NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Agony and Ecstasy: Party Drug or Breakthrough Treatment for PTSD?

by

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Part I – Background on Post-Traumatic Stress Disorder

Jake, age 21, was on his second tour of active duty in Iraq as a private first class when a roadside bomb flipped his convoy and resulted in his honorable discharge due to a severe spinal injury. He had returned home 10 months ago to his wife, Caroline, who supported him through months of rehabilitation at the VA hospital an hour from their home.

Throughout the recovery process, Caroline tried to overlook the changes she noticed in her husband's personality—he had just returned from war, after all, with a life-altering injury. Jake didn't speak to her about what he had been through or how he felt now that he was back on American soil. But his temper seemed shorter and his outbursts more fierce. All of this Caroline could understand. His rehabilitation was long and painful; it prevented him from finding a job and from getting back to the real world, and it was a constant reminder of the war. On top of that, Caroline had to give up shifts at work to get him to his appointments at the hospital and money was tight. Still, Caroline was patient during the months Jake spent silent and angry until his spinal injury was declared healed and visits to the hospital were no longer needed. Caroline had thought that as soon as Jake's body healed, he would become the man she had loved and remembered and that they would begin the life together that they had always planned.

But Jake did not return to normal. He barely slept, and when he did his nights were full of terror. Baghdad haunted him through his nightmares, forcing him to relive moments he wanted to forget. He spent his days in a haze with no will to move or do anything. He became infuriated when Caroline would try to talk to him about it, and he often found himself yelling at her for no reason. Alcohol was often the only relief he could find to cloud his mind and keep the memories out.

After six months at home, Jake was a shadow of his former self. He drank all the time, woke up sweating or screaming almost nightly, and hardly acknowledged his wife. Caroline realized that he was not getting better and that he needed help. She scheduled an appointment with a therapist, Dr. Reece, and forced an unwilling Jake to go.

Dr. Reece quickly recognized Jake's symptoms and diagnosed him with severe post-traumatic stress disorder (PTSD). The doctor provided Jake and Caroline with a pamphlet about PTSD and possible treatment options.

Resources

Consult the following resources to answer the questions further below.

1. PTSD patient information pamphlet (Appendix 1)
2. *Trauma Abuse Treatment.* GAD vs. PTSD [webpage]. Distinguishing between PTSD and generalized anxiety disorder (GAD): <http://traumaabusetreatment.com/gad-vs-ptsd>.

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3. *Level Black – PTSD and the War at Home*. Video by Staff Sgt. Robert Ham. Running time: 4:59 min. Personal account of PTSD: <https://www.youtu.be/Fc6_aTnRXQ>.
4. Criteria for diagnosis of PTSD, as published in the American Psychiatric Association's *Diagnostic and Statistical Manual V (DSM-5)* (Appendix 2).
5. Shin, L.M., S.L. Rauch, and R.K. Pitman. 2006. Amygdala, prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences* 1071: 67–79.
6. Alternate open-access reference, which can be used as a substitute for Resource 5 (Shin et al.): Morey, R., and V.M. Brown. 2012. Neural systems for cognitive and emotional processing in posttraumatic stress disorder. *Frontiers in Psychology* 3: 449. doi: <http://dx.doi.org/10.3389/fpsyg.2012.00449>.

Questions

1. In what ways do environmental circumstances, learning and cognition, and biology interact to result in the symptoms of PTSD?
2. In clinical diagnosis, how is PTSD distinguished from depression or anxiety?
3. How are brain structures such as the amygdala, hypothalamus, hippocampus, and prefrontal cortex involved in the manifestation of PTSD symptoms?

Part II – Selective Serotonin Reuptake Inhibitors to Treat PTSD

Physicians and psychotherapists use the guidance of governmental regulations, professional organizations, and their own clinical experience to determine what treatment or treatments is/are appropriate for each patient. PTSD, like all psychological disorders, is not a singular disorder; the causes, symptoms, and ideal treatments vary widely from individual to individual. However, basic and clinical scientific research is used to determine which treatments are the safest and most effective for "typical" PTSD sufferers.

The front-line treatment for PTSD is psychotherapy. Several evidence-based approaches to psychotherapy are effective in treating many individuals with PTSD. However when PTSD is resistant to psychotherapy alone, medications can be added to the treatment regimen. The selective serotonin reuptake inhibitors (SSRIs) paroxetine (brand name Paxil) and sertraline (brand name Zoloft) have been approved by the Food and Drug Administration (FDA) for use in PTSD. To be approved by the FDA, a drug must be shown in preclinical (animal model) trials and Phase I and Phase II clinical (human) trials to be both safe for use and effective in treating the condition for which it is indicated.

Resources

Consult the following resources to answer the questions below.

1. FDA drug approval process: <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm295473.htm>.
2. Excerpts from Zoloft drug label (Appendix 3)

Questions

1. Describe the general goals for each of the three major phases of clinical studies (Phases I, II, and III). Why does the FDA have different criteria for number and types of volunteer subjects for each phase of a clinical trial?
2. Explain the biological rationale for using SSRIs to treat PTSD.
3. Review the clinical trial data describing the safety and efficacy data of sertraline for PTSD (Zoloft drug label excerpts, Appendix 3). Based on the data reported in the drug label, what are the primary side effects or safety risks that Jake and Caroline should consider? Note the number of patients participating in the reported studies and any gender effects. Do the efficacy studies of sertraline for PTSD provide strong evidence that Jake is likely to benefit from this treatment? Explain your answer.
4. What course of treatment would you recommend for Jake? Explain your rationale for this recommendation.

Part III – An Alternate Treatment Option

After five months of intensive psychotherapy with Jake, Dr. Reece decided to also prescribe sertraline and a sleep aid. Jake had recently become more open to therapy and treatment and was sleeping more, but he had not seen any real changes in his other symptoms. He still jumped at even the smallest sound, was easily angered, and still haunted by nightmares.

