Post-Traumatic Stress Disorder (PTSD)

National Institute of Mental Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health

Contents

What is post-traumatic stress disorder, or PTSD?

PTSD is an anxiety disorder that some people get after seeing or living through a dangerous event.

When in danger, it's natural to feel afraid. This fear triggers many split-second changes in the body to prepare to defend against the danger or to avoid it. This "fight-or-flight" response is a healthy reaction meant to protect a person from harm. But in PTSD, this reaction is changed or damaged. People who have PTSD may feel stressed or frightened even when they're no longer in danger.

Who gets PTSD?

Anyone can get PTSD at any age. This includes war veterans and survivors of physical and sexual assault, abuse, accidents, disasters, and many other serious events.

Not everyone with PTSD has been through a dangerous event. Some people get PTSD after a friend or family member experiences danger or is harmed. The sudden, unexpected death of a loved one can also cause PTSD.

What are the symptoms of PTSD?

PTSD can cause many symptoms. These symptoms can be grouped into three categories:

1. **Re-experiencing symptoms:**

- Flashbacks—reliving the trauma over and over, including physical symptoms like a racing heart or sweating
- Bad dreams
- Frightening thoughts.

Re-experiencing symptoms may cause problems in a person's everyday routine. They can start from the person's own thoughts and feelings. Words, objects, or situations that are reminders of the event can also trigger re-experiencing.

2. Avoidance symptoms:

- Staying away from places, events, or objects that are reminders of the experience
- Feeling emotionally numb
- Feeling strong guilt, depression, or worry
- Losing interest in activities that were enjoyable in the past
- Having trouble remembering the dangerous event.

Things that remind a person of the traumatic event can trigger avoidance symptoms. These symptoms may cause a person to change his or her personal routine. For example, after a bad car accident, a person who usually drives may avoid driving or riding in a car.

3. Hyperarousal symptoms:

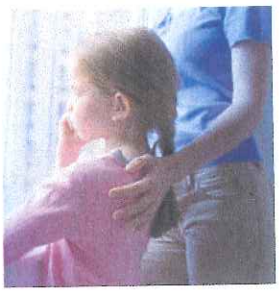
- Being easily startled
- Feeling tense or "on edge"
- Having difficulty sleeping, and/or having angry outbursts.

Hyperarousal symptoms are usually constant, instead of being triggered by things that remind one of the traumatic event. They can make the person feel stressed and angry. These symptoms may make it hard to do daily tasks, such as sleeping, eating, or concentrating.

It's natural to have some of these symptoms after a dangerous event. Sometimes people have very serious symptoms that go away after a few weeks. This is called acute stress disorder, or ASD. When the symptoms last more than a few weeks and become an ongoing problem, they might be PTSD. Some people with PTSD don't show any symptoms for weeks or months.

Do children react differently than adults?

Children and teens can have extreme reactions to trauma, but their symptoms may not be the same as adults.[1] In very young children, these symptoms can include:



- Bedwetting, when they'd learned how to use the toilet before
- Forgetting how or being unable to talk
- Acting out the scary event during playtime
- Being unusually clingy with a parent or other adult.

Older children and teens usually show symptoms more like those seen in adults. They may also develop disruptive, disrespectful, or destructive behaviors. Older children and teens may feel guilty for not preventing injury or deaths. They may also have thoughts of revenge. For more information, see the NIMH booklets on helping children cope with violence and disasters.

How is PTSD detected?

A doctor who has experience helping people with mental illnesses, such as a psychiatrist or psychologist, can diagnose PTSD. The diagnosis is made after the doctor talks with the person who has symptoms of PTSD.

To be diagnosed with PTSD, a person must have all of the following for at least 1 month:

- At least one re-experiencing symptom
- At least three avoidance symptoms
- At least two hyperarousal symptoms
- Symptoms that make it hard to go about daily life, go to school or work, be with friends, and take care of important tasks.

Why do some people get PTSD and other people do not?

It is important to remember that not everyone who lives through a dangerous event gets PTSD. In fact, most will not get the disorder.

Many factors play a part in whether a person will get PTSD. Some of these are **risk factors** that make a person more likely to get PTSD. Other factors, called **resilience factors**, can help reduce the risk of the disorder. Some of these risk and resilience factors are present before the trauma and others become important during and after a traumatic event.

Risk factors for PTSD include:[2]

- Living through dangerous events and traumas
- Having a history of mental illness
- Getting hurt
- Seeing people hurt or killed
- Feeling horror, helplessness, or extreme fear
- Having little or no social support after the event
- Dealing with extra stress after the event, such as loss of a loved one, pain and injury, or loss of a job or home.

Resilience factors that may reduce the risk of PTSD include:[3]

- Seeking out support from other people, such as friends and family
- Finding a support group after a traumatic event
- Feeling good about one's own actions in the face of danger
- Having a coping strategy, or a way of getting through the bad event and learning from it
- Being able to act and respond effectively despite feeling fear.

Researchers are studying the importance of various risk and resilience factors. With more study, it may be possible someday to predict who is likely to get PTSD and prevent it.

How is PTSD treated?

The main treatments for people with PTSD are psychotherapy ("talk" therapy), medications, or both. Everyone is different, so a treatment that works for one person may not work for another. It is important for anyone with PTSD to be treated by a mental health care provider who is experienced with PTSD. Some people with PTSD need to try different treatments to find what works for their symptoms.

If someone with PTSD is going through an ongoing trauma, such as being in an abusive relationship, both of the problems need to be treated. Other ongoing problems can include panic disorder, depression, substance abuse, and feeling suicidal.

Psychotherapy

Psychotherapy is "talk" therapy. It involves talking with a mental health professional to treat a mental illness. Psychotherapy can occur one-on-one or in a group. Talk therapy treatment for PTSD usually lasts 6 to 12 weeks, but can take more time. Research shows that support from family and friends can be an important part of therapy.

Many types of psychotherapy can help people with PTSD. Some types target the symptoms of PTSD directly. Other therapies focus on social, family, or job-related problems. The doctor or therapist may combine different therapies depending on each person's needs.

One helpful therapy is called **cognitive behavioral therapy**, or **CBT**. There are several parts to CBT, including:

- **Exposure therapy.** This therapy helps people face and control their fear. It exposes them to the trauma they experienced in a safe way. It uses mental imagery, writing, or visits to the place where the event happened. The therapist uses these tools to help people with PTSD cope with their feelings.
- **Cognitive restructuring.** This therapy helps people make sense of the bad memories. Sometimes people remember the event differently than how it happened. They may feel guilt or shame about what is not their fault. The therapist helps people with PTSD look at what happened in a realistic way.
- **Stress inoculation training.** This therapy tries to reduce PTSD symptoms by teaching a person how to reduce anxiety. Like cognitive restructuring, this treatment helps people look at their memories in a healthy way.

Other types of treatment can also help people with PTSD. People with PTSD should talk about all treatment options with their therapist.

How Talk Therapies Help People Overcome PTSD

Talk therapies teach people helpful ways to react to frightening events that trigger their PTSD symptoms. Based on this general goal, different types of therapy may:

- Teach about trauma and its effects.
- Use relaxation and anger control skills.
- Provide tips for better sleep, diet, and exercise habits.
- Help people identify and deal with guilt, shame, and other feelings about the event.
- Focus on changing how people react to their PTSD symptoms. For example, therapy helps people visit places and people that are reminders of the trauma.

Medications

The U.S. Food and Drug Administration (FDA) has approved two medications for treating adults with PTSD:

- sertraline (Zoloft)
- paroxetine (Paxil)

Both of these medications are **antidepressants**, which are also used to treat depression. They may help control PTSD symptoms such as sadness, worry, anger, and feeling numb inside. Taking these medications may make it easier to go through psychotherapy.

Sometimes people taking these medications have side effects. The effects can be annoying, but they usually go away. However, medications affect everyone differently. Any side effects or unusual reactions should be reported to a doctor immediately.

The most common side effects of antidepressants like sertraline and paroxetine are:

- Headache, which usually goes away within a few days.
- Nausea (feeling sick to your stomach), which usually goes away within a few days.

- Sleeplessness or drowsiness, which may occur during the first few weeks but then goes away. Sometimes the medication dose needs to be reduced or the time of day it is taken needs to be adjusted to help lessen these side effects.
- Agitation (feeling jittery).
- Sexual problems, which can affect both men and women, including reduced sex drive, and problems having and enjoying sex.

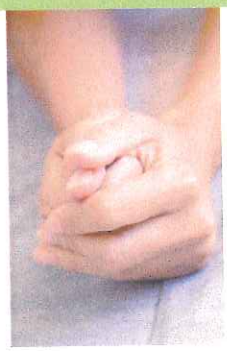
FDA Warning on Antidepressants

Despite the relative safety and popularity of SSRIs and other antidepressants, some studies have suggested that they may have unintentional effects on some people, especially adolescents and young adults. In 2004, the Food and Drug Administration (FDA) conducted a thorough review of published and unpublished controlled clinical trials of antidepressants that involved nearly 4,400 children and adolescents. The review revealed that 4 percent of those taking antidepressants thought about or attempted suicide (although no suicides occurred), compared to 2 percent of those receiving placebos.

This information prompted the FDA, in 2005, to adopt a "black box" warning label on all antidepressant medications to alert the public about the potential increased risk of suicidal thinking or attempts in children and adolescents taking antidepressants. In 2007, the FDA proposed that makers of all antidepressant medications extend the warning to include young adults up through age 24. A "black box" warning is the most serious type of warning on prescription drug labeling.

The warning emphasizes that patients of all ages taking antidepressants should be closely monitored, especially during the initial weeks of treatment. Possible side effects to look for are worsening depression, suicidal thinking or behavior, or any unusual changes in behavior such as sleeplessness, agitation, or withdrawal from normal social situations. The warning adds that families and caregivers should also be told of the need for close monitoring and report any changes to the physician. The latest information from the FDA can be found on their Web site at www.fda.gov.

Results of a comprehensive review of pediatric trials conducted between 1988 and 2006 suggested that the benefits of antidepressant medications likely outweigh their risks to children and adolescents with major depression and anxiety disorders.[4] The study was funded in part by the National Institute of Mental Health.



Other medications

Doctors may also prescribe other types of medications, such as the ones listed below. There is little information on how well these work for people with PTSD.

1. **Benzodiazepines.** These medications may be given to help people relax and sleep. People who take benzodiazepines may have memory problems or become dependent on the medication.[5]
2. **Antipsychotics.** These medications are usually given to people with other mental disorders, like schizophrenia. People who take antipsychotics may gain weight and have a higher chance of getting heart disease and diabetes.
3. **Other antidepressants.** Like sertraline and paroxetine, the antidepressants fluoxetine (Prozac) and citalopram (Celexa) can help people with PTSD feel less tense or sad. For people with PTSD who also have other anxiety disorders or depression, antidepressants may be useful in reducing symptoms of these co-occurring illnesses.

Treatment after mass trauma

Sometimes large numbers of people are affected by the same event. For example, a lot of people needed help after Hurricane Katrina in 2005 and the terrorist attacks of September 11, 2001. Most people will have some PTSD symptoms in the first few weeks after events like these. This is a normal and expected response to serious trauma, and for most people, symptoms generally lessen with time. Most people can be helped with basic support, such as:

- Getting to a safe place
- Seeing a doctor if injured
- Getting food and water
- Contacting loved ones or friends
- Learning what is being done to help.

But some people do not get better on their own. A study of Hurricane Katrina survivors found that, over time, more people were having problems with PTSD, depression, and related mental disorders.[6] This pattern is unlike the recovery from other natural disasters, where the number of people who have mental health problems gradually lessens. As communities try to rebuild after a mass trauma, people

may experience ongoing stress from loss of jobs and schools, and trouble paying bills, finding housing, and getting health care. This delay in community recovery may in turn delay recovery from PTSD.

In the first couple weeks after a mass trauma, brief versions of CBT may be helpful to some people who are having severe distress.[7] Sometimes other treatments are used, but their effectiveness is not known. For example, there is growing interest in an approach called *psychological first aid*. The goal of this approach is to make people feel safe and secure, connect people to health care and other resources, and reduce stress reactions.[8] There are guides for carrying out the treatment, but experts do not know yet if it helps prevent or treat PTSD.

In single-session *psychological debriefing*, another type of mass trauma treatment, survivors talk about the event and express their feelings one-on-one or in a group. Studies show that it is not likely to reduce distress or the risk for PTSD, and may actually increase distress and risk.[9]

Mass Trauma Affects Hospitals and Other Providers

Hospitals, health care systems, and health care providers are also affected by a mass trauma. The number of people who need immediate physical and psychological help may be too much for health systems to handle. Some patients may not find help when they need it because hospitals do not have enough staff or supplies. In some cases, health care providers themselves may be struggling to recover as well.

NIMH scientists are working on this problem. For example, researchers are testing how to give CBT and other treatments using the phone and the Internet. In one study, people with PTSD met with a therapist to learn about the disorder, made a list of things that trigger their symptoms, and learned basic ways to reduce stress. After this meeting, the participants could visit a Web site with more information about PTSD. Participants could keep a log of their symptoms and practice coping skills. Overall, the researchers found the Internet-based treatment helped reduce symptoms of PTSD and depression.[10] These effects lasted after treatment ended.

Researchers will carry out more studies to find out if other such approaches to therapy can be helpful after mass trauma.

What efforts are under way to improve the detection and treatment of PTSD?

Researchers have learned a lot in the last decade about fear, stress, and PTSD. Scientists are also learning about how people form memories. This is important because creating very powerful fear-related memories seems to be a major part of PTSD. Researchers are also exploring how people can create "safety" memories to replace the bad memories that form after a trauma. NIMH's goal in supporting this research is to improve treatment and find ways to prevent the disorder.

PTSD research also includes the following examples:

- Using powerful new research methods, such as brain imaging and the study of genes, to find out more about what leads to PTSD, when it happens, and who is most at risk.
- Trying to understand why some people get PTSD and others do not. Knowing this can help health care professionals predict who might get PTSD and provide early treatment.
- Focusing on ways to examine pre-trauma, trauma, and post-trauma risk and resilience factors all at once.
- Looking for treatments that reduce the impact traumatic memories have on our emotions.
- Improving the way people are screened for PTSD, given early treatment, and tracked after a mass trauma.
- Developing new approaches in self-testing and screening to help people know when it's time to call a doctor.
- Testing ways to help family doctors detect and treat PTSD or refer people with PTSD to mental health specialists.

For more information on PTSD research, please see NIMH's PTSD Research Fact Sheet (online at http://www.nimh.nih.gov/health/publications/post-traumatic-stress-disorder-research-fact-sheet.shtml) or the PTSD Clinical Trials Web site page at http://www.nimh.nih.gov/health/trials/post-traumatic-stress-disorder-ptsd.shtml.

How can I help a friend or relative who has PTSD?

If you know someone who has PTSD, it affects you too. The first and most important thing you can do to help a friend or relative is to help him or her get the right diagnosis and treatment. You may need to make an appointment for your friend or relative and go with him or her to see the doctor. Encourage him or her to stay in treatment, or to seek different treatment if his or her symptoms don't get better after 6 to 8 weeks.

To help a friend or relative, you can:

- Offer emotional support, understanding, patience, and encouragement.
- Learn about PTSD so you can understand what your friend or relative is experiencing.
- Talk to your friend or relative, and listen carefully.
- Listen to feelings your friend or relative expresses and be understanding of situations that may trigger PTSD symptoms.
- Invite your friend or relative out for positive distractions such as walks, outings, and other activities.
- Remind your friend or relative that, with time and treatment, he or she can get better.

Never ignore comments about your friend or relative harming him or herself, and report such comments to your friend's or relative's therapist or doctor.

How can I help myself?

It may be very hard to take that first step to help yourself. It is important to realize that although it may take some time, with treatment, you can get better.

To help yourself:

- Talk to your doctor about treatment options.
- Engage in mild activity or exercise to help reduce stress.
- Set realistic goals for yourself.
- Break up large tasks into small ones, set some priorities, and do what you can as you can.

- Try to spend time with other people and confide in a trusted friend or relative. Tell others about things that may trigger symptoms.
- Expect your symptoms to improve gradually, not immediately.
- Identify and seek out comforting situations, places, and people.

Where can I go for help?

If you are unsure where to go for help, ask your family doctor. Others who can help are listed below.

Mental health resources

- Mental health specialists, such as psychiatrists, psychologists, social workers, or mental health counselors
- Health maintenance organizations
- Community mental health centers
- Hospital psychiatry departments and outpatient clinics
- Mental health programs at universities or medical schools
- State hospital outpatient clinics
- Family services, social agencies, or clergy
- Peer support groups
- Private clinics and facilities
- Employee assistance programs
- Local medical and/or psychiatric societies.

You can also check the phone book under "mental health," "health," "social services," "hotlines," or "physicians" for phone numbers and addresses. An emergency room doctor can also provide temporary help and can tell you where and how to get further help.

What if I or someone I know is in crisis?

If you are thinking about harming yourself, or know someone who is, tell someone who can help immediately:

- Call your doctor.
- Call 911 or go to a hospital emergency room to get immediate help or ask a friend or family member to help you do these things.
- Call the toll-free, 24-hour hotline of the National Suicide Prevention Lifeline at 1–800–273–TALK (1–800–273–8255); TTY: 1–800–799–4TTY (4889) to talk to a trained counselor.
- Make sure you or the suicidal person is not left alone.

Citations

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For more information on post-traumatic stress disorder (PTSD)

Visit the National Library of Medicine's:

MedlinePlus:
http://medlineplus.gov

En Español:
http://medlineplus.gov/spanish

For information on clinical trials for PTSD:
http://www.nimh.nih.gov/health/trials/index.shtml

National Library of Medicine Clinical Trials Database:
http://clinicaltrials.gov

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Science Writing, Press & Dissemination Branch
6001 Executive Boulevard
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Phone: 301–443–4513 or
1–866–615–NIMH (6464) toll-free
TTY: 301–443–8431
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MAYO CLINIC

Post-traumatic stress disorder (PTSD)

By Mayo Clinic staff

Definition

Post-traumatic stress disorder (PTSD) is a mental health condition that's triggered by a terrifying event. Symptoms may include flashbacks, nightmares and severe anxiety, as well as uncontrollable thoughts about the event.

Many people who go through traumatic events have difficulty adjusting and coping for a while. But with time and taking care of yourself, such traumatic reactions usually get better. In some cases, though, the symptoms can get worse or last for months or even years. Sometimes they may completely shake up your life. In a case such as this, you may have post-traumatic stress disorder.

Getting treatment as soon as possible after post-traumatic stress disorder symptoms develop may prevent long-term post-traumatic stress disorder.

Symptoms

Post-traumatic stress disorder symptoms typically start within three months of a traumatic event. In a small number of cases, though, PTSD symptoms may not appear until years after the event.

Post-traumatic stress disorder symptoms are generally grouped into three types: intrusive memories, avoidance and numbing, and increased anxiety or emotional arousal (hyperarousal).

Symptoms of intrusive memories may include:

- Flashbacks, or reliving the traumatic event for minutes or even days at a time
- Upsetting dreams about the traumatic event

Symptoms of avoidance and emotional numbing may include:

- Trying to avoid thinking or talking about the traumatic event
- Feeling emotionally numb
- Avoiding activities you once enjoyed

- Hopelessness about the future
- Memory problems
- Trouble concentrating
- Difficulty maintaining close relationships

Symptoms of anxiety and increased emotional arousal may include:

- Irritability or anger
- Overwhelming guilt or shame
- Self-destructive behavior, such as drinking too much
- Trouble sleeping
- Being easily startled or frightened
- Hearing or seeing things that aren't there

Post-traumatic stress disorder symptoms can come and go. You may have more post-traumatic stress disorder symptoms when things are stressful in general, or when you run into reminders of what you went through. You may hear a car backfire and relive combat experiences, for instance. Or you may see a report on the news about a rape and feel overcome by memories of your own assault.

When to see a doctor

It's normal to have a wide range of feelings and emotions after a traumatic event. You might experience fear and anxiety, a lack of focus, sadness, changes in how well you sleep or how much you eat, or crying spells that catch you off guard. You may have nightmares or be unable to stop thinking about the event. This doesn't mean you have post-traumatic stress disorder.

But if you have these disturbing thoughts and feelings for more than a month, if they're severe, or if you feel you're having trouble getting your life back under control, talk to your health care professional. Getting treatment as soon as possible can help prevent PTSD symptoms from getting worse.

In some cases, post-traumatic stress disorder symptoms may be so severe that you need emergency help, especially if you're thinking about harming yourself or someone else. If this happens, call 911 or other emergency medical service, or ask a supportive family member or friend for help.

Causes

You can develop post-traumatic stress disorder when you go through, see or learn about an event that causes intense fear, helplessness or horror.

Doctors aren't sure why some people get post-traumatic stress disorder. As with most mental health problems, PTSD is probably caused by a complex mix of:

- Your inherited mental health risks, such as an increased risk of anxiety and depression
- Your life experiences, including the amount and severity of trauma you've gone through since early childhood
- The inherited aspects of your personality — often called your temperament
- The way your brain regulates the chemicals and hormones your body releases in response to stress

Risk factors

People of all ages can have post-traumatic stress disorder. However, some factors may make you more likely to develop PTSD after a traumatic event, including:

- Being female
- Experiencing intense or long-lasting trauma
- Having experienced other trauma earlier in life
- Having other mental health problems, such as anxiety or depression
- Lacking a good support system of family and friends
- Having first-degree relatives with mental health problems, including PTSD
- Having first-degree relatives with depression
- Having been abused or neglected as a child

Women may be at increased risk of PTSD because they are more likely to experience the kinds of trauma that can trigger the condition.

Kinds of traumatic events

Post-traumatic stress disorder is especially common among those who have served in combat. It's sometimes called "shell shock," "battle fatigue" or "combat stress."

The most common events leading to the development of PTSD include:

- Combat exposure
- Rape

- Childhood neglect and physical abuse
- Sexual molestation
- Physical attack
- Being threatened with a weapon

But many other traumatic events also can lead to post-traumatic stress disorder, including fire, natural disaster, mugging, robbery, assault, civil conflict, car accident, plane crash, torture, kidnapping, life-threatening medical diagnosis, terrorist attack and other extreme or life-threatening events.

Complications

Post-traumatic stress disorder can disrupt your whole life: your job, your relationships and even your enjoyment of everyday activities.

Having PTSD also may place you at a higher risk of other mental health problems, including:

- Depression
- Drug abuse
- Alcohol abuse
- Eating disorders
- Suicidal thoughts and actions

In addition, PTSD may increase your risk of certain medical illnesses, including:

- Cardiovascular disease
- Chronic pain
- Autoimmune diseases, such as rheumatoid arthritis and thyroid disease
- Musculoskeletal conditions

Preparing for your appointment

If you have thoughts of suicide, go to an emergency room or call 911 or your local emergency number immediately.

If you have less urgent symptoms of post-traumatic stress disorder, make an appointment with your family doctor or general practitioner. Your doctor can help you begin the process of understanding whether your physical and emotional symptoms may be related to a traumatic experience. In many cases, your doctor may

refer you to a mental health professional who can help make a diagnosis and create the right treatment plan for you.

Here's some information to help you prepare for your appointment, and what to expect from your doctor.

What you can do

- **Write down any symptoms you've been experiencing,** and for how long.
- **Write down your key personal information,** especially events or experiences — even in your distant past — that have made you feel intense fear, helplessness or horror. It will help your doctor to know if there are memories you can't directly access without feeling an overwhelming need to push them out of your mind.
- **Make a list of your medical information,** including other physical or mental health conditions with which you've been diagnosed. Also write down the names of any medications, including over-the-counter medications, you're taking.
- **Take a trusted family member or friend along,** if possible. Sometimes it can be difficult to soak up all 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 doctor in advance so that you can make the most of your appointment.

For PTSD, some basic questions to ask your doctor include:

- What do you believe is causing my symptoms?
- Are there any other possible causes?
- How will you determine my diagnosis?
- Is my condition likely temporary or chronic?
- Do you recommend treatment? If yes, with what types of therapy?
- I have other health problems. How should I manage these together with PTSD?
- How soon do you expect my symptoms to improve?
- Does PTSD increase my risk of other mental health problems?
- Should I see a mental health specialist?
- Do you recommend any temporary changes at home, work or school to encourage recovery?

- Would it help my recovery to tell my teachers or work colleagues about my diagnosis?
- 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 doctor, don't hesitate to ask questions during your appointment.

What to expect from your doctor

Being ready to answer your doctor's questions may reserve time to go over any points you want to talk about in-depth. You should be prepared to answer the following questions from your doctor:

- What are your symptoms?
- When did you or your loved ones first notice your symptoms?
- Have you ever experienced or witnessed an event that was life-threatening to you or someone else?
- Have you ever been physically, sexually or emotionally harmed?
- Do you have disturbing thoughts, memories or nightmares of the trauma you experienced?
- Do you ever feel as if you are reliving the traumatic event, through flashbacks or hallucinations?
- Do you avoid certain people, places or situations that remind you of the traumatic experience?
- Have you lost interest in things or felt numb?
- Do you feel jumpy, on guard, or easily startled?
- Do you frequently feel irritable or angry?
- Are you having trouble sleeping?
- Is anything happening in your life right now that is making you feel unsafe?
- Have you been having any problems at school or work?
- Have you been having problems in your personal relationships?
- Have you ever thought about harming yourself or others?
- Do you drink alcohol or use illegal drugs? How often?
- Have you been treated for other psychiatric symptoms or mental illness in the past? If yes, what type of therapy was most beneficial?

