MDH Minnesota Department *of* Health

Minnesota Medical Cannabis Program
Petition to Add a Qualifying Medical Condition

Making your petition

- ☐ Any person may petition the Minnesota Department of Health ("the department" or "MDH") to add a qualifying medical condition to those listed in subdivision 14 of Minnesota Statutes section 152.22.

Petitions are accepted only between June 1 and July 31, each year. Petitions received outside of these dates will not be reviewed.

Petitions must be sent by certified U.S. mail to:

Minnesota Department of Health
Office of Medical Cannabis
P.O. Box 64882
St. Paul, MN 55164-0882

- ☐ You must mail the original copy of the petition with an original signature.
- ☐ Complete each section of this petition and attach all supporting documents. Clearly indicate which section of the petition an attachment is for.
- ☐ Each petition is limited to one proposed qualifying medical condition.
- ☐ If a petition does not meet the standards for submission, it will be dismissed without being considered.
- ☐ If the petition is accepted for consideration, MDH will send the petition documents to the Medical Cannabis Review Panel ("Review Panel"). MDH staff will also provide information to the Review Panel about the proposed qualifying condition, its prevalence, and the effectiveness of current treatments.

Petition review process

- ☐ The Review Panel meets at least once a year to review all eligible petitions.
- ☐ MDH will post notice of the public hearing on its medical cannabis website.
- ☐ After the public meeting and by November 1, the Review Panel will provide the Commissioner of Health its written report of findings.
- ☐ The Commissioner will approve or deny the petition by December 1 of the year the petition is accepted for consideration.

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☐ You may withdraw the petition before the Review Panel's first public meeting of the year by submitting a written statement to the Department stating that you wish to withdraw it.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]		
Home Address (including Apartment or Suite #): [redacted]		
City: [redacted]	State: MN	Zip Code: [redacted]
Telephone Number: [redacted]	Email Address: [redacted]	

Section B: Medical Condition You Are Requesting Be Added

Please specify the name and provide a brief description of the proposed qualifying medical condition. Be as precise as possible in identifying the condition. **Optional:** Include diagnostic code(s), citing the associated ICD-9 or ICD-10 code(s), if you know them. *Attach additional pages as needed.*

PLEASE SEE ATTACHED DOCUMENTATION FOR REMAINING SECTIONS – B, C, D, & E, DUE TO MY HAND PAIN FROM MY MEDICAL CONDITION MAKES IT DIFFICULT TO WRITE – TYPING IS EASIER. THANK YOU FOR UNDERSTANDING.

Please accept this typed letter in place of the handwritten form- pain in my hands makes it difficult to write.

Section B: Medical Condition You Are Requesting Be Added

The medical condition I am petitioning to be added is Posttraumatic Stress Disorder, also known as PTSD. PTSD is medical condition where the sufferer experiences flash backs, anxiety, uncontrolled thoughts, panic, nightmares, and many more symptoms due to a traumatic event they have experienced. The symptoms cause a person to have problems with their daily life. PTSD affects everything in life from relationships to work to activities of daily living. PTSD related suicide is the 10th leading cause of death in the United States (*see note below). Anyone can develop PTSD at any age.
The ICD-9 code for PTSD is 309.81.

*According to Health Research Funding.org

Section C: Symptoms of the Proposed Medical Condition and/or Its Treatment

Per the Mayo clinic, PTSD symptoms are generally grouped into four types: intrusive memories, avoidance, negative changes in thinking and mood, or changes in emotional reactions.

Symptoms can include, but are not limited to:
1) Flashbacks- people experiencing PTSD have flashbacks of the traumatic event or events, essentially reliving the event over and over again. These flashbacks can be triggered by things such as a memory, a sound, a place, a person, or event. Triggers can be different for each person.
2) Nightmares that are reoccurring, disturbing, and cause sleep problems.
3) Emotional reactions that can manifests as irritability and being short-fused with others, self-destructive behaviors, easily startled or frightened, always on guard, overwhelming feelings of guilt or shame.
4) Trying to distance self from others or avoiding places, people, and activities that are reminders of the trauma.
5) Unable to or difficulties maintaining healthy relationships.
6) Trouble concentrating.

PTSD symptoms affect a persons life and those around them in every aspect of life.

Section D: Availability of conventional medical therapies.

PTSD therapies may include:

1) Oral medication, specifically selective serotonin reuptake inhibitors, also known as SSRI's. This class of medication can also cause suicidal ideation, which puts PTSD sufferers at further risk.
With oral medication, doses are often changing and come with side effects. It may take a person years or it may be a life long struggle to find the correct dose of medication or even the correct medication that will work for them. The problems arise due to the broad spectrum of SSRI's, therapeutic dose is hard to reach and maintain on a consistent level, and to get to that level may be difficult as you cannot make drastic increases with these types of medication. The other problem with oral medication is a pill doesn't fix the base of the issue, it only masks it.
I have attached a study discussing the risks associated with this class of medication.

2) CBT, also known as Cognitive Behavioral Therapy. According to the U.S. Department of Veterans Affairs, CBT is the most effective type of counseling for PTSD. With this type of therapy it is often done in a group and the mental health conditions of the group often vary as the therapy is done in a psychiatrist's office. For a PTSD sufferer, it is difficult to discuss the events, but to do it in a group of people, it becomes even more difficult if not impossible. It is extremely difficult to discuss the events or symptoms with a therapist one on one, let alone a group of people. What if a person cannot leave the house due to PTSD? Or be in public? This type of therapy may work for some, but not for others.