Dr. Reece told Jake about a new experimental treatment that he could try. It reduced anxiety and reportedly helped PTSD patients to cope with their traumatic experiences.

"What is it?" Jake asked.

"MDMA," Dr. Reece replied. "The technical name is methylenedioxymethamphetamine."

Jake was incredulous. "Like *ecstasy*? Isn't that illegal?"

"Well, technically it's true that MDMA is illegal, but it's also been investigated as an adjunct to psychotherapy in the treatment of PTSD," explained Dr. Reece. "A recent pilot study in the U.S. reported positive preliminary results. In healthy volunteers, MDMA seemed to lessen the impact of painful memories, which supports the idea that it could help patients with PTSD revisit their traumatic experiences in psychotherapy without being overwhelmed by negative emotions. This drug can help you to work through the traumatic events you experienced in Iraq. You'll never be able to heal completely enough to move on with your life if you cannot face those memories head on. We've tried several treatments with you and have had limited success. MDMA may be the one that works, but you need to decide if this is what you want. I can arrange to have you enrolled in the next clinical trial if you decide that you want to try this new avenue."

Jake didn't know what to think. He desperately wanted to get his PTSD under control and move on with his life. At the end of the session, the therapist gave Jake a recent news article and a pamphlet about MDMA and how it affects the brain. Jake knew Caroline would want to know every detail, so he took them home to discuss with her.

Resources

Consult the following resources to answer the questions below.

1. Skormorowsky, A. How Molly works in the brain. 2015. *Scientific American:* <http://www.scientificamerican.com/article/how-molly-works-in-the-brain/>.
2. MDMA informational pamphlet (Appendix 4).

Questions

1. What are the actions and effects of MDMA? How do these actions fit with the profile of an effective and desirable treatment for PTSD?
2. Evaluate the structure of MDMA in comparison with serotonin, norepinephrine, and dopamine. Identify key pharmacophore elements in MDMA that may mimic the endogenous neurotransmitters.
3. Compare and contrast how the different protein targets (receptors or neurotransmitter transporters) of sertraline (described in the Zoloft drug label) and MDMA (described in the MDMA pamphlet, Appendix 4) lead to differences in neurotransmitter levels and synaptic activity for the relevant neurotransmitter systems.
4. Review the potential safety risks vs. therapeutic benefit associated with the use of sertraline to treat PTSD (Part II, Question 3.) Using the information provided in the MDMA pamphlet, identify the potential risks and benefits of MDMA therapy for PTSD. Compare the risk-benefit profiles between these two drugs as potential therapeutic agents for treatment of PTSD.
5. How does the Drug Enforcement Administration (DEA) scheduling (described in Appendix 4) of MDMA impact its use in clinical practice and research?
6. Given the information we have reviewed today, what treatment plan would you recommend for Jake? What is your rationale for this recommendation? What remaining questions, concerns, and/or reservations do you have regarding this potential treatment?

Part IV – Panel Discussion

Jake and Caroline carefully read the PTSD literature given to them by Dr. Reece.

"You know, Caroline, I think this MDMA treatment might be worth a try. If it's been helping other patients get over their PTSD, maybe it will help me too. I'm willing to try pretty much anything, at this point, if it might help me get back to normal. I can't take much more of these nightmares and flashbacks of the war."

Although Jake's violent mood swings had been especially difficult for Caroline, she still worried that the experimental MDMA treatment would just make things worse.

She re-read the pamphlet on potential MDMA side effects and immediately voiced her objections. "There has to be another option. This experimental treatment seems too risky and I don't want you to have to go through more trauma. PTSD alone is hard enough on you; imagine adding an experimental drug to the mix. I want you to get better, but I don't know if this is the right route."

Jake and Caroline agreed to talk to Dr. Reece together. With his guidance, they hoped to find a course of treatment that they could agree on.

At their appointment with Dr. Reece, Jake and Caroline expressed their disagreements and concerns over MDMA treatment. Dr. Reece knew of a panel discussion on the experimental MDMA treatment led by some of the top doctors and psychologists in the field that was going to be held in a neighboring city next week. He invited Jake and Caroline to attend in the belief that it would be helpful for them to hear the opinions of several experts. Jake and Caroline were eager to hear the panel discussion and hoped that it may give them some much-needed answers.

Read panel information, and prepare for panel discussion.

Panel Discussion Guidelines

Your instructor will assign you and your team one "expert panelist," whom your team will collectively represent in the panel discussion.

1. Review the specialization and viewpoints of your assigned panelist and the suggested references (Appendix 5). Your goal is to represent your panelist's perspective while providing a persuasive, informative, and accurate argument.
2. Work with your team to prepare a brief PowerPoint presentation for Jake and Caroline using data from the provided literature. Each team member should prepare one PowerPoint slide to deliver in a 2-minute presentation. Coordinate with your group members for a cohesive team presentation.
3. Remember that Jake and Caroline are non-specialists who are trying to decide whether to proceed with experimental MDMA treatment/therapy for Jake. With your team, review the PTSD patient pamphlet that was provided for Part I of the case study. Compare the writing style and content of this pamphlet with the primary articles you have been assigned. Why are these writing styles so different? Make sure your presentation is aimed at your non-specialist (patient) audience. Be sure to present some key data from your assigned article(s), but in a way that is accessible to your audience. Work together with your team to decide what information is most important to convey to Jake and Caroline. The following references provide tips for communicating science to the general public:
   - Cahan, V. 2014. Explaining your science—tips for clear communication. *Inside NIA: A Blog for Researchers.* <https://www.nia.nih.gov/research/blog/2014/11/explaining-your-science-tips-clear-communication>.
   - Bearzi, M. 2013. Five simple tips for communicating science. *National Geographic Ocean Views.* <http://voices.nationalgeographic.com/2013/10/11/5-simple-tips-for-communicating-science/>.
   - *AAAS—Center for Public Engagement with Science and Technology.* n.d. Communication fundamentals. <https://www.aaas.org/page/communication-fundamentals-0>.
4. Be prepared to field questions! After each panelist has presented, Jake and Caroline will have questions for you.