What you can do in the meantime

There are steps you can take to improve your ability to cope while you're waiting for your appointment with a doctor. What works best for you is likely to be highly personal. Talking with friends or family about your feelings or trauma you've experienced may be helpful. However, don't push yourself to share more than you can actually tolerate.

You may find it especially helpful to talk with others who have gone through a traumatic experience similar to yours. Your doctor or mental health professional may be able to recommend a support group in your area. Exercise and relaxation techniques such as yoga or meditation also may improve your symptoms.

Tests and diagnosis

Post-traumatic stress disorder is diagnosed based on signs and symptoms and a thorough psychological evaluation. Your doctor or mental health professional will ask you to describe the signs and symptoms you're experiencing — what they are, when they occur, how intense they are and how long they last. Your doctor also might ask you to describe the event that led up to your symptoms. You may also have a physical exam to check for any other medical problems.

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

Criteria for post-traumatic stress disorder to be diagnosed include:

- You experienced or witnessed an event that involved death or serious injury, or the threat of death or serious injury
- Your response to the event involved intense fear, horror or a sense of helplessness
- You relive experiences of the event, such as having distressing images and memories, upsetting dreams, flashbacks or even physical reactions
- You try to avoid situations or things that remind you of the traumatic event or feel a sense of emotional numbness
- You feel as if you're constantly on guard or alert for signs of danger, which may make it difficult to sleep or concentrate
- Your symptoms last longer than one month
- The symptoms cause significant distress in your life or interfere with your ability to go about your normal daily tasks

Treatments and drugs

Post-traumatic stress disorder treatment can help you regain a sense of control over your life. With successful post-traumatic stress disorder treatment, you can also feel better about yourself and learn ways to cope if any symptoms arise again.

Post-traumatic stress disorder treatment often includes both medication and psychotherapy. Combining these treatments can help improve your symptoms and teach you skills to cope better with the traumatic event — and life beyond it.

Medications

Several types of medications can help symptoms of post-traumatic stress disorder improve.

- **Antipsychotics.** In some cases, you may be prescribed a short course of antipsychotics to relieve severe anxiety and related problems, such as difficulty sleeping or emotional outbursts.
- **Antidepressants.** These medications can help symptoms of both depression and anxiety. They can also help improve sleep problems and improve your concentration. The selective serotonin reuptake inhibitor (SSRI) medications sertraline (Zoloft) and paroxetine (Paxil) are FDA-approved for the treatment of PTSD.
- **Anti-anxiety medications.** These drugs also can improve feelings of anxiety and stress.
- **Prazosin.** If your symptoms include insomnia or recurrent nightmares, a drug called prazosin (Minipress) may help. Prazosin, which has been used for years in the treatment of hypertension, also blocks the brain's response to an adrenaline-like brain chemical called norepinephrine. Although this drug is not specifically approved for the treatment of PTSD, prazosin may reduce or suppress nightmares in many people with PTSD.

You and your doctor will need to work together to figure out the best treatment, with the fewest side effects, for your symptoms and situation. You may see an improvement in your mood and other symptoms within a few weeks.

Be sure to tell your health care professional about any side effects or problems you have with the medications, as you may be able to try something different.

Psychotherapy

Several types of therapy may be used to treat both children and adults with post-traumatic stress disorder. You may try more than one, or combine types, before finding the right fit for you. You may also try individual therapy, group therapy or both. Group therapy can offer a way to connect to others going through similar experiences.

Some types of therapy used in PTSD treatment include:

Cognitive therapy. This type of talk therapy helps you recognize the ways of thinking (cognitive patterns) that are keeping you stuck — for example, negative or inaccurate ways of perceiving normal situations.

In PTSD treatment, cognitive therapy often is used along with a behavioral therapy called exposure therapy.

Exposure therapy. This behavioral therapy technique helps you safely face the very thing that you find frightening, so that you can learn to cope with it effectively. A new approach to exposure therapy uses "virtual reality" programs that allow you to re-enter the setting in which you experienced trauma — for example, a "Virtual Iraq" program.

Eye movement desensitization and reprocessing (EMDR). This type of therapy combines exposure therapy with a series of guided eye movements that help you process traumatic memories.

All these approaches can help you gain control of lasting fear after a traumatic event. The type of therapy that may be best for you depends on a number of factors that you and your health care professional can discuss.

Medications and psychotherapy also can help you if you've developed other problems related to your traumatic experience, such as depression, anxiety, or alcohol or substance abuse. You don't have to try to handle the burden of PTSD on your own.

Alternative medicine

Acupuncture may be helpful in improving the symptoms of PTSD. More research is needed to fully understand the safety and effectiveness of acupuncture as a treatment for PTSD. Talk with your doctor if you're interested in adding acupuncture to your treatment plan.

Coping and support

If stress and other problems caused by a traumatic event affect your life, seeing your health care professional is an important first step. But you can take actions to help yourself cope as you continue with treatment for post-traumatic stress disorder. Things you can do include:

Follow your health professional's instructions. Although it may take a while to feel benefits from therapy or medications, most people do recover. Remind yourself that it takes time. Healing won't come overnight. Following your treatment plan will help move you forward.

Take care of yourself. Get enough rest, eat a balanced diet, exercise and take time to relax. Avoid caffeine and nicotine, which can worsen anxiety.

Don't self-medicate. Turning to alcohol or drugs to numb your feelings isn't healthy, even though it may be a tempting way to cope. It can lead to more problems down the road and prevent real healing.

- **Break the cycle.** When you feel anxious, take a brisk walk or jump into a hobby to re-focus.
- **Talk to someone.** Stay connected with supportive and caring family, friends, faith leaders or others. You don't have to talk about what happened, if you don't want to. Just sharing time with loved ones can offer healing and comfort.
- **Consider a support group.** Many communities have support groups geared to specific situations. Ask your health care professional for help finding one, look in your local phone book or contact your community's social services system.

When someone you love has PTSD

Post-traumatic stress disorder can significantly strain the emotional and mental health of the affected person's caregivers and loved ones. In fact, the term "compassion fatigue" was coined to describe the feelings, such as depression and helplessness, that commonly develop in those close to a person with PTSD.

Hearing about the trauma that led to your loved one's PTSD may be extremely painful for you, and may cause you to relive difficult events in your own life. The person you love may seem like a different person than you knew before the trauma — angry and irritable, for example, or withdrawn and depressed.

If someone you love has PTSD, you may find yourself avoiding his or her attempts to talk about the trauma or feeling hopeless that your loved one will get better. At the same time, you may feel guilty that you can't fix your loved one or hurry up his or her process of healing.

In order to take care of yourself and your loved one, it's critical that you make your own mental health a priority. Eat right, exercise and rest. Continue to take time alone or with friends, doing activities that help you recharge. If you continue to have difficulty coping, talk with your doctor. He or she may refer you to a therapist who can help you work through your emotions.

Prevention

After surviving a traumatic event, many people have PTSD-like symptoms at first, such as being unable to stop thinking about what's happened. Fear, anxiety, anger, depression, guilt — all are common reactions to trauma. Although you may not want to talk about it to anyone or you don't want to even think about what's happened, getting support can help you recover. This may mean turning to supportive family and friends who will listen and offer comfort. It may mean that you seek out a mental health professional for a brief course of therapy. Some people also may find it helpful to turn to their faith community or a pastoral crisis counselor.

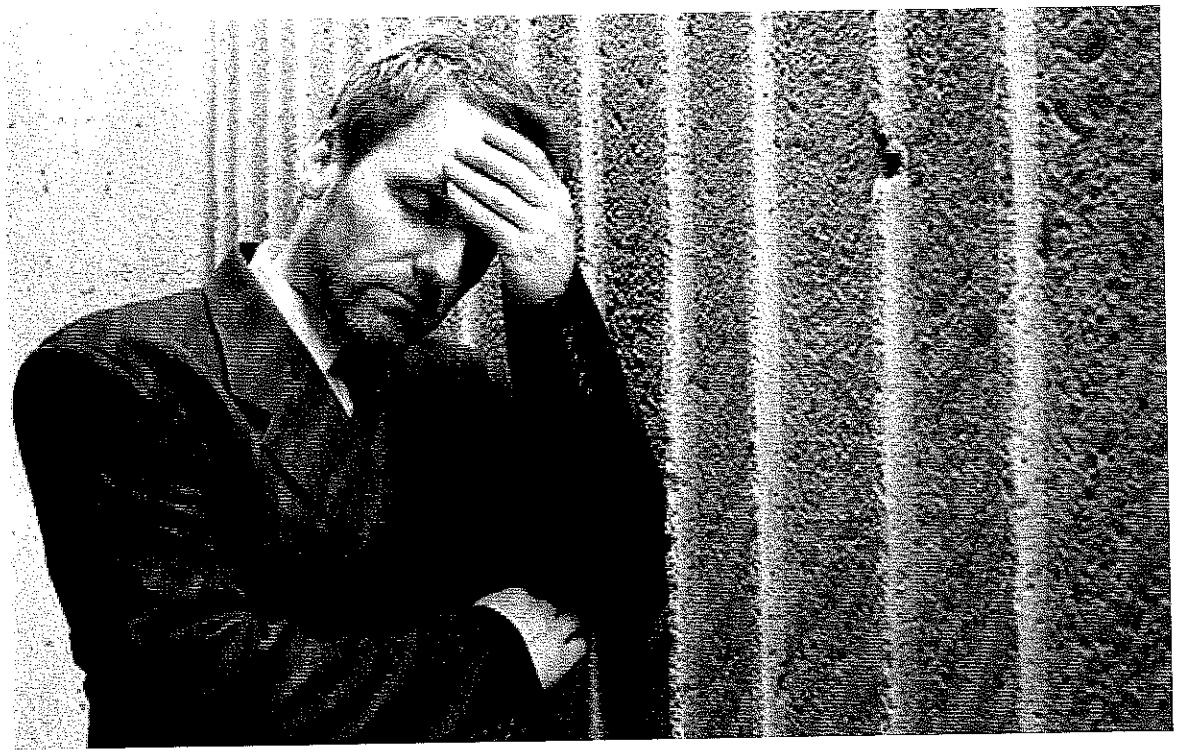
However you choose to get support and help, doing so can help prevent normal stress reactions from getting worse and developing into post-traumatic stress disorder. Getting support may also help prevent you from turning to unhealthy coping methods, such as alcohol use.

References

DS00246 April 8, 2011

Post Traumatic Stress Disorder: Long Term Effects

By dan • Sep 15th, 2009 • Category: Featured



Post Traumatic Stress Disorder was called "shell shock" during World War I. The term we use today – PTSD – is less vivid and more clinical-sounding. But it refers to the same phenomenon: psychological and physical after-effects associated with traumatic experiences.

The disorder has proven difficult to study because its symptoms and their severity vary widely and often present differently in women than they do in men.

Though PTSD is still most popularly associated with veterans of military combat, it is believed to affect civilians who suffer severe abuse or other heightened forms of psychological and physical stress, such as sexual abuse or car accidents.

A new study published in the September 2009 Archives of General Psychiatry focused on soldiers returning from combat in the Iraq war. The study found that PTSD causes chemical changes in the brain that can linger for at least a year. Other studies have found that symptoms persist well beyond one year.

PTSD victims tend to be in a continuous state of heightened alertness. The trauma that precipitates the disorder essentially conditions them to be ever-ready for a life threatening situation to arise at any moment. As a result, they have increased reaction times, which might be

characterized as a positive short-term gain. But the continuous release of brain chemicals that accompany this reaction time – and their inability to control when this heightened reactivity will occur – take psychological and biological tolls on PTSD victims over time.

The 2009 study also found that increased alertness was accompanied by a decrease in the ability to learn, retain or even pay attention to information not associated with combat situations. The chemical shift essentially redirects their brains to focus abnormally on immediate survival.

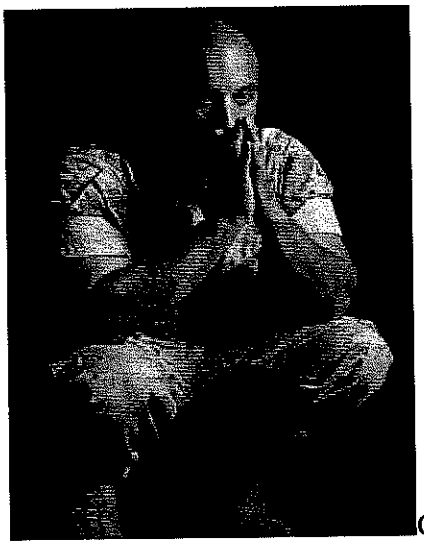
While the 2009 study did not find the soldiers' neurological changes had any connection with depression or alcohol and drug abuse, other studies over the past 25 years have found addiction and chronic depression to be common in PTSD sufferers.

Other long term side effects of PTSD include an inability to sleep, vivid nightmares and obsessive thoughts surrounding the trauma. Sufferers are also tormented by an "alarm reaction" (http://www.childtrauma.org/ctamaterials/memory_states.asp), becoming jittery or even terrified when loud noises resemble sounds they associate with the trauma. For example, combat veterans often react as if they are being fired at by guns when they are startled by the noise of a car backfiring. Repeated instances of the alarm reaction tax the autonomic nerve system over time – which could result in decreased motor skills and coordination.

Sleep deprivation and the physical strain of prolonged hyper-alertness may eventually lead to a weakening of the body's immune system. Other physical complications like cardiovascular disease could be directly related to the toll PTSD takes on the sufferer's body over an extended period of time.

Emotional disorders like depression seem to be more common in female PTSD sufferers, while men appear more likely to develop addiction problems. Both genders have been found to suffer from panic attacks and violent fits anger. They have difficulty developing or maintaining relationships with other people.Continuous study will give us a clearer picture of what PTSD does to its sufferers in the long term.

VA STUDY: Soldiers with PTSD More Likely to Experience Long-Term Psychological Effects



Combat-related post-traumatic stress disorder (PTSD) symptoms appear to be associated with longer-term physical (headache, tinnitus), emotional (irritability) and cognitive (diminished concentration or memory) symptoms, according to a report in the January issue of Archives of General Psychiatry, one of the JAMA/Archives journals. Conversely, concussion/mild traumatic brain injuries (MTBI) do not appear to have long-term negative effects on troops.

"Nearly 2 million troops have been deployed to Operation Enduring Freedom and Operation Iraqi Freedom since 2001," the authors write as background information in the article. "High levels of combat exposure have been documented among Operation Enduring Freedom/Operation Iraqi Freedom-deployed soldiers, with increased risk of blast exposure and injury and development of post-deployment mental and physical health problems."

Although there has been a focus by the Department of Defense and the Veterans Administration on early identification of concussion, little data exist on the long-term, functional effects of concussion on returning soldiers. To examine the associations between concussion and PTSD symptoms reported during deployment and long-term psychosocial outcomes, Melissa A. Polusny, Ph.D., of the Minneapolis Veterans Affairs Health Care System and the University of Minnesota Medical School, Minneapolis, and colleagues, surveyed 953 combat-deployed U.S. National Guard Soldiers.

Consistent with demographics of infantry soldiers deployed to Iraq, 92.5 percent of participants were male, 87.1 percent were white, 46.4 percent were younger than 30 and 86.5 percent were enlisted rank. Soldiers were surveyed in Iraq one month before returning home, and again one year later.

At the time of the first survey, 7.6 percent of all participating soldiers met criteria for probable PTSD. This rate increased to 18.2 percent at the time of the second survey. Change in PTSD symptoms between the two surveys was no different for those who reported concussion in the first survey and those who did not. Reporting of PTSD at the time of survey one strongly predicted post-deployment symptoms, including memory and balance problems, difficult concentrating and irritability.

The rate of reported concussion at the time of the first survey was 9.2 percent and increased to 22 percent at the second survey. Of those reporting concussion at the first survey, 30.2 percent had probable PTSD at the time of the second survey. Additionally, of the 22 percent who reported concussion during the second survey, 30.4 percent also had probable PTSD at that time. Soldiers with a history of reported concussion were also more likely to report post-concussive symptoms after deployment; however, after adjusting for PTSD symptoms, the association between these symptoms and concussion was not significant.

"Although combat-related PTSD was strongly associated with post-concussive symptoms and psychosocial outcomes one year after soldiers return from Iraq, there was little evidence of a long-term negative impact of concussion/mild traumatic brain injury history on these outcomes after accounting for PTSD," the authors conclude. "These findings and the two-fold increase in reports of deployment-related concussion/MTBI history have important implications for screening and treatment."

Source: **US Dept of Veteran Affairs**

PolicePTSD.com is the webs best resource for Police or Combat related traumatic stress. Regardless of your occupation or critcal incident PolicePTSD.com and its members can help.

Conventional Treatments 4 PTSd

Conventional therapy for PTSD typically spans several years and involves both individual and group therapy. Of the many varieties of therapy available for PTSD, almost all emphasize exposure to the frightening stimulus. This is a common treatment among many anxiety disorders.

The four most common treatments for PTSD include psychodynamic theory (Foa, Rothbaum, & Molnar, 1995), cognitive-behavior therapy (Foa, et al. 1995), pharmacotherapy (Friedman & Southwick, 1995), and group therapy (Foa, et al., 1995). There is alos the controversial eye-movement desensitization and reproccessing therapy (EMDR) (Shapiro, 1989). Because of the unique involvement of the trauma in the etiology of the disorder, therapists generally agree that therapy can be divided into three phases (Friedman, 1996):

- establishing trust, safety, and "earning a right to gain access" to carefully guarded traumatic material (Lindy, 1993).
- trauma-focused therapy, exploring traumatic material in depth, titrating intrusive recollections with avoidant/numbing symptoms (Horowitz, 1986).
- helping the patient disconnect from the trauma and reconnect with family, friends , and society.

Psychodynamic Therapy

Psychodynamic psychotherapy focuses on the traumatic event. The patient recounts the event to a caring, empathetic listener (the therpaist). This helps the patient develop more intense emotions (Marmar, Weiss, & Pynoos, 1995). The therapist helps the patient identify current life situaions that exacerbate PTSD symptoms.

Cognitive-Behavioral Therapy

The two cognitive-behavioral approaches include exposure therapy and cognitive-behavior therapy. Exposure therapy employs techniqies such as systematic desensitizaion and imaginal flooding. It should be noted that, due to the nature of the trauma in PTSD, in-vivo flooding is never used. Cognitive-behavioral therapy includes techniques designed to manage anxiety. These include relaxation training, stress inoculation training, cognitive restructuring, breathing retraining, biofeedback, social skills training, and distraction techniques (Fairbank, De Good, & Jenkins, 1981; Foa, et al., 1995; Hyer, 1994; Muse, 1986).

Pharmacotherapy

Practically speaking, the use of drugs in PTSD treatment can be very effective for symptomatic relief of anxiety, depression, and insomnia (Friedman, 1991; Murburg, 1994; Southwick, Krystal, Johnson, et al., 1992). Improvement has been achieved with imipramine, amitriptyline, phenelzine, fluoxetine (Prozac), and propranolol (Inderal). Southwick, et al. (1992) found that tricyclic antidepressants and monoamine oxidase inhibitors are generally helpful in PTSD patients, especially with regard to intrusion and avoidant

symptoms. Fluoxetine and amitriptyline have also shown efficacy against avoidant symptoms (Davidson, Kudler, Smith, et al., 1990; Fesler, 1991; Van der Kolk, Dryfus, Michaels, et al., 1994).

While no single drug has emerged as a treatment for the actual post-traumatic disorder, drug therapies are clearly useful for the relief of overwhelming symptoms. The alleviation of these symptoms may make it possible for the client to participate in individual and/or group therapy.

Group Therapy

Group therapy sessions (often called "rap groups") developed following the Vietnam War in response to pressure from the American Civil Liberties Union and Veterans-rights organizations. They typically employ many of hte same techniques as exposure therapy. These groups provide mutual support from others who have experienced similar traumas and encourage the patient to begin confronting their traumas (Davidson & Neale, 1998).

Eye-Movement Desensitization and Reprocessing (EMDR)

Shapiro (1989) has developed a controversial treatment for PTSD called eye-movement desensitization and reprocessing (EMDR). In EMDR the patient is instructed to imagine a painful traumatic memory while visually focusing on the rapid movements of the therapist's finger. Shapiro believes that such saccadic eye movements reprogram brain function so that the emotional impact of the trauma can finally be integrated. Many have suggested that EMDR is really exposure therapy and that the saccadic movements are irrelevant (Pitman, Orr, Altman, et al., 1993). Currently, there is little well-controlled empirical support for EMDR.

The Use of Medical Cannabis to Treat PTSD

by

Dr. Sue Sisley

Clinical Faculty, Internal Medicine/Psychiatry,
St. Joseph's Hospital & Medical Center
Assistant Professor, Arizona Telemedicine Program,
University of Arizona College of Medicine

I. Introduction

Currently, there are approximately 500 suicides a month in patients with Post Traumatic Stress Disorder (PTSD) and all other causes, and over three hundred thousand backlogged disability claims involving PTSD and depression. n1. Those suffering from PTSD also have a reduced quality of life, an increased number of hospitalizations, high frequency of depressions and alcohol drug abuse, and suffer in social, family, and work life. n2. For patients who are treated, many have poor responses to psychotherapy and pharmacological treatment and often turn to alcohol and drugs. n3.

Recent studies demonstrate the potential benefits of the use of cannabis for PTSD. These studies confirm that extinction of aversive memories and the adaptation to stress responses are in part, controlled by endocannabinoids. n4. There are two cannabinoid receptors in the brain, CB1 and CB2. These receptors are activated by: endocannabinoids, which are synthesized internally in the body, cannabinoids derived from the cannabis plant (such as THC), and synthetic cannabinoids that are synthesized in a laboratory. This natural system works much like our natural GABA system. Just as we produce our own endocannabinoids, we produce our own internal GABA, and we use synthetic benzodiazapines that bind to the receptors. Likewise, we have cannabinoid receptors, and we should be using cannabis to modulate them. Cannabinoids can act as a therapeutic target for the treatment of diseases associated with the inappropriate retention of aversive memories, such as PTSD. n5 Furthermore, because of the effects of the cannabis on the stress response, it is likely that potential patients treated with cannabinoids may also benefit from the stress-reversing effects of the drug. n6

While the state of Arizona has acknowledged and approved the use of cannabis for many physical illnesses such as multiple sclerosis and chronic pain, it has failed to acknowledge the use of cannabis for psychological disorders such as PTSD, in which the medical benefits of cannabis are scientifically proven. This reflects unfounded discrimination on mental illness and psychological disorders. As Nancy Pelosi stated in a recent address on health care, "Illness of the brain must be treated just like illness anywhere else in the body." n7. Recently, the federal government has expressly acknowledged this in its passage of the Mental Health Parity and Equalization Act of 2008, mandating that health care providers provide equal treatment for mental disorders/substance abuse disorders as it does for any other physical illness. n8 The stereotype that psychological illnesses are any less debilitating or credible than physical illnesses is unacceptable and has no basis in science or reality. In both cases people are sick and need care; in both cases there are treatments that can relieve them of pain. When

people receive the necessary treatment, people have the potential to get better and be productive and independent citizens. n9.

Hundreds of recent studies indicate that cannabis is an effective treatment for PTSD. Considering the high suicide rate associated with PTSD (50-100 suicides a month for veterans alone) n10, and that accepted psychotherapeutic and pharmacological treatments are often ineffective, n11, it is imperative that PTSD patients have access to another option that is effective, natural, safe, and can be regulated by a doctor. These are people, often veterans, whose chronic psychological trauma, depression, insomnia, and accompanying symptoms cannot be relived by conventional therapy or psychotherapeutics and is worsened by alcohol. n12. In fact, since the U.S. sent more than 1.6 million men and women into combat in Iraq and Afghanistan in 2001, 18.3% of those returning have PTSD or major depression. n13. These patients have fought for our country and are now plagued with horrible memories. Their health and quality of life should be of top priority, and studies show and patients have testified that cannabis is an effective, alternative treatment. Cannabis can help relieve these patients of psychological trauma, it can stop horrible nightmares and stress related sleep disorders, and it can provide them with a better quality of life. n14

II. The Effectiveness of Cannabis as a treatment for PTSD.

a) The endocannabinoid system reverses enhancing effects of stress and helps with retention of aversive memories.

Over the past few years, remarkable advances have been made in our understanding of the endocannabinoid system and its molecular and physiological functions. n15. The potential therapeutic value of cannabinoid modulation is highlighted by the dense expression of the cannabinoid CB1 receptor in regions known to be significant for anxiety and emotional learning, particularly the basolateral amygdala (BLA). n16.

The endocannabinoid system has specific involvement in the habituation component of fear extinction and mediates habituation to repeated stress, suggesting that augmentation of endocannabinoid signaling is a good target for the treatment of affective disorders. n18, n19. The endocannabinoid system has a direct effect on the natural brain's function of dealing with information and can in fact aid the brain in discarding unneeded information. n20.

