the treatment of depression. The Arizona Department of Health Services (ADHS), funded this report to assist in assessing depression as a condition to add to those that qualify for the use of medical marijuana in Arizona.

Background

Pursuant to A.R.S. § 36-2801.01, the public may petition the Arizona Department of Health Services (ADHS) to add debilitating medical conditions to those listed in A.R.S. 36-2801(3). The ADHS established the manner in which it shall consider petitions to add debilitating medical conditions in A.A.C. R9-17-106. A.A.C. R9-17-106(C) states, ADHS "shall accept requests for the addition of a medical condition to the list of debilitating medical conditions in R9-17-201 in January and July of each calendar year starting in January 2012". After receiving requests for adding conditions the ADHS requests a report on the scientific evidence on the use of cannabis for this condition from the University of Arizona College of Public Health. In addition the Department holds a public hearing to hear public testimony on the condition and its treatment with cannabis. The Department Medical Advisory Committee then considers the totality of the evidence in deciding to add a condition to the list, or not.

Scope of the Evidence Review

List of Key Questions

1. What evidence describes the benefits (including long-term benefits) of cannabis use for patients with depressive disorder? Is there evidence for the treatment of depression with medicinal marijuana or cannabis?
2. What are the approved recommended treatments for depression?
3. What is the relationship between marijuana use and depression?

Conflicts of Interest

The reviewers had no conflicts of interest to disclose.

Methods

Literature Search and Strategy

The topics of cannabis use and depression where searched in the following databases: The Cochrane Library, Ovid and PubMed MEDLINE®, Web of Science, Google Scholar, and PsycINFO. Bibliographies in the articles identified through these databases were hand searched for additional pertinent articles. A detailed description of the search terms can be found in Appendix 1.

Inclusion and Exclusion Criteria

Studies that met all of the following criteria were included:

1. Evaluated adults (≥ 18 years old) with depression
2. English language
3. Human study
4. Were relevant to one of the key questions

Studies that were excluded include those that were:

1. Animal studies
2. Editorials or opinions
3. Descriptions of biochemical and pathophysiological pathways
4. Not relevant to the key questions

The original intent was to restrict the search to clinical trials, cohort and case control studies. Due to the paucity of studies of this type found, we also included cross sectional studies and case reports.

Dates of Search

March 2012 to June 2012

Quality Assessment

Types of studies available to assess are listed and described in Appendix 2.
Observational studies were assessd using the main domains described in tools commonly used (Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomized intervention studies. Health Technology Assessment 2003;7(27)). The overall quality of the evidence is ranked using GRADE methodology demonstrated in Appendix 3. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.)

Results

The search resulted in a total of 155 articles between all databases. Out the 155 only 20 articles and 2 systematic reviews appeared to be relevant to the key questions. Out of the 20 articles, 9 did not meet the inclusion criteria or did not provide answers to our key questions. Each included article (total of 11) is summarized in Table 1. Systematic reviews (total of 2) are summarized in Table 2. The 9 reviewed and excluded articles are listed in Table 3.

There were a total of 11 articles that met the inclusion criteria. One was a series of case reports , two were cohort studies, 7 were cross sectional studies and one was a clinical trial of poor design.

Table 1
Articles Included in the Review

Author, Year, Title	***Description and Design of Study***	***Findings***	***Quality***
1. Denson, TF and Earleywine M. ; Decreased depression in marijuana users. Addictive Behaviors 2006;31:738-742.	Cross-Sectional Study. United States Participants solicited on internet from "drug policy organizations". Comparison via survey of 4494 people who either used either used marijuana daily (n=3323) or 1x/wk (n=861) with a control group (never used, n=310).	Users who consumed daily or occasionally had lower levels of depressive symptoms than those who never tried marijuana. Non-users had more depression than moderate users, ψ=3.2, p=.003 and heavy users ψ = 2.9, p<.001.	**Very Low Quality.** Study limitations include heavy selection bias, recall bias of participants, , and no control for confounders. It is a series of single variable analyses.
2. Gruber AJ, Pope HG, Brown M. ; Do Patients Use Marijuana As An Antidepressant? Depression 1996;4:77-80.	Case Series Review. Boston. Authors reviewed literature and presented 5 cases where they felt there was evidence of marijuana producing an antidepressant effect.	The five cases presented were of individuals ages 16 to 28, most of them with a college education. 5 cases, ages 16-28 that report anti depressant effects of marijuana. Soome used marijuana before onset of depression, some after. Most had co morbidities.	**Very Low Quality.** Article published in 1996 and is typically referenced in many updated systematic reviews on the topic.
3. Kotin J, Post RM, Goodwin FK, Δ^9 Tetrahydrocannabinol in depressed patients	Non randomized controlled clinical trial THC was given under double blind conditions to 8 depressed patients for a week and the outcomes were observed. Conducted at	Four patients showed little change in mood and reported drowsiness. Remaining four experienced adverse reactions and discontinued the intervention.	**Low Quality.** Study had a very small sample size. Inconsistency in administration of THC was noted. Duration of trial considered too short to document typical

	the NIH in Bethesda		antidepressant behavior.
4. Bovasso GB. Cannabis Use as a Risk Factor for Depressive Symptoms. American Journal of Psychiatry 2001;158:2033-2037.	**Longitudinal cohort, prospective.** **Participants (N=1,920) in the 1980 Baltimore Epidemiologic Catchment Area (ECA) study who were reassessed between 1994 and 1996 as part of a follow- up study.. The analysis focused on three groups: those who reported no depressive symptoms at baseline (N=849) and those with no diagnosis of cannabis abuse at baseline (N=1,837) vs those reporting baseline cannabis use (n=83).**	**Subjects with no history of depression but had a history of cannabis use at baseline were 4x more likely to develop depressive symptoms. Subjects with no history of cannabis use at baseline but had a history of depression did not develop cannabis abuse in the future.**	**Low to Moderate Quality.** **Depression symptomology and cannabis abuse is self reported. Imprecision is a problem as the odds ratios are found to have wide confidence Intervals. There is a large loss to follow up. Only 1920 of the original 3481 participated in the follow up. 848 had died. The study did control for multiple potential confounders.**
5. Chen CY, Wagner FA, Anthony JC. Marijuana use and the risk of major depressive episode (MDE) Epidemiological evidence from the United States National Comorbidity Survey. Social Psychiatry and Psychiatric Epidemiology 2002;37:199-206	**Cross-Sectional l Study.** **Data from 6,792 participants (15-45 yrs old) from the National Co morbidity Survey in the U.S. was analyzed.**	**The risk of first MDE was moderately associated with the number of occasions of marijuana use and with more advanced stages of marijuana use. The odds ratio was 1.6.**	**Low to Moderate Quality** **While the sample size was large and some possible confounders were controlled for, the cross sectional design is subject to recall bias from survey participants And the behaviors are self-reported .. Confounders identified: onset of marijuana use, frequency use, and social factors (unemployment status, marriage status, etc). Upgraded from very low to low-to moderate.**
6. Degenhardt L, Hall W, Lynskey M. . The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. Social Psychiatry and Psychiatric Epidemiology 2001;36:219-227.	Cross-Sectional Study. Data from the Australian National Survey of Mental Health and Well-Being was analyzed (N=10,641).	There was a moderate association between cannabis use in the past 12 months and the prevalence of affective and anxiety disorders. Cannabis use did not appear to be directly related to depression or anxiety when other drug use was considered as contributing factors.	**Low to Moderate quality** A large representative sample from Australia. Major potential confounders were controlled for. Large potential for recall bias from survey participants. Self-reported behaviors. Study did not directly measure depression but a plethora of other emotional health conditions. Upgraded from very low to

			low-to - moderate.
7. Fairman BJ, Anthony JC. Are early-onset cannabis smokers at an increased risk of depression spells? Journal of Affective Disorders 2012; 138-54-62.	**Cross-Sectional Study.** **The National Surveys on Drug Use and Health (NSDUH) was used and included 173,755 participants in a 4 year time frame.**	**Cannabis smoking initiated at any age signals a modest increased risk of a spell of depression in adulthood, even when adjusted for confounding variables. Delaying cannabis onset until adulthood does not appear to diminish the cannabis- associated risk. Odds ratios were 1.7 and 1.8.**	**Low to Moderate Quality.** **Self-reported (recall) bias present. Large sample size. Potential confounding variables from other comorbid conditions or habits (tobacco smoking) were controlled for. Upgraded from very low to low-to - moderate.**
8. Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: testing for causal associations. Addiction 2006;101:1463-1472.	**Longitudinal Cohort** **Study compared differences between users and non-users of marijuana. The data used came from the U.S. National Longitudinal Survey of Youth of 1979. The survey was re-administered every year between 1979 and 1994. The number of participants was 12,686 in 1979 and 8759 in 1994. 50 potential confounders controlled for.**	**Past-year marijuana use does not significantly predict later development of depression when other variable controlled for. The associations observed between marijuana use and depression status may be caused not by continued marijuana use, but by other factors associated with both the decision to use marijuana and to depression.**	**Moderate to High Quality.** **Large sample size. Confounding variables were controlled for. Sophisticated analysis. It is unclear what years are being studied. It appears that only those responding in 1994 were studied. Limitations identified were:** **- Current treatment of depression not considered in analysis.** **- Self-reported status instrument (recall bias)** **-**
9. Lynskey MT Glowinsi AL, Todorov AA, et al.. Major depressive disorder (MDD), suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. Archives of General Psychiatry 2004;61:1026-1032.	Cross-Sectional Study. A cross-sectional survey of 588 twin pairs over the age of 17 was conducted in Australia..	Individuals who were cannabis dependent had odds of suicidal ideation and suicide attempt that were 2.5 to 2.9 times higher than those of their non–cannabis dependent co-twin. Additionally, cannabis dependence was associated with elevated risks of MDD in dizygotic but not in monozygotic twins. Those who initiated cannabis use before age 17 years had elevated rates of subsequent suicide attempt (odds ratio, 3.5 [95% confidence	**Very Low Quality** Selection bias present. Possible confounders were not considered in data analysis. Article referenced in many systematic reviews.