3) EMDR, also known as eye movement desensitization and reprocessing, is another form of therapy where the PTSD sufferer will focus on other stimuli, like eye movements, hand taps, and sounds. There is some controversy regarding this therapy and whether or not there is a need for eye movement.

4) CPT, also known as Cognitive Processing Therapy, typically consist of twenty four sessions and contains elements of Cognitive Behavioral Therapy. With this therapy, PTSD sufferers block the natural recovery process by avoiding triggers in their day to day lives. The problem with this type of therapy is it limits a person's opportunity to process the traumatic experience and gain understanding of it. Think of this type of therapy as a band-aid approach: Would you put a band-aid on someone who had their hand cut off?

5) Exposure therapy can involve talking about the trauma repeatedly with a therapist or using a virtual reality program that allows a patient to re-enter the traumatic event. This goal is to help the patient cope effectively with their feelings. One of the issues with this

type of therapy, is the high turn around rate for therapists. Imagine finding a therapist you connect with, which is difficult to do, but then to have that therapist leave the office you are seeing them at, whether the reason be personal, work related, or something else, but to invest your time and trust as a patient and then have to start from scratch with someone new.

6) Family therapy is for the PTSD sufferer and their family members as PTSD doesn't just affect the sufferer. Family members are often at the receiving end of the symptoms displayed by a person suffering from PTSD. The hope of family therapy is for the PSTD sufferer's family members to gain understanding into why the person is acting the way they are, to help the family communicate better, cope with emotions, and maintain healthy relationships. One of the problems with this is health insurance often limits how many sessions family members can have together.

While these options may work for one person, it may not for another. Medication and therapy is not a one solution fits all. The mental health field is difficult to navigate in for PTSD patients as it is due to health insurance limitations, high therapist turn around rate, the personal nature of PTSD, and other potential problems. Due to the difficulties and obstacles in treating PTSD, shouldn't any option available be there for patients?
If we save one person's life who is suffering from PTSD by adding this medical condition to the Medical Marijuana in Minnesota, isn't it worth it?

Section E: Anticipated benefits from Medical Cannabis

The anticipated benefits are, but not limited:

1) It will help a PTSD suffer achieve better sleep by removing the intruding thoughts, flashbacks, and nightmares. By achieving better sleep, this will help with maintaining normal levels of activities of daily living.

2) It will help calm the agitation and hostility a PTSD sufferer projects.

3) It will decrease the anxiety or panic attacks.

4) It will help to stop the mind racing.

5) It will help maintain healthy relationships, work, and other areas of life.

6) It will give patients another option instead of pharmaceuticals.

7) It will help with social isolation.

I have no doubt I am missing anticipated benefits due to the personal nature of PTSD, as each person varies with their symptoms.

Section F: Scientific Evidence of Support for Medical Cannabis Treatment

I have attached some studies. Please be aware that medical cannabis studies are extremely limited due to the Federal government. I would encourage you to join online support groups, read forums, or go to a local support group. Hearing stories from personal experience is better than relying on studies that are extremely limited.

Thank you for your time and consideration with this matter.

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Section C: Symptoms of the Proposed Medical Condition and/or Its Treatment

Describe the extent to which the proposed qualifying medical condition or the treatments cause suffering and impair a person's daily life. *Attach additional pages if needed.*

PLEASE SEE ATTACHED SHEET.

Section D. Availability of conventional medical therapies

Describe conventional medical therapies available and the degree to which they ease the suffering caused by the proposed qualifying medical condition or its treatment. *Attach additional pages if needed.*

PLEASE SEE ATTACHED SHEET

MDH Minnesota Department *of* Health

Section E: Anticipated benefits from Medical Cannabis

Describe the anticipated benefits from the medical use of cannabis specific to the proposed qualifying medical condition. *Attach additional pages if needed.*

PLEASE SEE ATTACHED SHEET.

Section F (optional): Scientific Evidence of Support for Medical Cannabis Treatment

It will strengthen your petition to include evidence generally accepted by the medical community and other experts supporting the use of medical cannabis to alleviate suffering caused by the proposed medical disease or its treatment. This includes but is not limited to full text, peer-reviewed published journals or other completed medical studies. Please attach complete copies of any article or reference, not abstracts.

☒ ***I have attached relevant articles.*** *(check box if you have attached scientific articles or studies)*

Section G (optional): Letters in Support of Adding the Medical Condition

Attach letters of support for the use of medical cannabis from persons knowledgeable about the proposed qualifying medical condition, such as a licensed health care professional.

☒ ***I have attached letters of support.*** *(check box if you have attached letters of support)*

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Section H: Acknowledgement and Signature

Please Note: Any individually identifiable health information relating to any past, present, or future health condition or health care contained in this Petition is classified as a health record under Minnesota Statutes §144.291, and is not subject to public disclosure.

I certify that the information provided in this petition is true and accurate to the best of my knowledge.

S [redacted] 07/31/2016
DATE (mm/dd/yyyy)

To obtain this information in a different format, call:
(651) 201-5598 in the Metro area and (844) 879-3381 in the Non-metro.

Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials

Dean Fergusson, Steve Doucette, Kathleen Cranley Glass, Stan Shapiro, David Healy, Paul Hebert, Brian Hutton

Editorial by Cipriani et al and pp 385, 389

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BMJ 2005;330:396–9

Abstract

Objective To establish whether an association exists between use of selective serotonin reuptake inhibitors (SSRIs) and suicide attempts.
Design Systematic review of randomised controlled trials.
Data sources Medline and the Cochrane Collaboration's register of controlled trials (November 2004) for trials produced by the Cochrane depression, anxiety, and neurosis group.
Selection of studies Studies had to be randomised controlled trials comparing an SSRI with either placebo or an active non-SSRI control. We included clinical trials that evaluated SSRIs for any clinical condition. We excluded abstracts, crossover trials, and all trials whose follow up was less than one week.
Results Seven hundred and two trials met our inclusion criteria. A significant increase in the odds of suicide attempts (odds ratio 2.28, 95% confidence 1.14 to 4.55, number needed to treat to harm 684) was observed for patients receiving SSRIs compared with placebo. An increase in the odds ratio of suicide attempts was also observed in comparing SSRIs with therapeutic interventions other than tricyclic antidepressants (1.94, 1.06 to 3.57, 239). In the pooled analysis of SSRIs versus tricyclic antidepressants, we did not detect a difference in the odds ratio of suicide attempts (0.88, 0.54 to 1.42).
Discussion Our systematic review, which included a total of 87 650 patients, documented an association between suicide attempts and the use of SSRIs. We also observed several major methodological limitations in the published trials. A more accurate estimation of risks of suicide could be garnered from investigators fully disclosing all events.

Introduction

Selective serotonin reuptake inhibitors (SSRIs) rank among the most commonly prescribed medications in the world, in large part because they have been marketed as safe and effective in treating depression and an expanding list of additional conditions. Concerns related to safety were raised in the early 1990s, with reports describing a possible association with suicidality.[1–3] However, inferences regarding the plausibility and strength of the association have been divergent.[4–6] Because suicides and suicide attempts are rare events, the inability to document an important difference may be a function of the small number of patients in trials. Nevertheless, public health advisories concerning the use of antidepressants and suicidality have been issued.[7 8]

Given the controversy, we undertook a systematic review of all published randomised controlled trials regardless of treatment indication, to evaluate the association between suicide attempts and the use of SSRIs.

Methods

Literature search strategy

We conducted a systematic literature search to identify all randomised controlled trials of SSRIs indexed on Medline between 1967 and June 2003. We searched the Cochrane Collaboration's register of controlled trials (November 2004) (Cochrane depression, anxiety, and neurosis group) with the same strategy, and reviewed the bibliographies of three systematic reviews and identified trials to identify relevant reports. Three authors independently reviewed all citations. Each potentially relevant citation was reviewed by at least two individuals. Disagreements were resolved by consultation with a third reviewer.

Eligible studies had to be randomised controlled trials comparing an SSRI with either placebo or an active non-SSRI control, for any clinical condition. We excluded abstracts, crossover trials, and all trials whose follow up was less than one week. We abstracted information on to a standardised data abstraction form. See bmj.com for details of search strategy.

Outcomes

The primary outcome, suicide attempts, included both fatal and non-fatal acts of suicide. We documented rates of each separately. The authors had literally to use the term "suicide." The one exception was the use of the term "overdose." We made conservative assumptions to

This is the abridged version; the full version is on bmj.com

deal with the published reporting of non-fatal suicide attempts. If the authors explicitly reported that there were no adverse or serious adverse events we recorded that there were no fatal or non-fatal suicide attempts. If no suicide attempts were mentioned but the authors accounted for all adverse events and reasons for discontinuation we recorded zero suicide attempts. Subjects for which the authors did not indicate a reason for withdrawal or discontinuation we did not count as suicide attempts.

We documented how adverse events were reported, dropout rates, sample size, and the number of trials that did not report adverse events. We included a "not reported" category consisting of trials that did not mention adverse events or reasons for discontinuation of therapy, provided an incomplete listing of all adverse events, or did not explicitly state that no serious adverse events occurred.

Analysis

As an initial description of the risk of suicide overall and in major comparisons, we calculated the absolute risk per 1000 patients treated. To account for exposure time, we calculated the number of episodes of suicide attempts per 1000 person years of exposure by assuming a constant risk over the first year and using a weighted average of exposures.

We undertook three separate meta-analyses: SSRIs compared with placebo, with tricyclic antidepressants, and with other active forms of treatment excluding placebo and tricyclic antidepressants. Within each comparison, we tested the association between suicide attempts and the use of SSRIs by estimating summary odds ratios and 95% confidence intervals, using fixed effects models (Peto). We conducted separate meta-analyses for the number of fatal and non-fatal suicide attempts. We did not incorporate trials categorised as "not reported" into the analyses.

A priori subgroups of interest were based on age, the duration of the study follow up, proportion of women, and primary diagnosis of participants in the trials. We examined the reported partial or total funding source (funded by, compared with not funded by, the pharmaceutical industry). We also conducted a cumulative meta-analysis to evaluate the temporal sequence of evidence of effect.

Results

The literature search identified a total of 3717 citations. After exclusions, 624 met the inclusion criteria. A further 78 trials were identified from the Cochrane Collaboration register of controlled trials and the bibliographies of the three systematic reviews and of all eligible trials, giving a total of 702 trials (see bmj.com). As some trials had more than one comparison arm, the total number of comparisons exceeds the number of published trials. Of the 159 comparisons other than placebo or tricyclic antidepressants, the most common comparative treatments were moclobemide (21 trials), psychotherapy (20), maprotiline (18), and mianserin (16).