Understanding Post-Traumatic Stress Disorder

What is PTSD?

Post-traumatic Stress Disorder (PTSD) is caused by being exposed to one or more traumatic events, paired with an altered stress response system in the brain that affects one's perceptions of safety and danger. Symptoms of PTSD include:

- Intense anxiety in the form of flashbacks or nightmares
- Emotional numbness
- Anger and outbursts
- Avoidance of thoughts or situations that may bring up memories of the traumatic event.

Within the overall U.S. population, 7-8% of people will experience PTSD after a traumatic event at some point in their lifetime. This number is much higher for military personnel who have experienced combat. **Among U.S. veterans, the prevalence of PTSD is between 11 and 20%.**

For a Healthier Future

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What are the Treatments for PTSD?

Psychotherapy

Psychotherapy sessions, in which a patient speaks with a licensed therapist, are one of the primary treatment options for PTSD patients. A psychotherapy session may include exposure therapy, which exposes patients to their trauma in a controlled setting. The therapist can then help them to cope with the feelings that arise. Additionally, cognitive restructuring may be used to help patients make sense of their memories of a traumatic event. Using this method, the therapist helps patients look at what happened more objectively.

Other Treatments

Additional treatments focus on easing symptoms of PTSD rather than addressing the root cause of the disorder. For example, relaxation methods, such as meditation or breathing exercises, can help to reduce anxiety. Additionally, medications such as selective serotonin reuptake inhibitors (SSRIs) help to reduce the symptoms associated with depression. Sleep aids can also be helpful to normalize sleep patterns.

Are You or A Loved One Suffering?

What is a "normal" stress response?

Experiencing a fearful situation triggers a special program in the brain called the stress response. First, the stressful information enters parts of the brain devoted to processing vision, sound, and other sensory information. From there it is sent to the hippocampus, a part of the brain involved in memory and learning, to compare the situation with previous experiences. The hippocampus communicates the situation to the amygdala, an area of the brain that attaches emotional responses to memories. If the amygdala evaluates the situation as being dangerous, it sends a signal to the hypothalamus, which controls the autonomic (automatic) nervous system of the body.

In response to stress, the hypothalamus tells the autonomic nervous system to initiate the "fight or flight" response – causing the adrenal gland to release epinephrine (adrenaline). Epinephrine increases heart rate, blood pressure, breathing rate, and blood flow to the brain. Glucose and stored fats are released into the bloodstream to provide energy to every part of the body. The result of all of this is that the brain is alert, and muscles are primed for action.

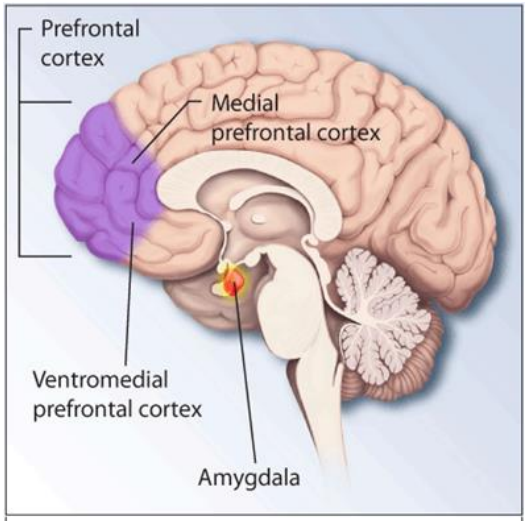
The fight or flight response then suppresses brain areas that are not critical to immediate survival, such as the hippocampus and an area of the cerebral cortex, the prefrontal cortex, that is specialized for short term memory, social cognition, and planning for the future.

The response is immediate and short-lived. In order to sustain the fight or flight response, the hypothalamus signals the release of additional cortisol by the adrenal gland, which prolongs the sympathetic nervous system response, and suppresses the immune system. When the threatening stimulus subsides, the autonomic nervous system returns the body to its normal resting rate.

How is PTSD different?

This "fight or flight" response is critical to short-term survival, but when a stressor is repetitive, prolonged, or extreme, the effects of the response can be damaging. In PTSD, the amygdala may continue to send stress-response signals to the hypothalamus, even when there is no longer a threat. This causes the body to stay primed for action, even when there is no reason for this.

Because the hippocampus is suppressed in the stress response, memories are not properly formed during a traumatic event, and may be fragmented, disconnected, or not remembered at all. The impaired memory processing, in combination with the hyperactivity of the amygdala, may cause a person with PTSD to experience the fear of their traumatic event as if it were happening to them in the present, long after the event has passed.



Brain Structures Involved in Dealing with Fear and Stress

The prefrontal cortex is another part of the brain that is suppressed during the stress response. Typically, the prefrontal cortex helps to regulate emotional responses and inhibits the amygdala during non-fearful events. Without this regulation from the prefrontal cortex, the amygdala can be hyper-activated even by non-threatening stimuli.

With decreased activity from the hippocampus and prefrontal cortex, a person suffering from PTSD cannot distinguish safe events from dangerous ones. Safe new events are perceived as dangerous, triggering the stress response all over again, keeping the person in a hyper-vigilant state.

Image References

"PTSD" by Q - http://www.dissociative-identity-disorder.net/w/images/PTSD.png. Licensed under CC0 via Wikimedia Commons https://commons.wikimedia.org/wiki/File:PTSD.png#/media/File:PTSD.png

"Ptsd-brain" by National Institutes of Health - http://www.nimh.nih.gov/health/publications/post-traumatic-stress-disorder-research-fact-sheet/index.shtml. Licensed under Public Domain via Wikimedia Commons - https://commons.wikimedia.org/wiki/File:Ptsd-brain.gif#/media/File:Ptsd-brain.gif

References

. Epidemiology of PTSD.http://www.ptsd.va.gov/professional/PTSD-overview/epidemiological-facts-ptsd.asp. Accessed June 6, 2016.