		interval, 1.4-8.6]) but not of MDD or suicidal ideation. Early MDD and suicidal ideation were significantly associated with subsequent risks of cannabis dependence in discordant dizygotic pairs but not in discordant monozygotic pairs.	
10. Green BE,Ritter C. Marijuana Use and Depression.Journal of Health and Social Behavior 2000;41:40-49.	Cross-Sectional Study. Data from the 1985 Young Men and Drugs Survey was used. N=1,941 men. National representative sample n U.S.	Results show that early onset (in adolescent years) of marijuana use is weakly associated with increased depression in adulthood. Adult frequency of marijuana use is not significantly associated with increased depression. Participants who indicate using marijuana to cope with issue are more depressed than those who do not use it for coping.	**Low Quality** Sample size is large and is representative of men. Women are not part of the Large potential for recall bias. Few potential confounders controlled for.
11. Musty RE, Kaback L. Relationships between motivation and depression in chronic marijuana users. Life Sciences 1995; 56:2151-2158.	Cross Sectional Study. Survey disseminated to university students, which measured substance use behaviors, depression symptomology, motivation, (N=70). Chronic users (with and without depression) were compared with light users (with and without depression).	Both light and heavy users with symptoms of depression had significantly lower scores in items pertaining to motivation and sense of purpose compared to those without depressive symptoms. Study concludes that amotivational symptoms observed in heavy marijuana users in treatment are due to depression.	**Very Low Quality.** Sampling bias. Self-reported data (recall bias). Very small sample size. No potential confounders controlled for. Very low number of references and short descriptions of methodology.

Systematic Reviews

Only two systematic reviews were found that directly attempted to explore the association specifically between depression and marijuana use. Both reviews were of low quality. They did not assess the quality of the studies found or use any system to rank the overall quality of the evidence.

Table 2
Systematic Reviews Included in the Review

Author, Year, Title	*Description*	*Findings*	*Quality*
1. Degenhardt L, Hall W, Lynskey M.. Exploring the association between cannabis use and depression. Addiction 2003;98;1493-1504.	Systematic review aimed at exploring the evidence on the association between cannabis use and depression.	A number of studies found a modest association between early-onset, regular cannabis use and later depression, which persisted after controlling for potential confounding variables. There was little evidence of an increased risk of later cannabis use among people with depression. They found a moderate association between heavy cannabis use and depression in cohort studies and cross-sectional studies in the general population. However, little evidence was found for an association between depression and light cannabis use. There have been a limited number of studies that have controlled for potential confounding variables in the association between heavy cannabis use and depression. These have found that the risk is much reduced by statistical control but a modest relationship remains. Heavy cannabis use and depression are associated and evidence from longitudinal studies suggests that heavy cannabis use may increase depressive symptoms among some users.	**Low quality** The search strategy and inclusion criteria were described but the articles were not systematically assessed for quality and no formal system of rating the overall quality of the evidence on each question was used.
2. Crippa JAS, Zuardi AW, & Hallak JEC. Theurapeutical use of the cannabinoids in psychiatry. Revista Brasileira de Psiquiatria • vol 32• Suppl I • may2010 • **S56-65**	The review – conducted in Brazil – reviewed the main advances related to the potential therapeutic use of cannabinoid compounds in psychiatry.	Cannabidiol compound was found to have therapeutic potential with antipsychotic, anxiolytic, and antidepressant properties. Further human control trials are necessary to confirm the findings.	**Very Low Quality** Review consisted of a search only in the PubMed, ScieELO, and Lilacs databases. Review focused primarily on animal study results. No inclusion criteria described, no system of assessing individual studies or rating the overall quality of the

Author, Year, Title	*Content*	*Reason Not Used*
1. Moore T, Zammit S, Lingfor-Hughes A, Barnes T, Jones P, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. The Lancet. 2007(370): 319-328.	The systematic review analyzed the evidence pertaining to cannabis use and occurrence of psychotic or affective mental health outcomes.	Did not fully include depression in its review. Greater focused on anxiety and psychotic conditions.
2. Gruber AJ, Pope HG, Brown M. Do Patients Use Marijuana As An Antidepressant? Depression 1996;4:77-80.	Reviews the evidence from RCTs for pharmacologic and psychological approaches to the treatment of cannabis use among individuals with psychotic or depressive disorders.	Does not address a key question.
3. Robson P. Therapeutic aspects of cannabis and cannabinoids. The British Journal of Psychology. 2001;178:107-115.	Review of the evidence to assess the therapeutic profile of cannabis and cannabinoids.	Content does not address the questions. Focus is primarily on anxiety, pain treatment, and analgesics effects of cannabis.
4. Ware MA, Adams H, Guy GW. The medicinal use of cannabis in the UK: Results of a nationwide survey. Int J Clin Pract. 2005;59(3):291-295.	Cross Sectional l Study. Report on the results of a self-administered questionnaire study conducted in the United Kingdom between 1998 and 2002. N=2969. Documented medicinal use of cannabis by patients with chronic pain, multiple sclerosis and depression, arthritis and neuropathy.	Article does not address the question.. Only use patterns are documented,
5. Zammit S, Moore T, Lingford-Hughes A, Barnes T, Jones P, Lewis G. Effects of cannabis use on outcomes of psychotic disorders: a systematic review. British Journal of Psychology. 2008;193:357-363.	The article is a systematic review of the evidence pertaining to whether cannabis affects outcome of psychotic disorders.	Article does not address depression.
6. Degenhardt L, Tennant C, Gilmour S, Schofield D, Nash L, Hall W, & McKay D. The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic	The aim of the study was to examine the temporal relationships over 10 months between cannabis use and symptoms of psychosis and depression in people with schizophrenia and related disorders.	Article did not fully address depression. The association between marijuana and depression is not clearly stated nor is it a major focus within the article. Does not

disorders: findings from a 10-month prospective study. Psychological Medicine. 2007;37:927-934.	N=101. The study discovered that cannabis use predicted a small but statistically significant increase in symptoms of psychosis, but not depression, after controlling for other differences between cannabis users and non-users. Symptoms of depression and psychosis did not predict cannabis use.	address a key question.
7. . Milani R, Parrot A, Turner J, Fox H. Gender differences in self-reported anxiety, depression, and somatization among ecstasy/MDMA polydrug users, alcohol/tobacco users, and nondrug users. Addictive Behaviros. 2004(29);965-971.	Cross-Sectional Study. The present investigation (N=768) explores gender variability in patterns of drug use in relation to self-reported depression, anxiety, and somatization. The study discovered that heavy illegal drug users are represented by a preponderance of males than females.	Does not answer key questions. Small communication format of article does not provide much detail.
8. Moreira, F, Grieb M, & Lutz B. Central side-effects of therapies based on CB1 cannabinoid receptor agonists and antagonists: focus on anxiety and depression. Best Practices and Research Clinical Endocronology and Metabolism. 2009(23);133-144.	A review of current therapies biopharmaceutical focus.	Article does not answer key questions. Review is on the therapeutic use of synthesized THC not medical marijuana.
9. Vlahov D, Galea S, Ahern J, Resnick H, Boscarino J, Gold J, Bucuvalas, M & Kilpatrick D. Consumption of Cigarettes, Alcohol, and Marijuana Among New York City Residents Six Months After the September 11 Terrorist Attacks. The American Journal of Drug and Alcohol Abuse. 2004(30);2:385-407.	Phone interview surveys of residents in New York City 6 to 9 months post 9/11 events. Interview asked consumption behavior questions. Study discovered that prevalence of PTSD and Depression in a segment of the population was declining over time while substance use was increasing.	Does not address key questions.

Conclusion

There is insufficient evidence to answer any of the key questions. There is no credible evidence regarding the effectiveness, or harms of marijuana for the treatment of depression. There may be an association between marijuana use and depression but it is not know if one causes the other or if both are linked to some unknown third factor. The one clinical trial found was so poorly designed that it provides no useful information. No other studies addressed the use of marijuana to treat depression. There appears to be a correlation between marijuana use and depression although the strength of this association is low to modest and it is not possible to tell if one causes the other if both are related to other variables.

Major Recommendations for the Effective Treatment of Depression

The National Guideline Clearinghouse was searched for guidelines on the treatment of depression. The most recent and pertinent guideline found was by the American Psychiatric Association (APA).

Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA);
2010 http://guideline.gov/content.aspx?id=24158&search=depression+and+major+depression+disorder

The guideline is attached as appendix 5.