A total of 345 trials representing 36 445 patients reported the number of suicide attempts (143 in total) and were included in the analysis. Of the 345 trials reporting suicide attempts as adverse events, 64 reported at least one suicide attempt. In comparing trial characteristics between trials that reported suicide attempts and those that did not, the only significant difference was that larger trials tended not to report (χ^2 test, df=2, P=0.001). The overall rate of suicide attempts was 3.9 (95% confidence interval 3.3 to 4.6) per 1000 patients treated in clinical trials. When we used study duration as exposure time, we found an incidence of 18.2 suicide attempts per 1000 patient years. For the trials conducted in patients with depression, the overall rate of suicide attempts was 4.9 (95% confidence interval 4.2 to 5.6 per 1000 patients). The table provides the reported numbers of fatal and non-fatal suicide attempts.

We found a significant increase in the odds of suicide attempts (odds ratio 2.28, 1.14 to 4.55, number needed to treat to harm 684; P=0.02) for patients receiving SSRIs compared with placebo (fig 1). Given reduced sample sizes, our ability to detect significant differences within subgroups was limited. However, all odds ratios exceeded 1.0 except for trials whose participants had a mean age of over 60 (fig 1). In comparing non-fatal suicide attempts, a significant difference overall remained (2.70, 1.22 to 5.97; P=0.01). In comparing fatal suicide attempts, we did not detect any differences between SSRIs and placebo (0.95, 0.24 to 3.78).

In the pooled analysis of SSRIs compared with tricyclic antidepressants, we did not detect differences in the odds of suicide attempt (0.88, 0.54 to 1.42). We found no clinically or statistically important differences in any subgroup analyses. The odds ratio of non-fatal suicide attempts was 0.85 (0.51 to 1.43) and the odds ratio of fatal suicide attempts for SSRIs compared with tricyclic antidepressants was 7.27 (1.26 to 42.03).

We found an increase in the odds of suicide attempts when comparing SSRIs with therapeutic interventions other than tricyclic antidepressants (1.94, 1.06 to 3.57, number needed to treat to harm 239). Again with smaller sample sizes, we found no subgroup specific differences that reached significance. All odds ratios exceeded 1.0, except for trials in which the proportion of women exceeded 75%. The odds ratio for fatal suicide attempts was 0.59 (0.16 to 2.24) and that for non-fatal suicide attempts 2.25 (1.16 to 4.35).

Fatal and non-fatal suicide attempts in the analysed trials

	No of trials*		No of patients				No of suicide attempts					
			All trials		Trials that report		Fatal		Non-fatal		Total	
	All trials	Trials that report	SSRI	Control	SSRI	Control	SSRI	Control	SSRI	Control	SSRI	Control
SSRI *v* placebo	411	189	28 803	21 767	10 557	7856	4	3	23	6	27	9
SSRI *v* tricyclic antidepressants	220	115	12 740	11 609	6126	5401	5	4	29	31	34	35
SSRI *v* other	159	83	8856	9059	4130	4233	3	5	24	13	27	18

SSRI=selective serotonin reuptake inhibitors. *Represents the number of comparisons, as some trials had more than one comparison arm.

Patient group	SSRI: No of patients	SSRI: No of attempts	Placebo: No of patients	Placebo: No of attempts
Overall	10557	27	7856	9
Condition				
Major depression	3641	13	3243	7
Depression	1665	4	1127	1
Other conditions	5251	10	3486	1
Trial duration				
≤6 weeks	3094	8	2096	3
7+ weeks	7413	19	5710	6
Age group				
<60 years old	9798	26	7110	8
>60 years old	759	1	746	1
Sex				
<25% female	620	0	426	0
25-50% female	1706	2	1331	2
50-75% female	5731	20	4598	6
75-100% female	2178	4	1250	1
Reported funding				
Funded by pharmaceutical industry	5965	16	4647	5
Not funded by pharmaceutical industry	4592	11	3209	4

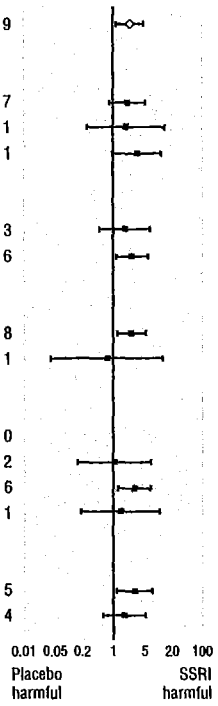

Fig 1 Fatal and non-fatal suicide attempts in SSRI trials and placebo trials

Discussion

We documented a more than twofold increase in the rate of suicide attempts in patients receiving SSRIs compared with placebo or therapeutic interventions other than tricyclic antidepressants. We documented a difference in absolute risk of 5.6 suicide attempts per 1000 patient years of SSRI exposure compared with placebo. Although small, the incremental risk remains an important population health issue because of the widespread use of SSRIs. Cumulative meta-analysis reinforces concern with the potential trend towards harm over the past several years (fig 2). It is unclear whether regulatory authorities were aware of this or not.

Possible explanations for our findings

The increase in the number of suicide attempts was not associated with a comparable increase in the risks of fatal suicide attempts. Several explanations are plausible. Estimates for patients with major depression favoured a decrease in suicides with SSRIs, whereas patients with depression and other clinical indications may have as much as an eightfold increase in the rates of suicide, thus resulting in an overall null effect. In all instances, the number of events was too small to generate sufficiently narrow confidence intervals. Alternatively, the agitation and akathasia known to occur with SSRIs may have induced more distress in patients with less severe clinical conditions and may account for the greater number of suicide attempts in patients without severe depression. Another explanation could be that treating more severely depressed patients with a higher inherent risk of suicide in a controlled environment may produce a more favourable ratio of risks to benefits. One implication from our findings is that patients with mild illness who are being treated without supervision in the community may require closer monitoring by general practitioners, family, friends, or work colleagues.