Harvard Mental Health Letter (2011). Understanding the stress response. http://www.health.harvard.edu/newsletters/Harvard_Mental_Health_Letter/2011/March/understanding-the-stress-response. Accessed June 6, 2016.

National Institutes of Health. PostTraumatic Stress Disorder research fact sheet. http://www.nimh.nih.gov/health/publications/post-traumatic-stress-disorder-research-fact-sheet/index.shtml. Accessed June 6, 2016.

Appendix 2

Diagnostic criteria for PTSD include a history of exposure to a traumatic event (Criterion A) and symptoms from each of four symptom clusters (Criteria B–E): intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity. Criteria F–H describe duration, impact on daily living, and exclusion parameters in diagnosing PTSD.

Criterion A: Stressor

The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: (one required)

1. Direct exposure.
2. Witnessing, in person.
3. Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental.
4. Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders, collecting body parts; professionals repeatedly exposed to details of child abuse). This does not include indirect non-professional exposure through electronic media, television, movies, or pictures.

Criterion B: Intrusion Symptoms

The traumatic event is persistently re-experienced in the following way(s): (one required)

1. Recurrent, involuntary, and intrusive memories. Note: Children older than six may express this symptom in repetitive play.
2. Traumatic nightmares. Note: Children may have frightening dreams without content related to the trauma(s).
3. Dissociative reactions (e.g., flashbacks) which may occur on a continuum from brief episodes to complete loss of consciousness. Note: Children may reenact the event in play.
4. Intense or prolonged distress after exposure to traumatic reminders.
5. Marked physiologic reactivity after exposure to trauma-related stimuli.

Criterion C: Avoidance

Persistent effortful avoidance of distressing trauma-related stimuli after the event: (one required)

1. Trauma-related thoughts or feelings.
2. Trauma-related external reminders (e.g., people, places, conversations, activities, objects, or situations).

Criterion D: Negative Alterations in Cognitions and Mood

Negative alterations in cognitions and mood that began or worsened after the traumatic event: (two required)

1. Inability to recall key features of the traumatic event (usually dissociative amnesia; not due to head injury, alcohol, or drugs).
2. Persistent (and often distorted) negative beliefs and expectations about oneself or the world (e.g., "I am bad," "The world is completely dangerous").
3. Persistent distorted blame of self or others for causing the traumatic event or for resulting consequences.
4. Persistent negative trauma-related emotions (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest in (pre-traumatic) significant activities.
6. Feeling alienated from others (e.g., detachment or estrangement).
7. Constricted affect: persistent inability to experience positive emotions.

Criterion E: Alterations in Arousal and Reactivity

Trauma-related alterations in arousal and reactivity that began or worsened after the traumatic event: (two required)

1. Irritable or aggressive behavior
2. Self-destructive or reckless behavior
3. Hypervigilance
4. Exaggerated startle response
5. Problems in concentration
6. Sleep disturbance

Criterion F: Duration

Persistence of symptoms (in Criteria B, C, D, and E) for more than one month.

Criterion G: Functional Significance

Significant symptom-related distress or functional impairment (e.g., social, occupational).

Criterion H: Exclusion

Disturbance is not due to medication, substance use, or other illness.

Reference

American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed.* Washington, DC: American Psychiatric Association.

Appendix 3 – Zoloft FDA Drug Label Excerpts

Source: <http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/019839s070,020990s032lbl.pdf> Accessed June 23, 2016.

ZOLOFT®

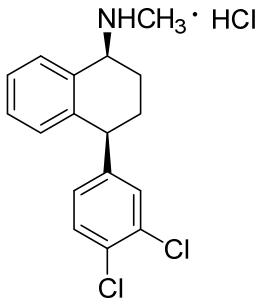
(sertraline hydrochloride)
Tablets and Oral Concentrate

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

DESCRIPTION

ZOLOFT® (sertraline hydrochloride) is a selective serotonin reuptake inhibitor (SSRI) for oral administration. It has a molecular weight of 342.7. Sertraline hydrochloride has the following chemical name: (1*S*-*cis*)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-*N*-methyl-1-naphthalenamine hydrochloride. The empirical formula C17H17NCl2•HCl is represented by the following structural formula:



CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of sertraline is presumed to be linked to its inhibition of CNS neuronal uptake of serotonin (5HT). Studies at clinically relevant doses in man have demonstrated that sertraline blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that sertraline is a potent and selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. *In vitro* studies have shown that sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), or benzodiazepine receptors; antagonism of such receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs. The chronic administration of sertraline was found in animals to down regulate brain norepinephrine receptors, as has been observed with other drugs effective in the treatment of major depressive disorder. Sertraline does not inhibit monoamine oxidase.

Posttraumatic Stress Disorder (PTSD)–The effectiveness of ZOLOFT in the treatment of PTSD was established in two multicenter placebo-controlled studies (Studies 1-2) of adult outpatients who met DSM-III-R criteria for PTSD. The mean duration of PTSD for these patients was 12 years (Studies 1 and 2 combined) and 44% of patients (169 of the 385 patients treated) had secondary depressive disorder.

Studies 1 and 2 were 12-week flexible dose studies. ZOLOFT was initiated at 25 mg/day for the first week, and patients were then dosed in the range of 50-200 mg/day on the basis of clinical response and toleration. The mean ZOLOFT dose for completers was 146 mg/day and 151 mg/day, respectively for Studies 1 and 2. Study outcome was assessed by the Clinician-Administered PTSD Scale Part 2 (CAPS) which is a multi-item instrument that measures the three PTSD diagnostic symptom clusters of re-experiencing/intrusion, avoidance/numbing, and hyperarousal as well as the patient-rated Impact of Event Scale (IES) which measures intrusion and avoidance symptoms. ZOLOFT was shown to be significantly more effective than placebo on change from baseline to endpoint on the CAPS, IES and on the Clinical Global Impressions (CGI) Severity of Illness and Global Improvement scores. In two additional placebo-controlled PTSD trials, the difference in response to treatment between patients receiving ZOLOFT and patients receiving placebo was not statistically significant. One of these additional studies was conducted in patients similar to those recruited for Studies 1 and 2, while the second additional study was conducted in predominantly male veterans.