Appendix 1: Search Terms

Initial Terms used

1. cannabis
2. depression
3. tetrahydrocannabinol

Mesh Terms

Marijuana Smoking

- Smoking, Marijuana
- Marihuana Smoking
- Smoking, Marihuana
- **Cannabis Smoking**
- Smoking, Cannabis
- Hashish Smoking
- Smoking, Hashish

Mesh Terms

Cannabis

Entry Terms:

- Cannabi
- Hemp Plant
- Hemp Plants
- Plant, Hemp
- Plants, Hemp
- Cannabis indica
- Cannabis indicas
- indica, Cannabis
- indicas, Cannabis
- Marihuana
- Marihuanas
- Marijuana
- Marijuanas
- Ganja
- Ganjas
- Hashish
- Hashishs
- Hemp
- Hemps
- Bhang
- Bhangs
- Cannabis sativa
- Cannabis sativas
- sativa, Cannabis
- sativas, Cannabis

Mesh Terms

Depression

Entry Terms:

- Depressions
- Depressive Symptoms
- Depressive Symptom
- Symptom, Depressive
- Symptoms, Depressive
- Emotional Depression
- Depression, Emotional
- Depressions, Emotional
- Emotional Depressions

Mesh Terms
Depressive Disorder
Entry Terms
- Depression, Postpartum
- Depressive Disorder, Major
- Depressive Disorder, Treatment-Resistant
- Dysthymic Disorder
- Seasonal Affective Disorder

Appendix 2: Taxonomy of Study Designs

BOX 1 *Taxonomy of study designs to assess the effectiveness of an intervention*

Experimental designs
A study in which the investigator has control over at least some study conditions, particularly decisions concerning the allocation of participants to different intervention groups.

1. ***Randomised controlled trial***
   Participants are randomly allocated to intervention or control groups and followed up over time to assess any differences in outcome rates. Randomisation with allocation concealment ensures that on average known and unknown determinants of outcome are evenly distributed between groups.
2. ***Quasi-randomised trial***
   Participants are allocated to intervention or control groups by the investigator, but the method of allocation falls short of genuine randomisation and allocation concealment (e.g. allocated by date of birth, hospital record number, etc.)
3. ***Non-randomised trial/quasi-experimental study***
   The investigator has control over the allocation of participants to groups, but does not attempt randomisation (e.g. patient or physician preference). Differs from a 'cohort study' in that the intention is experimental rather than observational.

Observational designs
A study in which natural variation in interventions (or exposure) among study participants is investigated to explore the effect of the interventions (or exposure) on health outcomes.

4. ***Controlled before-and-after study***
   A follow-up study of participants who have received an intervention and those who have not, measuring the outcome variable both at baseline and after the intervention period, comparing either final values if the groups are comparable at baseline, or change scores. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
5. ***Concurrent cohort study***
   A follow-up study that compares outcomes between participants who have received an intervention and those who have not. Participants are studied during the same (concurrent) period either prospectively or, more commonly, retrospectively.
6. ***Historical cohort study***
   A variation on the traditional cohort study where the outcome from a new intervention is established for participants studied in one period and compared with those who did not receive the intervention in a previous period, i.e. participants are not studied concurrently.
7. ***Case–control study***
   Participants with and without a given outcome are identified (cases and controls respectively) and exposure to a given intervention(s) between the two groups compared.
8. ***Before-and-after study***
   Comparison of outcomes from study participants before and after an intervention is introduced. The before and after measurements may be made in the same participants, or in different samples. It can also be considered an experimental design if the investigator has control over, or can deliberately manipulate, the introduction of the intervention.
9. ***Cross-sectional study***
   Examination of the relationship between disease and other variables of interest as they exist in a defined population at one particular time point.
10. ***Case series***
    Description of a number of cases of an intervention and outcome (no comparison with a control group).

Appendix 3: GRADE Method

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or
	Very low	Imprecision -1 Serious -2 Very serious	+1 Would suggest a spurious effect when results show no effect
		Publication bias -1 Likely -2 Very likely	

Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. Methods Guide for Comparative Effectiveness Reviews. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60.

Appendix 4: Articles Found in the Search

1

1. Abel EL. Retrieval of information after use of marihuana. *Nature*. 1971;231(5297):58.
2. Ablon SL, Goodwin FK. High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients. *Am J Psychiatry*. 1974;131(4):448-453.
3. Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. Survey of cannabis use in patients with amyotrophic lateral sclerosis. *Am J Hosp Palliat Care*. 2004;21(2):95-104.
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10.1016/j.addbeh.2010.02.004.
27. Crippa JAS, Zuardi AW, Hallak JEC. Theurapeutical use of the cannabinoids in psychiatry. *Revista Brasileira de Psiquiatria.* 2010(32);1:S56-65.
28. Crowley TJ, Macdonald MJ, Whitmore EA, Mikulich SK. Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders. *Drug Alcohol Depend.* 1998;50(1):27-37.
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NGC banner

Guideline Summary NGC-8093

Guideline Title

Practice guideline for the treatment of patients with major depressive disorder, third edition.

Bibliographic Source(s)

American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152 p. [1170 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry 2000 Apr;157(4 Suppl):1-45. [325 references]

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- March 28, 2012 – Celexa (citalopram hydrobromide) [x] : The U.S. Food and Drug Administration (FDA) is clarifying dosing and warning recommendations for the antidepressant Celexa (citalopram hydrobromide; also available in generic form). In August 2011, FDA issued a Drug Safety Communication (DSC) stating that citalopram should no longer be used at doses greater than 40 mg per day because it could cause potentially dangerous abnormalities in the electrical activity of the heart. Citalopram use at any dose is discouraged in patients with certain conditions because of the risk of QT prolongation, but because it may be important for some of those patients to use citalopram, the drug label has been changed to describe the particular caution that needs to be taken when citalopram is used in such patients. The revised drug label also describes lower doses that should be used in patients over 60 years of age.

Scope

Disease/Condition(s)

Major depressive disorder

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Psychiatry

Intended Users

Physicians

Guideline Objective(s)

To summarize the specific approaches to treatment of individuals with major depressive disorder

Target Population

Individuals with major depressive disorder

Interventions and Practices Considered

Evaluation/Management

1. Establishing and maintaining a therapeutic alliance
2. Psychiatric assessment
3. Safety evaluation including evaluation of suicide risk, level of self-care and dependent care, and risk or harm to self and others
4. Establishing appropriate treatment setting including hospitalization if appropriate
5. Evaluation of functional impairment and quality of life
6. Coordinating care with other clinicians, monitoring status, and tailoring treatment to specific patient needs
7. Assessment of and acknowledgment of potential barriers to treatment

8. Patient and family education

Treatment

1. Pharmacotherapy
   - Selective serotonin reuptake inhibitors (SSRI)
   - Serotonin norepinephrine reuptake inhibitors (SNRI)
   - Mirtazapine
   - Bupropion
   - Nonselective monoamine oxidase inhibitors (MAOIs)
2. Somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), vagus nerve stimulation
3. Psychotherapy
   - Cognitive-behavioral therapy (CBT)
   - Interpersonal psychotherapy
   - Psychodynamic therapy
   - Marital and family therapy
   - Problem-solving therapy in individual and in group formats
4. Combination of medications and psychotherapy
5. Complementary and alternative therapies
   - St. John's wort
   - *S*-adenosyl methionine
   - Omega-3 fatty acids
   - Folate
   - Light therapy
   - Acupuncture

Major Outcomes Considered

- Control of depressive symptoms
- Rate of remission, relapse, and recurrence of major depression
- Morbidity and mortality due to major depression
- Side effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Relevant updates to the literature were identified through a MEDLINE literature search for articles published since the second edition of the guideline, published in 2000. For this edition of the guideline, literature was identified through a computerized search of MEDLINE, using PubMed, for the period from January 1999 to December 2006. Using the MeSH headings depression or depressive disorder, as well as the key words major depression, major depressive disorder, neurotic depression, neurotic depressive, dysthymia, dysthymic, dysthymic disorder, endogenous depression, endogenous depressive, melancholia, melancholic, psychotic depression, atypical depression, seasonal depression, postpartum depression, postpartum depressive symptoms, unipolar depression, unipolar depressive, or pseudodementia yielded 39,157 citations. An additional 8,272 citations were identified by using the key words depression or depressive in combination with the MeSH headings affective disorders or psychotic or the key words psychosis, psychotic, catatonic, catatonia, mood disorder, mood disorders, affective disorder, or affective disorders. These citations were limited to English language articles on human treatments using the MeSH headings central nervous system stimulants, hypnotics and sedatives, anticonvulsants, tranquilizing agents, electric stimulation therapy, electroconvulsive therapy, psychotherapy, antidepressive agents, and monoamine oxidase inhibitors or the key words antidepressant, antidepressants, antidepressive, antidepressive agents, antidepressive agents, second generation, antidepressive agents tricyclic, antidepressive agents, tricyclic, fluoxetine, citalopram, escitalopram, paroxetine, sertraline, venlafaxine, duloxetine, mirtazapine, nefazodone, trazodone, imipramine, desipramine, nortriptyline, protriptyline, doxepin, trimipramine, amitriptyline, phenelzine, tranylcypromine, isocarboxazid, moclobemide, antipsychotic agents, testosterone, thyroid, tri iodothyronine, thyroxine, omega 3, *s* adenosyl methionine, *s* adenosylmethionine, St. John's wort, hypericum, selegiline, anticonvulsant, anticonvulsants, antipsychotic, antipsychotic agent, antianxiety, anti anxiety, benzodiazepine, benzodiazepines, zolpidem, sedative, sedatives, hypnotic, hypnotics, zalepion, eszopiclone, valproate, valproic acid, divalproex, carbamazepine, oxcarbazepine, gabapentin, topiramate, lamotrigine, lithium, modafinil, methylphenidate, Adderall, amphetamine, amphetamines, dextroamphetamine, atomoxetine, electroconvulsive, vagal nerve stimulation, vagus nerve stimulation, VNS, rTMS, rapid transcranial magnetic, repetitive transcranial magnetic stimulation, magnetic stimulation, deep brain stimulation, psychotherapy, psychotherapeutic, psychotherapies, behavior therapy, behaviour therapy, cognitive therapy, cognitive behavior therapy, cognitive behavioral analysis system, cognitive behavioral therapy, cognitive

behaviour therapy, cognitive behavioural therapy, psychoanalytic, interpersonal therapy, interpersonal psychotherapy, group therapy, family therapy, marital therapy, couples therapy, psychoanalysis, psychodynamic, aversive therapy, desensitization, exposure therapy, relaxation techniques, or progressive muscle relaxation. This yielded 13,506 abstracts, which were screened for relevance with a very modest threshold for inclusion, then reviewed by the Work Group.