A review of published and unpublished sources documented increased rates of suicide in patients with depression when records from the Food and Drug Administration (FDA) were considered, of approximately 15.3 episodes per 1000 patients treated with SSRIs.[9] Our review noted suicide attempts at a rate of 3.9 episodes per 1000 patients. The difference in rates implies that a substantial proportion of suicide attempts have gone unreported.[5 10]

Limitations

As additional evidence of difficulties in reporting, we were unable to find documentation confirming or refuting suicide attempts in 51 205 of the 87 650 patients. We conducted a survey of a random sample of 35 (10%) of these trials. Of those responding, 22.2% of trials (n=2) reported a suicide attempt compared with 18.6% of trials (n=64) in our entire sample.

Only one trial (0.14%) mentioned a potential association between suicidality or any aspect of self inflicted injuries and SSRIs in their background or discussion sections. One hundred and four of the 702 trials reported adverse events that occurred in excess of a prespecified threshold of either 3%, 5%, or 10% of patients or above a certain number of patients. As a consequence, rare but lethal complications may have gone unreported or under-reported.

We also documented other important limitations. Of 493 trials that reported dropout rates, 28.7% (n=18 217) of the 63 478 patients dropped out. In most study areas, patients who are lost to follow up tend to be less compliant, do not derive comparable

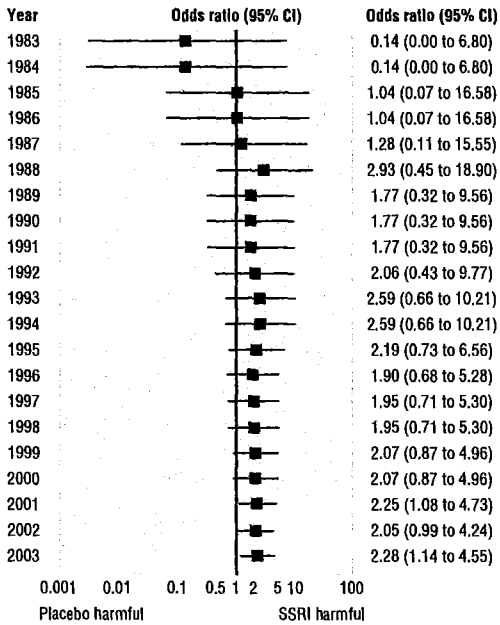

Fig 2 Cumulative meta-analysis of fatal and non-fatal suicide attempts in placebo controlled trials

benefits, and have a greater frequency of adverse outcomes compared with other patients in trials.[11] High rates of losses to follow up may therefore have hindered the ability to detect risks of suicide.

Trial size and duration of follow up are obstacles to detecting associations between SSRIs and rare adverse events. Clinical trials have focused largely on symptoms rather than long term outcomes, such as resolution of depression, prevention of relapse, and long term quality of life. In our review, 62.3% of trials (n=437) enrolled fewer than 100 patients and the mean duration of treatment and follow up in published trials was 10.8 weeks. It is therefore impossible to infer rates of long term risks and benefits of treatment, especially in relation to other therapies.

In 29 trials representing 4243 patients, investigators limited trial entry to those patients who were known to respond to and tolerate SSRIs. This would effectively diminish adverse events during the conduct of the trial. In addition, some trials enrolled patients receiving SSRIs into a placebo arm without an adequate washout period, thereby potentially attributing adverse events associated with the discontinuation of treatment to the placebo or attributing adverse events to placebo in patients who were successfully treated by SSRIs.

Conclusions

We documented an association between suicide attempts and the use of SSRIs. A more accurate estimation of the risks of suicide would be garnered from investigators fully and accurately disclosing all events. Our review also showed major limitations in the published medical literature. Doctors rely on published reports for their treatment decisions, making open and complete reporting scientifically and ethically essential.

We thank Michelle Grondin for her help in retrieving articles and abstracting data and Nancy Cleary for her administrative assistance. In addition, we thank all authors and investigators who responded to our survey of the non-reporting trials.

Contributors: See bmj.com

Funding: Canadian Institutes of Health Research.

Competing interests: DH has had consultancies with, been a principal investigator or clinical trialist for, been a chairman or speaker at international symposia for, or been in receipt of support to attend foreign meetings from: Astra, Astra-Zeneca, Boots/Knoll, Eli Lilly, Janssen-Cilag, Lorex-Synthelabo, Lundbeck, Organon, Pharmacia & Upjohn, Pierre-Fabre, Pfizer, Rhone-Poulenc Rorer, Roche, SmithKline Beecham, Solvay, and Zeneca. DH has been an expert witness for the plaintiff in eight legal actions involving SSRIs and has been consulted on several cases of attempted suicide, suicide, and suicide-homicide after antidepressant medication, in most of which he has offered the view that the treatment was not involved. He has also been an expert witness for the defendants (the British NHS) in a large series of lysergic acid diethylamide (LSD) and electroconvulsive therapy (ECT) cases.