As PTSD is a more common disorder in women than men, the majority (76%) of patients in these trials were women (152 and 139 women on sertraline and placebo versus 39 and 55 men on sertraline and placebo; Studies 1 and 2 combined). Post hoc exploratory analyses revealed a significant difference between ZOLOFT and placebo on the CAPS, IES and CGI in women, regardless of baseline diagnosis of comorbid major depressive disorder, but essentially no effect in the relatively smaller number of men in these studies. The clinical significance of this apparent gender interaction is unknown at this time. There was insufficient information to determine the effect of race or age on outcome.

In a longer-term study, patients meeting DSM-III-R criteria for PTSD who had responded during a 24-week open trial on ZOLOFT 50-200 mg/day (n=96) were randomized to continuation of ZOLOFT or to substitution of placebo for up to 28 weeks of observation for relapse. Response during

the open phase was defined as a CGI-I of 1 (very much improved) or 2 (much improved), and a decrease in the CAPS-2 score of > 30% compared to baseline. Relapse during the double-blind phase was defined as the following conditions being met on two consecutive visits: (1) CGI-I ≥ 3; (2) CAPS-2 score increased by ≥ 30% and by ≥ 15 points relative to baseline; and (3) worsening of the patient's condition in the investigator's judgment. Patients receiving continued ZOLOFT treatment experienced significantly lower relapse rates over the subsequent 28 weeks compared to those receiving placebo. This pattern was demonstrated in male and female subjects.

ADVERSE REACTIONS

During its premarketing assessment, multiple doses of ZOLOFT were administered to over 4000 adult subjects as of February 18, 2000. The conditions and duration of exposure to ZOLOFT varied greatly, and included (in overlapping categories) clinical pharmacology studies, open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and studies for multiple indications, including major depressive disorder, OCD, panic disorder, PTSD, PMDD and social anxiety disorder.

Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, a World Health Organization dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 4000 adult individuals exposed to multiple doses of ZOLOFT who experienced a treatment-emergent adverse event of the type cited on at least one occasion while receiving ZOLOFT. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

Incidence in Placebo-Controlled Trials–Table 2 enumerates the most common treatment-emergent adverse events associated with the use of ZOLOFT (incidence of at least 5% for ZOLOFT and at least twice that for placebo within at least one of the indications) for the treatment of adult patients with major depressive disorder/other*, OCD, panic disorder, PTSD, PMDD and social anxiety disorder in placebo-controlled clinical trials. Most patients in major depressive disorder/other*, OCD, panic disorder, PTSD and social anxiety disorder studies received doses of 50 to 200 mg/day.

TABLE 2
MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

	Percentage of Patients Reporting Event							
	Major Depressive Disorder/Other*		OCD		Panic Disorder		PTSD	
Body System/Adverse Event	ZOLOFT (N=861)	Placebo (N=853)	ZOLOFT (N=533)	Placebo (N=373)	ZOLOFT (N=430)	Placebo (N=275)	ZOLOFT (N=374)	Placebo (N=376)
Autonomic Nervous System Disorders								
Ejaculation Failure[1]	7	<1	17	2	19	1	11	1
Mouth Dry	16	9	14	9	15	10	11	6
Sweating Increased	8	3	6	1	5	1	4	2
Center. & Periph. Nerv. System Disorders								
Somnolence	13	6	15	8	15	9	13	9
Tremor	11	3	8	1	5	1	5	1
Dizziness	12	7	17	9	10	10	8	5
General								
Fatigue	11	8	14	10	11	6	10	5
Pain	1	2	3	1	3	3	4	6
Malaise	<1	1	1	1	7	14	10	10
Gastrointestinal Disorders								
Abdominal Pain	2	2	5	5	6	7	6	5
Anorexia	3	2	11	2	7	2	8	2
Constipation	8	6	6	4	7	3	3	3
Diarrhea/Loose Stools	18	9	24	10	20	9	24	15
Dyspepsia	6	3	10	4	10	8	6	6
Nausea	26	12	30	11	29	18	21	11
Psychiatric Disorders								
Agitation	6	4	6	3	6	2	5	5
Insomnia	16	9	28	12	25	18	20	11
Libido Decreased	1	<1	11	2	7	1	7	2

[1] Primarily ejaculatory delay. Denominator used was for male patients only (N=271 ZOLOFT major depressive disorder/other*; N=271 placebo major depressive disorder/other*; N=296 ZOLOFT OCD; N=219 placebo OCD; N=216 ZOLOFT panic disorder; N=134 placebo panic disorder; N=130 ZOLOFT PTSD; N=149 placebo PTSD; No male patients in PMDD studies; N=205 ZOLOFT social anxiety disorder; N=153 placebo social anxiety disorder). *Major depressive disorder and other premarketing controlled trials.

DOSAGE AND ADMINISTRATION

Panic Disorder, Posttraumatic Stress Disorder and Social Anxiety Disorder–ZOLOFT treatment should be initiated with a dose of 25 mg once daily. After one week, the dose should be increased to 50 mg once daily.

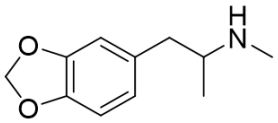
While a relationship between dose and effect has not been established for major depressive disorder, OCD, panic disorder, PTSD or social anxiety disorder, patients were dosed in a range of 50-200 mg/day in the clinical trials demonstrating the effectiveness of ZOLOFT for the treatment of these indications. Consequently, a dose of 50 mg, administered once daily, is recommended as the initial therapeutic dose. Patients not responding to a 50 mg dose may benefit from dose increases up to a maximum of 200 mg/day. Given the 24 hour elimination half-life of ZOLOFT, dose changes should not occur at intervals of less than 1 week.