The Psychoanalytic Electronic Publishing database (http://www.p-e-p.org) was also searched using the terms major depression or major depressive. This search yielded 112 references. The Cochrane databases were also searched for the key word depression, and 168 meta-analyses were identified. Additional, less formal, literature searches were conducted by American Psychiatric Association (APA) staff and individual Work Group members and included references through May 2009. Sources of funding were considered when the Work Group reviewed the literature.

The broad scope of this guideline and the substantial evidence base resulted in some practical tradeoffs. One such tradeoff worth highlighting is the decision to build upon literature reviews of the first and second editions of the guideline, rather than re-do them. This decision is acknowledged to have resulted in an emphasis of study in this guideline on newer treatments, because the majority of studies about older treatments, including tricyclic antidepressants and monoamine oxidase inhibitors, were published in decades prior to 1999. Readers are advised that the reviews of this older literature are described in the previous editions of the guideline. The Work Group for this edition considered the previous editions during their evidence review, but for practical reasons, that effort is less well documented than the group's analysis of the newer literature. The treatment recommendations of this guideline, however, were developed to reflect the complete evidence base.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence tables were developed that reviewed the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

This practice guideline was developed under the direction of the Steering Committee on Practice Guidelines. The development process is detailed in a document entitled "APA Guideline Development Process," which is available from the American Psychiatric Association (APA) Department of Quality Improvement and Psychiatric Services. Key features of this process include the following:

- A comprehensive literature review to identify all relevant randomized clinical trials as well as less rigorously designed clinical trials and case series when evidence from randomized trials was unavailable.
- Development of evidence tables that reviewed the key features of each identified study, including funding source, study design, sample sizes, subject characteristics, treatment characteristics, and treatment outcomes.
- Initial drafting of the guideline by a work group ("Work Group") that included psychiatrists with clinical and research expertise in major depressive disorder.
- Production of multiple revised drafts with widespread review; 15 organizations and 71 individuals submitted comments.
- Review of the final draft by an Independent Review Panel of experts with no relationships with industry, who were charged to evaluate the guideline recommendations for bias from potential conflicts of interest.
- Approval by the APA Assembly and Board of Trustees.
- Planned revisions at regular intervals.

This document represents a synthesis of current scientific knowledge and rational clinical practice regarding the treatment of patients with major depressive disorder. It strives to be as free as possible of bias toward any theoretical approach to treatment. In order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each recommendation, the summary of treatment recommendations is keyed according to the level of confidence with which each recommendation is made. Each rating of clinical confidence considers the strength of the available evidence. When evidence from randomized controlled trials and meta-analyses is limited, the level of confidence may also incorporate other clinical trials and case reports as well as clinical consensus with regard to a particular clinical decision. In the listing of cited references, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence.

Rating Scheme for the Strength of the Recommendations

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence:

[I] Recommended with substantial clinical confidence.

[II] Recommended with moderate clinical confidence.

[III] May be recommended on the basis of individual circumstances.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Iterative guideline drafts were broadly circulated to and reviewed by the Steering Committee, other experts, allied organizations, and the American Psychiatric Association (APA) membership; reviewers were asked to disclose their own potential conflicts of interest relevant to evaluating their comments. Over 1,000 comments were received and were addressed by substantive revisions by the Work Group. Oversight of the draft review and revision process was provided by the chair and vice-chair of the Steering Committee and by the Medical Editor, none of whom had relationships with industry.

In response to a 2009 report by the Institute of Medicine, which advocated that professional organizations that develop and disseminate practice guidelines should adopt a new policy that members of guideline work groups have no significant relationships with industry, the following process was implemented: An independent review panel of experts ("Independent Review Panel") having no current relationships with industry also reviewed the guideline and was charged with identifying any possible bias. The Independent Review Panel found no evidence of bias.

This practice guideline was approved in May 2010 and published in October 2010.

Recommendations

Major Recommendations

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. Definitions of the categories of endorsement are provided at the end of the "Major Recommendations" field.

Psychiatric Management

Psychiatric management consists of a broad array of interventions and activities that psychiatrists should initiate and continue to provide to patients with major depressive disorder through all phases of treatment **[I]**.

Establish and Maintain a Therapeutic Alliance

In establishing and maintaining a therapeutic alliance, it is important to collaborate with the patient in decision making and attend to the patient's preferences and concerns about treatment **[I]**. Management of the therapeutic alliance should include awareness of transference and counter-transference issues, even if these are not directly addressed in treatment **[II]**. Severe or persistent problems of poor alliance or nonadherence to treatment may be caused by the depressive symptoms themselves or may represent psychological conflicts or psychopathology for which psychotherapy should be considered **[II]**.

Complete the Psychiatric Assessment

Patients should receive a thorough diagnostic assessment in order to establish the diagnosis of major depressive disorder, identify other psychiatric or general medical conditions that may require attention, and develop a comprehensive plan for treatment **[I]**. This evaluation generally includes a history of the present illness and current symptoms; a psychiatric history, including identification of past symptoms of mania, hypomania, or mixed episodes and responses to previous treatments; a general medical history; a personal history including information about psychological development and responses to life transitions and major life events; a social, occupational, and family history (including mood disorders and suicide); review of the patient's prescribed and over-the-counter medications; a review of systems; a mental status examination; a physical examination; and appropriate diagnostic tests as indicated to rule out possible general medical causes of depressive symptoms **[I]**. Assessment of substance use should evaluate past and current use of illicit drugs and other substances that may trigger or exacerbate depressive symptoms **[I]**.

Evaluate the Safety of the Patient

A careful and ongoing evaluation of suicide risk is necessary for all patients with major depressive disorder **[I]**. Such an assessment includes specific inquiry about suicidal thoughts, intent, plans, means, and behaviors; identification of specific psychiatric symptoms (e.g., psychosis, severe anxiety, substance use) or general medical conditions that may increase the likelihood of acting on suicidal ideas; assessment of past and, particularly, recent suicidal behavior; delineation of current stressors and potential protective factors (e.g., positive reasons for living, strong social support); and identification of any family history of suicide or mental illness **[I]**. In addition to assessing suicide risk per se, it is important to assess the patient's level of self-care, hydration, and nutrition, each of which can be compromised by severe depressive symptoms **[I]**. As part of the assessment process, impulsivity and potential for risk to others should also be evaluated, including any history of violence or violent or homicidal ideas, plans, or intentions **[I]**. An evaluation of the impact of the depression on the patient's ability to care for dependents is an important component of the safety

evaluation [I]. The patient's risk of harm to him- or herself and to others should also be monitored as treatment proceeds [I].

Establish the Appropriate Setting for Treatment

The psychiatrist should determine the least restrictive setting for treatment that will be most likely not only to address the patient's safety, but also to promote improvement in the patient's condition [I]. The determination of an appropriate setting for treatment should include consideration of the patient's symptom severity, co-occurring psychiatric or general medical conditions, available support system, and level of functioning [I]. The determination of a treatment setting should also include consideration of the patient's ability to adequately care for him- or herself, to provide reliable feedback to the psychiatrist, and to cooperate with treatment of the major depressive disorder [I]. Measures such as hospitalization should be considered for patients who pose a serious threat of harm to themselves or others [I]. Patients who refuse inpatient treatment can be hospitalized involuntarily if their condition meets the criteria of the local jurisdiction for involuntary admission [I]. Admission to a hospital or, if available, an intensive day program, may also be indicated for severely ill patients who lack adequate social support outside of a hospital setting, who have complicating psychiatric or general medical conditions, or who have not responded adequately to outpatient treatment [I]. The optimal treatment setting and the patient's likelihood of benefit from a different level of care should be reevaluated on an ongoing basis throughout the course of treatment [I].

Evaluate Functional Impairment and Quality of Life

Major depressive disorder can alter functioning in numerous spheres of life including work, school, family, social relationships, leisure activities, or maintenance of health and hygiene. The psychiatrist should evaluate the patient's activity in each of these domains and determine the presence, type, severity, and chronicity of any dysfunction [I]. In developing a treatment plan, interventions should be aimed at maximizing the patient's level of functioning as well as helping the patient to set specific goals appropriate to his or her functional impairments and symptom severity [I].

Coordinate the Patient's Care with Other Clinicians

Many patients with major depressive disorder will be evaluated by or receive treatment from other health care professionals in addition to the psychiatrist. If more than one clinician is involved in providing the care, all treating clinicians should have sufficient ongoing contact with the patient and with each other to ensure that care is coordinated, relevant information is available to guide treatment decisions, and treatments are synchronized [I].

In ruling out general medical causes of depressive symptoms, it is important to ensure that a general medical evaluation has been done [I], either by the psychiatrist or by another health care professional. Extensive or specialized testing for general medical causes of depressive symptoms may be conducted based on individual characteristics of the patient [III].