What is already known on this topic

Selective serotonin reuptake inhibitors (SSRIs) are a widely prescribed medication

SSRIs are used to treat an expanding list of indications

Divergent studies exist on whether SSRIs are associated with an increase in suicidal events

What this study adds

Evidence from this study supports the association between the use of SSRIs and increased risk of fatal and non-fatal suicide attempts

While the incremental risk is low, the widespread use of SSRIs makes this a population health concern

A number of major methodological limitations of the published trials may have led to an underestimate of the risk of suicide attempts

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(Accepted 4 January 2005)

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Cannabinoid Science Sheds New Light on the Darkness of PTSD

MARTIN LEE

Martin Lee

A RECENT ARTICLE IN THE journal *Neuroendocrinology* highlights the crucial role of the endocannabinoid system in protecting against posttraumatic stress disorder (PTSD), a debilitating chronic condition involving horrific memories that cannot be erased.

In an effort to understand the neurobiological mechanisms that underlie the onset and development of PTSD, a team of U.S. and Canadian scientists analyzed 46 subjects who were near the World Trade Center in New York City during the September 11 terrorist attacks. Twenty-four of these subjects suffered from PTSD following the attacks; 22 did not.

The researchers found that people with PTSD had lower serum levels of anandamide, an endogenous cannabinoid compound, compared to those who did not show signs of PTSD after 9/11. Innate to all mammals, anandamide (our inner cannabis, so to speak) triggers the same brain receptors that are activated by THC (tetrahydrocannabinol: The High Causer) and other components of the marijuana plant.

Concentrated in the brain and central nervous system, the cannabinoid receptor known as CB-1 mediates a broad range of physiological functions, including emotional learning, stress adaption, and fear extinction. Scientists have determined that normal CB-1 receptor signaling deactivates traumatic memories and endows us with the gift of forgetting.

But skewed CB-1 signaling, due to endocannabinoid deficits (low serum levels of anandamide), results in impaired fear extinction, aversive memory consolidation, and chronic anxiety, the hallmarks of PTSD.

PTSD is one of many enigmatic conditions that may arise because of a dysfunctional endocannabinoid system. A 2009 report by Virginia Commonwealth University scientists discerned a link between the dysregulation of the endocannabinoid system and the development of epilepsy. Researchers at the University of Rome in Italy have documented low levels of anandamide in the cerebrospinal fluid in patients with untreated newly diagnosed temporal lobe epilepsy.

Dr. Ethan Russo postulates that clinical endocannabinoid deficiency underlies migraines, fibromyalgia, irritable bowel disease, and a cluster of related degenerative conditions—which may respond favorably to cannabinoid therapies.

Individuals have different congenital endocannabinoid levels and sensitivities that factor into how one responds to stress and trauma. Alcoholism induces endocannabinoid deficits. So does lack of exercise and a diet laden with corn syrup and artificial sweeteners.

Additional research has established that clinical depression is an endocannabinoid deficiency disease. Canadian scientist and Rockefeller University post-doc Matthew Hill analyzed the serum endocannabinoid content in depressed women and found that it was "significantly reduced" compared with controls.

Animal studies show that chronic stress is associated with decreased endocannabinoid levels. Cannabinoid receptor signaling has been identified as a key modulator of adaptation to stress.

In healthy individuals, acute stress triggers a spike in endocannabinoid levels. Scientists view this as a protective response—the fleeting uptick of anandamide eases stress and facilitates homeostasis (a return to baseline) by dialing down the production of stress hormones through a process known as "pre-synaptic inhibition."

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But chronic stress has a different effect than acute stress. Chronic stress depletes endocannabinoid tone and sets the stage for all manner of illness. Chronically elevated stress levels boost anxiety and significantly hasten the progression of Alzheimer's dementia. Emotional stress has been shown to accelerate the spread of cancer. Stress also alters how we assimilate fats.

In 2012, a team of Brazilian scientists found that chronic stress decreases CB-1 receptor binding and expression in the hippocampus, an area of the brain that plays a major role in short and long-term memory consolidation. This has major implications for treating PTSD.

Chronic stress impairs endocannabinoid signaling and impedes fear extinction, according to NYU Medical Center professor Alexander Neumeister. In a recent scientific paper Neumeister argued for PTSD treatments that target the endocannabinoid system.

Neumeister notes that "chronic stress produces an upregulation" of a crucial metabolic enzyme—fatty acid amide hydrolase, otherwise known as FAAH—which decisively influences endocannabinoid signaling.

Various enzymes are involved in the biosynthesis and creation of anandamide; other enzymes break down endogenous cannabinoid compounds. The FAAH enzyme figures prominently in the metabolic breakdown of anandamide and several other fatty acid messenger molecules. FAAH degrades these endogenous compounds; this is part of the normal, fleeting life cycle of anandamide and its fatty acid cousins.

Polymorphisms or unusual amino acid sequence repeats in the genes that encode FAAH are associated with a propensity for drug addiction and predisposition toward various afflictions. But it is the aberrant upregulation and/or down-regulation of genes—more so than the genes themselves—that drives disease vectors. Stress messes with gene expression.

Chronic stress upregulates FAAH, and more FAAH results in lower endocannabinoid levels. Conversely, less FAAH means more anandamide, and more anandamide means elevated cannabinoid receptor signaling.

Cannabidiol—CBD—is a nonpsychoactive component of marijuana and hemp that enhances endocannabinoid tone by inhibiting the FAAH enzyme. And this is just one of the ways that CBD shows promise as a treatment for PTSD.