Posttraumatic Stress Disorder–It is generally agreed that PTSD requires several months or longer of sustained pharmacological therapy beyond response to initial treatment. Systematic evaluation of ZOLOFT has demonstrated that its efficacy in PTSD is maintained for periods of up to 28 weeks following 24 weeks of treatment at a dose of 50-200 mg/day (see Clinical Trials under CLINICAL PHARMACOLOGY). It is not known whether the dose of ZOLOFT needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment.

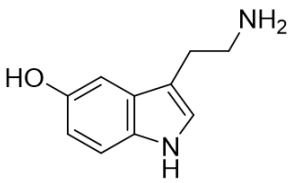
Appendix 4 – Patient Information Sheet: Pharmacology of MDMA ("Ecstasy")

What Is MDMA and What Is Its History?

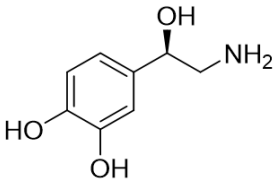
MDMA (±3,4-Methylenedioxymethamphetamine; street name "ecstasy" or "Molly") is a member of a class of psychotropic drugs called enactogens or empathogens. Entactogens are phenethylamines; their chemical structure resembles those of monoamine neurotransmitters, such as serotonin, norepinephrine, and dopamine. The subjective effects of MDMA are described as being a hybrid of the effects of psychedelics (hallucinogens, such as LSD) and stimulants (such as amphetamines), drug classes that also have a phenethylamine structure; but the property that makes enactogens such as MDMA unique is their ability to produce subjective experiences of social communion and emotional openness.



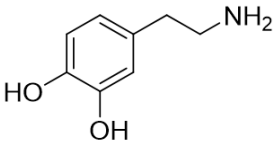
MDMA



Serotonin



Norepinephrine



Dopamine

MDMA

MDMA was first synthesized and patented by Merck in 1912, but its patent has expired. Psychotherapists in the US began to use MDMA as an adjunct to psychotherapy in the 1970s, citing that MDMA helped traumatized clients relive and discuss emotional memories without being overwhelmed by the negative emotions that usually accompany such memories.

In the United States, the Drug Enforcement Administration (DEA) classifies drugs and potential synthetic precursors to drugs into five categories, termed schedules, defined by the drug's acceptable medical use and its abuse potential (Table 1). In response to rising recreational ecstasy use in the 1980s, and deaths that resulted from this use in hot, crowded settings such as clubs, the U.S. DEA added MDMA to the list of Schedule I controlled substances, described as having "a high potential for abuse and no accepted medical use." Because Schedule I drugs are illegal to obtain and possess without a special license, the DEA's action almost completely eliminated the use of MDMA in clinical and research settings. Additionally, even substances that are not included on the DEA list may be treated as a Schedule I substance for criminal prosecution by the DEA: "A controlled substance analogue is a substance which is intended for human consumption and is structurally or pharmacologically substantially similar to or is represented as being similar to a Schedule I or Schedule II substance and is not an approved medication in the United States." (<http://www.dea.gov/druginfo/ds.shtml>)

There are no large-scale clinical studies of the safety and efficacy of MDMA in psychotherapeutic settings. Very recently, however, a small number of placebo-controlled studies have been conducted on the effects of MDMA-assisted psychotherapy in individuals with posttraumatic stress disorder (PTSD) and other mood disorders (Mithoefer et al., 2011, 2013). These studies have reported significant decreases in PTSD symptom severity that have persisted beyond the period of treatment, in clients who had not seen benefit from psychotherapy alone or traditional pharmaceutical treatments.

Table 1. DEA Schedule Categories, Definitions and Examples of Scheduled Drugs

Schedule Category	*Definition*	*Drug Examples*
Schedule I	No currently accepted medical use; high potential for abuse	Heroin, LSD, marijuana, MDMA
Schedule II	High potential for abuse, with use potentially leading to severe psychological or physical dependence	Cocaine, methamphetamine, methadone, hydromorphone, oxycodone (OxyContin), Adderall, and Ritalin
Schedule III	Moderate to low potential for physical and psychological dependence	Products containing < 90 mg of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, testosterone
Schedule IV	Low potential for abuse and low risk of dependence	Xanax, Valium, Ambien
Schedule V	Lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics	Cough preparations with < 200 mg of codeine or per 100 mL(Robitussin AC), Lomotil, Motofen, Lyrica

What Do People Experience When They Take MDMA?

Individuals who consume a single clinical dose of MDMA most frequently report feelings of positive mood, enhanced empathy for self and others, increased mental vigor, and positively experienced derealization (Hysek et al., 2014). Occasionally, individuals report mild to moderate anxiety, tension, and dysphoria, sometimes in conjunction with the positive effects. Onset of drug effects is approximately 30 to 60 minutes following administration, with effects lasting approximately 3–6 hours.

In some individuals, MDMA alters visual or auditory perception, causing visual distortions, changes in colors or brightness, or alterations in perceived distances of sounds. Perception of time or the significance of events can also change. However, people maintain insight as to their experience, and sense of self remains intact (Liechti & Vollenweider, 2001).

MDMA impacts emotional and perceptual processes that are particularly relevant to clinical settings. It increases emotional empathy and prosocial behavior (Hysek et al., 2014), facilitates recognition of and attention to positive social cues, dampens recognition of and attention to negative social cues (Hysek et al., 2012; Wardle & de Wit, 2014), increases perceived safety and security, and enhances collaborative behaviors.

How Does MDMA Interact with the Brain to Produce These Effects?

MDMA increases levels of the neurotransmitters serotonin (5-HT), norepinephrine (NE), and dopamine (DA) in the synaptic cleft between nervous system cells. As a result, cells that respond to these neurotransmitters (i.e., have receptors for them) demonstrate an increased response to this amplified "signal." MDMA increases transmitter levels by interfering with proteins in cell membranes called reuptake transporters, the job of which is to clear transmitters out of the synapse after they have been released. MDMA affects the 5-HT transporter most strongly, followed by NE and then DA. In addition to preventing serotonin reuptake, MDMA reverses the serotonin transporter, enabling serotonin to diffuse out of the neuron rather than being transported into the neuron.

