SCOPING REVIEW PROTOCOL

Therapeutic Cannabis in the treatment of Post-Traumatic Stress Disorder: Protocol for a Scoping Review

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About this protocol:

- *The protocol of a scoping review according to the methodology of the Joanna Briggs Institute (JBI) is described.*

- *At the protocol submission, data collection has not yet started.*

ABSTRACT

BACKGROUND: Recent results from several studies seem to find improvements in the symptomatology of PTSD patients undergoing treatment with therapeutic cannabis (THC, CBD and NABILONE). However, some reviews have highlighted that different methods of use and different forms of the therapeutic agent were found, and that the included studies presented various biases. Given this evidence, it makes sense to conduct a new Scoping Review aimed at mapping the primary studies in the literature reporting evidence of efficacy of cannabis for the treatment of PTSD, in order to describe the mode of use, dosage, patient adherence to therapy and some specific characteristics of the sample that could be relevant such as previous alcohol and drug abuse and adherence to previous therapies.

METHODS AND ANALYSIS: This scoping review will follow the methodology of the Joanna Briggs Institute, contained in the JBI Manual for Evidence Synthesis. The literature search will be performed through PubMed, Scopus, Web Of Science, Cochrane Library, Elsevier, Psycinfo databases; in addition, grey literature sources will be consulted. Only clinical trials (randomised and non-randomised) and quasi-experimental studies will be included in Italian or English language and available in full text version. Key information of the studies will be extracted and presented both in narrative and summary form with tables to give an adequate overview of the contents of the existing scientific literature on the topic.

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BACKGROUND

Post-traumatic stress disorder (PTSD) is a mental health disorder included in the DSM since 1980. When it comes to PTSD it is usually associated with its risk only those patients who have personally suffered a traumatic event, in a rather restrictive of the phenomenon. In reality, any event that harms the psycho-physical health of the patient can potentially constitute a source of PTSD risk: it can be easily found, for example, in those who witness traumatic events and also in those who are continuously exposed. in situations of great emotional stress. We can note that in epidemiology the greatest incidence of the disease is found in rescuers, health workers and the military. According to a study on the causes of PTSD carried out on epidemiological investigations of the WHO in 24 countries with a sample of 68,894 people and 29 types of trauma analyzed, about 70.4% of the subjects interviewed suffered at least one serious trauma in life and per capita average of the traumas suffered is about 3 traumatic events. The most frequent traumatic events are rape (13.1%), other sexual assaults (15.1%), being persecuted (9.8%) and the unexpected death of a loved one (11.6%). (1)

The symptoms that are found in these subjects are many and affect different aspects of a person's life, including, in a pre-eminent way, the relational ones. Some of these symptoms involve memories, dreams, dissociative reactions related to the traumatic event experienced (flashback), *avoidance reactions* of people, places and sensations that can bring to mind the traumatic event. Other symptoms affect the subject's consideration of himself and of those around him such as, for example, a persistent negative emotional state, a noticeable decrease in interest or participation in meaningful activities, feelings of detachment or distancing from others and the persistent inability to experience positive emotions. Finally, some symptoms affect the patient's behavioral sphere, who thus finds hyper-vigilance, sleep disturbances, irritability and irascibility. (2)

It is known in these cases that, after diagnosis, it is essential to act promptly to avoid the chronicization of symptoms and pathology. There are many treatments for post-traumatic stress disorder and are articulated with both pharmacological and psychotherapeutic therapies. The treatment of this disorder, however, does not require a "standard therapy" but each clinical situation must be thoroughly evaluated for a personalization of the therapy based on the symptoms presented by the patient.

The cornerstone of the therapy is Cognitive Behavioral Therapy (CBT), lasting 6/12 weeks, which through the help of the family and loved ones helps the patient to recognize the symptoms, to manage them and to treat them, both at home. than in the workplace.