The functions of the endocannabinoid system are especially relevant to the treatment of conditions associated with retention of aversive memories and stress related disorders, such as PTSD. A recent study examining the cannabinoid receptor activation in the BLA found that it reverses the enhancing effects of environmental stress on inhibitory avoidance (IA) conditioning and its impairing effects on extinction. n21. The study tested rats, known for their love of dark places, who were given electric shocks when entering the darkened region of their cage. Shortly thereafter, the rats became afraid of the dark area and began to remain in the brighter part of the cage. The researchers then

stopped giving the electric shock treatment and the rats returned to the dark area. The length of time between the shocks stopping and the rats returning was measured. In the next phase of the study, a new group of rats were used. These rats were shocked as they entered the dark area of the cage and were placed on an elevated grid. (Most animals, including rats, avoid walking over elevated grids as they find the distressing). It took longer for this group of rats to trust the dark region again. The researchers then tested a third group of rats, who were treated in the same way as the second group, except in this group a synthetic THC-like compound was injected into a the BLA, the region of their brains associated with fear. This medical-marijuana receiving group of rats returned just as quickly to the dark spot in the cage as the rats in group one. n22.

The beneficial effects of cannabinoids in the BA are extremely significant. Specifically, the study found that: 1) cannabinoid receptor activation in the BA blocks the effects of stress on the conditioning and extinction of inhibitory avoidance (IA); 2); cannabinoid receptor stimulation in the BLA reduces stress-induced elevations in corticosteroid levels (this is significant because most people with PTSD show a high secretion of cortisol), n23; and (3) the CB_1 receptor has an extremely important role in the BLA in the extinction of avoidance behavior because the receptor antagonist impairs IA extinction. n24. These findings show that cannabinoid receptor activation can act *to reverse the effects of stress on memory*. These results support a wide therapeutic application for the cannabis cannabinoids in the treatment of conditions in which patients suffer from aversive memories and stress. PTSD patients should be entitled to a treatment that can have such a profound beneficial effect on relieving traumatic memories.

b) Cannabinoids are effective in cessation of nightmares and a reduction in nightmare intensity

The disruption of sleep is often one of the most debilitating parts of PTSD and patients are often unable to find relief through pharmaceutical treatment. n25. Particularly, nightmares and sleep disorders are frequent symptoms of PTSD, with some patients experiencing even more severe problems such as violent or injurious behaviors during sleep, sleep paralysis, and hypnagogic and hypnopompic hallucinations. n26, n27.

Recent studies have shown that cannabis is effective in cessation of nightmares and reduction of nightmare intensity. In a study evaluating the effects of an endocannabinoid receptor agonist on treatment-resistant nightmares in patients diagnosed with PTSD, patients who had continued nightmares despite treatment with conventional anti-depressants and hypnotics were reviewed after treatment with nabilone, an endocannabinoid receptor agonist. n28. A large majority (72%) of patients experienced either cessation of nightmares or a significant reduction in nightmare intensity. n29. Furthermore, patients noted improvement in sleep time, the quality of sleep, and the reduction of daytime flashbacks and night sweats. n30.

These findings are extremely significant because they not only illustrate the many benefits of cannabis on PTSD symptoms, but also that cannabis can be an effective option for patients who are unable to find relief with the currently accepted treatments.

Dr. Tod Mikuriya, psychiatrist, author, and former marijuana research for the National Institute of Health, emphasized the importance of treating sleep deficits in those with PTSD when he explained, "PTSD often involves irritability and inability to concentrate, which is aggravated by sleep deficit. Cannabis use enhances the quality of sleep through modulation of emotional reactivity. It eases the triggered flashbacks and accompanying emotional reactions, including nightmares. The importance of restoring circadian rhythm of sleep cannot be overestimated in the management of PTSD." n31.

c) Cannabinoids promote neurogenesis and produce anxiolytic and antidepressant like effects.

The hippocampus is able to generate new neurons (neurogenesis) throughout the lifespan of mammals. n32. Studies teach us that newborn hippocampal neurons are functionally integrated into the existing circuitry and are positively correlated with learning and memory processes and the developmental mechanisms of stress and mood disorders. n33. Recent studies have shown that chronic treatment with synthetic cannabinoids produces antidepressant and anxiolyic effects. The anxiolytic effects are achieved by promoting hippocampal neurogenesis, which is in turn promoted by cannabinoids. n34. By finding that embryonic and adult rat hippocampal neural stem/progenitor cells are immunoreactive for CB1 cannabinoid receptors, studies demonstrate that cannabinoids can act on CB1 receptors to regulate neurogenesis. n35. This is further corroborated by findings that cannabinoids promote proliferation, but not differentiation, of embryonic hippocampal neural stem/progenitor cells via activation of CB1 receptors combined with G proteins and ERK signaling. n36.

The anti-depressant and anxiolytic effects of cannabis are important as anxiety and depression are frequent symptoms of PTSD and can be very debilitating. n37. It is well-founded that cannabis and its major psychoactive component, (-)-*trans*-Δ^9-tetrahydrocannabinol, have profound effects on mood and can modulate anxiety and mood states. n38. Thus, stimulating the endogenous cannabinoid system with natural cannabinoids could be a major therapeutic target for the treatment of anxiety-related and mood disorders. n39. In a study that looked at treating anxiety with cannabinoids, blocking the CB1 receptor resulted in the rats having more fear, demonstrating that modulation may be useful treatment for blocking fear, as seen in the blockade mice. n40. These results indicate that the endocannabinoid system can be modulated to enhance emotional learning and that endocannabinoid modulators may be therapeutically useful for exposure based psychotherapies such as those used to treat PTSD and other anxiety disorders. n41.

Based on its efficacy alone, cannabis should be considered an acceptable treatment for PTSD. As Dr. Mikuriya said "Cannabis relieves pain, enables sleep, normalizes gastrointestinal function and restores peristalsis. Fortified by improved digestion and adequate rest, the patient can resist being overwhelmed by triggering stimuli. There is no other psychotherapeutic drug with these synergistic and complementary effects." n42. Dr. Mikuriya also emphasizes that cannabis can relieve many other symptoms of PTSD such as physical pain, fatigue, and sleep deficit.

Furthermore, restorative exercise and diet are requisite components of PTSD treatment and depression treatment, and cannabis, unlike some analgesics, sedatives, and benzodiazepines, does not leave the patient too immobile to exercise. n43.

III. PTSD and substance abuse

Many PTSD patients have poor responses to psychotherapy and often turn to alcohol and drugs. n44. Moreover, many suffer from chronic pain and become addicted to opiate pain medications. n45. Due to continuous problems such as depression, anxiety, secondary alcoholism, and substance abuse that PSTD patients suffer from and the numerous poor responses to pharmacological and psychological treatments, alternative treatments such as cannabis are imperative.

While many studies, and many State Departments of Health, cite cannabis use as substance abuse in PTSD patients, they ignore the positive effects of cannabis on the brain and the reality that patients may not be abusing cannabis, but using it as an alternative, effective treatment. Abuse can occur with any drug, including medically prescribed Oxycontin or Vicodin as well as an over the counter drug like Tylenol. But the possibility that these drugs can be abused does not make them illegal. The possibility that some people might abuse cannabis should not make it illegal, when, like these other drugs, it is scientifically proven to effectively treat a condition. In fact, "it is generally appreciated that the use of cannabinoids is related to their positive modulatory effects on brain-rewarding processes along with their ability to positively influence emotional states and remove stress responses." n46.

The differing effects of cannabis and other drugs of abuse on the brain highlight the difference between using a drug as an effective treatment versus substance abuse. Chronic administration of the major drugs of abuse including opiates, alcohol, nicotine, and cocaine has been reported to suppress hippocampal neurogenesis in rats. n47. Unlike these major drugs that inhibit neurogenesis, studies demonstrate that cannabis *promotes* hippocampal neurogenesis. n48. This suggests a role of hippocampal neurogenesis in the initiation, maintenance, and treatment of drug addiction.

The specific effect of the cannabinoid system on the fear response is significant and suggests the potential for long-term relief. n49. Current acceptable treatments such as behavior therapy, on the other hand, are ineffective for many. While behavior therapy for human anxiety disorders is often effective, extinction-like treatments require repeated cue exposures and are vulnerable to reversal by a number of environmental factors, particularly stress. n50. Thus, cannabis has the potential to be an effective alternative to often-ineffective behavior therapy and extinction treatment. n51.

The ineffectiveness of currently acceptable treatments leads to substance abuse. Patients unable to find relief seek it elsewhere, with substances that are not regulated or monitored by a physician. Moreover, psychiatrist-advised use of medical marijuana can actually *help* PTSD patients reduce their alcohol intake. Marijuana addiction potential is

a fraction of that of alcohol (3% vs. 10%). n52. Dr. Christopher Ficthner, section chief for PTSD at Hines V.A. Hospital in Illinois, explained that the use of medical cannabis can reduce the physical and psychological harm for those who self-medicate with alcohol. n53.

IV. New Mexico: Taking the lead in treating PTSD with cannabis.

New Mexico has taken the lead in explicitly allowing people with PTSD to have access to marijuana under its medical marijuana law. PTSD accounts for more patients than any other of the state's 16 eligible debilitating conditions approved for medical marijuana treatment. n54. After a review of the evidence of the effectiveness of marijuana in treating PTSD, health professionals in New Mexico agreed that medical marijuana could be beneficial for patients with PTSD. On the other hand, health officials in Colorado are denying veterans and other patients suffering from PTSD a legitimate, safe, treatment alternative.

The chief medical officer of the Colorado health department said, "There is no evidence of efficacy of marijuana for treatment of PTSD in the medical literature." n50. This statement is outright false, inconsistent with evidence-based medicine and demonstrates ignorance of the hundreds of medical studies on the efficacy of marijuana for PTSD treatment. To deny the enormous body of medical literature is outrageous and offensive to the suffering PTSD patients who are now the victims of the health department's ignorance. Dr. Eve Elting, a New Mexico physician, emphasized the offensiveness of the Colorado Health Department when she said, "It's bad enough they have something that makes life so challenging. On top of that they're discriminated against, made to feel like they're doing something wrong." n55.

New Mexico is not alone in recognizing cannabis as an effective treatment for PTSD. In Canada, the government *pays* for medical marijuana for their veterans, acknowledging that for many, its is more effective than available alternatives, with fewer side effects. n56. In Israel, the Ministry of Health is currently granting licenses for people who have PTSD to use medical marijuana. n57

Even Croatia acknowledges cannabis as a treatment for PTSD. In 2009, Croatia's Supreme Court threw out a jail sentence given to a veteran who used marijuana for his PTSD. n58. This ruling is extremely significant considering Croatia's "zero tolerance" drug policy. In its ruling, the court noted that "the defendant suffers from PTSD, and marijuana relaxes him and helps him to overcome psychological problems." n59.

V. Conclusion

To deny those with PTSD suffering from psychological trauma and terrifying flashbacks access to a natural herb that is scientifically proven to provide them with relief is simply outrageous. By allowing PTSD to be treated with medical marijuana, physicians

can help patients treat their condition with cannabis and assist the patient in using cannabis in a manner that is safe and most effective for the particular patient. Physicians can be re-assured that there is an ample body of medical literature that supports the beneficial use of cannabinoids. Studies teach us that we have our own cannabinoid receptors in our internal cannabinoids, and these should be modulated as they are proven to reverse effects of stress and help with retention of aversive memories, promote neurogenesis, and can reduce nightmares, fear, anxiety, mood disorders and other PTSD symptoms. The importance of the endocannabinoid system and the large body of medical literature supporting the beneficial use of cannabis should be acknowledged. Without the acceptance of cannabis to treat PTSD, patients who cannot find relief with pharmaceuticals and psychotherapy are forced to turn to the streets to have access to cannabis. They are denied the very important role of the doctor in helping them treat their condition. These patients will often turn to substance abuse and many turn to suicide.

We are sending millions of our citizens to Iraq and Afghanistan, and many are coming back afflicted with PTSD and other psychological trauma. n60. We should give them all of the tools available to regain their health. The enormous volume of scientific research and data proves that the use of medical marijuana for PTSD is safe and effective. To deny patients access to a treatment whose efficacy is well founded with scientific evidence is callous and discriminatory at best.

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Cannabis Eases Post Traumatic Stress

By Tod Mikuriya, MD

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William Woodward, MD, of the American Medical Association, testifying before Congress in 1937 against the Prohibition of cannabis, paraphrased a French author (F. Pascal, 1934) to the effect that "Indian hemp has remarkable properties in revealing the subconscious." A Congressman asked, "Are there any substitutes for that latter psychological use?" Woodward replied, "I know of none. That use, by the way, was recognized by John Stuart Mill in his work on psychology, where he referred to the ability of Cannabis or Indian hemp to revive old memories —and psychoanalysis depends on revivivification of hidden memories."

For including that reference to Mill (1867) in the list I have been compiling of conditions amenable to treatment by cannabis, I was ridiculed by Drug Czar Barry McCaffrey in 1996. I stand by its inclusion, of course, and in the 10 years since California physicians have been approving cannabis use by patients, I have found myself appreciating and confirming Mill's insight with every report that cannabis has eased symptoms of post-traumatic stress disorder.

PTSD As a Dissociative Disorder

PTSD—a chronic condition involving horrific memories that cannot be erased—is a dissociative identity disorder. The victims's psyche is fragmented in response to contradictory inputs that cannot be resolved.

Dissociative identity disorders are expressed in bizarre or inappropriate behaviors with intense sadness, fear, and anger. Repression or "forgetting" of the experiences may develop as a coping mechanism.

When traumatic or abusive experiences cannot be integrated into normal consciousness —as in the case of the Jekyl-Hyde behaviors of abusive parents or caregivers— creation of separate personalities or identities may occur.

For example, the woman who was molested by a family member may have both superfically-compliant and repressed-raging identities. The persona that's presented to the world can be swept away when a stimulus calls forth the overwhelming rage.

Such fragmenting of the individual personality causes tremendous stress. The psyche is

incomplete because of repression and denial. The person tries to appear normal and logical but in fact is in turmoil, angry and depressed. The inability to deal directly with emotional issues results in ongoing splitting and compartmentalization of the personality —and in extreme cases, multiple personalities, hysterical fugue (a separate state of consciousness that the individual may not recall), blindness, paralysis, and other functional disruptions.
In 1994 the term "Multiple Personality Disorder" was replaced with the more widely applicable "Dissociative Identity Disorder." As an article (by Foote et al) and editorial (Spiegel) in the April 2006 American Journal of Psychiatry attest, it is only relatively recently that PTSD has been characterized as a dissociative disorder.

Easement by Cannabis
Approximately eight percent of the >9,000 Californians whose cannabis use I have monitored presented with PTSD (309.81) as a primary diagnosis. Many of them are Vietnam veterans whose chronic depression, insomnia, and accompanying irritability cannot be relieved by conventional psychotherapeutics and is worsened by alcohol. For many of these veterans, chronic pain from old physical injury compounds problems with narcotic dependence and side effects of opioids.
Survivors of childhood abuse and other traumatic experiences form a second group manifesting the same symptoms —loss of control and recurrent episodes of anxiety, depression, panic attacks and mood swings, chronic sleep deficit and nightmares.
The brief case reports in the box at the right of this page, unique though the subjects may be, typify two different forms that PTSD takes, both of which are eased by cannabis. The recurrent nightmares from the vet's traumatic episode took on a life of their own, causing nocturnal turmoil and dread. The repressed memories of the sexually abused and beaten woman were symptoms of a fragmented, dissociative response to the disorder.
Easement by cannabis helped both —the vet by toning down his reaction to the nightmares and restoration of his sleep, the woman by modulating her emotional reactivity and permitting her to process and integrate the experience and give up the fragmented, dissociative defense mechanisms, which in due course she no longer needed.

Repression and suppression are defense mechanisms that break down when the victim is fatigued and/or hurting and subjected to triggering stimuli. With cannabis, vegetative functions necessary for recovery, growth and repair are normalized.
Cannabis relieves pain, enables sleep, normalizes gastrointestinal function and restores peristalsis. Fortified by improved digestion and adequate rest, the patient can resist being overwhelmed by triggering stimuli. There is no other psychotherapeutic drug with these synergistic and complementary effects.

Practical Treatment Goals
In treating PTSD, psychotherapy should focus on improving how the patient deals with resurgent symptoms rather than revisitation of the events. Decreasing vulnerability to symptoms and restoring control to the individual take priority over insight as treatment goals. Revisiting the traumatic events without closure and support is not useful but

prolongs and exacerbates pain and fear of loss of control. To repeat: cathartic revisiting of the traumatic experience(s) without support and closure is anti-therapeutic and can exacerbate symptoms.
Physical pain, fatigue, and sleep deficit are symptoms that can be ameliorated. Restorative exercise and diet are requisite components of treatment of PTSD and depression. Cannabis does not leave the patient too immobile to exercise, as do some analgesics, sedatives biodi-azapenes, etc. Regular aerobic exercise (where injury does not interfere) relieves tension and restores control through kinesthetic involvement. Exercise also internalizes the locus of control and diminishes drug-seeking to manage emotional response.

The importance of sound sleep

PTSD often involves irritability and inability to concentrate, which is aggravated by sleep deficit. Cannabis use enhances the quality of sleep through modulation of emotional reactivity. It eases the triggered flashbacks and accompanying emotional reactions, including nightmares.
The importance of restoring circadian rhythm of sleep cannot be overestimated in the management of PTSD. Avoidance of alcohol is important in large part because of the adverse effects on sleep. The short-lived relaxation and relief provided by alcohol are replaced by withdrawal symptoms at night, causing anxiety and the worsening of musculoskeletal pain.
Evening oral cannabis may be a useful substitute for alcohol. With proper dosage, the quality and length of sleep can be improved without morning dullness or hangover. For naïve patients, use of oral cannabis should be gradually titrated upward in a supportive setting; this is the key to avoiding unwanted mental side effects.
I recommend the protocol J. Russell Reynolds M.D., commended to Queen Victoria: "The dose should be given in minimum quantity, repeated in not less than four to six hours, and gradually increased by one drop every third or fourth day, until either relief is obtained, or the drug is proved, in such case to be useless. With these precautions I have never met with any toxic effects, and have rarely failed to find, after a comparatively short time, either the value or the uselessness of the drug."
The advantage of oral over inhaled cannabis for sleep is duration of effect; a disadvantage is the time of onset (45-60 minutes). When there is severe recurrent insomnia with frequent awakening it is possible to medicate with inhaled cannabis and return to sleep.
An unfortunate result of cannabis prohibition is that researchers and plant breeders have not been able to develop strains in which sedative components of the plant predominate.

Modulation, Not Extinction

Although it is now widely accepted that cannabinoids help extinguish painful memories, my clinical experience suggests that "extinguish" is a misnomer.
Cannabis modulates emotional reactivity, enabling people to integrate painful memories —to look at them and begin to deal with them, instead of suppressing them until a stimulus calls them forth with overwhelming force.
The modulation of emotional response relieves the flooding of negative affect. The

skeletal and smooth muscle relaxation decreases the release of corticosteroids and escalating "fight-or-flight" agitation. The modulation of mood prevents or significantly decreases the symptoms of anxiety attacks, mood swings, and insomnia.
While decreasing the intensity of affectual response, cannabis increases introspection as evidenced by the slowing of the EEG after initial stimulation. Unique anti-depressive effects are experienced immediately with an alteration in cognition. Obsessive and pressured thinking give way to introspective free associations (given relaxed circumstances). Emotional reactivity is calmed, worries become less pressing.
Used on a continuing basis, cannabis can hold depressive symptoms at bay. Agitated depression appears to respond to the anxiolytic component of the drug. Social withdrawal and emotional shutting down are reversed.
The short-term memory loss induced by cannabis that may be undesirable in other contexts is therapeutic in controlling obsessive ideation, amplified anxiety and fear of loss of control ignited by the triggering stimuli.

Easement Effects of Cannabis
In treating PTSD, cannabis provides control and amelioration of chronic stressors without adverse side effects. Mainstream medicine treats PTSD symptoms such as hyperalertness, insomnia, and nightmares with an array of SSRI and tricyclic anti-depressants, sedatives, analgesics, muscle relaxants, etc., all of which provide inadequate relief and have side effects that soon become problematic. Sedatives, both prescribed and over-the-counter, when used chronically, commonly cause hangovers, dullness, sedation, constipation, weight gain, and depression. See chart at right.
Cannabis is a unique psychotropic immunomodulator which can best be categorized as an "easement." Modulating the overwhelming flood of negative affect in PTSD is analogous to the release of specific tension, a process of "unclenching" or release. As when a physical spasm is relieved, there is a perception of "wholeness" or integration of the afflicted system with the self. For some, this perceptual perspective is changed in other ways such as distancing (separating the reaction from the stimulus, which can involve either lessening the reaction, as with modulation, or repressing/suppressing the memory; walling it off; forgetting).
The modulation of emotional response relieves the flooding of negative affect. The skeletal and smooth muscle relaxation decreases the sympathetic nervous reactivity and kindling component of agitation. Fight/flight responses and anger symptoms are significantly ameliorated. The fear of loss of control diminishes as episodes of agitation and feeling overwhelmed are lessened. Experiences of control then come to prevail. Thinking is freed from attachment to the past and permitted to fix on the present and future. Instead of being transfixed by nightmares, the sufferer is freed to realize dreams.

Based on both safety and efficacy, cannabis should be considered first in the treatment of post-traumatic stress disorder. As part of a restorative program with exercise, diet, and psychotherapy, it should be substituted for "mainstream" anti-depressants, sedatives, muscle relaxants, tricyclics, etc.

Case Report:
A 52-year-old retired executive secretary brought her 20-year-old daughter along to her follow-up interview two years after starting cannabis therapy. During her initial visit she had not disclosed fully the causality of her chronic depression with symptoms of PTSD (nightmares, chronic insomnia, dissociative episodes, rage).
She was experiencing loss of emotional control with crisis psychiatric interventions. Hypervigilance characterized her presentation; she described herself as being "all clenched up."
On follow-up she reported being able to recover and process repressed memories of sexual abuse from age five to 15 by her father (a preacher) and having been beaten by her enraged mother. She reported the diminution and cessation of dissociative reactions to the painful memories. This permitted her to process and resolve —or come to an accord with— these unthinkable memories. Her continuing psychotherapy focused on these issues. She no longer experienced episodes of loss of control. She was able to relax her hypervigilance. Her self-esteem was significantly improved and she seemed happy and optimistic
Her daughter confirmed that her mother was less irritable and more emotionally available since starting cannabis therapy. Both described improvement in their relationship.

Case Report:
A 55-year-old disabled male veteran had been a naval air crewman on patrol during the Vietnam war. A P2V turbo-prop engine failed to reverse properly on landing. A propeller broke loose, pierced the fuselage, and instantly killed his crew mate who was two feet away. He brought a large binder of documentation of the incident.
His PTSD was expressed primarily through a haunting, recurrent flashback nightmares that replayed the traumatic event. Attendant were the feelings of being emotionally overwhelmed. Sleep deficit was a salient aggravating factor for increasing vulnerability. Cannabis restored sleep and controlled nightmares. Depression and irritability had been eased.

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Cannabinoids Prevent the Development of Behavioral and Endocrine Alterations in a Rat Model of Intense Stress

Eti Ganon-Elazar[1] and Irit Akirav*[,1]

[1]*Department of Psychology, University of Haifa, Haifa, Israel*

Cannabinoids have recently emerged as a possible treatment of stress- and anxiety-related disorders such as post-traumatic stress disorder (PTSD). Here, we examined whether cannabinoid receptor activation could prevent the effects of traumatic stress on the development of behavioral and neuroendocrine measures in a rat model of PTSD, the single-prolonged stress (SPS) model. Rats were injected with the CB1/CB2 receptor agonist WIN55,212-2 (WIN) systemically or into the basolateral amygdala (BLA) at different time points following SPS exposure and were tested 1 week later for inhibitory avoidance (IA) conditioning and extinction, acoustic startle response (ASR), hypothalamic-pituitary-adrenal (HPA) axis function, and anxiety levels. Exposure to SPS enhanced conditioned avoidance and impaired extinction while enhancing ASR, negative feedback on the HPA axis, and anxiety. WIN (0.5 mg/kg) administered intraperitoneally 2 or 24 h (but not 48 h) after SPS prevented the trauma-induced alterations in IA conditioning and extinction, ASR potentiation, and HPA axis inhibition. WIN microinjected into the BLA (5 μg/side) prevented SPS-induced alterations in IA and ASR. These effects were blocked by intra-BLA co-administration of the CB1 receptor antagonist AM251 (0.3 ng/side), suggesting the involvement of CB1 receptors. These findings suggest that (i) there may be an optimal time window for intervention treatment with cannabinoids after exposure to a highly stressful event, (ii) some of the preventive effects induced by WIN are mediated by an activation of CB1 receptors in the BLA, and (iii) cannabinoids could serve as a pharmacological treatment of stress- and trauma-related disorders. *Neuropsychopharmacology* (2012) **37,** 456–466; doi:10.1038/npp.2011.204; published online 14 September 2011

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INTRODUCTION

The cannabinoid system is part of the complex circuitry that regulates anxiety and stress and is a crucial mediator of emotional learning (Marsicano *et al*, 2002; Viveros *et al*, 2005; Patel *et al*, 2005, 2005a; Laviolette and Grace, 2006; Varvel *et al*, 2007; Ganon-Elazar and Akirav, 2009; Lutz, 2009; Hill *et al*, 2009; Abush and Akirav, 2010; Akirav, 2011). Recently, it has been suggested that the cannabinoid system could represent a therapeutic target for the treatment of stress- and anxiety-related disorders such as post-traumatic stress disorder (PTSD) (Porter and Felder, 2001; Marsicano *et al*, 2002; Kathuria *et al*, 2003). In humans, potential benefits of the synthetic cannabinoid nabilone were demonstrated in PTSD patients (Fraser, 2009).