Brazilian scientists report that CBD reduces anxiety in animal models by binding directly to the 5HT1A serotonin receptor; activating this receptor confers an anxiolytic and anti-depressant effect. Preclinical research in Brazil indicates that "CBD has beneficial potential for PTSD treatment and the 5-HT1A

receptors could be a therapeutic target in this disorder."

CBD and other therapeutic interventions that enhance cannabinoid receptor signaling could become breakthrough treatments for PTSD. CB-1 receptor transmission, in particular, has emerged as a target of novel cannabinoid-based remedies for anxiety and other mood disorders tied to stressful life events.

Smoking marijuana is one method of augmenting CB-1 receptor transmission. Numerous combat veterans and other PTSD patients claim that nothing can calm the storm that rages in their heads like a few puffs of pot. A 2011 observational study by Israeli scientists found that smoked cannabis, which directly activates the CB-1 receptor, improved symptoms of PTSD.

The National Institute on Drug Abuse continues to block FDA-approved research proposed by MAPS, which seeks to study the effects of smoked and vaporized cannabis—including a CBD-rich variety—on military veterans with PTSD.

CBD and other therapeutic interventions that enhance cannabinoid receptor signaling could become breakthrough treatments for PTSD.

Some scientists aren't high on marijuana as a PTSD treatment option. NYU's Neumeister contends that despite "their potential therapeutic value, direct-acting cannabinoid receptor compounds [such as THC] have very limited medical applications, mainly because of their undesirable psychotropic side effects and ability to cause addiction."

This assertion reflects politically correct assumptions rather than scientific fact. The operative premise—that the marijuana high is an adverse side effect—doesn't pass the unbiased smell test. Cannabis doesn't cause addiction any more than food causes a person to become a compulsive eater.

Dismissing smoked cannabis as "an appealing short-term 'solution' that will more likely create longer term problems," Neumeister favors "blocking endocannabinoid deactivation" by inhibiting FAAH, which "may lead to a more circumscribed and beneficial spectrum of biological responses than those produced by direct CB-1 receptor activation."

That is (some of) what CBD does: it inhibits FAAH. Big Pharma, meanwhile, has its sights set on developing and patenting synthetic FAAH-inhibitors to treat PTSD, depression, and other pathological conditions—the very same conditions for which whole plant cannabis provides politically incorrect relief.

Cannabis is often the remedy of choice for people coping with PTSD and other stress-induced maladies. Some are already using CBD-rich extracts and flowers. Many others self-medicate with THC-dominant strains to ease posttraumatic stress. PTSD sufferers can't afford to wait for whatever benefits synthetic FAAH-inhibitors may offer in the years ahead. They need help now. ●

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ScienceDaily
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How the federal government limits valid scientific research on Cannabis sativa

Researchers attempt to navigate difficult system

Date: June 24, 2016

Source: University of New Mexico

Summary: The use of medical marijuana for millions of patients suffering from a wide range of health conditions and the subsequent therapeutic benefits has long been documented. Cannabis sativa can benefit patients suffering from a wide range of conditions, including cancer, epilepsy, chronic pain, and post-traumatic stress disorder. So given all the health benefits for people experiencing debilitating health issues, why does the federal government continue to stifle valid, externally valid scientific research on Cannabis sativa?

FULL STORY

The use of medical marijuana for millions of patients suffering from a wide range of health conditions and the subsequent therapeutic benefits has long been documented. Twenty-three states, the District of Columbia, Puerto Rico, and Guam, have determined that Cannabis sativa (a.k.a. marijuana) can benefit patients suffering from a wide range of conditions, including cancer, epilepsy, chronic pain, and post-traumatic stress disorder.

So given all the health benefits for people experiencing debilitating health issues, why does the federal government continue to stifle valid, externally valid scientific research on Cannabis sativa?

In a recent paper published in *Science*, researchers at The University of New Mexico including Associate Professor Jacob Vigil in the Department of Psychology and Assistant Professor Sarah Stith in the Department of Economics, concluded that the federal government continues to make it extremely difficult to conduct any meaningful research on the risks and benefits of medicinal use of Cannabis sativa.

"Millions of patients have been granted the authorization to use medical Cannabis and Cannabis-based products by their respective state Health Departments and four states have begun taxing and regulating Cannabis sold for 'recreational' purposes," said Vigil and Stith. "However, the federal government continues to categorize Cannabis sativa as a Schedule I drug under the Controlled Substances Act, a more restrictive categorization than that used for cocaine, methamphetamine and PCP."

The definition of a Schedule I drug includes a "high potential for abuse," and "no currently accepted medical use," implying "a lack of accepted safety use of the drug or other substance under medical supervision, according to Vigil and Stith.

National Institute on Drug Abuse control

The National Institute on Drug Abuse (NIDA) controls the supply of Cannabis sativa to researchers. The active agent in Cannabis, Tetrahydrocannabinol or THC, has potency levels in the products that NIDA supplies that fall far below those of medical Cannabis sativa regularly sold and used in the U.S., significantly limiting the external validity of most clinical research designed to study the effects of Cannabis sativa on health, both positive and negative.

"This has created a truly unique and an unnecessary paradox in modern medicine, in which physicians are authorizing treatments to patients, and patients are regularly using medication without a scientific basis of knowledge on patient outcomes, forced rather to rely only on scientifically invalid or anecdotal information," Vigil and Stith said.