The increased serotonin levels are responsible for most of the self-reported effects of MDMA, with increased norepinephrine and dopamine levels playing a lesser role (Liechti & Vollenweider, 2001). Elevated mood is primarily dependent on increased activation of 5HT2A serotonin receptors, and effects on empathy and social function are due to increased activation of 5HT1A and 5HT2A receptors, and to serotonin- and norepinephrine-induced release of the hormones oxytocin, vasopressin, prolactin, and cortisol. Oxytocin increases trust and improves accuracy of emotion perception, and increased cortisol, in some circumstances, may serve as a signal to seek affiliation or to increase positive mood. Dopamine binding to D2 receptors contributes to euphoric effects of MDMA consumption.

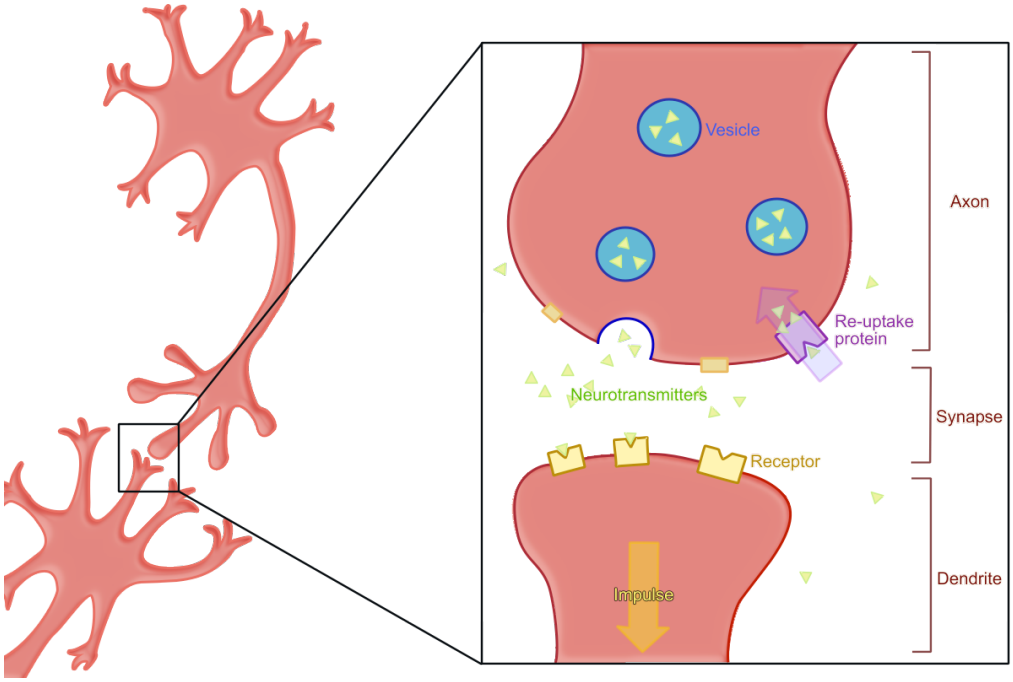


Figure 1. Illustration of a synapse, a point of communication between two neurons. The top cell releases a chemical signal (a neurotransmitter, such as serotonin) onto the bottom receiving cell, which detects the signal with the use of receptor proteins. The sending cell can remove neurotransmitter from the synapse via reuptake proteins (shown here in lavender), thus stopping the signal. MDMA blocks reuptake transporters, resulting in neurotransmitter accumulating in the synapse and the signal between the cells being more pronounced and sustained.
Source: "Reuptake both" by Sabar [p.d.] via Wikimedia Commons <https://commons.wikimedia.org/wiki/File%3AReuptake_both.png>.

Specific effects of MDMA can also be tied to increased or decreased activity in brain regions that contribute to emotional experience, memory, and social functioning. MDMA increases brain activity in the ventromedial prefrontal cortex (important for socioemotional processing) and inferior temporal cortex (responsible for facial recognition), while decreasing activity in the amygdala and hippocampus (Carhart-Harris et al., 2014). The changes in amygdala and hippocampus could be indicative of individuals' decreased subjective responses to negative stimuli and memories (Bedi et al., 2009), as the amygdala infuses memories with emotional content, particularly negative content, and the hippocampus consolidates or lays down those memories in preparation for storage.

Is MDMA Use Safe?

All medications carry a degree of risk associated with taking them. In the case of MDMA, illicit use carries particular risk as the dose and purity of the MDMA cannot be assured. Adverse effects can also arise from improper MDMA dose, interactions with other medications, and environmental conditions that are stressful, crowded, and/or hot. In clinical settings, the most common adverse effects include increased anxiety or panic, hyperthermia, and serotonin syndrome (McCann & Ricaurte, 1992; Mithoefer et al., 2011). Panic and anxiety can be treated with a benzodiazepine and continued presence of the therapist. Serotonin syndrome symptoms include agitation, confusion, rapid heart rate and high blood pressure, and, in severe cases, high fever, seizures, and unconsciousness.

In the 1980s and 1990s, several reports of MDMA-induced damage to serotonergic (i.e., serotonin-containing) neurons in users of MDMA were published (e.g., McCann et al., 1998; Parrott, 2002). However, participants were either polydrug users, abusers of MDMA, and/or administered doses in excess of those that would be used in a clinical setting. Therefore, they are not an accurate model of MDMA use in psychotherapy. There is no evidence that single, clinically relevant doses of MDMA produce toxic effects on the nervous system, nor is there any evidence of addiction risk when MDMA is taken in this context (Sessa & Nutt, 2007).