The single-prolonged stress (SPS) model (Liberzon *et al*, 1997) is a valuable tool to examine the neural and endocrine circuitry related to the effects of intense stress on fear learning and regulation of stress responsivity that are relevant to PTSD. Exposure to SPS involves three different stress paradigms and, after an undisturbed period of 7 or 14 days, rats show enhanced negative feedback on the hypothalamic-pituitary-adrenal (HPA) axis and an exaggerated acoustic startle response (ASR) (Liberzon *et al*, 1997; Khan and Liberzon, 2004; Kohda *et al*, 2007). Enhanced ASR and HPA-negative feedback have been reliably observed in patients with PTSD (Shalev *et al*, 1992; Yehuda *et al*, 1993; Orr *et al*, 1997).

SPS exposure also results in impaired extinction of contextual fear (Yamamoto *et al*, 2007). Impaired fear extinction is a major symptom of anxiety disorders caused by emotional trauma, such as PTSD. Moreover, it has been suggested that the continued ability of conditioned stimuli to elicit traumatic memories and flashbacks in PTSD results from a deficit in the neural mechanisms involved in extinction (Charney *et al*, 1993). PTSD patients also demonstrate impaired extinction in the aftermath of the trauma (Orr *et al*, 2000; Milad *et al*, 2008). For example, Milad *et al* (2008) have shown deficient extinction recall as measured in skin conductance response in a 2-day fear conditioning and extinction procedure in PTSD patients.

We have recently found that cannabinoid receptor activation in the basolateral amygdala (BLA) using the

*Correspondence: Dr I Akirav, Department of Psychology, University of Haifa, Haifa 31905, Israel, Tel: +972 4 828 8268, Fax: +972 4 824 9157, E-mail: iakirav@psy.haifa.ac.il
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CB1/2 receptor agonist WIN55,212-2 (WIN) can prevent the stress-induced enhancement of inhibitory avoidance (IA) conditioning as well as the stress-induced disruption of IA extinction. This reversal effect was found to be associated with alterations in the HPA axis, as intra-BLA WIN inhibited the stress-induced increase in plasma corticosterone (CORT) levels (Ganon-Elazar and Akirav, 2009). Other studies have suggested that, in non-stressed rats, cannabinoid systemic activation facilitates fear extinction (Chhatwal *et al*, 2005). We have recently shown that WIN administered into the CA1 facilitates IA extinction, with no effect on conditioned avoidance (Abush and Akirav, 2010).

In the current study, we aimed to examine whether cannabinoid receptor activation, using WIN administered systemically or into the BLA, could prevent SPS-induced alterations in IA conditioning and extinction, ASR, HPA axis function, and anxiety levels.

MATERIALS AND METHODS

Subjects

A total of 637 male Sprague Dawley rats (~60 days old, 250–300 g) were used for the experiments. Animals were caged individually at 22 ± 2 °C under 12 h light/dark cycles (lights turned on at 0700 h and turned off at 1900 h). Rats had access to water and laboratory rodent chow *ad libitum*. All experiments were carried out between 0900 and 1500 h.

The experiments were approved by the University of Haifa Ethics and Animal Care Committee, and adequate measures were taken to minimize pain or discomfort.

Drug Treatment

WIN (i.p.: 0.5 mg/kg or 3 mg/kg; intra-BLA: 5 μg/side) and the CB1 receptor antagonist AM251 (0.3 ng/side) (Tocris Bioscience) were dissolved in dimethylsulfoxide (DMSO) and then diluted with saline (0.9% NaCl) and Tween-80 to achieve the final volume. Controls were given the vehicle only (1% DMSO, 1% Tween-80, and 98% saline). Drug concentrations were based on reports in the literature and our previous results (Martin *et al*, 1999; Ganon-Elazar and Akirav, 2009; Campolongo *et al*, 2009; Abush and Akirav, 2010; Segev and Akirav, 2011).

Cannulation and Drug Microinjection

Rats were anesthetized with 4.8 ml/kg Equithesin (2.12% w/v $MgSO_4$, 10% ethanol, 39.1% v/v propylene glycol, 0.98% w/v sodium pentobarbital, and 4.2% w/v chloral hydrate) and implanted bilaterally with a stainless steel guide cannula (23 gauge, thin walled) aimed at the BLA (anteroposterior, −3 mm; lateral, ±5 mm; ventral, −6.7 mm). Animals were allowed 1 week to recuperate before being subjected to experimental manipulations. Microinjection was performed bilaterally in a 0.5-μl volume per side delivered over 1 min. The injection cannula was left in position for an additional 60 s before withdrawal to minimize dragging of the injected liquid along the injection tract. The injection cannula was connected via polyethylene PE20 tubing to a Hamilton microsyringe driven by a microinfusion pump (PHD1000, Harvard Apparatus).

Single-Prolonged Stress

Rats were (i) restrained (7 cm diameter, 21 cm length) for 2 h, (ii) individually placed in a clear acrylic cylinder (20 cm diameter) filled to two thirds (35 cm) of its height with water (24 °C) and forced to swim for 15 min, and (iii) following 15 min recuperation, exposed to the inhalation anesthetic isoflurane (Nicholas Piramal) until the loss of consciousness. A cotton ball soaked in isoflurane was placed in a transparent test tube (to avoid any skin irritation to the rat caused by contact with the soaked cotton) that was placed near the rat's nose until deep anesthesia (indicated by a 50% reduction in respiratory rate and loss of the righting reflex). Control rats remained in a room adjacent to the SPS rats for the duration of SPS and were handled twice for several minutes.

Light-Dark IA

Described in Ganon-Elazar and Akirav (2009). Briefly, animals were placed in the light side of the IA apparatus. For conditioning (*Cond*), when the rat crossed over to the dark side of the box it received a 2 s, 0.7 mA scrambled footshock. After administration of the footshock, the opening between the two sides of the box was blocked, and the rats remained in the dark side for an additional 60 s, after which they were removed back to the home cage.

For extinction, rats were submitted to a non-reinforced test trial every 24 h for 3 days (*Ext1–Ext3*), beginning 24 h after conditioning. The latency to cross over to the dark side was measured. If, after 180 s, the rat did not cross over on its own, the experimenter gently guided it to the dark side. The opening between the two sides of the shuttle was then blocked, no footshock was administered, and the rat was allowed to explore the dark side freely for 180 s, after which it was removed back to the home cage.

Acoustic Startle Response

An acrylic animal holder (9 cm in diameter and 20 cm in length) connected to a piezoelectric accelerometer was placed in a sound proof chamber (25 × 25 × 25 cm). A high-frequency loudspeaker inside the chamber produced both continuous background noise (68 dB) and acoustic stimuli. Illumination was provided by a white bulb located on the ceiling of the chamber. The animals were placed in the holder and a startle session started following a 5-min habituation period. Sound stimuli consisting of a 50-ms burst of 120 dB white noise were delivered 30 times every 30 s. The background noise level of 68 dB was maintained throughout each session. The maximal amplitudes of ASR (%) were measured during a 1-s interval from the second the sound stimuli were delivered and were transferred to a computer using Harvard software (Panlab, Barcelona, Spain). The system allows recording and analysis of the signal generated by the animal movement through a high sensitivity Weight Transducer System. The maximal startle reflex response for each animal was

calculated as the average of the responses to the 30 auditory stimuli.

Open Field

The floor was white and divided by 1 cm wide black lines into 25 squares measuring 10×10 cm each ($50 \times 50 \times 38$) and placed under dim red light (<10 lux) (Ganon-Elazar and Akirav, 2009). Recordings were made of the time the rat spent in the central and the peripheral squares and the total distance covered over a period of 5 min. The open-field arena was thoroughly cleaned between each trial.

Light-Dark Test

Rats were placed in a box divided into two sides that were connected to each other through a small opening. One side was dark (black walls) and the other side was brightly lit (white walls; 80–90 lux). The rat was placed in the dark compartment facing away from the opening to the light side, and the number of entries into the light side and time spent in the light side were measured for 5 min.

Corticosterone Measurements and Dexamethasone Suppression Test

To test alterations in resting CORT levels following SPS, CORT was measured 2 min, 2, 24 h, or 1 week after SPS exposure.

To assess HPA-negative feedback, we used the dexamethasone (Dex) suppression test (DST) (Kohda *et al*, 2007). Rats were exposed to SPS and then administered with vehicle or with WIN at different time points. One week after SPS, Dex (0.05 mg/kg; Sigma, IL) was administered subcutaneously 2 h before a second stress exposure (elevated platform (EP), see below).

Trunk blood was collected after decapitation between 0900 and 1100 h. Samples were centrifuged at 3000 r.p.m. for 20 min at 4 °C. Serum was stored at −80 °C and analyzed for CORT using ELISA kits (DSL).

Elevated Platform

An EP (12×12 cm) stressor was used as the second stress exposure in the DST. Individual animals were placed on an EP for 30 min (height: 150 cm). The EP elicits stress responses in the form of behavioral 'freezing,' that is, immobility for up to 10 min, defecation, and urination (Maroun and Akirav, 2008; Ganon-Elazar and Akirav, 2009).

Histology

Following completion of the behavioral experiments, animals were deeply anesthetized and microinjected into the BLA with 0.5 μl of India ink. Brains were removed and brain slices (60 μm) were examined under a light microscope following Nissl staining to verify the cannula location. Placements of the cannulae were found to be incorrect in <10% of injected rats. Only data from animals with correct cannula placements were included in the analyses (Figure 1).

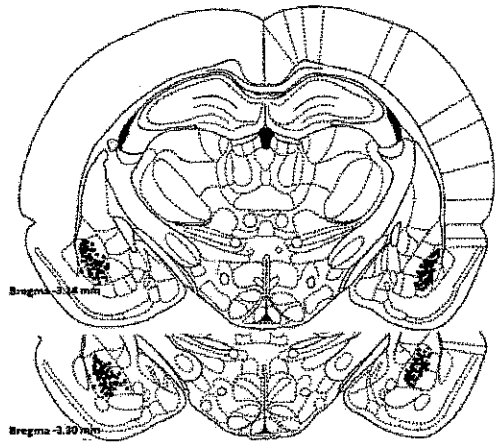

Figure 1 Representative schematic drawings of cannulae tip positions in the BLA. Solid black circles indicate cannula locations in a subset of animals (not all animals are shown in light of the large number of rats involved in the experiments). Two coronal views from positions 3.14 and 3.30 mm posterior to bregma.

Statistical Analysis

The results are expressed as mean values ± SEM. For statistical analysis, *t*-test, one-way ANOVA, and mixed design ANOVA were used. All *post hoc* comparisons were made using the least significant difference multiple-comparison test (LSD). Values are reported as mean values ± SEM.

RESULTS

The Effects of SPS and WIN55,212-2 Administered Systemically on IA

In our first experiment, we examined whether the cannabinoid receptor agonist WIN administered systemically (0.5 mg/kg) 2 min, 2, 24, or 48 h after SPS exposure would prevent the effects of SPS on conditioned avoidance and extinction tested a week later (Figure 2; data are shown in four different panels due to the number of groups involved).

When WIN was administered 2 min after SPS (Figure 2a), mixed ANOVA (groups × days (3×4)) revealed a significant difference between the groups in terms of their latency to enter the dark side of the box ($F_{(2,28)} = 6.10$; $p = 0.006$). A significant within-subject difference in the latency between the days was found ($F_{(1,28)} = 22.31$; $p = 0.0001$) but no significant interaction ($F_{(2,28)} < 1$; NS). One-way ANOVA applied on each day revealed that the significant main effect stemmed from a difference in latency between the groups on Cond ($F_{(2,28)} = 7.28$; $p = 0.003$), Ext1 ($F_{(2,28)} = 4.48$; $p = 0.02$), and Ext2 ($F_{(2,28)} = 3.59$; $p = 0.041$). The SPS + Veh group demonstrated increased latency compared with the two other groups on Cond (Veh: $p = 0.002$; SPS + WIN2 min: $p = 0.005$) and Ext2 (Veh: $p = 0.026$; SPS + WIN2 min: $p = 0.043$). The Veh group demonstrated decreased latency compared with the two other groups on Ext1 (SPS + Veh: $p = 0.01$; SPS + WIN2 min: $p = 0.01$). This suggests that SPS rats (SPS + Veh and SPS + WIN2 min)

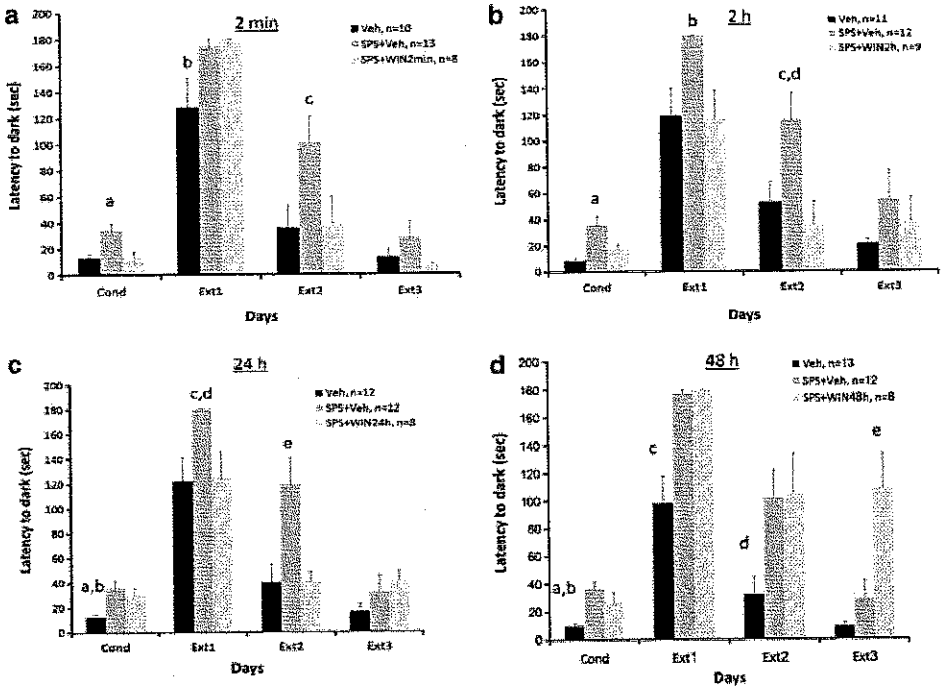

Figure 2 The effects of single-prolonged stress (SPS) exposure and systemic WIN55,212-2 administration on inhibitory avoidance (IA) conditioning and extinction. Rats were administered with vehicle (SPS + Veh) or WIN (SPS + WIN; 0.5 mg/kg) 2 min, 2, 24, or 48 h after SPS exposure and compared with a non-stressed group (Veh). The SPS + Veh groups demonstrated a significantly longer latency until they crossed over to the dark side of the IA apparatus on conditioning (Cond) day, fear retrieval (Ext1) and extinction (Ext2) than the Veh groups. (a) WIN administered 2 min after SPS exposure prevented the SPS-induced alterations in extinction (a, $p<0.01$; c, $p<0.05$: compared with Veh and SPS + WIN2 min; b, $p=0.01$: compared with SPS + Veh and SPS + WIN2 min). (b) WIN administered 2 h after SPS exposure prevented the SPS-induced alterations in conditioned avoidance and extinction (a, $p<0.01$; b, $p<0.05$: compared with Veh and SPS + WIN2 h; c, $p<0.05$: compared with Veh; d, $p<0.01$: compared with SPS + WIN2 h). (c) WIN administered 24 h after SPS exposure prevented the SPS-induced alterations in conditioned avoidance and extinction (a, $p<0.01$: compared with SPS + Veh; b, $p<0.05$: compared with SPS + WIN24 h; c, $p<0.01$: compared with Veh; d, $p<0.05$: compared with SPS + WIN24 h; e, $p<0.01$: compared with Veh and SPS + WIN24 h). (d) WIN administered 48 h after SPS exposure did not prevent the SPS-induced alterations in fear retrieval or extinction (a, $p<0.01$: compared with SPS + Veh; b, $p<0.05$: compared with SPS + WIN48 h; c, $p<0.01$; d, $p<0.05$: compared with SPS + Veh and SPS + WIN48 h; e, $p<0.01$: compared with Veh and SPS + Veh).

show enhanced fear retrieval than the Veh group (Ext1) and that WIN administered 2 min post-SPS prevented the impairing effects of stress on extinction (Ext2).

When WIN was administered 2 h after SPS (Figure 2b), mixed ANOVA (groups × days (3 × 4)) revealed a significant difference between the groups in terms of their latency to enter the dark side of the box ($F_{(2,29)}=5.93$; $p=0.007$). There was no within-subject difference in the latency between the days ($F_{(1,29)}<1$; NS), nor was there an interaction effect ($F_{(2,29)}<1$; NS). However, analyzing the days of extinction (Ext2–3) revealed a significant interaction effect ($F_{(2,29)}=3.34$; $p=0.049$), further suggesting that exposure to SPS impaired extinction. One-way ANOVA applied on each day revealed that the significant main effect stemmed from a difference in latency between the groups on Cond ($F_{(2,29)}=11.21$; $p=0.001$), Ext1 ($F_{(2,29)}=4.77$; $p=0.016$), and Ext2 ($F_{(2,29)}=4.59$; $p=0.019$). The SPS + Veh group demonstrated increased latency compared with the two other groups on Cond (Veh: $p=0.001$; SPS + WIN2 h: $p=0.004$), Ext1 (Veh: $p=0.013$; SPS + WIN2 h: $p=0.014$), and Ext2 (Veh: $p=0.029$; SPS + WIN2 h: $p=0.009$). This suggests that WIN administered 2 h post-SPS prevented the effects of stress on fear retrieval (Ext1) and extinction (Ext2).

When WIN was administered 24 h after SPS (Figure 2c), mixed ANOVA (groups × days (3 × 4)) revealed a significant difference between the groups in terms of their latency to enter the dark side of the box ($F_{(2,29)}=9.13$; $p=0.001$). A significant within-subject difference in the latency between the days was found ($F_{(1,29)}=6.31$; $p=0.018$) but no significant interaction ($F_{(2,29)}<1$; NS). However, analyzing the days of extinction (Ext2–3) revealed a significant interaction effect ($F_{(2,29)}=7.08$; $p=0.003$), further suggesting that exposure to SPS impaired extinction. One-way ANOVA applied on each day revealed that the significant main effect stemmed from a difference in latency between the groups on Cond ($F_{(2,29)}=6.91$; $p=0.003$), Ext1 ($F_{(2,29)}=4.69$; $p=0.017$), and Ext2 ($F_{(2,29)}=7.24$; $p=0.003$). The Veh group demonstrated decreased latency compared with the two other groups on Cond (SPS + Veh: $p=0.001$; SPS + WIN24 h: $p=0.023$). The SPS + Veh group demonstrated increased latency compared with the two other groups on Ext1 (Veh: $p=0.009$; SPS + WIN24 h: $p=0.024$) and Ext2 (Veh: $p=0.002$; SPS + WIN24 h: $p=0.005$). This suggests that WIN administered 24 h post-SPS prevented the effects of stress on fear retrieval (Ext1) and extinction (Ext2).

When WIN was administered 48 h after SPS (Figure 2d), mixed ANOVA (groups × days (3 × 4)) revealed a significant difference between the groups in terms of their latency to enter the dark side of the box ($F_{(2,30)}=15.99$; $p=0.0001$).

There was no within-subject difference in the latency between the days but there was a significant interaction ($F_{(2,30)}=6.91$; $p=0.003$). Also, analyzing the days of extinction (Ext2–3) revealed a significant interaction effect ($F_{(2,30)}=3.79$; $p=0.034$). One-way ANOVA applied on each day revealed that the significant main effect stemmed from a difference in latency between the groups on Cond ($F_{(2,30)}=9.06$; $p=0.001$), Ext1 ($F_{(2,30)}=12.41$; $p=0.001$), Ext2 ($F_{(2,30)}=4.47$; $p=0.02$), and Ext3 ($F_{(2,30)}=7.50$; $p=0.002$). The Veh group demonstrated decreased latency compared with the two other groups on Cond (SPS + Veh: $p=0.001$; SPS + WIN48 h: $p=0.026$), Ext1 (SPS + Veh: $p=0.001$; SPS + WIN48 h: $p=0.001$), and Ext2 (SPS + Veh: $p=0.014$; SPS + WIN48 h: $p=0.021$). The SPS + WIN48 h group demonstrated increased latency compared with the two other groups on Ext3 (Veh: $p=0.001$; SPS + Veh: $p=0.001$). This suggests that WIN administered 48 h post-SPS did not prevent the effects of stress on fear retrieval or extinction.

The Effects of SPS and WIN55,212-2 Administered into the BLA on IA

We have recently shown (Ganon-Elazar and Akirav, 2009) that WIN could prevent the effects of acute stress on IA conditioning and extinction when microinjected into the BLA.

In the current study, we examined whether intra-BLA WIN would prevent the effects of SPS exposure on IA conditioning and extinction and whether this effect is mediated by the CB1 receptor (Figure 3). Rats were exposed to SPS and treated with intra-BLA vehicle or WIN 2 min (Figure 3a) or 2 h (Figure 3b) after SPS exposure. Another set of rats was treated with Vehicle, WIN, AM251, or a combination of WIN + AM251 2 min after SPS exposure (Figure 3c). All rats were tested in the IA paradigm 1 week after SPS.

When WIN was administered into the BLA 2 min after SPS (Figure 3a), mixed ANOVA (groups × days (3 × 4)) revealed a significant difference between the groups in terms of their latency to enter the dark side of the box ($F_{(1,29)}=125.03$; $p=0.0001$). There was a within-subject difference in the latency between the days ($F_{(1,29)}=7.30$; $p=0.011$), with no significant interaction ($F_{(2,29)}<1$; NS). One-way ANOVA applied on each day revealed that the significant main effect stemmed from a difference in latency between the groups on Cond ($F_{(2,29)}=4.33$; $p=0.023$), Ext1 ($F_{(2,29)}=4.25$; $p=0.024$), and Ext3 ($F_{(2,29)}=3.21$; $p=0.05$). The SPS + Veh BLA group demonstrated increased latency compared with the Veh BLA group on Cond ($p=0.007$). The SPS + Veh BLA group demonstrated increased latency compared with the two other groups on Ext1 (Veh BLA: $p=0.035$; SPS + WIN2 min BLA: $p=0.012$) and Ext3 (Veh BLA: $p=0.04$; SPS + WIN2 min BLA: $p=0.039$). This suggests that WIN administered into the BLA 2 min post-SPS prevented the effects of stress on fear retrieval (Ext1) and extinction (Ext3).

When WIN was administered into the BLA 2 h after SPS (Figure 3b), mixed ANOVA (groups × days (3 × 4)) revealed a significant difference between the groups in terms of their latency to enter the dark side of the box ($F_{(1,29)}=231.65$; $p=0.0001$). There was a within-subject difference in the

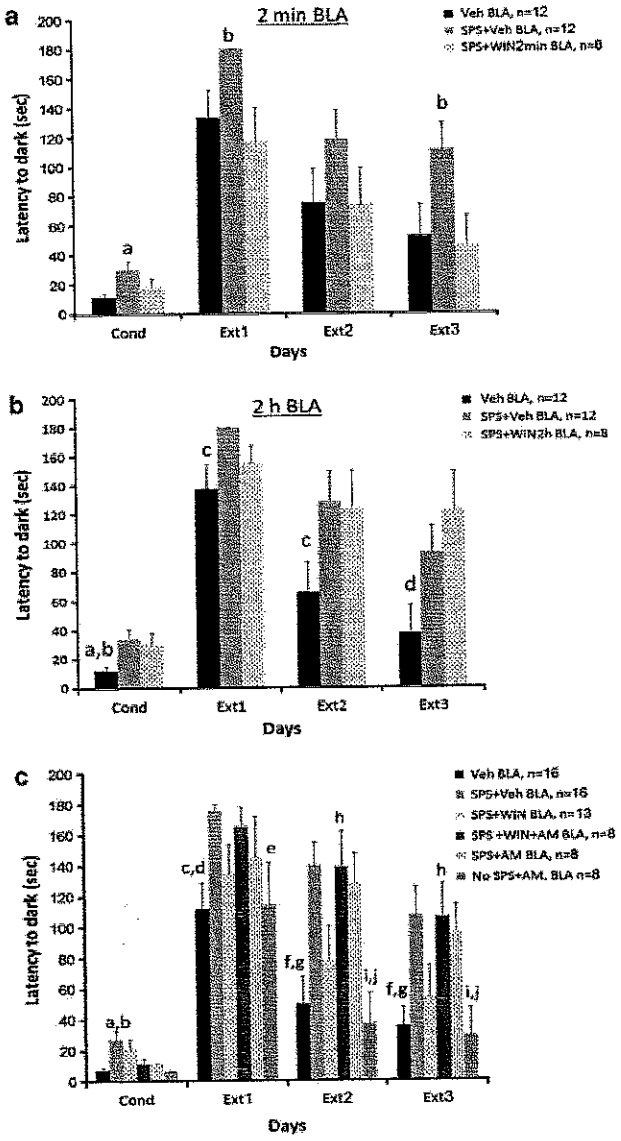

Figure 3 The effects of single-prolonged stress (SPS) exposure and intra-BLA WIN55,212-2 administration on inhibitory avoidance conditioning and extinction. Rats were administered with vehicle or WIN (5 μg/side) or AM251 (0.3 ng/side) or a combination of WIN + AM251 into the BLA. (a) WIN administered into the BLA 2 min after SPS exposure prevented the SPS-induced alterations in conditioned avoidance and extinction (a, $p<0.01$: compared with Veh BLA; b, $p<0.05$: compared with Veh BLA and SPS + WIN2 min BLA). (b) WIN administered into the BLA 2 h after SPS exposure did not prevent the SPS-induced alterations in conditioned avoidance and extinction (a, $p<0.01$: compared with SPS + Veh BLA; b, $p<0.05$: compared with SPS + WIN2 h BLA; c, $p<0.05$: compared with SPS + Veh BLA; d, $p<0.05$: compared with both groups). (c) AM251 (0.3 ng/side), co-administered with WIN (5 μg/side) into the BLA after SPS prevented the effects of WIN on SPS-induced alterations in extinction (a, $p<0.01$: different from Veh and NO SPS + AM; b, $p<0.05$: different from SPS + WIN + AM and SPS + AM; c, $p<0.01$ different from SPS + Veh; d, $p<0.05$: different from SPS + WIN + AM and SPS + AM; e, $p<0.05$: different from SPS + Veh; f, $p<0.01$: different from SPS + Veh and SPS + WIN + AM; g, $p<0.05$: different from SPS + AM; h, $p<0.05$: different from SPS + WIN; i, $p<0.05$: different from SPS + WIN + AM and SPS + AM; j, $p<0.01$: different from SPS + Veh).

latency between the days ($F_{(1,29)} = 4.39$; $p = 0.045$), with no significant interaction ($F_{(2,29)} = 1.35$; NS). One-way ANOVA applied on each day revealed that the significant main effect stemmed from a difference in latency between the groups on Cond ($F_{(2,29)} = 4.57$; $p = 0.019$), Ext1 ($F_{(2,29)} = 3.32$; $p = 0.05$), and Ext3 ($F_{(2,29)} = 4.08$; $p = 0.027$). The Veh BLA group demonstrated decreased latency compared with the two other groups on Cond (SPS + Veh BLA: $p = 0.008$; SPS + WIN2 h BLA: $p = 0.041$) and Ext3 (SPS + Veh: $p = 0.05$; SPS + WIN2 h BLA $p = 0.011$). Also, the Veh BLA group demonstrated decreased latency compared with the SPS + Veh BLA group on Ext1 ($p = 0.016$) and Ext2 ($p = 0.041$). This suggests that WIN administered into the BLA 2 h post-SPS did not prevent the effects of stress on extinction.