Monitor the Patient's Psychiatric Status

The patient's response to treatment should be carefully monitored [I]. Continued monitoring of co-occurring psychiatric and/or medical conditions is also essential to developing and refining a treatment plan for an individual patient [I].

Integrate Measurements into Psychiatric Management

Tailoring the treatment plan to match the needs of the particular patient requires a careful and systematic assessment of the type, frequency, and magnitude of psychiatric symptoms as well as ongoing determination of the therapeutic benefits and side effects of treatment [I]. Such assessments can be facilitated by integrating clinician- and/or patient-administered rating scale measurements into initial and ongoing evaluation [II].

Enhance Treatment Adherence

The psychiatrist should assess and acknowledge potential barriers to treatment adherence (e.g., lack of motivation or excessive pessimism due to depression; side effects of treatment; problems in the therapeutic relationship; logistical, economic, or cultural barriers to treatment) and collaborate with the patient (and if possible, the family) to minimize the impact of these potential barriers [I]. In addition, the psychiatrist should encourage patients to articulate any fears or concerns about treatment or its side effects [I]. Patients should be given a realistic notion of what can be expected during the different phases of treatment, including the likely time course of symptom response and the importance of adherence for successful treatment and prophylaxis [I].

Provide Education to the Patient and the Family

Education about the symptoms and treatment of major depressive disorder should be provided in language that is readily understandable to the patient [I]. With the patient's permission, family members and others involved in the patient's day-to-day life may also benefit from education about the illness, its effects on functioning (including family and other interpersonal relationships), and its treatment [I]. Common misperceptions about antidepressants (e.g., they are addictive) should be clarified [I]. In addition, education about major depressive disorder should address the need for a full acute course of treatment, the risk of relapse, the early recognition of recurrent symptoms, and the need to seek treatment as early as possible to reduce the risk of complications or a full-blown episode of major depression [I]. Patients should also be told about the need to taper antidepressants, rather than discontinuing them precipitously, to minimize the risk of withdrawal symptoms or symptom recurrence [I]. Patient education also includes general promotion of healthy behaviors such as exercise, good sleep hygiene, good nutrition, and decreased use of tobacco, alcohol, and other potentially deleterious substances [I]. Educational tools such as books, pamphlets, and trusted web sites can augment the face-to-face education provided by the clinician [I].

Acute Phase

Choice of an Initial Treatment Modality

Treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning [I]. Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy, as described in the sections that follow. Selection of an initial treatment modality should be influenced by clinical features (e.g., severity of symptoms, presence of co-occurring disorders or psychosocial stressors) as well as other factors (e.g., patient preference, prior treatment experiences) [I]. Any treatment should be integrated with psychiatric management and any other treatments being provided for other diagnoses [I].

Pharmacotherapy

An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [**I**] and definitely should be provided for those with severe major depressive disorder unless ECT is planned [**I**]. Because the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects, the safety or tolerability of these side effects for the individual patient, pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions), and additional factors such as medication response in prior episodes, cost, and patient preference [**I**]. For most patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion is optimal [**I**]. In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, tranylcypromine, isocarboxazid) should be restricted to patients who do not respond to other treatments [**I**], given the necessity for dietary restrictions with these medications and the potential for deleterious drug-drug interactions. In patients who prefer complementary and alternative therapies, S-adenosyl methionine (SAMe) [**III**] or St. John's wort [**III**] might be considered, although evidence for their efficacy is modest at best, and careful attention to drug-drug interactions is needed with St. John's wort [**I**].

Once an antidepressant medication has been initiated, the rate at which it is titrated to a full therapeutic dose should depend upon the patient's age, the treatment setting, and the presence of co-occurring illnesses, concomitant pharmacotherapy, or medication side effects [**I**]. During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy, identify the emergence of side effects (e.g., gastrointestinal symptoms, sedation, insomnia, activation, changes in weight, and cardiovascular, neurological, anticholinergic, or sexual side effects), and assess patient safety [**I**]. The frequency of patient monitoring should be determined based upon the patient's symptom severity (including suicidal ideas), co-occurring disorders (including general medical conditions), cooperation with treatment, availability of social supports, and the frequency and severity of side effects with the chosen treatment [**II**]. If antidepressant side effects do occur, an initial strategy is to lower the dose of the antidepressant or to change to an antidepressant that is not associated with that side effect [**I**].

Other Somatic Therapies

ECT is recommended as a treatment of choice for patients with severe major depressive disorder that is not responsive to psychotherapeutic and/or pharmacological interventions, particularly in those who have significant functional impairment or have not responded to numerous medication trials [**I**]. ECT is also recommended for individuals with major depressive disorder who have associated psychotic or catatonic features [**I**], for those with an urgent need for response (e.g., patients who are suicidal or nutritionally compromised due to refusal of food or fluids) [**I**], and for those who prefer ECT or have had a previous positive response to ECT [**II**].

Bright light therapy might be used to treat seasonal affective disorder as well as nonseasonal depression [**III**].

Psychotherapy

Use of a depression-focused psychotherapy alone is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder [**I**], with clinical evidence supporting the use of cognitive-behavioral therapy (CBT) [**I**], interpersonal psychotherapy [**I**], psychodynamic therapy [**II**], and problem-solving therapy [**III**] in individual [**I**] and in group [**III**] formats. Factors that may suggest the use of psychotherapeutic interventions include the presence of significant psychosocial stressors, intrapsychic conflict, interpersonal difficulties, a co-occurring axis II disorder, treatment availability, or—most important—patient preference [**II**]. In women who are pregnant, wish to become pregnant, or are breastfeeding, a depression-focused psychotherapy alone is recommended [**II**] and depending on the severity of symptoms, should be considered as an initial option [**I**]. Considerations in the choice of a specific type of psychotherapy include the goals of treatment (in addition to resolving major depressive symptoms), prior positive response to a specific type of psychotherapy, patient preference, and the availability of clinicians skilled in the specific psychotherapeutic approach [**II**]. As with patients who are receiving pharmacotherapy, patients receiving psychotherapy should be carefully and systematically monitored on a regular basis to assess their response to treatment and assess patient safety [**I**]. When determining the frequency of psychotherapy sessions for an individual patient, the psychiatrist should consider multiple factors, including the specific type and goals of psychotherapy, symptom severity (including suicidal ideas), co-occurring disorders, cooperation with treatment, availability of social supports, and the frequency of visits necessary to create and maintain a therapeutic relationship, ensure treatment adherence, and monitor and address depressive symptoms and suicide risk [**II**]. Marital and family problems are common in the course of major depressive disorder, and such problems should be identified and addressed, using marital or family therapy when indicated [**II**].

Psychotherapy Plus Antidepressant Medication

The combination of psychotherapy and antidepressant medication may be used as an initial treatment for patients with moderate to severe major depressive disorder [**I**]. In addition, combining psychotherapy and medication may be a useful initial treatment even in milder cases for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder [**II**]. In general, when choosing an antidepressant or psychotherapeutic approach for combination treatment, the same issues should be considered as when selecting a medication or psychotherapy for use alone [**I**].

Assessing the Adequacy of Treatment Response

In assessing the adequacy of a therapeutic intervention, it is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose [**I**]. Onset of benefit from psychotherapy tends to be a bit more gradual than that from medication, but no treatment should continue unmodified if there has been no symptomatic improvement after 1 month [**I**]. Generally, 4–8 weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention [**II**].

Strategies to Address Nonresponse

For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely [**I**], as an incomplete response to treatment is often associated with poor functional outcomes. If at least a moderate improvement in symptoms is not observed within 4–8 weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial factors reviewed, and the treatment plan adjusted [**I**]. It is also important to assess the quality of the therapeutic alliance and treatment adherence [**I**]. For patients in psychotherapy, additional factors to be assessed include the frequency of sessions and whether the specific approach to psychotherapy is adequately addressing the patient's needs [**I**]. If medications are

prescribed, the psychiatrist should determine whether pharmacokinetic [I] or pharmacodynamic [III] factors suggest a need to adjust medication doses. With some TCAs, a drug blood level can help determine if additional dose adjustments are required [I].

After an additional 4–8 weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan [I]. Consultation should also be considered [II].

A number of strategies are available when a change in the treatment plan seems necessary. For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached [II]. Particularly for those who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy [I] or with other agents [II] or changing to another non-MAOI antidepressant [I]. Patients may be changed to an antidepressant from the same pharmacological class (e.g., from one SSRI to another SSRI) or to one from a different class (e.g., from an SSRI to a tricyclic antidepressant [TCA]) [II]. For patients who have not responded to trials of SSRIs, a trial of an SNRI may be helpful [II]. Augmentation of antidepressant medications can utilize another non-MAOI antidepressant [II], generally from a different pharmacological class, or a non-antidepressant medication such as lithium [II], thyroid hormone [II], or a second-generation antipsychotic [II]. Additional strategies with less evidence for efficacy include augmentation using an anticonvulsant [III], omega-3 fatty acids [III], folate [III], or a psychostimulant medication [III], including modafinil [III]. If anxiety or insomnia are prominent features, consideration can be given to anxiolytic and sedative-hypnotic medications [III], including buspirone, benzodiazepines, and selective gamma-aminobutyric acid (GABA) agonist hypnotics (e.g., zolpidem, eszopiclone). For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered [I]. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a nonselective MAOI [II] after allowing sufficient time between medications to avoid deleterious interactions [I]. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered [II]. Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [III].