In aid of psychotherapy, antidepressants (SSRIs) are the most used drugs for the treatment of the main symptoms such as sadness, anxiety, anger and inner emptiness. Antidepressants are often supported by drugs to treat secondary symptoms such as insomnia, self-esteem and hyper-vigilance. (3)

However, due to the high number of drug classes used, annoying side effects typical of psychotropic drugs are often highlighted, which combine to create an imbalance between therapeutic effects and adverse effects. In addition, classic psychiatric drugs often cause resistance and risk of addiction. (4)

In recent years, especially in the USA, research has been carried out on the possible use of cannabis in the treatment of certain diseases, including PTSD. Often, many patients diagnosed with the disease already used cannabis to seek relief from their disorder for its anxiolytic, relaxing, sleep-promoting and antidepressant properties, avoiding the side effects of drugs. The results of some researches appear to be promising, finding that many of the patients with mild and moderate PTSD treated with

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different modalities of cannabis use (THC, CBD and NABILONE) reported an improvement in symptoms and a lowering of secondary symptoms. On the other hand, people with severe PTSD and chronic use of cannabis / drugs / alcohol would not seem to have had much benefit. However, it would seem that the associated use of cannabis with cognitive behavioral therapy is very effective, compared to the use of classical therapy. (5)

A preliminary search was carried out within the PubMed biomedical database regarding the possible treatment of PTSD with Cannabis, looking for scoping reviews and systematic reviews to see if similar searches had already been carried out. This preliminary research was carried out in the period from 11 November 2021 to 20 November 2021. The results of the research found a number of systematic reviews that mostly investigate some specific aspects of the therapy.

A first systematic review of controlled trials delves into the use of THC and CBD in the treatment of various diseases such as affective disorders, anxiety disorders and post-traumatic stress disorder (6). A second review analyzes the clinical evidence on the efficiency of cannabinoids to treat PTSD (7).

A third review delves into the effectiveness of cannabis on PTSD symptoms, the quality of life of patients undergoing this therapy and reintegration into the world of work, probing the various side effects of the therapy (8). Finally, the latest review found has set itself the goal of determining the clinical and therapeutic potential of cannabis and synthetic cannabinoids for PTSD. (5)

All the systematic reviews found have highlighted the existence of different methods of recruitment and different forms of therapeutic agent; the authors then indicated, among the limitations of the studies, a limited number of sources used, a certain risk of bias

in the studies involved and the need for more in-depth studies in everything in this area.

In the face of these evidences, it makes sense to carry out a new *Scoping Review* aimed at mapping the primary studies in the literature, the evidence of efficacy of cannabis for the treatment of PTSD found to date, the methods of use and the posologies that were used, reporting any patient adherence to therapy and some specific characteristics of the sample that could be influential such as previous alcohol and drug abuse and adherence to previous therapies.

RESEARCH QUESTION:

What are the approaches adopted for treatment with medical cannabis in the symptoms of Post-Traumatic Stress Disorder?

Sub-Questions:

- What pharmaceutical forms / methods of administration have been studied in the literature?
- What posologies have been studied in the literature?

INCLUSION CRITERIA

- Studies on adult patients diagnosed with PTSD;
- Inclusion of all studies belonging to primary literature;
- Treatment with medical cannabis, in any dosage and form of intake;
- Availability in *Full Text format*

EXCLUSION CRITERIA

- Patients with psychiatric comorbidities in addition to PTSD;
- Drug addicts or patients with current alcohol abuse.

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CONTEXT

No geographic restrictions will be applied in order to examine the full number of studies available in the field; however, it must be considered that the use of cannabis for therapeutic purposes is not legalized in all countries. Currently, the aforementioned use seems to be legal in Australia, Canada, Chile, Colombia, Germany, Israel, Italy, the Netherlands, Peru, Poland, the United Kingdom and in 31 federal states of the United States.

SEARCH STRATEGY

The search will be carried out according to the criteria of the JBI Manual for Evidence Synthesis (9). Regarding the search strategies, the search for data useful for the review will be carried out in three phases.

First phase:

After having decided to base the review on quasi-experimental studies and clinical trials, following the JBI indications, an initial search will be carried out on two medical-scientific databases such as MEDLINE (PubMed) and Scopus. The selection of the articles will be carried out through the evaluation of the title and the Abstract. Following the selection process, an analysis of the words contained in the title, the abstract and the keywords used to define the article will be carried out. Table 1 shows an example of a search on MEDLINE (Pubmed)

Second phase:

Following the first phase, all the keywords and descriptors extracted previously will be used to carry out a complete search on the PubMed, Scopus, Web Of Science, Cochrane Library, Elsevier, Psycinfo databases. The selection of the articles will be made through the evaluation of title and abstract. Eligibility

will be assessed through the complete reading of the articles. The reasons will be given for each item rejected at this stage.