Next, we examined whether microinjecting a low dose of the CB1 receptor antagonist AM251 (AM; 0.3 ng/0.5 μl) into the BLA would block the effects of WIN on SPS-induced alterations in IA conditioning and extinction. WIN and AM251 were administered into the BLA alone (SPS + WIN BLA and SPS + AM BLA) or co-administered in a single injection (SPS + WIN + AM BLA) 2 min after SPS (Figure 3c).

Mixed ANOVA (groups × days (6 × 4)) revealed a significant difference between the groups in terms of their latency to enter the dark side of the box ($F_{(5,63)} = 263.59$; $p = 0.0001$). There was a within-subject difference in the latency between the days ($F_{(1,63)} = 20.28$; $p = 0.0001$) and a significant interaction ($F_{(5,63)} = 3.03$; $p = 0.016$). One-way ANOVA applied on each day revealed that the significant main effect stemmed from a difference in latency between the groups on Cond ($F_{(5,63)} = 4.00$; $p = 0.003$), Ext1 ($F_{(5,63)} = 2.74$; $p = 0.027$), Ext2 ($F_{(5,63)} = 5.16$; $p = 0.0001$), and Ext3 ($F_{(5,63)} = 3.51$; $p = 0.007$). On Cond, the SPS + Veh BLA group demonstrated increased latency compared with Veh BLA ($p = 0.001$), SPS + WIN + AM BLA ($p = 0.021$), SPS + AM BLA ($p = 0.020$), and NO SPS + AM BLA ($p = 0.002$). The Veh BLA group demonstrated decreased latency compared with the SPS + Veh BLA, SPS + WIN + AM BLA, and SPS + AM BLA groups on Ext1 ($p = 0.002$, $p = 0.027$, and $p = 0.049$, respectively), Ext2 ($p = 0.001$, $p = 0.004$, and $p = 0.011$, respectively), and Ext3 ($p = 0.003$, $p = 0.014$, and $p = 0.033$, respectively). Hence, SPS rats injected with vehicle, AM, or a combination of AM + WIN after SPS exposure showed increased fear retrieval (Ext1) and impaired extinction (Ext2–3). Importantly, the SPS + WIN + AM BLA group demonstrated increased latencies compared with the SPS + WIN BLA on Ext2 ($p = 0.030$), and Ext3 ($p = 0.038$), indicating that AM251 blocked the effects of WIN on extinction after SPS. The NO SPS + AM BLA group demonstrated decreased latency compared with the SPS + Veh BLA on Ext1 ($p = 0.016$), Ext2 ($p = 0.001$), and Ext3 ($p = 0.007$) and compared with the SPS + WIN + AM BLA and the SPS + AM BLA on Ext2 ($p = 0.004$ and $p = 0.01$, respectively), and Ext3 ($p = 0.021$ and $p = 0.042$, respectively), suggesting that AM by itself had no effect on extinction.

The Effects of SPS and WIN55,212-2 on ASR

Rats were exposed to SPS and then treated with vehicle or with WIN 2 min, 2, 24, or 48 h after SPS exposure. All rats were tested for their ASR levels 1 week after SPS (Figure 4a). One-way ANOVA revealed significant differences in mean ASR levels between the groups (all groups are presented in one graph; 2 min: $F_{(2,27)} = 10.79$, $p < 0.001$; 2 h: $F_{(2,26)} = 23.31$, $p < 0.001$; 24 h: $F_{(2,27)} = 7.88$, $p < 0.002$;

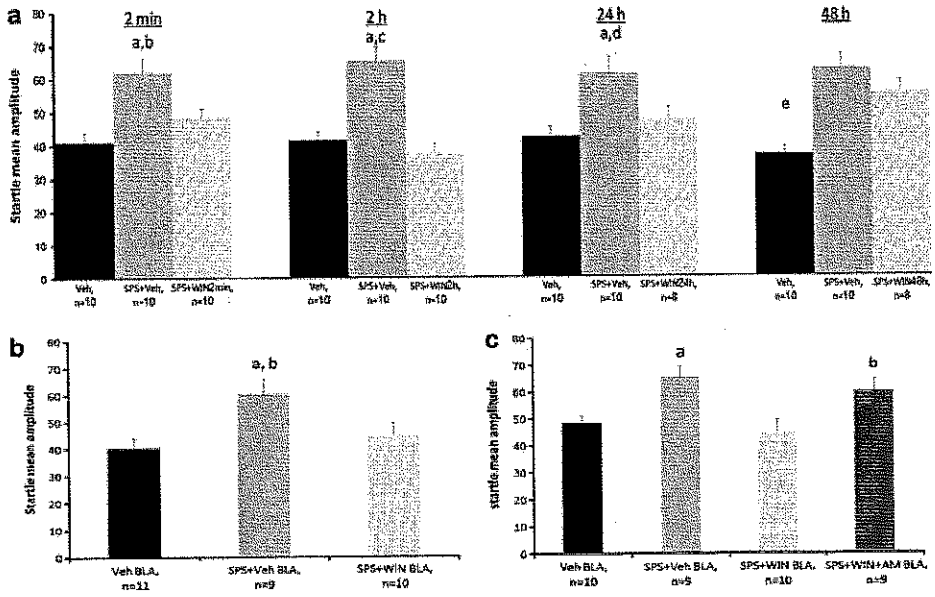

Figure 4 The effects of single-prolonged stress (SPS) exposure and WIN55,212-2 administration on acoustic startle response (ASR). (a) The SPS + Veh groups demonstrated a significantly enhanced ASR than the Veh groups and the SPS + WIN2 min, SPS + WIN2 h and SPS + WIN24 h groups (WIN: 0.5 mg/kg) (a, $p < 0.01$ compared with Veh; b, $p < 0.05$: compared with SPS + WIN2 min; c, $p < 0.01$: compared with SPS + WIN2 h; d, $p < 0.05$ compared with SPS + WIN24 h; e, $p < 0.01$: compared with SPS + Veh and SPS + WIN48 h). (b) WIN administered into the BLA (5 μg/side) 2 min after SPS exposure prevented the SPS-induced enhancement in ASR (a, $p < 0.01$: compared with Veh BLA; b, $p < 0.05$: compared with SPS + WIN BLA). (c) AM251 (0.3 ng/side), co-administered with WIN into the BLA after SPS exposure, blocked the effect of WIN on ASR (a, $p < 0.01$; b, $p < 0.05$: compared with Veh BLA and SPS + WIN BLA).

48 h: $F_{(2,27)} = 7.78$, $p < 0.002$). *Post hoc* comparison revealed that the SPS + Veh group demonstrated significantly potentiated ASR levels compared with the Vehicle groups ($p = 0.001$). Importantly, the SPS + Veh group demonstrated significantly potentiated ASR levels compared with the SPS + WIN2 min ($p = 0.011$), SPS + WIN2 h ($p = 0.001$), and SPS + WIN24 h ($p = 0.022$) groups, suggesting that WIN administered 2 min, 2 or 24 h post-SPS, but not 48 h post-SPS, prevented the enhancing effects of stress on ASR.

Injecting a higher dose of WIN (3 mg/kg) 2 h after SPS exposure also prevented the SPS-induced potentiation of ASR levels. One-way ANOVA revealed significant differences in mean ASR levels between the groups ($F_{(2,24)} = 7.5$, $p < 0.05$). *Post hoc* comparison revealed that the SPS + Veh group demonstrated significantly potentiated ASR levels (63.42 ± 2.81) compared with the Vehicle (40.91 ± 2.81, $p = 0.001$) and SPS + WIN2 h (49.48 ± 5.54) ($p < 0.05$) groups.

Next, we examined whether intra-BLA WIN would prevent the effects of SPS exposure on ASR potentiation. Rats were exposed to SPS and treated with vehicle or with WIN 2 min after SPS exposure. A vehicle group was used as control (Figure 4b). All rats were tested in the ASR paradigm 1 week after SPS. One-way ANOVA revealed significant differences in mean ASR levels between the groups ($F_{(2,30)} = 5.59$; $p < 0.009$). *Post hoc* comparison revealed that the SPS + Veh BLA group demonstrated significantly potentiated ASR levels compared with the Veh BLA ($p = 0.003$) and the SPS + WIN BLA ($p = 0.021$) groups.

Finally, to examine whether intra-BLA AM251 would block the effects of WIN on SPS-induced potentiation of ASR levels, rats were treated with Vehicle, or WIN, or AM251 in combination with WIN 2 min after SPS exposure (Figure 4c).

One-way ANOVA revealed significant differences in mean ASR levels between the groups ($F_{(3,37)} = 5.74$; $p < 0.003$). *Post hoc* comparison revealed that the SPS + Veh BLA group demonstrated significantly potentiated ASR levels compared with Veh BLA ($p = 0.006$) and SPS + WIN BLA ($p = 0.001$). The SPS + WIN + AM BLA group showed a significantly increased ASR compared with Veh BLA ($p = 0.05$) and SPS + WIN BLA ($p = 0.011$). Hence, AM251 microinjected into the BLA blocked the effects of WIN on ASR after SPS.

The Effects of SPS and WIN55,212-2 on HPA Axis Function

In our third experiment, we tested the effects of SPS on HPA axis function by measuring plasma CORT levels at rest and following the DST (Figure 5). CORT levels *at rest* were measured 2 min, 2, 24 h, or 1 week after SPS exposure and were compared with a control group. One-way ANOVA revealed significant differences in CORT levels between the groups ($F_{(4,31)} = 129.82$; $p < 0.001$; Figure 5a). *Post hoc* comparison revealed that the 2-min SPS and 2-h SPS groups demonstrated significantly increased CORT levels compared with the control group ($p = 0.001$ and $p = 0.005$,

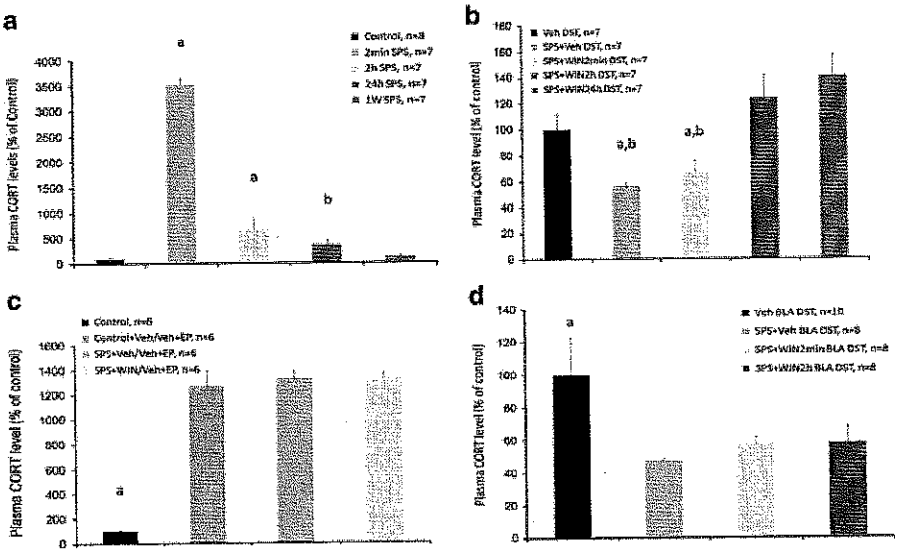

Figure 5 The effects of single-prolonged stress (SPS) and WIN55,212-2 administration on HPA axis function. (a) Rats decapitated 2 min, 2, or 24 h, but not 1 week (1W), after SPS exposure showed significantly increased levels of CORT compared with control rats. Data represent the mean values ± SEM expressed as a percentage of the CORT values of the control rats (132 ± 15 ng/ml) (a, $p < 0.01$; b, $p < 0.05$: compared with control). (b) SPS + Veh DST and SPS + WIN2 min DST groups show significantly enhanced negative feedback on the HPA axis as indicated by reduced CORT levels compared with the other groups following DEX injection and EP exposure (see Materials and methods). Data represent the mean values ± SEM expressed as a percentage of the CORT values of the Veh DST rats (46 ± 6 ng/ml) (a, $p < 0.05$: compared with Veh DST; b, $p < 0.01$: compared with SPS + WIN2 h DST and SPS + WIN24 h DST). (c) Control or SPS rats that were injected with vehicle or WIN and after 1 week treated with vehicle before EP exposure (no Dex) showed significantly increased levels of CORT compared with control rats (control; no exposure to EP or Dex). Data represent the mean values ± SEM expressed as a percentage of the CORT values of the control rats (116 ± 11 ng/ml) (a, $p < 0.01$: compared with all groups). (d) SPS rats injected with vehicle (SPS + Veh BLA DST) or WIN (SPS + WIN2 min BLA DST and SPS + WIN2 h BLA DST) into the BLA show significantly enhanced negative feedback on the HPA axis as indicated by reduced CORT levels compared with the control group (Veh BLA DST) following exposure to EP and DEX injection (see Materials and methods). Data represent the mean values ± SEM expressed as a percentage of the CORT values of the Veh rats (60 ± 13 ng/ml) (a, $p < 0.05$: compared with all groups).

respectively). Since the 24-h SPS group showed high CORT levels (367 ± 79) compared with the control group (100 ± 37), the two groups were compared using an independent samples *t*-test ($t_{(13)} = 4.30$, $p < 0.05$).

For the DST, rats were exposed to SPS and treated i.p. with vehicle or WIN 2 min, 2, or 24 h after SPS exposure. A vehicle group was used as control. One week after handling or SPS, Dex was administered before a second stress exposure, the elevated platform stress, and CORT levels were measured (Figure 5b). Note that in this figure, we are measuring CORT levels *in response to DST*. Reduced levels of CORT in response to DST indicate HPA axis inhibition. One-way ANOVA revealed significant differences in CORT levels between the groups in response to DST ($F_{(4,30)} = 8.19$; $p < 0.001$). *Post hoc* comparison revealed that the SPS + Veh DST group demonstrated significantly reduced CORT levels compared with the Veh DST ($p = 0.021$), SPS + WIN2 h DST ($p = 0.001$), and SPS + WIN24 h DST ($p = 0.0001$) groups. The SPS + WIN2 min DST group demonstrated significantly reduced CORT levels compared with the Veh DST ($p = 0.05$), SPS + WIN2 h DST ($p = 0.003$), and SPS + WIN24 h DST ($p = 0.001$) groups. Hence, the SPS group showed enhanced inhibition of the HPA axis in response to DST; WIN administered 2 or 24 h, but not 2 min, after SPS exposure, prevented this enhanced inhibition.

Next, we demonstrated that SPS exposure by itself does not change the responsiveness to subsequent EP stress when no Dex is injected. Hence, control or SPS rats were injected with vehicle or WIN. After 1 week, rats were treated with vehicle before EP exposure (no Dex) and were compared with a control group (control; with no exposure to EP or Dex) (Figure 5c). One-way ANOVA revealed significant differences in CORT levels between the groups ($F_{(3,20)} = 69.017$; $p = 0.001$). *Post hoc* comparison revealed that the control group demonstrated significantly decreased CORT levels compared with all groups ($p < 0.001$). Hence, a similar response was observed in rats that were exposed to SPS and EP and rats that were exposed to EP without prior SPS exposure.

Finally, we examined whether intra-BLA WIN would prevent the effects of SPS exposure on HPA axis inhibition. Rats were exposed to SPS and microinjected into the BLA with vehicle or WIN 2 min or 2 h after SPS exposure. A vehicle group was used as control. One week after SPS, Dex was administered before a second stress exposure and CORT levels were measured (Figure 5d). One-way ANOVA revealed significant differences in CORT levels between the groups ($F_{(3,30)} = 2.96$; $p = 0.048$). *Post hoc* comparison revealed that the Veh BLA group demonstrated significantly increased CORT levels compared with SPS + Veh BLA DST ($p = 0.012$), SPS + WIN2 min BLA DST ($p = 0.038$), and SPS + WIN2 h BLA DST ($p = 0.042$). Hence, the SPS group showed enhanced inhibition of the HPA axis in response to DST and WIN administered into the BLA 2 min or 2 h after SPS exposure did not prevent this enhanced inhibition.

The Effects of SPS and WIN55,212-2 on Anxiety and Locomotion

We used the open field arena and the light-dark test to examine the effects of SPS and WIN (0.5 mg/kg) on anxiety and locomotion.

Table 1 The Effects of Single-Prolonged Stress (SPS) Exposure and WIN55,212-2 Administration on Locomotion and Anxiety in the Open-Field Test

	Time in center (s)	Distance covered (cm)
Veh ($n = 14$)	6.15 ± 1.56*	1350 ± 101.77
SPS+Veh ($n = 7$)	0.90 ± 0.36	1314.28 ± 162.45
SPS+WIN 2 min ($n = 7$)	1.36 ± 0.50	1550 ± 48.79
SPS+WIN 2 h ($n = 7$)	2.23 ± 0.65	1482.85 ± 100.99
SPS+WIN 24 h ($n = 8$)	2.86 ± 0.73	1221.37 ± 220.36
SPS+WIN 48 h ($n = 7$)	1.21 ± 1.21	1300 ± 124.4

The Veh group spent more time in the center of an open field compared with all other groups. *$p < 0.05$.

Table 2 The Effects of Single-Prolonged Stress (SPS) Exposure and WIN55,212-2 Administration on Anxiety in the Light-dark Test

	Time in light side (s)	Entries to light side
Veh ($n = 9$)	39.97 ± 8.36*	2.55 ± 046
SPS+Veh ($n = 8$)	7.28 ± 2.68	1.28 ± 0.45
SPS+WIN 2 min ($n = 8$)	19.06 ± 7.86	1.7 ± 0.52
SPS+WIN 2 h ($n = 8$)	13.23 ± 9.57	1.28 ± 0.56

The Veh group spent more time in the light side in the light-dark test compared with all other groups. *$p < 0.05$.

Rats were tested in the open field 1 week after SPS (Table 1). One-way ANOVA revealed significant differences in time in center between the groups ($F_{(5,44)} = 3.33$; $p < 0.05$). *Post hoc* comparison revealed that the Veh group spent significantly more time in the center than all groups ($p < 0.05$). As for the distance covered, one-way ANOVA did not reveal a significant difference between the groups ($F_{(5,44)} < 1$; NS), suggesting that neither SPS nor WIN administration affected gross motoric behavior.

A similar effect was found in the light-dark test conducted 1 week after SPS (Table 2). One-way ANOVA revealed significant differences in time in the light side between the groups ($F_{(3,29)} = 5.04$; $p < 0.05$). *Post hoc* comparison revealed that the Vehicle group spent significantly more time in the light side than all groups ($p < 0.05$).

DISCUSSION

The main findings of the current study are that exogenous systemic or intra-BLA administration of the CB1/CB2 cannabinoid receptor agonist WIN55,212-2 normalizes behavioral and neuroendocrine abnormalities resulting from prior stress exposure in a rat model of PTSD. We also demonstrate that there may be an optimal time window for treatment with cannabinoids after exposure to a highly stressful event and that CB1 receptors in the BLA contribute to some of the preventive effects of WIN.

Cannabinoid Receptor Activation Prevents the Effects of Stress on IA Extinction and ASR

WIN administered systemically 2 min, 2, or 24 h after SPS exposure prevented the stress-induced disruption of extinction learning and enhancement of ASR. When WIN was injected 48 h after trauma exposure, it was too late to reverse the effects of stress, and in fact resulted in the impairment of extinction. These findings suggest that there may be an optimal time window for pharmacological intervention following trauma exposure.

Importantly, WIN administered *into the BLA* 2 min after SPS also reversed the stress-induced effects on IA and ASR. This suggests the possible involvement of cannabinoid receptors in the BLA in preventing the effects of stress on IA and ASR, when the activation takes place in close proximity to stress exposure. This is consistent with studies suggesting that cannabinoids in the amygdala serve to attenuate neuronal and behavioral responses to aversive environmental stimuli (Patel *et al*, 2005; Ganon-Elazar and Akirav, 2009). The different time table for the systemic and intra-BLA effects of WIN may suggest that there are other brain areas besides the BLA that are involved in the preventive effect of WIN on SPS-induced symptoms (eg, hippocampus and prefrontal cortex).

When a low and non-impairing dose of the CB1 receptor antagonist AM251 was co-administered with WIN into the BLA after SPS, it blocked the effects of WIN on IA and ASR, suggesting that the preventive effects of WIN are mediated via an activation of CB1 receptors in the BLA. Yet, we cannot completely rule out the possibility that other targets of WIN (eg, CB2 receptors) contributed to its effects.

Systemic Cannabinoid Receptor Activation Prevents the Effects of Stress on HPA axis Function

Rats exposed to SPS showed enhanced inhibition of the HPA axis as indicated by reduced CORT levels in response to the DST, corroborating previous studies (Liberzon *et al*, 1997; Kohda *et al*, 2007). Importantly, WIN administered systemically 2 or 24 h, but not 2 min, after SPS exposure prevented the enhancement of HPA axis inhibition. However, WIN microinjected into the BLA 2 min or 2 h after SPS exposure did not prevent the stress-induced alterations to HPA axis function. The DST assesses CORT levels following negative feedback to the pituitary to suppress the secretion of adrenocorticotropic hormone. Thus, activating cannabinoid receptors in the BLA may not affect the DST-induced HPA axis inhibition.

Several studies have shown that activating CB1 receptors or increasing *N*-arachidonylethanolamine (AEA) signaling prevents some of the effects of stress in the amygdala and hippocampus and can reduce stress-induced HPA axis activation (Ganon-Elazar and Akirav, 2009; Patel *et al*, 2004; Gorzalka *et al*, 2008). On the other hand, exposure to stress causes significant reductions in amygdalar and hippocampal AEA content (Patel *et al*, 2005a; Hill *et al*, 2005; Rademacher *et al*, 2008; Gorzalka *et al*, 2008). Hence, there are probably non-amygdala brain areas that are also involved in suppressing stress-induced behaviors and reducing HPA axis output following cannabinoids enhancement (eg, the hippocampus). Specifically, the finding that AEA content is reduced within the amygdala at the termination of stress exposure (Hill *et al*, 2009) may support a temporary role for cannabinoid receptor activation in the BLA in modulating the stress response.

Interestingly, resting CORT levels measured at different time points following SPS exposure were extremely high immediately after the trauma and remained significantly high up to 24 h thereafter. We have previously shown that intra-BLA WIN reversed the stress-induced increase in CORT levels (Ganon-elazar and Akirav, 2009). Hence, it is possible that the preventive effects of cannabinoids within a time window ranging from 2 min to 24 h after SPS are associated with their inhibition of the elevated CORT levels that follow stress exposure.

The Effects of Cannabinoid Receptor Activation on SPS-Induced Anxiety

WIN administration did not prevent the SPS-induced enhancement of anxiety as measured in the open field and dark-light tests 1 week after trauma. This lack of effect is particularly interesting since it may indicate that cannabinoid receptor activation reverses the effects of SPS on PTSD-like behavioral and neuroendocrine measures (ie, disrupted extinction, enhanced ASR, and HPA inhibition), but that it is not necessarily effective in blocking all the effects of stress exposure.