For patients treated with psychotherapy, consideration should be given to increasing the intensity of treatment or changing the type of therapy [II]. If psychotherapy is used alone, the possible need for medications in addition to or in lieu of psychotherapy should be assessed [I]. Patients who have a history of poor treatment adherence or incomplete response to adequate trials of single treatment modalities may benefit from combined treatment with medication and a depression-focused psychotherapy [II].

Continuation Phase

During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse [I]. Systematic assessment of symptoms, side effects, adherence, and functional status is essential [I] and may be facilitated through the use of clinician- and/or patient-administered rating scales [II]. To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for 4–9 months [I]. In general, the dose used in the acute phase should be used in the continuation phase [II]. To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended [I], with the best evidence available for cognitive-behavioral therapy.

Patients who respond to an acute course of ECT should receive continuation pharmacotherapy [I], with the best evidence available for the combination of lithium and nortriptyline. Alternatively, patients who have responded to an acute course of ECT may be given continuation ECT, particularly if medication or psychotherapy has been ineffective in maintaining remission [II].

Maintenance Phase

In order to reduce the risk of a recurrent depressive episode, patients who have had three or more prior major depressive episodes or who have chronic major depressive disorder should proceed to the maintenance phase of treatment after completing the continuation phase [I]. Maintenance therapy should also be considered for patients with additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders [II]. Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes (including factors such as psychosis or suicide risk), the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders [II]. Such factors also contribute to decisions about the duration of the maintenance phase [II]. For many patients, particularly for those with chronic and recurrent major depressive disorder or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely [I].

During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose [II]. If a depression-focused psychotherapy has been used during the acute and continuation phases of treatment, maintenance treatment should be considered, with a reduced frequency of sessions [II]. For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to ECT, maintenance ECT may be considered [III]. Maintenance treatment with vagus nerve stimulation is also appropriate for individuals whose symptoms have responded to this treatment modality [III].

Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase [I]. Use of standardized measurement aids in the early detection of recurrent symptoms [II].

Discontinuation of Treatment

When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks [I]. To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home [I]. A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome [II] when discontinuing antidepressants or reducing antidepressant doses. Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms [I]. After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur [I].

For patients receiving psychotherapy, it is important to raise the issue of treatment discontinuation well in advance of the final session [I], although the exact process by which this occurs will vary with the type of therapy.

Clinical Factors Influencing Treatment

Psychiatric Factors

For suicidal patients, psychiatrists should consider an increased intensity of treatment, including hospitalization when warranted [I] and/or combined treatment with pharmacotherapy and psychotherapy [II]. Factors to consider in determining the nature and intensity of treatment include (but are not limited to) the nature of the doctor-patient alliance, the availability and adequacy of social supports, access to and lethality of suicide means, the presence of a co-occurring substance use disorder, and past and family history of suicidal behavior [I].

For patients who exhibit psychotic symptoms during an episode of major depressive disorder, treatment should include a combination of antipsychotic and antidepressant medications or ECT [I]. When patients exhibit cognitive dysfunction during a major depressive episode, they may have an increased likelihood of future dementia, making it important to assess cognition in a systematic fashion over the course of treatment [I].

Catatonic features that occur as part of a major depressive episode should be treated with a benzodiazepine [I] or barbiturate [II], typically in conjunction with an antidepressant [II]. If catatonic symptoms persist, ECT is recommended [I]. To reduce the likelihood of general medical complications, patients with catatonia may also require supportive medical interventions, such as hydration, nutritional support, prophylaxis against deep vein thrombosis, turning to reduce risks of decubitus ulcers, and passive range of motion to reduce risk of contractures [I]. If antipsychotic medication is needed, it is important to monitor for signs of neuroleptic malignant syndrome, to which patients with catatonia may have a heightened sensitivity [II].

When patients with a major depressive disorder also have a co-occurring psychiatric illness, the clinician should address each disorder as part of the treatment plan [I]. Benzodiazepines may be used adjunctively in individuals with major depressive disorder and co-occurring anxiety [II], although these agents do not treat depressive symptoms, and careful selection and monitoring is needed in individuals with co-occurring substance use disorders [I].

In patients who smoke, bupropion [I] or nortriptyline [II] may be options to simultaneously treat depression and assist with smoking cessation. When possible, a period of substance abstinence can help determine whether the depressive episode is related to substance intoxication or withdrawal [II]. Factors that suggest a need for antidepressant treatment soon after cessation of substance use include a family history of major depressive disorder and a history of major depressive disorder preceding the onset of the substance use disorder or during periods of sobriety [II].

For patients who have a personality disorder as well as major depressive disorder, psychiatrists should institute treatment for the major depressive disorder [I] and consider psychotherapeutic and adjunctive pharmacotherapeutic treatment for personality disorder symptoms [II].

Demographic and Psychosocial Factors

Several aspects of assessment and treatment differ between women and men. Because the symptoms of some women may fluctuate with gonadal hormone levels, the evaluation should include a detailed assessment of mood changes across the reproductive life history (e.g., menstruation, pregnancy, birth control including oral contraception use, abortions, menopause) [I]. When prescribing medications to women who are taking oral contraceptives, the potential effects of drug-drug interactions must be considered [I]. For women in the perimenopausal period, SSRI and SNRI antidepressants are useful in ameliorating depression as well as in reducing somatic symptoms such as hot flashes [II]. Both men and women who are taking antidepressants should be asked whether sexual side effects are occurring with these medications [I]. Men for whom trazodone is prescribed should be warned of the risk of priapism [I].

The treatment of major depressive disorder in women who are pregnant or planning to become pregnant requires a careful consideration of the benefits and risks of available treatment options for the patient and the fetus [I]. For women who are currently receiving treatment for depression, a pregnancy should be planned, whenever possible, in consultation with the treating psychiatrist, who may wish to consult with a specialist in perinatal psychiatry [I]. In women who are pregnant, planning to become pregnant, or breast-feeding, depression-focused psychotherapy alone is recommended [II] and should always be considered as an initial option, particularly for mild to moderate depression, for patients who prefer psychotherapy, or for those with a prior positive response to psychotherapy [I]. Antidepressant medication should be considered for pregnant women who have moderate to severe major depressive disorder as well as for those who are in remission from major depressive disorder, are receiving maintenance medication, and are deemed to be at high risk for a recurrence if the medication is discontinued [II]. When antidepressants are prescribed to a pregnant woman, changes in pharmacokinetics during pregnancy may require adjustments in medication doses [I]. Electroconvulsive therapy may be considered for the treatment of depression during pregnancy in patients who have psychotic or catatonic features, whose symptoms are severe or have not responded to medications, or who prefer treatment with ECT [II]. When a woman decides to nurse, the potential benefits of antidepressant medications for the mother should be balanced against the potential risks to the newborn from receiving antidepressant in the mother's milk [I]. For women who are depressed during the postpartum period, it is important to evaluate for the presence of suicidal ideas, homicidal ideas, and psychotic symptoms [I]. The evaluation should also assess parenting skills for the newborn and for other children in the patient's care [I].

In individuals with late-life depression, identification of co-occurring general medical conditions is essential, as these disorders may mimic depression or affect choice or dosing of medications [I]. Older individuals may also be particularly sensitive to medication side effects (e.g., hypotension, anticholinergic effects) and require adjustment of medication doses for hepatic or renal dysfunction [I]. In other respects, treatment for depression should parallel that used in younger age groups [I].

The assessment and treatment of major depressive disorder should consider the impact of language barriers, as well as cultural variables that may influence symptom presentation, treatment preferences, and the degree to which psychiatric illness is stigmatized [I]. When antidepressants are prescribed, the psychiatrist should recognize that ethnic groups may differ in their metabolism and response to medications [II].

Issues relating to the family situation and family history, including mood disorders and suicide, can also affect treatment planning and are an important element of the initial evaluation [I]. A family history of bipolar disorder or acute psychosis suggests a need for increased attention to possible signs of bipolar illness in the patient (e.g., with antidepressant treatment) [I]. A family history of recurrent major depressive disorder increases the likelihood of recurrent episodes in the patient and supports a need for maintenance treatment [II]. Family history of a response to a particular antidepressant may sometimes help in choosing a specific antidepressant for the patient [III]. Because

problems within the family may become an ongoing stressor that hampers the patient's response to treatment, and because depression in a family is a major stress in itself, such factors should be identified and strong consideration given to educating the family about the nature of the illness, enlisting the family's support, and providing family therapy, when indicated [**II**].

For patients who have experienced a recent bereavement, psychotherapy or antidepressant treatment should be used when the reaction to a loss is particularly prolonged or accompanied by significant psychopathology and functional impairment [**I**]. Support groups may be helpful for some bereaved individuals [**III**].

Co-occurring General Medical Conditions

In patients with major depressive disorder, it is important to recognize and address the potential interplay between major depressive disorder and any co-occurring general medical conditions [**I**]. Communication with other clinicians who are providing treatment for general medical conditions is recommended [**I**]. The clinical assessment should include identifying any potential interactions between medications used to treat depression and those used to treat general medical conditions [**I**]. Assessment of pain is also important as it can contribute to and co-occur with depression [**I**]. In addition, the psychiatrist should consider the effects of prescribed psychotropic medications on the patient's general medical conditions, as well as the effects of interventions for such disorders on the patient's psychiatric condition [**I**].