Apart from following internal human subject protection procedures, such as Institutional Review Board (IRB) approval, a scientist designing a clinical trial on the effects of Cannabis sativa using human subjects must conduct several independent and lengthy procedures that include filing for an Investigational New Drug (IND) with the Food and Drug Administration (FDA), registering the study and obtaining approval from the Drug Enforcement Agency (DEA), and purchasing the Cannabis sativa to be used in the study through NIDA.

"An IND requires a level of specificity that may be difficult to achieve with a plant product or even undesirable when one takes into account the variation of natural phenotypes and the range of products used by patients, Vigil and Stith said. "In the case of new drug development with the intent to commercialize, such oversight may be prudent, but it is unclear why a study on, for example, the effects of smoked Cannabis sativa on driving impairment would also require an IND after receiving approval by a qualified Institutional Review Board."

DEA approval

After filing for and receiving IND approval from the FDA, the scientist must also register the study and receive approval from the DEA, an organization tasked with the conflicting interest of "enforcing controlled substances laws and regulations," which currently prohibit possession or distribution of Cannabis sativa, obvious components of any clinical investigation. The only exception is for Cannabis sativa purchased through NIDA. In other words, all Cannabis sativa used for research purposes must be purchased through NIDA, despite the fact that NIDA's stated mission is to bring "the power of science to bear on drug abuse and addiction." No mention is made of research related to therapeutic benefits or the potential for non-addictive recreational use.

Despite petitions from other universities, the NIDA Cannabis sativa supply is grown exclusively at the University of Mississippi since the passage of the Controlled Substances Act in 1970. It is not uncommon for researchers to invest several years navigating this system only to receive a rejection from one of the controlling federal entities, and typically the DEA, which carries a notorious record of stalling, impeding, or otherwise obstructing sound medical Cannabis research, according to the U.S. Drug Policy Alliance (Drug Policy Alliance, accessed January, 2016).

Potency issues

Another issue with what little research the U.S. government has approved is the limited potency of the Cannabis sativa products available through the University of Mississippi. Reliance on this single source completely restricts researchers from conducting clinical trials using products that match the potency levels of products used in vivo, i.e., studies that would enable scientists to assess the therapeutic benefits and negative side effects of the medicinal Cannabis sativa actually used by tens of millions of people in the U.S.

The highest level of THC currently available through NIDA is 12.4 percent (National Institute on Drug Abuse, accessed January 2016). As of December, 2015, out of all the currently funded NIH grants with the term 'Marijuana' (n = 51) or 'Cannabis' (n = 50) in the Project title, nearly every study addressed Cannabis use as a problem behavior, and only two studies measured the (analgesic) effects of Cannabis sativa in real time, each using products with potency levels between 3.5 percent and 7 percent THC. In contrast, a study presented by the owner of a state-certified Cannabis sativa testing laboratory at the 249th National Meeting and Exposition of the American Chemical Society found that the Cannabis sativa sold in Colorado averaged 18.7 percent THC levels with some strains registering as high as 35 percent THC.

In addition to dosing directly with the plant product, a variety of concentrates have been developed for vaporizing or ingesting edibles, both arguably healthier options than smoking. In New Mexico, the Department of Health has presently capped the THC potency levels in such products at 70 percent (a level that was widely protested as to low by visibly ill patients that attended a recent public medical advisory board hearing).

"Clearly, results from studies using Cannabis sativa obtained from the University of Mississippi offer little to no insight into the effects actually experienced by medical marijuana patients in terms of both therapeutic benefits and negative side effects, if any," Vigil and Stith said.

What physicians think

A recent poll conducted by the New England Journal of Medicine showed the vast majority of physicians in the U.S. believe that medical Cannabis is a safe and effective pharmacological agent for certain mental and physical health conditions (Adler & Colbert, 2013).

"With increasing morbidity rates associated with prescribed narcotic abuse (particularly among non-Hispanic Whites) there is a legitimate place for Cannabis sativa as an alternative and perhaps primary therapeutic option for patients with a broad range and severity of negative health symptoms," Vigil and Stith said.

The substitutability of Cannabis sativa for alcohol might also reduce the exorbitant number of deaths and costs associated with alcohol abuse and drunk driving.

"Unfortunately, both the costs and benefits of medicinal use of Cannabis sativa remain essentially unknown, and because the federal government effectively bans clinical research on Cannabis sativa, citizens, including many severely ill individuals, may suffer and die unnecessarily from both the unknown risks and the unknown benefits of consuming Cannabis sativa," Vigil and Stith added.

Story Source:

The above post is reprinted from materials provided by **University of New Mexico**. *Note: Materials may be edited for content and length.*

Journal Reference:

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Cite This Page:

MLA APA Chicago

University of New Mexico. "How the federal government limits valid scientific research on Cannabis sativa: Researchers attempt to navigate difficult system." ScienceDaily. ScienceDaily, 24 June 2016. <www.sciencedaily.com/releases/2016/06/160624154712.htm>.

Anonymous

I suffer from PTSD, as a child I dealt with sexual abuse, physical abuse as well as emotional abuse. Because of that it was hard to sleep at night & I lived with a great deal of fear. I was put in therapy and given medications that half ways worked but had bad sideeffects. As I was growing older I was getting into trouble all the time. I was being suspended in school, I got charged with domestic assualt. And up until I was in my 20's this was continuing except as I got older my mind would get fixated on the things in my childhood. 1 month after my 23rd birthday I realized nothing was working and I was about to have a melt down but was offered Marijuana. I tried it, and slowly my mind became free, it wasn't hung up like it had been. That was 3 years ago and I now live alone in my own apartment I am holding down a job and pretty much function because I use marijuana medically.