Because of its activity as a monoamine releaser, MDMA administration is contraindicated in participants requiring medication with inhibitors of monoamine oxidase (MAO; Freezer et al., 2005). Co-administration with an SSRI may eliminate or greatly attenuate the effects of MDMA. Therefore, patients should be tapered off of existing psychiatric medications before beginning MDMA-assisted therapy.

The success of MDMA use in psychotherapy is dependent upon the skill and sensitivity of the therapist. Adverse effects are minimized when a supportive, consistent, healing atmosphere is provided in the context of the MDMA administration, and when the MDMA-assisted session is preceded by several non-drug psychotherapy sessions.

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Mithoefer, M.C., M.T. Wagner, A.T. Mithoefer, et al. 2013. Durability of improvement in posttraumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3, 4-methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study. *Journal of Psychopharmacology* 27: 28–39.

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Wardle, M.C., and H. de Wit. 2014. MDMA alters emotional processing and facilitates positive social interaction. *Psychopharmacology* 231: 4219–4229.

Appendix 5 – Expert Panelists on Treatment of PTSD

Emmett Jackson, M.D. – Clinical Investigator, MDMA-Assisted Psychotherapy for PTSD

Emmett Jackson, M.D., is a psychiatrist who conducts clinical research and owns a clinical practice specializing in treating posttraumatic stress disorder (PTSD) with an emphasis on holistic psychotherapy. He recently completed a Phase II clinical trial testing MDMA-assisted psychotherapy for PTSD with positive results. For this panel, Dr. Jackson will share his perspectives on the need for more research on MDMA in therapeutic settings, and he will explain what study designs are most effective for determining the efficacy and safety of MDMA for treatment in PTSD.

Suggested References

Mithoefer, M.C., M.T. Wagner, and A.T. Mithoefer, et al. 2011. The safety and efficacy of {+/-} 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Journal of Psychopharmacology* 25: 439–452.

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Angelina Martinez, Ph.D. – Department of Pharmacology, Collegiate College, London

Angelina Martinez, Ph.D., is a Professor of Neuropsychopharmacology at Collegiate College. In 2004 she led a UK government-sponsored initiative on "Drugs, the brain, and society" with the goal of evaluating drug scheduling policies. She is a public advocate for changing MDMA from Schedule 1 to Schedule 2 to facilitate new research on the possible therapeutic uses of MDMA within psychiatry. For the panel, Dr. Martinez will explain the politics and science that drive the scheduling of psychoactive drugs in the United States.

Suggested References

Carhart-Harris, R. L., K. Murphy, R. Leech, D. Erritzoe, M.B. Wall, B. Ferguson, ... and M. Tanner. 2014. The effects of acutely administered 3, 4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level–dependent resting state functional connectivity. *Biological Psychiatry* 78: 554–562.

Oehen, P., R. Traber, V. Widmer, and U. Schnyder. 2013. A randomized, controlled pilot study of MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of Psychopharmacology* 27: 40–52.

Anna Kim, Ph.D. – Scientific Analyst and Advisor, United States Drug Enforcement Administration

Anna Kim, Ph.D. has completed numerous meta-analyses on clinical studies of psychotropic drugs over her thirty-year career in the DEA. Based on her analysis of the scientific data on MDMA she has concluded that the current Schedule 1 status of MDMA is appropriate as there is insufficient data to support a valid medical application of this substance. For this panel, Dr. Kim will explain that changing MDMA to Schedule 2 would not be in the best interest of the public health and could potentially lead to a new epidemic of abuse related to this substance. She will highlight recent data showing evidence of long-term brain damage caused by MDMA use.

Suggested References

Di Iorio, C.R., T.J. Watkins, M.S. Dietrich, A. Cao, J.U. Blackford, B. Rogers, ... and R.M. Salomon. 2012. Evidence for chronically altered serotonin function in the cerebral cortex of female 3, 4-methylenedioxymethamphetamine polydrug users. *Archives of General Psychiatry* 69: 399–409.

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Frederick Williams, Ph.D. – Associate Professor, Major University, Departments of Psychology and Psychiatry

Frederick Williams, Ph.D. is an Associate Professor of Psychology and Psychiatry at Major University. His research has explored the use of cognitive-behavioral therapy to treat PTSD. Dr. Williams believes that for most PTSD patients, adjunctive pharmacotherapy is not necessary and can even exacerbate symptoms. For this panel discussion, Dr. Williams will provide evidence for the efficacy of cognitive-behavioral therapy for PTSD when it is used by carefully trained specialists.

Suggested References

Foa, E.B., B.O. Rothbaum, and C. Molnar. 1995. Cognitive-behavioral therapy of PTSD. In: Friedman, M.J. et al., 1995, *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD*, 483–494.

Karlin, B.E., J.I. Ruzek, K.M. Chard, A. Eftekhari, C.M. Monson, E.A. Hembree, ... and E.B. Foa. 2010. Dissemination of evidence-based psychological treatments for posttraumatic stress disorder in the Veterans Health Administration. *Journal of Traumatic Stress* 23: 663–673.

Feryan Ahmad, MD, MPH – Department of Clinical Psychiatry, Midwest University School of Medicine

Dr. Feryan Ahmad is board certified in Psychiatry and is an instructor at the Midwest University School of Medicine, where he provides clinical services to children, adolescents and adults at the Depression Center. Dr. Ahmad served as an expert consultant to the U.S. Drug Enforcement Agency panel that reviewed requests to allow MDMA to be used in clinical studies for PTSD. Dr. Ahmad recommended against these requests. For this panel, Dr. Ahmad will describe the deficiencies in the designs and outcomes of recent clinical studies.

Suggested References

Mithoefer, M.C., M.T. Wagner, A.T. Mithoefer, et al. 2011. The safety and efficacy of {+/-} 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Journal of Psychopharmacology* 25: 439–452.

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Oehen, P., R. Traber, V. Widmer, and U. Schnyder. 2013. A randomized, controlled pilot study of MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of Psychopharmacology* 27: 40–52.