In patients with preexisting hypertension or cardiac conditions, treatment with specific antidepressant agents may suggest a need for monitoring of vital signs or cardiac rhythm (e.g., electrocardiogram [ECG] with TCA treatment; heart rate and blood pressure assessment with SNRIs and TCAs) [**I**]. When using antidepressant medications with anticholinergic side effects, it is important to consider the potential for increases in heart rate in individuals with cardiac disease, worsening cognition in individuals with dementia, development of bladder outlet obstruction in men with prostatic hypertrophy, and precipitation or worsening of narrow angle glaucoma [**I**]. Some antidepressant drugs (e.g., bupropion, clomipramine, maprotiline) reduce the seizure threshold and should be used with caution in individuals with preexisting seizure disorders [**II**]. In individuals with Parkinson's disease, the choice of an antidepressant should consider that serotonergic agents may worsen symptoms of the disease [**II**], that bupropion has potential dopamine agonist effects (benefitting symptoms of Parkinson's disease but potentially worsening psychosis) [**II**], and that selegiline has antiparkinsonian and antidepressant effects but may interact with L-dopa and with other antidepressant agents [**I**]. In treating the depressive syndrome that commonly occurs following a stroke, consideration should be given to the potential for interactions between antidepressants and anticoagulating (including antiplatelet) medications [**I**]. Given the health risks associated with obesity and the tendency of some antidepressant medications to contribute to weight gain, longitudinal monitoring of weight (either by direct measurement or patient report) is recommended [**I**], as well as calculation of body mass index (BMI) [**II**]. If significant increases are noted in the patient's weight or BMI, the clinician and patient should discuss potential approaches to weight control such as diet, exercise, change in medication, nutrition consultation, or collaboration with the patient's primary care physician [**I**]. In patients who have undergone bariatric surgery to treat obesity, adjustment of medication formulations or doses may be required because of altered medication absorption [**I**]. For diabetic patients, it is useful to collaborate with the patient's primary care physician in monitoring diabetic control when initiating antidepressant therapy or making significant dosing adjustments [**II**]. Clinicians should be alert to the possibility of sleep apnea in patients with depression, particularly those who present with daytime sleepiness, fatigue, or treatment-resistant symptoms [**II**]. In patients with known sleep apnea, treatment choice should consider the sedative side effects of medication, with minimally sedating options chosen whenever possible [**I**]. Given the significant numbers of individuals with unrecognized human immunodeficiency virus (HIV) infection and the availability of effective treatment, consideration should be given to HIV risk assessment and screening [**I**]. For patients with HIV infection who are receiving antiretroviral therapy, the potential for drug-drug interactions needs to be assessed before initiating any psychotropic medications [**I**]. Patients who are being treated with antiretroviral medications should be cautioned about drug-drug interactions with St. John's wort that can reduce the effectiveness of HIV treatments [**I**]. In patients with hepatitis C infection, interferon can exacerbate depressive symptoms, making it important to monitor patients carefully for worsening depressive symptoms during the course of interferon treatment [**I**]. Because tamoxifen requires active 2D6 enzyme function to be clinically efficacious, patients who receive tamoxifen for breast cancer or other indications should generally be treated with an antidepressant (e.g., citalopram, escitalopram, venlafaxine, desvenlafaxine) that has minimal effect on metabolism through the cytochrome P450 2D6 isoenzyme [**I**]. When depression occurs in the context of chronic pain, SNRIs and TCAs may be preferable to other antidepressive agents [**II**]. When ECT is used to treat major depressive disorder in an individual with a co-occurring general medical condition, the evaluation should identify conditions that could require modifications in ECT technique (e.g., cardiac conditions, hypertension, central nervous system lesions) [**I**]; these should be addressed insofar as possible and discussed with the patient as part of the informed consent process [**I**].

Definitions:

Categories of Endorsement

[**I**] Recommended with substantial clinical confidence.

[**II**] Recommended with moderate clinical confidence.

[**III**] May be recommended on the basis of individual circumstances.

Clinical Algorithm(s)

None provided

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

This document represents a synthesis of current scientific knowledge and rational clinical practice regarding the treatment of patients with major depressive disorder.

In order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each recommendation, the summary of treatment recommendations is keyed according to the level

of confidence with which each recommendation is made (see "Major Recommendations" field). Each rating of clinical confidence considers the strength of the available evidence. When evidence from randomized controlled trials and meta-analyses is limited, the level of confidence may also incorporate other clinical trials and case reports as well as clinical consensus with regard to a particular clinical decision. In the listing of cited references, each reference is followed by a letter code in brackets that indicates the nature of the supporting evidence:

- **[A]** *Randomized, double-blind clinical trial*. A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.
- **[A-]** *Randomized clinical trial*. Same as above but not double-blind.
- **[B]** *Clinical trial*. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.
- **[C]** *Cohort or longitudinal study*. A study in which subjects are prospectively followed over time without any specific intervention.
- **[D]** *Case-control study*. A study in which a group of patients and a group of control subjects are identified in the present and information about them is pursued retrospectively or backward in time.
- **[E]** *Review with secondary data analysis*. A structured analytic review of existing data, e.g., a meta-analysis or a decision analysis.
- **[F]** *Review*. A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.
- **[G]** *Other*. Textbooks, expert opinion, case reports, and other reports not included above.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of major depressive disorder

Potential Harms

Antidepressants

- *Selective Serotonin Reuptake Inhibitors (SSRIs)*: Side effects include gastrointestinal issues, activation/insomnia, sexual side effects, headaches, extrapyramidal side effects, falls, effects on weight, serotonin syndrome, drug interactions, and discontinuation syndrome.
- *Serotonin norepinephrine reuptake inhibitors (SNRIs)*: Side effects are similar to SSRIs. Dose-related hypertension may occur. Discontinuation symptoms are sometime protracted.
- *Bupropion*: Side effects include headaches, tremors, and seizures.
- *Mirtazapine*: The most common side effects include dry mouth, sedation, and weight gain. Mirtazapine increases cholesterol levels in some patients.
- *Trazodone*: The most common side effect is sedation. Trazodone can also cause cardiovascular side effects.
- *Nefazodone*: Side effects include dry mouth, nausea, constipation, orthostasis, and visual alterations. Sedation is also common. Hepatic toxicity has also been reported. These reports led the U.S. Food and Drug Administration to require a black box warning in the labeling of nefazodone, warning of possible liver failure leading to transplant and/or death.
- *Tricyclic Antidepressants (TCAs)*: Side effects include cardiovascular effects, anticholinergic effects, sedation, weight gain, myoclonus, seizures, falls, and medication interactions.
- *Monoamine Oxidase Inhibitors*: Side effects include cardiovascular effects, weight gain, sexual side effects, and headaches, insomnia, and sedation. Food-drug and drug-drug interactions can produce hypertensive crises and serotonin syndrome, which can be life-threatening.

See the original guideline document for further details on potential side effects of antidepressants, including information about risk of suicidal thoughts and behaviors.

Somatic Therapies

- *Electroconvulsive Therapy (ECT)*: Headaches and muscle aches are common. ECT may have cardiovascular side effects. It can also be associated with cognitive effects and anterograde amnesia.
- *Transcranial Magnetic Stimulation (TMS)*: Transient scalp discomfort and headaches were the most commonly reported side effects.

Other Non-pharmacological Therapies

- *Psychotherapy* carries its own "side effects." A psychotherapy that requires considerable time or patients may be poorly tolerated. The work of psychotherapy itself may generate anxiety or other strong feelings, which may be difficult for patients to manage.
- *Complementary and Alternative Treatments*: An important consideration with St. John's wort is the potential for drug-drug interactions.
- *Light Therapy*: Monitoring for mania and hypomania may be appropriate with initiation of light therapy, as hypomania was been reported.

Contraindications

Contraindications

- The combined use of a monoamine oxidase inhibitor (MAOI) with a selective serotonin reuptake inhibitor (SSRI) is contraindicated because it can lead to a potentially lethal interaction: the serotonin syndrome. Combining other serotonergic agents with an MAOI, including serotonin norepinephrine reuptake inhibitors (SNRIs), St. John's wort, or tricyclic antidepressants (TCAs), can also lead to the serotonin syndrome. When an SSRI is being changed to an MAOI or vice versa, a minimum washout time must be allowed.
- The vagus nerve stimulation (VNS) device may affect the operation of other implanted devices such as cardiac pacemakers or defibrillators and other procedures such as diathermy, and whole body or radiofrequency receive-only magnetic resonance imaging (MRI) are contraindicated. VNS is also contraindicated in the presence of bilateral or left cervical vagotomy.
- Enlarged prostate size and other causes of bladder outlet obstruction are relative contraindications to the use of antidepressant medication compounds with antimuscarinic effects.
- Bupropion is contraindicated in patients who have had anorexia nervosa or bulimia nervosa because of elevated risk of seizures.