Importantly, this result suggests that the effects of WIN in preventing PTSD-like symptoms are not due to a general 'relaxation effect' or to an erasure of the stressful event, since rats injected with WIN after SPS still exhibit unconditioned anxiety. Hence, rats that were injected with WIN after SPS are still anxious, but do not demonstrate the two main PTSD-like symptoms (ie, enhanced ASR and HPA-negative feedback).

The Involvement of Cannabinoid Receptor Activation in the BLA in Preventing the Effects of SPS on Behavioral and Neuroendocrine Measures

Our findings suggest that at least some of the beneficial effects of cannabinoids administered following trauma exposure are mediated by the BLA. Patel *et al* (2004) found a synergistic interaction between environmental stress and CB1 receptor activation in the amygdala by demonstrating robust Fos induction within the BLA and the central amygdala following restraint stress and CB1 agonist administration. Hill *et al* (2009) have recently shown that the content of AEA in the BLA is reduced at the termination of restraint stress (also see Patel *et al*, 2005a and Rademacher *et al*, 2008) and that AEA content is negatively correlated with the magnitude of the CORT response to stress. Inhibiting fatty acid amide hydrolase (an endocannabinoid-deactivating enzyme) activity within the BLA reduces the CORT response to stress, suggesting that AEA content in the BLA has a function in constraining HPA axis activation. Together with our findings that intra-BLA WIN reduces the CORT response to stress (Ganon-Elazar and Akirav, 2009), these studies suggest cannabinoid modulation in the BLA of HPA axis activation in proximity to stress exposure. This could explain why WIN injected into the

BLA after stress termination (ie, 2 min, but not 2 h, after SPS exposure) blocked the stress-induced effects on behavior.

The cannulae were implanted into the BLA and although we used a small volume of infusion (0.5 μl), the possibility of injection spread to other structures, especially the central amygdala nucleus, cannot be completely ruled out. Yet, CB1 receptors are expressed at high levels in the BLA (Herkenham *et al*, 1990; Katona *et al*, 2001; Tsou *et al*, 1997) but their expression in the central amygdala is less clear (Katona *et al*, 2001; Tsou *et al*, 1997; Cota *et al*, 2007; but see Kamprath *et al*, 2011).

Conclusions

Our findings are of considerable interest since they indicate a relatively broad therapeutic time window in the aftermath of trauma exposure for preventive treatment with CB1 agonists. Although the precise mechanism by which cannabinoid receptor activation prevents the stress-induced behavioral and neuroendocrine modifications remains to be clarified, our findings suggest a crucial contribution of CB1 receptors in the BLA.

Furthermore, the results extend previous findings to another stress model and to a post-trauma treatment configuration that are more relevant to clinical context and add to the growing body of data pointing to a therapeutic potential of cannabinoids for treatment of PTSD.

DISCLOSURE

The authors declare no conflict of interest.

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Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients

Mateus M Bergamaschi[1,2,3], Regina Helena Costa Queiroz[2,3], Marcos Hortes Nisihara Chagas[1,3], Danielle Chaves Gomes de Oliveira[1,3], Bruno Spinosa De Martinis[3,4], Flávio Kapczinski[3,5], João Quevedo[3,6], Rafael Roesler[3,7], Nadja Schröder[3,8], Antonio E Nardi[3,9], Rocio Martín-Santos[3,10], Jaime Eduardo Cecílio Hallak[1,3], Antonio Waldo Zuardi[1,3] and José Alexandre S Crippa*[,1,3]

[1]Department of Neuroscience and Behavior, School of Medicine of Ribeirão Preto, University of São Paulo, SP, Brazil; [2]Department of Clinical, Toxicological and Food Sciences Analysis, School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, SP, Brazil; [3]National Institute for Translational Medicine (INCT-TM), CNPq, Brazil; [4]Department of Chemistry, School of Philosophy, Science and Literature of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil; [5]Bipolar Disorder Program, Hospital de Clínicas de Porto Alegre, RS, Brazil; [6]Laboratory of Neurosciences, Health Sciences Unit, University of Southern Santa Catarina, Criciúma, SC, Brazil; [7]Laboratory of Molecular Neuropharmacology, Department of Pharmacology, Institute for Basic Health Sciences, Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil; [8]Neurobiology and Developmental Biology Laboratory, School of Biosciences, Pontifical Catholic University, Porto Alegre, RS, Brazil; [9]Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil; [10]Department of Psychiatry, Institute of Neurosciences, Hospital Clínic, IDIBAPS, CIBERSAM, Barcelona, Spain

Generalized Social Anxiety Disorder (SAD) is one of the most common anxiety conditions with impairment in social life. Cannabidiol (CBD), one major non-psychotomimetic compound of the *cannabis sativa* plant, has shown anxiolytic effects both in humans and in animals. This preliminary study aimed to compare the effects of a simulation public speaking test (SPST) on healthy control (HC) patients and treatment-naïve SAD patients who received a single dose of CBD or placebo. A total of 24 never-treated patients with SAD were allocated to receive either CBD (600 mg; $n = 12$) or placebo (placebo; $n = 12$) in a double-blind randomized design 1 h and a half before the test. The same number of HC ($n = 12$) performed the SPST without receiving any medication. Each volunteer participated in only one experimental session in a double-blind procedure. Subjective ratings on the Visual Analogue Mood Scale (VAMS) and Negative Self-Statement scale (SSPS-N) and physiological measures (blood pressure, heart rate, and skin conductance) were measured at six different time points during the SPST. The results were submitted to a repeated-measures analysis of variance. Pretreatment with CBD significantly reduced anxiety, cognitive impairment and discomfort in their speech performance, and significantly decreased alert in their anticipatory speech. The placebo group presented higher anxiety, cognitive impairment, discomfort, and alert levels when compared with the control group as assessed with the VAMS. The SSPS-N scores evidenced significant increases during the testing of placebo group that was almost abolished in the CBD group. No significant differences were observed between CBD and HC in SSPS-N scores or in the cognitive impairment, discomfort, and alert factors of VAMS. The increase in anxiety induced by the SPST on subjects with SAD was reduced with the use of CBD, resulting in a similar response as the HC.
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Keywords: cannabidiol; CBD; anxiety; simulation of public speaking test; SPST; social anxiety disorder

INTRODUCTION

Generalized Social Anxiety Disorder (SAD) is one of the most common anxiety conditions and is associated with impairment in social adjustment to the usual aspects of daily life, increased disability, dysfunction, and a loss of productivity (Kessler, 2007; Filho *et al*, 2010). SAD tends to follow a long-term and unremitting course and is rarely resolved without treatment (Crippa *et al*, 2007; Chagas *et al*, 2010).

The pharmacological management of SAD remains problematic, despite several guidelines or consensus statements issued over the past few years (Canadian Psychiatric Association, 2006; Montgomery *et al*, 2004). As this anxiety disorder is often poorly controlled by the currently available drugs (only about 30% of the subjects achieve true recovery

*Correspondence: Professor Dr JAS Crippa, Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Hospital das Clínicas, Terceiro Andar, Av. Bandeirantes, 3900, Ribeirão Preto, São Paulo, Brazil, Tel: +5 51 63 602 2201, Fax: +5 51 63 602 0713, E-mail: jcrippa@fmrp.usp.br
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or remission without residual symptomatology (Blanco *et al*, 2002)), there is a clear need to search for novel therapeutic agents.

Subjects with SAD seem to be more likely to use *cannabis sativa* (*cannabis*) than those without other anxiety disorders to 'self-medicate' anxiety reactions (Buckner *et al*, 2008). However, the relationship of *cannabis* with anxiety is paradoxical. *Cannabis* users reported the reduction of anxiety as one of the motivations for its use; on the other hand, episodes of intense anxiety or panic are among the most common undesirable effects of the drug (Crippa *et al*, 2009). These apparently conflicting statements may partly reflect the fact that low doses of the best-known constituent of the plant, Δ9-tetrahydrocannabinol (Δ9-THC), engender anxiolytic-like effects, whereas higher doses produce anxiogenic reactions (Crippa *et al*, 2009).

Moreover, other components of the plant can influence its pharmacological activity; in particular, cannabidiol (CBD), one major non-psychotomimetic compound of the plant, has psychological effects substantially different from those of 9-THC (Zuardi, 2008). Oral administration of CBD to healthy volunteers has been shown to attenuate the anxiogenic effect of Δ9-THC and does not seem to involve any pharmacokinetic interactions (Zuardi *et al*, 1982). In animal studies, CBD has similar effects to anxiolytic drugs in different paradigms including conditioned emotional response, the Vogel conflict test, and the elevated plus-maze test (Zuardi, 2008). In human studies, the anxiolytic effects of CBD have been elicited in subjects submitted to the Simulation Public Speaking Test (SPST) (Zuardi *et al*, 1993). Using functional neuroimaging in healthy volunteers, we have observed that CBD has anxiolytic properties and that these effects are associated with an action on the limbic and paralimbic brain areas (Fusar-Poli *et al*, 2009a; Crippa *et al*, 2004).

Recently, we investigated the central effects of CBD on regional cerebral blood flow (rCBF), using single photon emission computed tomography (SPECT) in patients with SAD. Relative to placebo, CBD was associated with significant decreases in subjective anxiety induced by the SPECT procedure and modulated the same brain areas as the healthy volunteers (Crippa *et al*, 2010, 2011).

The data reviewed above led to the hypothesis that CBD may be an effective compound in the treatment of SAD symptoms. As a first step to investigate this hypothesis, we used the SPST, an experimental model for the induction of anxiety. SPST has apparent and predictive validity for SAD because the fear of speaking in public is a cardinal manifestation of SAD, and there is pharmacological evidence that the response pattern to some substances in the SPST is similar to the clinical response presented by patients with SAD (Graeff *et al*, 2003; Brunello *et al*, 2000). In this preliminary study, we aimed to measure the subjective and physiological effects of SPST on healthy control (HC) and on treatment-naïve SAD patients, who received a single dose of CBD or placebo, in a double-blind design. We have decided to use a single dose of CBD because of ethical and economical constraints, as a first step in the investigation of a possible anxiolytic action of this cannabinoid in patients with pathological anxiety. For instance, it is important to confirm whether CBD has the advantage of a rapid onset of action, making it particularly suitable for individuals who have episodic performance-related social phobia and who are able to predict the need for treatment well in advance. Considering previous results from a single dose of CBD, it is expected that this cannabinoid will reduce the level of fear provoked by the SPST.

METHODS

Subjects

A total of 24 subjects with generalized SAD and 12 HC subjects were selected by the screening procedure described below (see section). The SAD patients were randomly assigned to the two groups with 12 subjects each to receive CBD (600 mg—SAD-CBD) or placebo (SAD-PLAC), in a double-blind study design. To ensure the adequacy of the matching procedure, the first participant had his treatment blindly chosen between the two treatment options available; the next participant (whose characteristics were matched to the first one's) had his treatment drawn from the remaining option. An equal number of healthy controls ($n = 12$) performed the test without receiving any medication (HC). The groups were matched according to gender, age, years of education, and socioeconomic status. Moreover, the two SAD groups were balanced according to the Social Phobia Inventory (SPIN (Connor *et al*, 2000)). All participants were treatment-naïve (either with pharmacotherapy or psychotherapy) and did not present any other concomitant psychiatric disorder. No subject had a history of head trauma, neurological illness, ECT, substance abuse, or major medical illnesses, based on a semi-standardized medical questionnaire and physical examination. They were all non-smokers (of tobacco) and had not taken any medications for at least 3 months before the study. None of the subject had used marijuana more than five times in their lives (no use in the last year) and none had ever used any other illegal drug. All subjects gave written informed consent after being fully informed about the research procedure, following approval by the local ethical committee (HCRP No. 12407/2009).

Screening Procedure and Clinical Assessment

As an initial step, 2319 undergraduate students were screened by a self-assessment diagnostic instrument, the short version of the Social Phobia Inventory named MINI-SPIN (Osório Fde *et al*, 2010; Connor *et al*, 2001). This led to the identification of subjects with probable SAD, who scored a minimum of six points in the three items that compose the MINI-SPIN. Using this cut-off score, the MINI-SPIN has been previously shown to provide high sensitivity and specificity for the detection of SAD (de Lima Osório *et al*, 2007; Connor *et al*, 2001). A total of 237 subjects with a positive MINI-SPIN and an equal number of subjects with zero points in the three items that compose this instrument were contacted by telephone in order to respond to the general revision and the social anxiety module of the Structured Clinical Interview for the DSM-IV, clinical version (SCID-CV (First *et al*, 1997), translated into Portuguese (Del-Ben *et al*, 2001)). The volunteers who fulfilled SAD criteria and scored 'very much' or 'extremely'

in the 11th item of SPIN (avoids speeches) and those who fulfilled the HC criteria were randomly invited to attend an interview for diagnosis confirmation through the full SCID-CV, applied by two examiners familiar with the instrument (the Kappa coefficient between the two interviewers was 0.84 (Crippa *et al*, 2008a)).

CBD Preparation

CBD (600 mg) in powder, ~99.9% pure (kindly supplied by STI-Pharm, Brentwood, UK and THC-Pharm, Frankfurt, Germany), was dissolved in corn oil (Crippa *et al*, 2004; Zuardi *et al*, 1993). The same amount of corn oil was used as placebo. The drug and placebo were packed inside identical gelatin capsules. We have chosen the dose of 600 mg based on the fact that acute anxiolytic effects of CBD have been observed in healthy controls with doses ranging from 300 (Zuardi *et al*, 1993) to 600 mg (Fusar-Poli *et al*, 2009a, b). Although we have recently observed that 400 mg of CBD significantly decreased subjective anxiety induced by the SPECT procedure in SAD patients, the SPST has face validity for SAD and the fear of speaking in public is considered to be the most stressful situation in this condition, in contrast with the neuroimaging procedure. Therefore, we have decided to use the highest dose of CBD previously found to have anxiolytic effects. The time of assessment after the procedure was chosen based on previous studies that showed that the plasma peak of an oral dose of CBD usually occurs 1–2 h after ingestion (Agurell *et al*, 1981; Crippa *et al*, 2004, 2010, 2011; Borgwardt *et al*, 2008; Fusar-Poli *et al*, 2009a, b)

Psychological Measurements

The state-anxiety level and other subjective states were evaluated during the test through the Visual Analogue Mood Scale—VAMS (Norris, 1971), translated into Portuguese (Zuardi and Karniol, 1981). In this scale, the subject is told to mark a point that identifies his/her present subjective state on a 100-mm straight line placed between two words that describe opposite mood states. VAMS contains 16 items that Norris grouped into four factors. A factorial analysis performed with the Portuguese version of the VAMS also yielded four factors with similar item composition (Zuardi *et al*, 1993). The original name of the anxiety factor was preserved, but the names of the remaining factors have been changed to fit the meaning of the items with the highest loads in that particular factor. Thus, the present factors are: (1) anxiety, comprising the items *calm–excited*, *relaxed–tense*, and *tranquil–troubled*; (2) sedation (former mental sedation), including the items *alert–drowsy*, and *attentive–dreamy*; (3) cognitive impairment (former physical sedation), including *quick-witted–mentally slow*, *proficient–incompetent*, *energetic–lethargic*, *clear-headed–muzzy*, *gregarious–withdrawn*, *well-coordinated–clumsy*, and *strong–feeble*; and (4) discomfort (former other feelings and attitudes), made of the items *interested–bored*, *happy–sad*, *contented–discontented*, and *amicable–antagonistic* (Parente *et al*, 2005).

The Self-Statements during Public Speaking Scale (Hoffmann and Di Bartolo, 2000) (SSPS), translated into Portuguese (de Lima Osório *et al*, 2008) is a self-report instrument that aims to measure the self-perception of performance in the specific situation of public speaking. It is based upon cognitive theories that propose that social anxiety is the result of a negative perception of oneself and of others towards oneself. The scale is comprised of 10 items, rated on a *likert* scale from 0 (strongly disagree) to 5 (strongly agree), which are organized into two subscales of five items each, for positive or negative self-evaluation. In this study, we applied the negative self-evaluation subscale (SSPS-N).

The Bodily Symptoms Scale (BSS) was designed to detect physical symptoms that can, indirectly, influence anxiety measures (Zuardi *et al*, 1993). It is organized into 21 items, and the intensity of each symptom is rated from 0 (no symptom) to 5 (highest).

Physiological Measurements

Skin conductance. A computer-controlled, voltage-constant (0.6 V) module with automatic back off (Contact Precision Instruments, UK) measured skin conductance. Two electrodes (Beckman, UK) were fixed with adhesive tape. Contact with the skin was made through high conductance gel (KY gel, Johnson and Johnson, Brazil). The skin conductance level (SCL) and the number of spontaneous fluctuations (SF) of the skin conductance were recorded.

Arterial blood pressure. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by a mercury sphygmomanometer (Becton Dickinson, Brazil).

Heart rate. Heart rate (HR) was estimated by manually counting the pulse rate.

Procedure

The SPST was the same as used by McNair *et al* (1982) with some modifications (Hallak *et al*, 2010).

The procedure is summarized in Table 1. After a 15-min adaptation period, baseline measurements (B) were taken and followed by a single dose of oral CBD or placebo in a double-blind procedure. Pretest measurements (P) were made 80 min after the drug ingestion. Immediately thereafter, the subject received the instructions and had 2 min to prepare a 4-min speech about 'the public transportation system of your city'. He/she was also told that the speech would be recorded on videotape and later analyzed by a psychologist. Anticipatory speech measurements (A) were taken before the subject started speaking. Thus, the subject started speaking in front of the camera while viewing his/her own image on the TV screen. The speech was interrupted in the middle and speech performance measurements (S) were taken. The speech was recorded for a further 2 min. Post-test measurements (F1 and F2) were made 15 and 35 min after the end of the speech, respectively.

Statistical Analysis

Clinical and demographical characteristics were analyzed with the non-parametric tests (gender and socioeconomic level) and by the analysis of variance for one factor

Table 1 Timetable of the Experimental Session

Session (min)	Phase	Procedure
−0:30		Adaptation to the laboratory; instructions about the interview and measurements
−0:15	Baseline (B)	SCL, SF, HR, AP, VAMS, SSPS and BSS
0		Drug intake: CBD or placebo capsules
+1:20	Pre-stress (P)	SCL, SF, HR, AP, VAMS, SSPS and BSS
+1:30		Instructions about the SPST
+1:32		Speech preparation
+1:34	Anticipatory speech (A)	SCL, SF, HR, AP, VAMS, SSPS and BSS
+1:45		Start of speech
+1:47	Speech performance (S)	SCL, SF, HR, AP, VAMS, SSPS and BSS
+1:53		Continuation of speech
+1:55		End of speech
+2:10	Post-stress 1 (F1)	SCL, SF, HR, AP, VAMS, SSPS and BSS
+2:30	Post-stress 2 (F2)	SCL, SF, HR, AP, VAMS, SSPS and BSS

(ANOVA), followed by post-hoc Bonferroni's test for multiple comparisons (age, age of SAD onset and SPIN).

Scores of VAMS's factors, SSPS-N, BSS, arterial diastolic and systolic pressure, heart rate, as well as the SCL and the total number of SF, were transformed by calculating the difference between the score in each phase and the pretest score in the same volunteer. For the analysis, SCL values were converted into natural logarithms (logn). These delta scores were submitted to a repeated-measures analysis of variance (repeated-measures ANOVA), analyzing the factors of phases, groups, and phases by groups' interaction. In the case where sphericity conditions were not reached, the degrees of freedom of the repeated factor were corrected with the Huynh–Feldt epsilon. Whenever a significant phase by group interaction occurred, comparisons among the groups were made at each phase using a one-factor ANOVA followed by multiple comparisons with the Bonferroni's test.

Data analysis was performed using the SPSS-17 program, and the significance level adopted was $p<0.05$.

RESULTS

Subjects

The clinical and demographical characteristics of the subjects are shown in Table 2. The only significant differences among the groups were found in the mean scores of SPIN ($F_{2,\ 35}=34.3$; $p<0.001$). The SPIN scores were significantly lower in healthy volunteers than in subjects with SAD who received CBD or placebo. No significant difference was observed between the two groups with SAD.

Psychological Measures

No differences were observed among the initial measures of the three groups on anxiety ($F_{2,35}=1.4$; $p=0.27$), sedation ($F_{2,35}=0.4$; $p=0.70$), cognitive impairment ($F_{2,35}=1.9$; $p=0.16$), and discomfort ($F_{2,35}=0.6$; $p=0.55$) VAMS factors. Changes in relation to the pretest phase of VAMS factors in the three groups are shown in Figure 1.

Table 2 Clinical and Demographical Characteristics of the Groups

	Sad-placebo	Sad-cbd	Healthy	p
Male/female	6/6	6/6	6/6	1.0
Age (mean (SD))	22.9 (2.4)	24.6 (3.6)	23.3 (1.7)	0.36
Socioeconomic levels[a] (Median)	2	2.5	2	0.66
Age of SAD onset (mean (SD))	12.2 (5.8)	9.6 (6.9)	—	0.36
SPIN (mean (SD))	36.3 (11.2)	30.9 (12.0)	5.75 (3.3)	<0.001

Abbreviations: SAD, social anxiety disorder; SPIN, Social Phobia Inventory.
[a]Socioeconomic levels were assessed by the Brazil Socioeconomic Classification Criteria.

Regarding the VAMS anxiety factor, the repeated-measures ANOVA showed a significant effect of phases ($F_{3.6,118.5}=32.7$; $p<0.001$), group ($F_{2,33}=13.5$; $p<0.001$) and phases by group interaction ($F_{7.2,118.5}=6.4$; $p<0.001$). Comparisons among the groups evidenced significant differences between SAD-PLAC and HC at the initial ($p=0.018$), anticipatory ($p<0.001$), speech ($p<0.001$) and post-speech (0.018) phases. The SAD-CBD differs from the SAD-PLAC ($p=0.012$) and HC ($p=0.007$) during the speech phase. Regarding cognitive impairment, repeated-measures ANOVA showed a significant effect of phases ($F_{3.2,105.8}=5.6$; $p=0.001$) and phases by group interaction ($F_{6.4,105.8}=5.1$; $p<0.001$). Comparisons among the groups evidenced that SAD-PLAC differed significantly from SAD-CBD ($p=0.009$) and HC ($p=0.001$) at the speech phase. Regarding discomfort, there are significant effects of phases ($F_{4,132}=7.1$; $p<0.001$), group ($F_{2,33}=4.7$; $p=0.016$) and phases by group interaction ($F_{4,132}=2.2$; $p=0.036$). Comparisons among the groups evidenced that SAD-PLAC differed significantly from HC at the anticipatory phase ($p=0.047$) and from SAD-CBD ($p=0.029$) and HC ($p=0.001$) at speech phases. On the sedation factor, there are significant effects of phases ($F_{3.1,102.1}=27.1$; $p<0.001$), group ($F_{2,33}=5.3$; $p=0.010$) and phases by group interaction ($F_{6.2,102.1}=2.4$; $p=0.032$). Comparisons among the groups evidenced that SAD-PLAC differed significantly from SAD-CBD ($p=0.016$) and HC ($p=0.001$) at the anticipatory phase and from HC at speech phases ($p=0.005$).

The scores of the SSPS-N at the initial phase differ significantly among the groups ($F_{2,35}=14.8$; $p<0.001$), with the SAS-PLAC and SAD-CBD higher than HC ($p<0.001$). Changes in relation to the pretest phase of SSPS-N in the three groups are shown in Figure 2. The repeated-measures ANOVA showed a significant effect of phases ($F_{3.1,101.6}=9.7$; $p<0.001$), group ($F_{2,33}=6.6$; $p=0.004$) and phases by group interaction ($F_{6.2,101.6}=3.2$; $p=0.006$). Comparisons among the groups evidenced significant differences between SAD-PLAC and SAD-CBD at the anticipatory ($p=0.043$) and speech ($p=0.001$) phases and between SAD-PLAC and HC at the speech ($p<0.001$) phases. No significant differences were observed between SAD-CBD and HC.

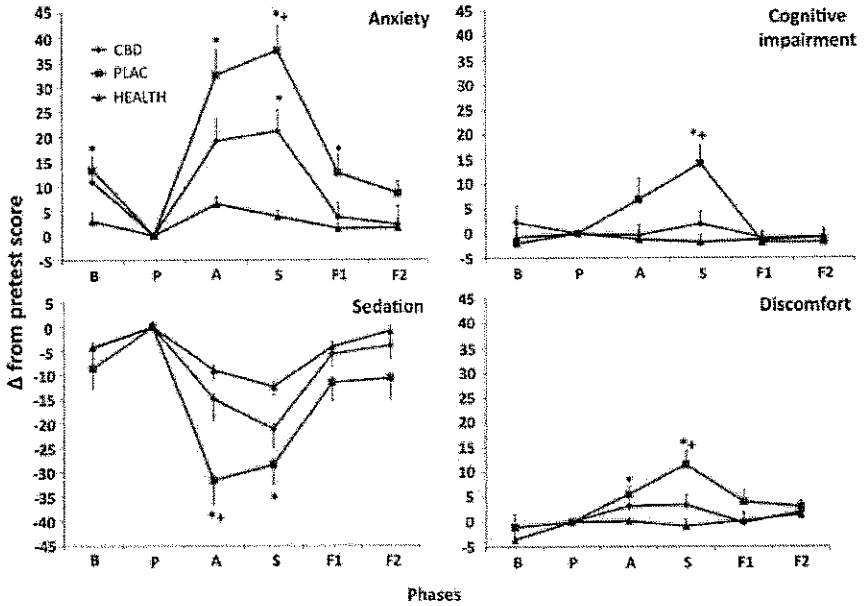

Figure 1 Changes in Visual Analogue Mood Scale (VAMS) factors induced by simulated public speaking test (SPST), measured in 12 social anxiety patients who received cannabidiol (—●—), 12 social anxiety patients who received placebo (—■—) and 12 healthy controls (—▲—). The phases of the experimental session are: b, basal; P, pretest; a, anticipation; S, speech performance; F1, post-speech measures 1; F2, post-speech measures 2. Points in the curves indicate mean and vertical bars SEM. *Indicates significant differences from healthy control and + from social anxiety patients who received cannabidiol.

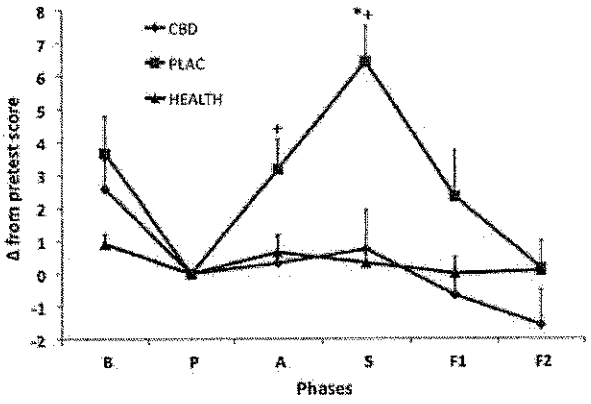

Figure 2 Changes in SSPS-N scores induced by simulated public speaking test (SPST). Other specifications are in the legend of Figure 1. *Indicates significant differences from healthy control and + from social anxiety patients who received cannabidiol.

No differences were observed among the initial measures of the three groups on BSS ($F_{2,35} = 1.4$; $p = 0.25$). Changes in relation to the pretest phase of BSS in the three groups showed a significant effect of phases ($F_{3.3,110.2} = 8.1$; $p < 0.001$) and phases by group interaction ($F_{6.7,110.2} = 2.3$; $p = 0.035$). Comparisons among the groups evidenced significant differences between SAD-PLAC and HC at the speech phase ($p = 0.05$). In this phase the changes in relation to the pretest phase were 8.2 for SAD-PLAC and 0.3 for HC. SAD-CBD group had an intermediate score, which did not differ from SAD-PLAC or HC.

The observed powers for the tests used in the statistical analysis of the anxiety VAMS factor and in the negative SSPS, were 0.996 and 0.881, respectively.

Physiological Measures

Systolic pressure ($F_{2,35} = 1.159$; $p = 0.33$), diastolic pressure ($F_{2,35} = 1.7$; $p = 0.20$), heart rate ($F_{2,35} = 0.4$; $p = 0.67$), SCL ($F_{2,5} = 1.6$; $p = 0.22$), and SF ($F_{2,35} = 0.1$; $p = 0.90$) did not show significant differences among the three groups in the initial measures. Changes in relation to the pretest showed significant repeated-measures ANOVA effect only in phases for the following physiological measures: systolic pressure ($F_{3.7,122.5} = 5.9$; $p < 0.001$), diastolic pressure ($F_{4,132} = 5.1$; $p < 0.001$), SCL ($F_{3.2,84.9} = 2.8$; $p = 0.045$), and SF ($F_{3.6,92.4} = 3.8$; $p = 0.009$). In these measures, the values were significantly elevated during SPS without differences among the groups. For the heart rates, the repeated-measures ANOVA showed a significant effect of phases ($F_{3.9,127.1} = 6.9$; $p < 0.001$) and phases by group interaction ($F_{7.7,127.1} = 4.6$; $p < 0.001$). Comparisons among the groups showed a reduction in heart rates from the initial to the pretest measures significantly greater ($p < 0.001$) for the SAD-PLAC (delta mean = 9.17; SE = 1.77) than for HD (delta mean = 0.5; SE = 0.56) group. The SAD-CBD group (delta mean = 4.3; SE = 1.56) did not differ significantly from the other two groups.

DISCUSSION

As observed in another study of SAD patients' performance on SPST (Crippa *et al*, 2008b), the present results of the

VAMS scale showed that the SAD-PLAC group presented a significantly higher anxiety level and greater cognitive impairment, discomfort, and alert compared with the control group during the test. This was expected as the fear of speaking in public is a cardinal manifestation of SAD (Brunello *et al*, 2000).

Pretreatment of SAD patients with CBD significantly reduced anxiety, cognitive impairment, and discomfort in their speech performance (S) and significantly decreased alert in their anticipatory speech (A). The cognitive impairment, discomfort, and alert of SAD patients that received CBD had similar results to the HC during the SPST. These preliminary results indicate that a single dose of CBD can reduce the anxiety-enhancing effect provoked by SPST in SAD patients, indicating that this cannabinoid inhibits the fear of speaking in public, one of the main symptoms of the disorder.

The anxiolytic effects of CBD had been extensively demonstrated in animal studies and in healthy volunteers submitted to anxiety induced by several procedures, including the simulation of public speaking (Crippa *et al*, 2010, 2011). However, there is only one published report of the anxiolytic effect of CBD in an anxiety disorder (Crippa *et al*, 2010, 2011). This study was performed with SAD patients and the anxiolyic effects of CBD were detected before provoking anxiety by the tracer injection and scanning procedure of SPECT, suggesting that CBD facilitates habituation of anticipatory anxiety. The SPECT analysis of this study and of a previous one with healthy volunteers (Crippa *et al*, 2004) showed that the CBD effects were associated with the activity of the parahippocampal gyrus and hippocampus. Functional magnetic resonance imaging (fMRI) detected attenuated responses in the amygdala and in the cingulated cortex induced by CBD (600 mg) during the viewing of fearful facial stimuli (Fusar-Poli *et al*, 2009a). Moreover, CBD has shown to disrupt forward intrinsic connectivity between the amygdala and the anterior cingulate during the neural response to fearful faces (Fusar-Poli *et al*, 2009b). Taken together, these studies demonstrate the action of CBD in limbic and paralimbic brain areas, which are known to be associated with anxiety.

The anxiolytic action of CBD may be mediated by 5-HT_{1A} receptors, as it displaces the agonist [3H]8-OHDPAT from the cloned human 5-HT1A receptor in a concentration-dependent manner and exerts an effect as an agonist at the human 5-HT1A receptor in signal-transduction studies (Russo *et al*, 2005). Additionally, CBD injected into the dorsolateral periaqueductal gray of rats produced anxiolytic-like effects in the elevated plus-maze and elevated T-maze, and these effects were prevented by a 5HT1A receptor antagonist (Soares *et al*, 2010; Campos and Guimaraes, 2008).

Another important observation of this study was that the increase of negative self-evaluation during public speaking was almost abolished by CBD. In a previous study, we suggested that the negative self-evaluation during the phobic situation of public speaking would be important for the avoidance and impairment in social functioning that support the diagnosis of SAD (Freitas-Ferrari *et al*, submitted). In that way, the observed effect of CBD for improving the self-evaluation during public speaking, which is one of the pivotal aspects of SAD, will influence the therapy of SAD patients.

Although physiological measures have not shown significant differences among the groups, the self-report of somatic symptoms (BSS) increased significantly only for the SAD patients who received placebo during the test. Following the same rationale as above, it is well-known that more pronounced bodily symptoms may contribute to the clinical diagnosis of SAD, and this result suggests that CBD also protects the patients from their subjective physiological abnormalities induced by the SPST.

The findings reported herein need to be interpreted with caution, given the limitations of the study. First, it would have been desirable to measure plasma levels of CBD and to relate such measurements to changes in the VAMS scores; however, it should be pointed out that previous investigations have not been able to confirm whether there is a direct relationship between plasma levels of cannabinoids, in particular CBD, and their clinical effects (Agurell *et al*, 1986). Another limitation refers to the size of the sample included; however, the statistical power of the data from the VAMS and SSPS was shown to be relatively robust even with small subject numbers.

An extensive list of medications for the pharmacological treatment of SAD was made available in recent years, including selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitor (SSNRI), antidepressants and benzodiazepines (Schneier, 2001). However, both SSRIs and SSNRIs have an initial activation and a long latency period of response, and benzodiazepines are limited by their potential to produce motor impairment, sedation, and to induce dependence and withdrawal symptoms following discontinuation (Blanco *et al*, 2002). Conversely, CBD has important advantages in comparison with the currently available pharmacological agents for the treatment of SAD, such as an early onset of action and lack of important side effects both with acute and chronic administration to healthy subjects (Crippa *et al*, 2010, 2011). Moreover, it was shown that repeated treatment with CBD (but not 9-THC) does not develop tolerance or dependence (Hayakawa *et al*, 2007) and possibly reduces drug-seeking behaviors (Parker *et al*, 2004; Ren *et al*, 2009; Morgan *et al*, 2010). Thus, because of the absence of psychoactive or cognitive effects, to its safety and tolerability profiles, and to its broad pharmacological spectrum, CBD is possibly the cannabinoid that is most likely to have initial findings in anxiety translated into clinical practice.

Therefore, the effects of a single dose of CBD, observed in this study in the face of one of the main SAD's phobic stimuli, is a promising indication of a rapid onset of therapeutic effect in patients with SAD. However, randomized, double-blind, placebo-controlled, clinical trials with larger samples and chronic use are still needed to confirm these statements. Likewise, because CBD effects are biphasic, the determination of adequate treatment ranges for each disorder remains a challenge. Further research to determine the precise mechanisms of action of CBD in the different anxiety disorders is desirable and opportune.

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DISCLOSURE

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Catch the Buzz

By David Jay Brown

May 13, 2011

FDA Approves New PTSD Study with Medical Marijuana

The Santa Cruz Multidisciplinary Association for Psychedelic Studies just received permission from the FDA to study the effects of cannabis on posttraumatic stress disorder.

Several months ago, I reported on how the Santa Cruz Multidisciplinary Association for Psychedelic Studies (MAPS) was beginning the first experimental sessions in their second MDMA study on posttraumatic stress disorder (PTSD).

PTSD is an extremely difficult medical condition to treat, and it currently effects around 7.8 percent of Americans. It is caused by exposure to dangerous and highly stressful situations, which can result in lasting symptoms that include disturbing flashbacks, distressful emotions, panic attacks, and nightmares.

On April 28th the U.S. Food and Drug Administration (FDA) accepted MAPS' protocol design for their study of cannabis as a treatment for symptoms of PTSD in war veterans. This approval from the FDA represents another important step forward in PTSD research, although there is still a major hurdle to overcome before the research can actually begin. The FDA stated that MAPS' current protocol successfully addresses all of their concerns, as long as the researchers can obtain cannabis for the study.

Living here in Santa Cruz, with medical cannabis dispensaries popping up like fast food restaurants, you'd think that access to marijuana would be the easy part. However, there is only one place to legally obtain cannabis for a medical study in the U.S.--from the government itself, which has had an unconstitutional monopoly on the plant for research purposes since 1968. So, in order to obtain cannabis for the PTSD study, yet another government review process needs to take place.

The National Institute on Drug Abuse/Public Health Service (NIDA/PHS) also has to approve the cannabis/PTSD study before it can begin. Although the FDA has repeatedly demonstrated its willingness to evaluate studies on the basis of scientific merit, NIDA/PHS appears to continually position politics over science, and has consequently blocked medical marijuana studies from moving forward.

"This redundant review, which may take another year or more, is required solely because NIDA has a monopoly on the supply of marijuana for research. NIDA/PHS must review and accept the protocol before allowing us to purchase marijuana from NIDA. This process is biased from the start, since NIDA's mission does not include exploring the potential beneficial uses of marijuana," said MAPS Director of Communications Brad Burge.

MAPS has been trying for years to continue their medical marijuana vaporizer research, and although the FDA has approved that next study as well, the DEA has prevented them from conducting it by not allowing the researchers to obtain the necessary cannabis. (For more information about this, see the in-depth article that I wrote for High Times on the subject: www.maps.org/media/view/crop_blockers/) There is concern that this could happen again with the PTSD study that was just approved by the FDA.

According to Burge, many U.S. veterans already use medical marijuana to deal with their symptoms of PTSD. "MAPS is seeking to conduct the first clinical trial testing the use of the smoked or vaporized marijuana plant in PTSD patients. Now PHS/NIDA will decide if MAPS can obtain marijuana for 50 suffering veterans," said Burge.

January 17, 2012

The Case for Treating PTSD in Veterans with Medical Marijuana

By: Martin Mulcahey

The Atlantic

The Atlantic makes a compelling case for the federal government to allow MAPS' FDA-cleared study of marijuana for veterans with PTSD to move forward: In the struggle between legitimate medical research and irrational government fear, veterans are the ones caught in the crossfire.

Correction: The Atlantic writes: "The plan is contingent upon final approval by a Department of Health and Human Services (HHS) scientific review panel, which is likely to ratify the proposal after the project leader, Dr. Sue Sisley, alleviated the Food and Drug Administration's concerns over safety precautions." In fact, the FDA cleared the protocol in April 2011, and the National Institute on Drug Abuse and Public Health Service (which are part of HHS) review committee later rejected it, refusing to sell MAPS the marijuana needed to conduct the study. The study is on hold either until NIDA agrees to sell our researchers the marijuana, until MAPS succeeds in growing its own marijuana for research, or until the marijuana can be legally imported.

Researchers are one bureaucratic hurdle away from gaining approval for the first clinical examination on the benefits of marijuana for veterans suffering from post-traumatic stress disorder (PTSD). The Multidisciplinary Association for Psychedelic Studies (MAPS), working under the auspices of the University of Arizona College of Medicine, are preparing a three-month study of combat veterans who served in Iraq and Afghanistan. The plan is contingent upon final approval by a Department of Health and Human Services (HHS) scientific review panel, which is likely to ratify the proposal after the project leader, Dr. Sue Sisley, alleviated the Food and Drug Administration's concerns over safety precautions. Social and political intrigue surrounding this research is far reaching, attracting opposing factions who must cede biases for the greater good and well-being of servicemen and servicewomen.

The University-controlled study Sisley advocates calls for a triple-blind and placebo-controlled environment. A meticulously prepared proposal recommends a sample base of 50 veterans, whose PTSD symptoms have not improved under current standard medical practices. All participants must agree to abstain from marijuana use for 30 days prior to participation. In two ensuing 60-day periods, the veterans are asked to either smoke or vaporize a maximum of 1.8 grams of marijuana a day (the equivalent of two marijuana cigarettes). The test group will be furnished a weekly supply of various strains of marijuana, with THC levels ranging from 0 percent to 12 percent. Sisley's study objectives are

twofold. "With this research, we can actually figure out which symptoms it might help with, and what an optimal dosing strategy might look like." She is also mindful of public opinion regarding medical marijuana. "If we get a chance to do this, we're not taking liberties. This is a carefully controlled, rigorous scientific study. We're not sitting around trying to get these vets high."

If anecdotal evidence were the standard, acceptance of marijuana's calming properties among psychologically scarred soldiers would be a topic relegated to the past. Statistical evidence to support that hypothesis could be petitioned from the state of New Mexico, where medical marijuana is legally prescribed for PTSD. The state's number one diagnosis for a medical marijuana license, a noteworthy 27 percent of the total, lists PTSD as the qualifying criteria for issuance. That statistic comes as no surprise to Sisley, but she stresses circumstantial evidence is not enough to sway the wide range of government agencies she deals with. "We really believe science should supersede politics," she said. "This illness needs to be treated in a multidisciplinary way. Drugs like Zoloft and Paxil have proven entirely inadequate."

"If we get a chance to do this, we're not taking liberties. This is a carefully controlled, rigorous scientific study. We're not sitting around trying to get these vets high."

In neighboring Colorado, the state's legislature failed to pass a proposal mirroring New Mexico's. It effectively forbade Colorado's large veteran population from citing PTSD on medical marijuana applications. Brian Vicente, of the Sensible Colorado organization, became an advocate for veterans after the legislative rejection. Vicente has watched the government fight itself over this issue. "The federal government is, in some ways, divided," Vicente said. "Agencies like the Veterans Administration have taken some fairly decent stances of medical marijuana." Quickly, he adds a qualifier: "But, then you have the DEA [Drug Enforcement Administration] and NIDA [the National Institute on Drug Abuse] and organizations like them blocking research that other parts of the government are authorizing. It's another example of the federal government being schizophrenic and flat-out wrong on marijuana as medicine." This is a frustrating scenario Sisley has encountered first-hand. "I can't help but think they simply don't want to move forward," she said. "Maybe they figure if they stall long enough, we'll give up and go away."

As arguments among American government agencies continue, other nations are taking the lead generating medical arguments that advance Sisley's theory. A study at Israel's University of Haifa showed that marijuana administered to rats within 24 hours of suffering psychological trauma effectively blocked the development of post-traumatic stress disorder. Dr. Irit Akirav's study even concludes there is a time-frame that has to be taken into consideration. "There is a critical window of time after trauma, during which synthetic marijuana can help prevent symptoms similar to PTSD in rats," Akirav stated at the time. "It does not erase the experience, but can help prevent the development of PTSD symptoms." In Germany, Switzerland, and Spain there are currently programs, some government funded, utilizing MDMA (from which the "ecstasy" drug is derived) as a possible inhibitor of PTSD symptoms.

A governmental lack of decisiveness has created unintended consequences and casualties in the medical field. One is Dr. Phil Leveque, a World War II veteran who had his medical license revoked based on the large number of medical marijuana permits he issued for PTSD in Oregon. Leveque estimates he signed 1,000 permits for PTSD, and said he did so with a clear conscience. "Whether they were World War II, Korea, Vietnam or vets from the current conflicts, 100 percent of my patients said it was better than any drug they were prescribed for PTSD," he said. Sixteen states and the District of Columbia currently have laws permitting marijuana for medical use. However, Veterans Affairs physicians are expressly prohibited from recommending patients for enrollment in any state's medical marijuana program. This, again, highlights contradictions at different levels of government agencies.

Veterans Affairs data disclosed that from 2002 to 2009 one million troops left active duty in Iraq or Afghanistan and became eligible for VA care. That's a number that will rise annually, revealing a need for effective treatment of PTSD that cannot be overstated. PTSD remains an enormous consideration with combat troops still serving in Afghanistan, where an estimated six to 11 percent are currently suffering symptoms of PTSD. Statistics among Iraq War veterans are more disturbing, with between 12 to 20 percent of returning vets suffering PTSD-related anxieties. Those are government statistics, and some non-governmental studies suggest that as many as one in every five military personnel returning from Iraq and Afghanistan could suffer various forms of PTSD. Veteran Affairs recognizes these facts, and to its credit funds unconventional studies of PTSD, employing therapy dogs and yoga.

Sisley has found an ally in Rick Doblin, executive director of the leading psychedelic studies group. Doblin has the unenviable job of lobbying Congress under the umbrella of the non-profit MAPS. The pair share a common frustration dealing with the multitude of government agencies, some of whose interests are diametrically opposed. Doblin addresses apprehensions from the administrative standpoint: "We're asking for marijuana from an agency [National Institute on Drug Abuse] designed to prevent people from using marijuana. There's something fundamental that just doesn't work here," he said. Sisley's concerns revolve around medical studies in the field, which often fail to gain approval because of political motives instead of science. "The doctors I know think this war on marijuana is awful, and they're tired of being in the middle of it," she said. "They just want to do real research, or read real research, and not operate around all of these agendas."

Veterans endure a framework of care for PTSD that has not changed since 1980, when PTSD was added to American Psychiatric Association's dictionary of maladies. Federal agencies are clearly confused, unable to reconcile the illegality of marijuana with the benefits it could have on the lives of soldiers and their extended families. These issues are not being addressed in an open forum; instead, they remain hidden behind committee doors or special panels of anonymous voices with unknown prejudices. Medical marijuana remains one of the nation's biggest political hot potatoes, and when combined with our veterans' health creates a unique conundrum for politicians. Disturbingly, the people caught in this crossfire of self-interest are veterans who risked their lives for the system that may be stifling their medical options now.

Medical Marijuana for PTSD

By Rick Nauert PhD *Senior News Editor*
Reviewed by John M. Grohol, Psy.D. on November 5, 2009

A new study carried out by Dr. Irit Akirav and research student Eti Ganon-Elazar, working at the Learning and Memory Lab in the University of Haifa's Department of Psychology, suggests the use of cannabinoids may help in the treatment of post-traumatic stress disorder patients.

The study was published in the prestigious *Journal of Neuroscience*.

According to background information, the result of experiencing a traumatic event — such as a car accident or terror attack — is the appearance of medical and psychological symptoms that affect various functions. While these conditions normally abate, 10 to 30 percent of people who experience a traumatic event develop post-traumatic stress disorder, a condition in which the patient continues to suffer stress symptoms for months and even years after the traumatic event.

Symptoms include reawakened trauma, avoidance of anything that could recall the trauma, and psychological and physiological disturbances. One of the problems in the course of treating trauma patients is that a person is frequently exposed to additional stress, which hinders the patient's overcoming the trauma.

The researchers used a synthetic form of marijuana, which has similar properties to the natural plant, and they chose to use a rat model, which presents similar physiological responses to stress to that of humans.

The first stage of the research examined how long it took for the rats to overcome a traumatic experience, without any intervention. A cell colored white on one side and black on the other was prepared. The rats were placed in the white area, and as soon as they moved over to the black area, which they prefer, they received a light electric shock.

Each day they were brought to the cell and placed back in the white area. Immediately following exposure to the traumatic experience, the rats would not move to the black area voluntarily, but a few days later, after not receiving further electric shocks in the black area, they learned that it was safe again and moved there without hesitation.

Next, the researchers introduced an element of stress. A second group of rats was placed on a small, elevated platform after receiving the electric shock, which added stress to the traumatic experience. These rats abstained from returning to the black area in the cell for much longer, which showed that the exposure to additional stress does indeed hinder the process of overcoming trauma.

The third stage of the research examined yet another group of rats. These rats were exposed to the traumatic and additional stress events, but just before being elevated on the platform they received an injection of synthetic marijuana in the amygdala – an area of the brain known to be connected to emotive memory. These rats agreed to enter the black area after the same amount of time as the first group, showing that the synthetic marijuana canceled out the symptoms of stress.

Refining the results of this study, the researchers then administered marijuana injections at different points in time on additional groups of rats, and found that regardless of when the injection was administered, it prevented the surfacing of stress symptoms.

Dr. Akirav and Ganon-Elazar also examined hormonal changes in the course of the experiment and found that synthetic marijuana prevents increased release of the stress hormone that the body produces in response to stress.

According to Dr. Akirav, the results of this study show that cannabinoids can play an important role in stress-related disorders.

"The results of our research should encourage psychiatric investigation into the use of cannabinoids in post-traumatic stress patients," she concludes.

APA Reference

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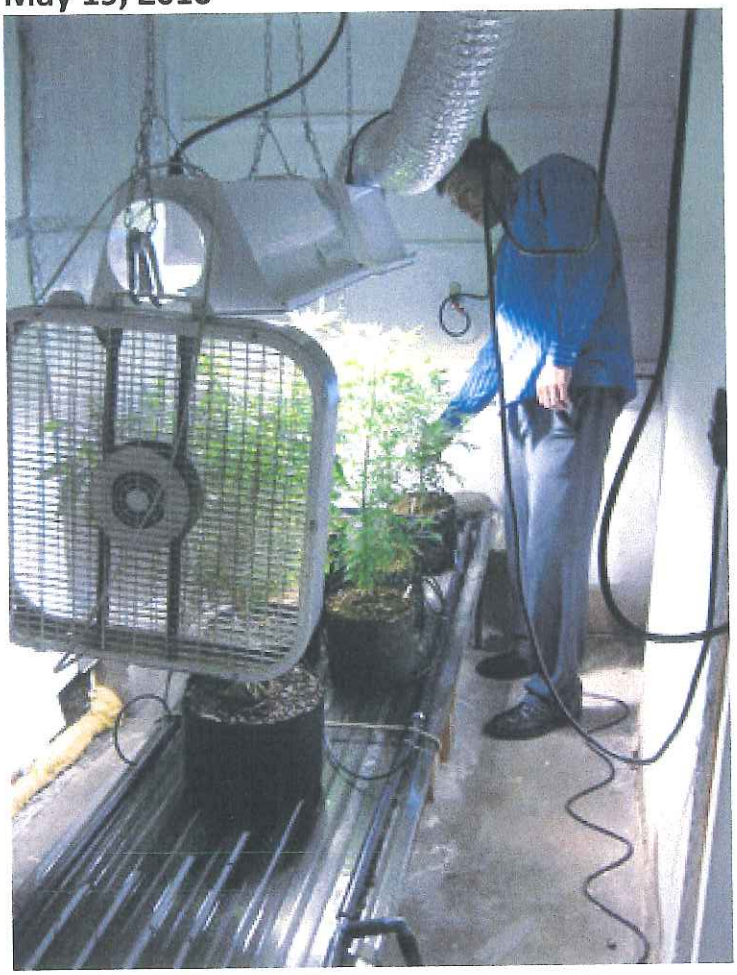
January 22, 2012

Can Marijuana Ease PTSD? A Debate Brews

by Jeff Brady

May 19, 2010



Veteran Paul Culkin created a small marijuana-growing operation in the garage of his suburban Albuquerque, N.M., home to help ease his PTSD.