Qualifying Statements

Qualifying Statements

- The American Psychiatric Association (APA) Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate recommendation regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data, the psychiatric evaluation, and the diagnostic and treatment options available. Such recommendations should incorporate the patient's personal and sociocultural preferences and values in order to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes.
- The Work Group and the Steering Committee differed on how to rate the strength of recommendation for psychodynamic psychotherapy. Based on their review of the available empirical evidence on the use of psychodynamic psychotherapy in individuals with major depressive disorder, the Work Group gave this treatment a level III rating, i.e., "may be recommended on the basis of individual circumstances." The Steering Committee gave a level II rating, "recommended with moderate clinical confidence," based on the long history of clinical experience with psychodynamic psychotherapy as well as findings from several studies of patients who had depressive symptoms but not major depressive disorder per se.
- The broad scope of this guideline and the substantial evidence base resulted in some practical tradeoffs. One such tradeoff worth highlighting is the decision to build upon literature reviews of the first and second editions of the guideline, rather than re-do them. This decision is acknowledged to have resulted in an emphasis of study in this guideline on newer treatments, because the majority of studies about older treatments, including tricyclic antidepressants and monoamine oxidase inhibitors, were published in decades prior to 1999. Readers are advised that the reviews of this older literature are described in the previous editions of the guideline. The Work Group for this edition considered the previous editions during their evidence review, but for practical reasons, that effort is less well documented than the group's analysis of the newer literature. The treatment recommendations of this guideline, however, were developed to reflect the complete evidence base.
- Medications discussed in this practice guideline may not have an indication from the U.S. Food and Drug Administration for the disorder or condition for which they are recommended. Off-label use of medications by individual physicians is permitted and common. Decisions about off-label use can be guided by the evidence provided in the APA practice guideline, other scientific literature, and clinical experience.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington (VA): American Psychiatric Association (APA); 2010 Oct. 152 p. [1170 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1993 (revised 2010 Oct)

Guideline Developer(s)

American Psychiatric Association - Medical Specialty Society

Source(s) of Funding

American Psychiatric Association (APA)

Guideline Committee

Work Group on Major Depressive Disorder

Composition of Group That Authored the Guideline

Work Group Members: Alan J. Gelenberg, MD, Chair; Marlene P. Freeman, MD; John C. Markowitz, MD; Jerrold F. Rosenbaum, MD; Michael E. Thase, MD; Madhukar H. Trivedi, MD; Richard S. Van Rhoads, MD, Consultant

Financial Disclosures/Conflicts of Interest

Work Group members were selected on the basis of their expertise and integrity, and they agreed to disclose all potential conflicts of interest before and during their work on this guideline to the Steering Committee on Practice Guidelines and to each other. Employees of industry were not included on the group, and the group was balanced to include some persons with minimal industry relationships. As disclosed below, from initiation of work in 2005 to approval of the guideline in 2010, some members of the Work Group on Major Depressive Disorder had relationships with industry for which they received research grants or income from consulting or speaking related to treatments discussed in the guideline.

The Work Group on Major Depressive Disorder reports the following potentially competing interests for the period from May 2005 to May 2010:

- Dr. Gelenberg reports consulting for Eli Lilly and Company, Pfizer, Best Practice, AstraZeneca, Wyeth, Cyberonics, Novartis, Forest Pharmaceuticals, Inc., GlaxoSmithKline, ZARS Pharma, Jazz Pharmaceuticals, Lundbeck, Takeda Pharmaceuticals North America, Inc., eResearch Technology, Dey Pharma, PGxHealth, and Myriad Genetics. He reports serving on speakers bureaus for Pfizer, GlaxoSmithKline, and Wyeth. He reports receiving research grant funding from Eli Lilly and Company, Pfizer, and GlaxoSmithKline. He reports stock ownership in Healthcare Technology Systems.
- Dr. Freeman reports that she received research support from the Meadows Foundation, the National Institute for Mental Health, the U.S. Food and Drug Administration, the Institute for Mental Health Research, Forest, GlaxoSmithKline and Eli Lilly and Company (investigator-initiated trials), and Pronova Biocare (research materials). She received an honorarium for case-based peer-reviewed material for AstraZeneca's website. She reports consulting for Ther-Rx, Reliant, and Pamlab. She reports receiving an honorarium for speaking at an APA continuing medical education program that was sponsored by Forest and an honorarium for speaking at a continuing medication education program sponsored by KV Pharmaceuticals. She reports receiving an honorarium from Leerink Swann for participating in a focus group.
- Dr. Markowitz reports consulting for Ono Pharmaceutical Co., Ltd. (2005). He reports receiving research support from Forest Pharmaceuticals, Inc. (2005). He reports receiving grant support from the National Institute of Mental Health (2005–2013), the National Alliance for Research in Schizophrenia and Depression (2005), and MINT: Mental Health Initiative (2005). He reports receiving royalties from American Psychiatric Publishing, Inc. (2005–2010), Basic Books (2005–2010), Elsevier (2005–2010), and Oxford University Press (2007–2010).
- Dr. Rosenbaum reports attending advisory boards for Bristol-Myers Squibb, Cephalon, Cyberonics, Forest Pharmaceuticals, Inc., Eli Lilly and Company, MedAvante, Neuronetics, Inc., Novartis, Orexigen Therapeutics, Inc., Organon BioSciences, Pfizer, Roche Diagnostics, Sanofi-aventis, Shire, and Wyeth. He reports consulting for Auspex Pharmaceuticals, Compellis Pharmaceuticals, EPIX Pharmaceuticals, Neuronetics, Inc., Organon BioSciences, Somaxon, and Supernus Pharmaceuticals, Inc. He reports receiving honoraria from lectureships for Boehringer Ingleheim, Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, Inc., Eli Lilly and Company, and Schwartz Pharma. He was involved in the creation of the Massachusetts General Hospital Psychiatry Academy (MGH-PA) and has served as a panelist in four satellite broadcast programs. MGH-PA programs that have industry support are always multi-sponsored, and curriculum development by the Academy is independent of sponsorship; the curricula from January 2005 to March 2009 included sponsorship support from AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly and Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Medical Affairs LLC, Ortho-McNeil Pharmaceutical, sanofi-aventis, Shire, and Wyeth. He reports equity holdings in Compellis Pharmaceuticals, MedAvante, and Somaxon.
- Dr. Thase reports that he provided scientific consultation to AstraZeneca, Bristol-Myers Squibb, Eli Lilly &

Company, Forest Pharmaceuticals, Inc., Gerson Lehman Group, GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Inc., Neuronetics, Inc., Novartis, Otsuka, Ortho-McNeil Pharmaceuticals, PamLab, L.L.C., Pfizer (formerly Wyeth-Ayerst Laboratories), Schering-Plough (formerly Organon), Shire U.S., Inc., Supernus Pharmaceuticals, Takeda (Lundbeck), and Transcept Pharmaceuticals. He was a member of the speakers bureaus for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Pfizer (formerly Wyeth-Ayerst Laboratories), and Schering-Plough (formerly Organon). He received grant funding from Eli Lilly and Company, GlaxoSmithKline, the National Institute of Mental Health, the Agency for Healthcare Research and Quality, and Sepracor, Inc. He had equity holdings in MedAvante, Inc., and received royalty income from American Psychiatric Publishing, Inc., Guilford Publications, Herald House, Oxford University Press, and W.W. Norton and Company. His wife was employed as the group scientific director for Embryon (formerly Advogent), which does business with Bristol-Myers Squibb and Pfizer/Wyeth.

- Dr. Trivedi reports that he was a consultant to or on speaker bureaus for Abbott Laboratories, Inc., Abdi Ibrahim, Akzo (Organon Pharmaceuticals, Inc.), AstraZeneca, Bristol-Myers Squibb Company, Cephalon, Inc., Cyberonics, Inc., Eli Lilly and Company, Evotec, Fabre Kramer Pharmaceuticals, Inc., Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica Products, L.P., Johnson & Johnson P.R.D., Meade-Johnson, Medtronic, Neuronetics, Otsuka Pharmaceuticals, Parke-Davis Pharmaceuticals, Inc., Pfizer, Inc., Sepracor, Shire Development, Solvay Pharmaceuticals, VantagePoint, and Wyeth-Ayerst Laboratories. He received research support from the Agency for Healthcare Research and Quality, Corcept Therapeutics, Inc., Cyberonics, Inc., Merck, National Alliance for Research in Schizophrenia and Depression, National Institute of Mental Health, National Institute on Drug Abuse, Novartis, Pharmacia & Upjohn, Predix Pharmaceuticals (Epix), Solvay Pharmaceuticals, Inc., and Targacept.
- Dr. Van Rhoads reports no competing interests.

The Independent Review Panel, including Drs. Reus, DePaulo, Fawcett, Schneck, and Silbersweig, report no competing interests. The Independent Review Panel reviewed this guideline to assess potential biases and found no evidence of influence from the industry and other relationships of the Work Group disclosed above. The Steering Committee on Practice Guidelines also reviewed this guideline and found no evidence of influence from these relationships. The development process for this guideline, including the roles of the Work Group, Independent Review Panel, Steering Committee, American Psychiatric Association (APA) Assembly, and APA Board of Trustees is described in "Overview of Guideline Development Process" on p. 11 in the original guideline document.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry 2000 Apr;157(4 Suppl):1-45. [325 references]

Guideline Availability

Electronic copies: Available from the American Psychiatric Association's Web site.

Availability of Companion Documents

The following are available:

- Treating major depressive disorder. A quick reference guide. Washington (DC): American Psychiatric Association (APA); 2010. 28 p. Electronic copies: Available from the American Psychiatric Association (APA) Web site (by subscription only).
- American Psychiatric Association practice guideline development process. Arlington (VA): APA; 2004. Available from the APA Web site. Also available in a PDA version.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 15, 2010. The information was verified by the guideline developer on January 7, 2011. This summary was updated by ECRI Institute on May 20, 2011 following the U.S. Food and Drug Administration advisory on antipsychotic drugs. This summary was updated by ECRI Institute on September 12, 2011 following the U.S. Food and Drug Administration advisory on Celexa (citalopram hydrobromide). This summary was updated by ECRI Institute on April 16, 2012 following the updated U.S. Food and Drug Administration advisory on Celexa (citalopram hydrobromide).

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