The Department of Veterans Affairs finds itself in a difficult position because some vets want to use marijuana to treat symptoms of post-traumatic stress disorder. Pot possession remains illegal under federal law. The VA says that as a federal agency its doctors can't recommend using it.

The problem is especially acute in New Mexico, where one-fourth of the state's more than 1,600 medical marijuana patients are PTSD sufferers.

'Medical Cannabis Saved Our Marriage'

Paul Culkin of Rio Rancho, N.M., traces his PTSD back to 2004 when he was in Kosovo and part of an Army bomb squad. A car crashed into a business. The manager was inside trying to put out a fire. Culkin went in once to try to get him to leave, but he wouldn't go.

"The second time when I went in to get him out of there — that's when the car bomb exploded and the glass hit me," Culkin says.

He recovered from the physical wounds, but years later the trauma of that moment can come back without warning.

"Sometimes you'll see a car that's just not in the right place and it'll send me back to that thinking that it could, possibly, be a car bomb," Culkin says.

Culkin started avoiding social situations and was quick to anger. He says the treatment he's received from the VA — mostly counseling and antidepressant medication — has helped. But, he says, marijuana also works well to relieve his anxiety.

To be legal in New Mexico, he had to go outside the VA system and pay for another doctor and a psychiatrist to recommend him for the state's medical marijuana program. Then he spent more than $1,500 to set up a small growing operation in his garage.

Victoria Culkin says that her husband Paul's marijuana use saved their marriage.

Culkin says he doesn't usually smoke the marijuana, instead choosing to dissolve an extract in hot chocolate or tea so he can control the dose better.

His wife, Victoria, says the marijuana has made a big difference.

"He's a different person. He's a better person. He's more open. He's more communicative," she says. "At one point, we almost got a divorce, and I can honestly say that I think medical cannabis saved our marriage and our family."

The Quest For Solid Research

Anecdotal evidence such as this hasn't swayed the VA. The agency responded to NPR's questions on the matter with this statement: "Based on guidance issued by the Drug Enforcement Administration and the Department of Justice, VA General Counsel has advised that completion of a state medical marijuana form is in violation of the Controlled Substances Act and subject to its enforcement provisions.

Therefore VA physicians and practitioners may not participate in state medical marijuana programs. VA has addressed issues/questions regarding medical marijuana separately as they have arisen but is in the process of developing national policy."

Meanwhile there are still questions about marijuana's effectiveness, especially in the medical community.

Instead of smoking marijuana, Culkin stirs a homemade extract of marijuana into hot chocolate or tea to control the dosage. Culkin says he doesn't use marijuana to a level that he loses control.

"There is no solid evidence that cannabinoids — that marijuana — is, in itself, an effective treatment for post-traumatic stress disorder," says Dr. David Spiegel, director of the Stanford Center on Stress and Health. "Before anyone can claim that, there needs to be some more solid research on that topic."

Spiegel says recovery from trauma begins with the victims regaining control, over both their bodies and their mental reactions to the traumatic event. Smoking marijuana could make that more difficult, he says.

"The last thing you want is to be losing control at a time when you're remembering an event in which you lost control," Spiegel says.

Culkin says he doesn't use marijuana to a level that he loses control.

"There is a difference between medical cannabis and what you did back in college," Culkin says. "Smoking in the dorm room and listening to Pink Floyd is not what medical cannabis is about."

Culkin's experience has turned him into an activist. He started an informal patients group a few months back and has become a spokesman for others who believe they were helped by marijuana.

The arguments around marijuana and PTSD start running in circles at a certain point. Scientists say more research is needed. Activists counter that the federal government has blocked research because marijuana is illegal. The American Medical Association has called for controlled studies to settle this and other questions about the effectiveness of marijuana.

Meanwhile, policymakers in states with medical marijuana programs have to make decisions now, and they're reaching different conclusions. While New Mexico found there's enough evidence to approve marijuana use for PTSD, next door in Colorado lawmakers recently rejected a similar proposal.

Veterans Need and Deserve Medical Marijuana

September 29, 2011
By Lanny Swerdlow, RN

Although the medical use of marijuana has been legal in the state of California since 1996, veterans using VA hospitals have found themselves between a rock and a hard place as VA doctors refused to recognize their right to this medicine and would refuse medical services, especially pain management treatments, if they used marijuana. This conundrum seems to be resolved as on July 6, 2010 the Veterans Affairs Department announced that they will be issuing a directive to all VA hospitals that allows for the use of marijuana medicinally in states where its use has been legalized when recommended by a physician.

In a letter to Michael Krawitz, director of Veterans for Medical Marijuana Access, Under Secretary for Health for the Department of Veterans Affairs Robert Petzel, M.D. wrote "if a Veteran obtains and uses medical marijuana in a manner consistent with state law, testing positive for marijuana would not preclude the Veteran from receiving opioids for pain management in a Department of Veterans Affairs (VA) facility."

Due to federal law, VA doctors would still be prohibited from providing recommendations to use marijuana for their patients, but patients who obtain recommendations from other doctors would no longer have to choose between receiving care at VA facilities and using marijuana.

Dr. Petzel advised veterans to inform doctors of the use of medical marijuana just as they would inform their doctor of the use of any other non-VA prescribed medications or supplements. VA physicians would retain the discretion to prescribe or not prescribe medications in conjunction with the use of marijuana medicinally.

The medicinal use of marijuana is legendary, dating back almost 5,000 years when a Chinese physician wrote of using cannabis to treat pain, mental problems and female ailments such as menopause and menstrual cramps. The medicinal use of marijuana is now being revived and substantiated through a virtual litany of published peer-reviewed evidentiary-based research demonstrating marijuana effective in reducing pain, facilitating sleep, relieving depression and fighting cancer.

One of the debilitating ailments plaguing many soldiers returning from duty in Iraq and Afghanistan is PTSD—Post-Traumatic Stress Disorder, once known as "battle fatigue" or "shell shock." PTSD is a chronic condition that follows from exposure to a single terrifying event or continuous emotional trauma. The symptoms of PTSD include persistent frightening thoughts with memories of the ordeal causing chronic depression, insomnia and irritability. These problems are compounded by alcohol which many veterans turn to for relief.

Chronic pain from old physical injuries compounds these problems with narcotic dependence and the debilitating side effects of opioid medications provided by physicians. Marijuana excels in its ability to treat all of these symptoms effectively and safely and with none of the dangerous and nausea inducing

side effects of many prescription pharmaceuticals. The only notable side effect of marijuana use is a mild euphoric state of feeling good which most consider a positive and beneficial ancillary effect.

Pioneering medical marijuana physician Dr. Tod Mikuriya, MD, has written that "Cannabis relieves pain, enables sleep, normalizes gastrointestinal function and restores peristalsis. Fortified by improved digestion and adequate rest, the patient can resist being overwhelmed by triggering stimuli. There is no other psychotherapeutic drug with these synergistic and complementary effects."

For all these reasons and many more, veterans in the 16 states that allow the use of marijuana medicinally are relieved that they no longer have to make the decision between giving up their VA medical benefits and using marijuana.

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Should we be treating PTSD with THC?

Women suffering from post-traumatic stress as a result of sexual assaults are being prescribed psychiatric medicines, even though there's plenty of anecdotal evidence that medical cannabis is another potential solution

By Ariela Bankier

D., a 26-year-old woman from the north of Israel, says she began to suffer from nightmares about seven years ago, after her partner raped her. After undergoing various forms of therapy, she thought she had largely put the trauma behind her. Then, two years ago, she chanced to see the rapist not far from her home. The nightmares came swarming back.

"I fell into a depression that went on until not long ago, during which I hardly slept or ate," she says in a quiet voice. "My whole life turned upside down. I left my job. Everything came to a stop. I went back to taking antidepressants and tranquilizers - Cipralex, Lustral and Prozac; sleeping pills that made me addicted. It was a nightmare. There was no way I could get through the day without those pills. Then I discovered cannabis."

Of approximately 6,000 Israelis currently being treated with medical cannabis (aka medical marijuana), most suffer from chronic pain and terminal illnesses. The therapeutic potential of cannabis has been known for many years and is recognized by the Health Ministry. But many patients - for example, victims of sexual assault who suffer from post-traumatic stress disorder (PTSD) and have a psychiatric recommendation for treatment with medical cannabis - encounter bureaucratic obstacles.

A year and a half ago, Dr. Yehuda Baruch - the chair of the Health Ministry's advisory board for medical cannabis - recognized the effectiveness of the substance for PTSD sufferers. Within a year, 142 requests by such patients for treatment were approved. Dozens of soldiers who suffer from PTSD as a result of their army service were, and continue to be, treated with medical cannabis, with the authorization and support of the Health Ministry and the Ministry of Defense. However, victims of sexual assault have been left out in the cold.

For D., marijuana is not a drug but a medicine. "When I smoked, I didn't need medicines," she says. "It didn't make my life good and beautiful, but it did make it bearable." She now shuns the array of medicines and sleeping pills she took because of the side effects. "If you take sleeping pills, you will bring yourself into sleep mode, you will succeed in getting yourself into bed and shutting off the light, but in the morning you are not the same person. You don't function. The quantity of pills I need in order to fall asleep will turn me into a zombie the next day. My brain is erased; people speak to me but I don't function. How can you live like that? How can you work like that, study, go out of the house, communicate with people?

"I refuse to take antidepressants because of the huge amount of weight I put on, and which I was able to shed only after I stopped taking them," she adds. "They also gave me constant stomachaches, made me nauseous and itchy, and caused dry skin and headaches. That's what life with medicinal drugs is like. So, yes, I'm not depressed. I don't want to die, but I also don't want to live. I'm not me, I don't feel anything, I'm some kind of robot - not happy, not sad, not anything. I am a straight line. It's not a life."

In June 2010, D. and the psychiatrist who was treating her requested a permit for the use of medical cannabis from the Health Ministry. A year later, she is still waiting for an answer. With no alternative, she smokes cannabis obtained illegally. "I am not a criminal," she says. "I need treatment and I can't go back to the serious side effects, which only make things worse."

The cannabis is effective, but fear of the police leaves her in a constant state of anxiety. "These days, most of my nightmares have to do with the police arriving and entering my home," D. says. "It's like rape, as though this is the only safe place I still have but it's not actually safe."

Perchance to dream

Tens of thousands of Israelis are afflicted by a wide variety of traumas every year, caused by everything from battle fatigue, terrorist attacks and road accidents to life threatening diseases. And about 3,000 sexual assaults are perpetrated each year. A small percentage of people, unable to liberate themselves from the trauma, are classified as suffering from PTSD. The conventional treatment in hospitals fuses psychology - in the form of cognitive therapy techniques - with psychiatric medicines, including antianxiety medications, sleeping pills and antidepressants. In recent years, researchers around the world have begun to probe more natural treatments, notably medical marijuana. New Mexico, for example, has passed legislation authorizing medical cannabis for soldiers who returned from a tour of duty in Iraq or Afghanistan suffering from PTSD. A number of interesting studies have been carried out on this subject in Israel. Prof. Rafael

Meshulam, an Israel Prize laureate for chemistry and one of the country's leading experts in medical cannabis, and Dr. Irit Akirav, from the Department of Psychology at the University of Haifa, have shown, in separate research, some of the marked advantages of the treatment. "At this stage we are talking only about rats," Dr. Akirav explains, "but the model is relevant for humans, too."

According to Prof. Meshulam, "The active material in marijuana, tetrahydrocannibinol (THC), emulates activity of materials that are bound up with an important system in the body - the endocannabinoid system. This system plays a critical role in regulating proper eating functions and various mental states, including forgetting. Forgetting is not necessarily something negative. If you enter a department store where there are a thousand people, do you want to remember what each of them looked like? Of course not. It's the same with trauma. What is post-trauma, actually? Something terrible happened and left a very strong impression. A week passes, a month passes, and it doesn't go away. You are unable to forget."

The experiments conducted by Prof. Meshulam and his colleagues were based on administering medical cannabis to mice that had been exposed to a trauma (electric shock) after their endocannabinoid system was neutralized. The results were clearly positive. The hypothesis was confirmed in subsequent experiments, including a famous experiment carried out by Dr. George Fraser, a Canadian psychiatrist with abundant experience in treating soldiers with PTSD. "A significant improvement was observed in 70 percent of the soldiers who took part in that research, particularly in regard to their sleep," Prof. Meshulam notes. "And why do we examine forgetting and sleep in particular? Because they are essential. One of the most terrible phenomena among PTSD sufferers is that they are unable to sleep: They are afflicted by nightmares and are afraid to fall asleep."

In a similar experiment using rats, Dr. Akirav examined the effect of medical cannabis on a mechanism known as "extinction learning," which serves humans and animals to overcome past trauma. In this experiment, the medical cannabis is injected directly into the part of the brain called the amygdala, which is responsible for emotional memory and the sensation of fear. The rats were also exposed to additional pressure, resembling the permanent stress to which post-trauma patients are subject.

"The medical cannabis helped the rats with extinction learning, despite the trauma and the additional pressure," Dr. Akirav says. "That is extremely important, because researchers and psychiatrists maintain that in human beings who develop post-trauma, something has gone awry in the extinction learning mechanism - that is, they do not succeed in learning that something that was once dangerous is now safe." She emphasizes that the aim of treatment with medical cannabis is not to generate a high or a state of euphoria. "It is a tool," she explains. "The animals do not get a high, nor is their memory completely erased. The aim is simply to influence the element in the emotional memory that is responsible for extinction learning."

More dangerous and addictive

Cannabis is a medicine in every respect, Prof. Meshulam says. He does not understand the reluctance of many psychiatrists to make use of the substance on the grounds that it is dangerous and addictive. "The great majority of them are simply uninformed, period," he believes. "With psychiatric drugs, it's also hard to know what will help who, because it's hard to know which mechanism has gone wrong and which medicine will help. But to say marijuana can't help is from sheer lack of knowledge."

Even though the Health Ministry is aware of the findings of the experiments conducted in Israel and abroad, patients now face increasing obstacles instead of benefiting from solutions. "It is amazing that for my post-trauma I easily - and without unnecessary arguments - get hard drugs such as opiates," says N., a 27-year-old woman from the south of the country who was a victim of sexual assault. "I call it medical heroin, because there isn't much difference between the heroin that's sold on the street and the OxyContin that is prescribed for me. I also get sleeping pills from the benzaprine family, and for dessert I am offered Ritalin. The paradox is that all these medicines are far more dangerous and addictive than marijuana."

The situation is "absurd," says Dr. Ilya Reznik, an expert on the subject and medical director of the Israel Institute for Diagnostic Neuropsychiatry. "Cannabis was approved for post-trauma [treatment] in the past, and then suddenly Dr. Baruch demanded that those applying for approval for post-trauma treatment be recognized as disabled by the National Insurance Institute or by the Defense Ministry, and show proven experience with at least three psychiatric drugs for a very long period - at least half a year with each drug. He also demanded that we refer to cannabis only those patients who are resistant to all the other drugs, and that cannabis constitute a third - or fourth-line treatment for post-trauma. He was actually stipulating far harsher conditions than those demanded by clinical experiments, because cannabis is no more than a medicinal herb, and you can't compare a medicinal herb to Prozac and its like, which had all the wisdom of the scientific world invested in their development."

For whom is cannabis suitable?

Reznik: "Cannabis is suitable for intermediate cases; there is no point demanding that it be used only in the hardest cases, in which no medicine helps. That is just wrong. People diagnosed with cancer receive cannabis straightaway. So why, in cases of post-trauma, is it necessary to wait for the most difficult cases before they are ready to allow its use, if at all? The Health Ministry's approach in this matter is insensitive and without any scientific basis - and I say this on the record, because Dr. Baruch and I talked about it in several scientific conferences and I told him then that what the ministry is doing is not right. What if someone does not want to be officially categorized as disabled? Some people are ashamed to go before committees. Does that mean they are not entitled? That cannot be a Health Ministry criterion."

What do your physician colleagues say?

"On this issue, the medical establishment is divided into two: 95 percent are neutral-to-negative about cannabis, and the rest are neutral -to-positive. No more. Why? It's conservatism. They were always taught that cannabis is bad, that cannabis is a drug, and the moment they hear the word 'cannabis' they see handcuffs looming on the horizon. So they run from it.

"Very few in Israel have experience with medical cannabis. Yehuda Baruch allows himself to set criteria, but he says, 'Persuade me, I am receptive.' He is not a bad person - we have friendly relations - and he is open to suggestions, but the criterion he set is not based on scientific data, period."

Like a walking zombie

"We do not get authorization," D. says. "Apparently only men get such authorization for PTSD. We women are not heroic soldiers who were traumatized while trying to defend the homeland. It's only now that I understand that I am a second-class citizen: I am a woman, I am the victim of a sexual assault, I suffer from depression, but I am apparently not as good as someone who has a backache."

The Health Ministry says no more permits are being issued for the use of medical cannabis in post-trauma therapy, unless the patient is also suffering from a disease that might justify its use (see box). Disabled army veterans who received authorization in the past are continuing with cannabis therapy but are loath to be interviewed, even anonymously, for fear they will lose the authorization.

One former soldier who did agree to speak on the record is Avraham Sherwood, who was wounded in an incident in which two armored personnel carriers were destroyed and 13 soldiers killed in attacks by Palestinians in the Gaza Strip on successive days in May 2004. He saw his buddies killed and since then has suffered from physical problems and PTSD. "My previous doctor was dead set against the use of marijuana," Sherwood says. "In every meeting he would just give me a prescription for something new or raise the dosage of what I was taking. The problem with these medicines is they cause extreme side effects. They contain cortisone, you start to put on weight, everything is stored up in the body, your face bloats and you look like a walking zombie.

"The antipsychotic drugs cause all kinds of stomach problems - to this day I suffer from heartburn because of them," Sherwood adds. "From my point of view - I say only from my point of view, I don't know about other people - the psychiatric drugs failed to treat my PTSD. Then one day a friend saw that I was walking around with a whole case of medicines - for morning, afternoon and evening - and suggested that maybe I should get a second opinion. That's how I got to Dr. Baruch and told him I wanted to cut down the medicinal dosage and start functioning again." According to Sherwood, Dr. Baruch - the same Dr. Baruch who is preventing other PTSD victims from getting medical cannabis - was his salvation. "From my point of view, the man is a saint," Sherwood says. "He saved me. He asked me if I wanted to try medical marijuana, and I got very uptight. I was afraid of the side effects, things that I now know are nonsense, but which absolutely made me shake when he said the word 'marijuana.' My previous doctor had totally frightened both me and my father: He said I would become addicted and that I would move on to hard drugs, to heroin. But actually I had already used heroin, because the pills I was taking contained morphine - and what is morphine?"

Despite his fears, Sherwood decided to try medical cannabis for a month. "My life changed completely," he says with visible emotion. "My face went back to what it was, I lost weight, I became a human being again. People are afraid, but there are problems caused by taking so many medicines that it's hard to know what a person is suffering from. In the meantime, I am with marijuana. Dr. Baruch left me with one psychiatric drug, which he says is keeping me in balance for now, and he will gradually lower its dosage. I went down from 17 medicines to five, including those against pains, against the nerve damage in my hand and against heartburn."

Dr. Baruch's response makes no mention of Sherwood, but it can be gleaned from it that, even if one of his patients received authorization to be treated with medical cannabis, this was not due to post-traumatic symptoms but to some other medical problem.

"Not one of [my] private patients received authorization for treatment with medical cannabis for PTSD," Dr. Baruch stated. "As a rule, I do not take patients who want treatment with medical cannabis in my private clinic. To the best of my knowledge, only three patients who went through my private clinic in the six years during which I have dealt with the subject have received authorization to use medical cannabis. The vast majority of the 142 people [who received authorization] are requests from other psychiatrists."

Like magic

In the wake of Sherwood's favorable reaction and the positive experience that soldiers suffering from PTSD have had with medical cannabis, it is difficult to understand the refusal of the Health Ministry to provide the same effective treatment to victims of sexual assault - who suffer from equally debilitating post-traumatic symptoms. That is exactly the question that L. asked for many long months. A self-employed woman in her thirties from the north of the country, she has been suffering from PTSD for years as a result of childhood sexual assault.

"That is how I grew up. I don't know the meaning of being normal," she says. "I know what it means to be depressed and have nightmares and anxieties and feel uncomfortable among people. For years I didn't tell anyone. It took many years before I told my parents, and they were very uncomfortable with it. It's the kind of thing you don't talk about at home. All the talk is about my problems, and it's hard for them to make the connection. I had psychological therapy but nothing helped. It's not easy." She falls silent.

After composing herself, L. continues: "About six years ago, someone gave me medical cannabis, which he had, and it really helped me. Suddenly I was able to obtain a master's degree, find a job and have a social life. It was like magic. [Previously] I had a great many nightmares - I woke from sleep shouting - and it helped me stop being wound up all the time."

She also continued to receive medicinal treatment. "My doctor kept switching my drugs. I would tell her that they caused side effects and that I felt no change, but she would say, 'Take this, it will help you' - she just wasn't listening to me. Two years ago, I looked at all kinds of websites about medical cannabis and I saw that it was used in treatment for PTSD. Hey, I thought, this can really help me. Then I found Dr. S. and told him about my condition. He said medical cannabis could help me a great deal."

Despite the unreserved recommendation of Dr. S. - an expert in post-traumatic therapy - L. discovered that the Health Ministry wasn't about to come to her aid. "There were delays for six months," she remembers. "Dr. S. kept telling me he wanted to help but couldn't, because of all kinds of restraints imposed on him from above. In the end he got a green light to recommend me, and then another half a year went by. In the meantime, other people told me they had received authorization, and it drove me crazy.

"People tell me, 'What's the problem? Tell them you have cluster headaches. What, you don't know you have them? They're a terrific thing. There are no tests for it. You just say you have the symptoms that you read about on the Internet and try. They'll give you Voltaren, you'll take it a couple of times and then throw it away and say it doesn't help. Then you ask for medical cannabis.' So, do I have to lie to get proper medical treatment?"

This month, L. was informed that her request has been approved. That's good news for her, but many patients - including the other women interviewed for this article - are still waiting.

Sexual favors

An egregious by-product of the Health Ministry's confused policy is the involvement of people who exploit patients' distress for their own personal benefit. One of the people L. encountered while looking for someone to help her was a man who presented himself as a volunteer with the Health Ministry. The ministry says volunteers are an integral part of its work, but it's not clear what training they get, whether background checks are run on them and what medical secrets they have access to.

According to L., the volunteer told her he could help her get a speedy authorization, but he wanted a quid pro quo. "He told me, 'You will have to come here and we will have to interview you.' I asked him what he was talking about. 'I have a doctor,' I said, 'I have a recommendation, I have to know whether you can help me or not.' He replied, 'Yes. Maybe I will come to your place.' In short, I understood that things were heading in an unpleasant direction."

A tape recording of their conversation makes it clear that the unpleasant direction was heading toward sexual favors:

Volunteer: "Do you hear? Like I did with a woman friend of mine who suffered from depression ... I got her a permit, the good life, I pampered her."

L.: "But I don't like people to touch me."

Volunteer: "You like my work."

L.: "No, no, I don't. I don't like it when people touch me."

Volunteer: "It's not about getting laid. I told you already back then, I don't want to sleep with you."

L.: "I can't..."

Volunteer: "Whatever you like. You can smoke before, so you'll be in a good mood."

L.: "What does this have to do with it? There is an authorization that gets signed by the ministry, no? So what's the connection?"

Volunteer: "Fine, e-mail me your request."

A spokesperson for the Health Ministry said in response: "That man is no longer a volunteer with us. At this stage, the ministry's work [in the area of medical cannabis] is based on volunteers, because until late 2010 there was no budgeting for professional staff. In the 2011 budget we expect to receive budgetary allocations to hire manpower, but not for permanent positions. Volunteers will therefore continue to work in the ministry; volunteering is valuable as such for patients."

One big mess

"Many people ask me why I don't pretend to have a disease in order to get cannabis," D. says. "There may be some people who do that, but I don't want to. I am afraid as it is, because I am treating myself, albeit under medical supervision - my psychiatrist knows that I smoke [cannabis] and accepts it and understands the situation."

All the women who were interviewed for this article say that, at one stage or another, they were told they would have to wait for the results of an experiment being conducted by the Health Ministry to examine the effect of medical cannabis on PTSD patients; any information about the experiment is shrouded in mystery.

According to a psychiatrist who asked for anonymity, the experiment is problematic: "Patients were told that if they wanted authorization, they should take part in the study," he says. "But it is wrong and illegal to say anything like that. And then, after some had agreed to take part, they were told, 'Just a minute, we are still organizing a group. Wait. We'll let you know.' One big mess.

"Yehuda Baruch decided to do a study precisely on post-trauma patients. I say that it is a conflict of interest for the regulator to conduct a study. The situation now is that people can't get authorization until the study is completed, and it hasn't yet begun. In the meantime, people are left dangling, with no answer, and are suffering."

D. is left feeling despair about the situation: "At last we found something that helps, but we are not getting it," she says. "From their point of view, I guess it's preferable for us to be in a situation of 'Another second and I will kill myself,' than 'Things are good but I am a criminal.' To whom are women like me - who had such terrible things done to them by men - supposed to turn in order to get the medicine they need? To drug dealers! It's like going back into this circle of scary psychopathic men who, in a second, can change totally. It's going to criminals to get medicine. Totally absurd."

This story is by: Ariela Bankier