1	"Medical Marijuana"[Mesh] OR "Cannabis"[Mesh] OR "Marijuana Smoking"[Mesh] OR "Cannabidiol"[Mesh] OR "Dronabinol"[Mesh] OR "nabilone" [Supplementary Concept] OR "Cannabinoids/administration and dosage"[Mesh] OR "Cannabinoids/therapeutic use"[Mesh] OR "Medical Marijuana" OR "Cannabis" OR "Marijuana Smoking" OR "Cannabidiol" OR "Dronabinol" OR "nabilone" OR "Cannabinoids"
2	"Stress Disorders, Post-Traumatic/drug therapy"[Mesh] OR "Stress Disorders, Post-Traumatic/nursing"[Mesh] OR "Stress Disorders, Post-Traumatic/organization and administration"[Mesh] OR "Stress Disorders, Post-Traumatic/prevention and control"[Mesh] OR "Stress Disorders, Post-Traumatic/therapy"[Mesh] OR "Stress Disorders, Post-Traumatic" OR "Post Traumatic Stress Disorders" OR "PTSD"
4	#1 AND #2
5	Limits: English and Italian language, adult population

Table 1 - Literature search strategy for MEDLINE (PubMed)

Third phase:

In the last phase, the bibliographic references contained only in the included articles will be analyzed, searching for new evidence to be evaluated for inclusion. Finally, a search will also be carried out in the gray literature consulting the databases of the FDA, EMA, ClincialTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and Google Scholar. The search strategy is described in *Image 1*. The languages chosen to carry out the research will be Italian and English, currently the most widespread language in the scientific field. Only primary literature sources will be included. The research will be carried out on studies drawn up in the last five years, therefore, from 2016 until today as studies on the therapeutic use of cannabis in PTSD have started relatively recently.

Source selection:

The selection of bibliographic sources will be carried out separately by two researchers; differences between the two researchers will be resolved through

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a discussion with a third researcher. The collected data will be managed through tables created in Microsoft Excel. As recommended by the Johanna Briggs Institute, a pilot research will be carried out before the start of the official research and will be carried out according to this scheme:

- Random selection of about 20 titles / abstracts of articles searched on the chosen databases;
- The group of researchers will carry out a screening of these data according to the inclusion criteria;
- The group will discuss possible changes to the inclusion criteria;
- It will be possible to continue with the main research only when an agreement is reached in at least 75% of cases.

DATA EXTRACTION

Data will be extracted with reference to the protocol inclusion criteria and selected based on the research question. The data will be extracted according to the JBI methodology for scoping review and reported in a virtual table to allow quick consultation and comparison. The categories of data that will be extracted and reported are the following:

- Author name;
- Year of publication;
- Geographical place where the research is carried out;
- Type of study carried out (randomized clinical trial or quasi-experimental study);
- Previous therapy for PTSD (psychotherapy, drug therapy);
- Previous alcohol or substance abuse;
- Type of treatment proposed in the study (nabilone, thc, cbd, etc.);
- Pharmaceutical form / method of intake used.

Prior to the data extraction, a pilot extraction on three studies will be conducted by at least two researchers in order to define any further categories of data to be extracted and to optimize the extraction process, ensuring that all relevant data for research are reported.

EVIDENCE ANALYSIS

Once the data has been extracted, they will be analyzed in an analytical and descriptive way, through the frequency measures of the concepts, the sample characteristics, the frequency of treatments, how many times a certain dosage is used, how many times that posology was found to be effective, the detection of side effects to the treatment, any data concerning the possible cost of the treatment, the possible use of the treatment in association with other forms of therapy. If a certain homogeneity between the studies will be found, the possibility of carrying out a random effects meta-analysis using the R 4.0 statistical software (R Foundation).

RESULTS PRESENTATION

The presentation of the results will be done through a table that will extrapolate the useful results according to the Population, Concept and Context (PCC) method. The objective of this table is to identify, characterize and summarize the results on the topic according to the inclusion criteria, the question asked at the beginning of the review and the intended objective. The table will be diagrammatic, with a descriptive section that will align with the objectives and questions posed by the review (table 2).

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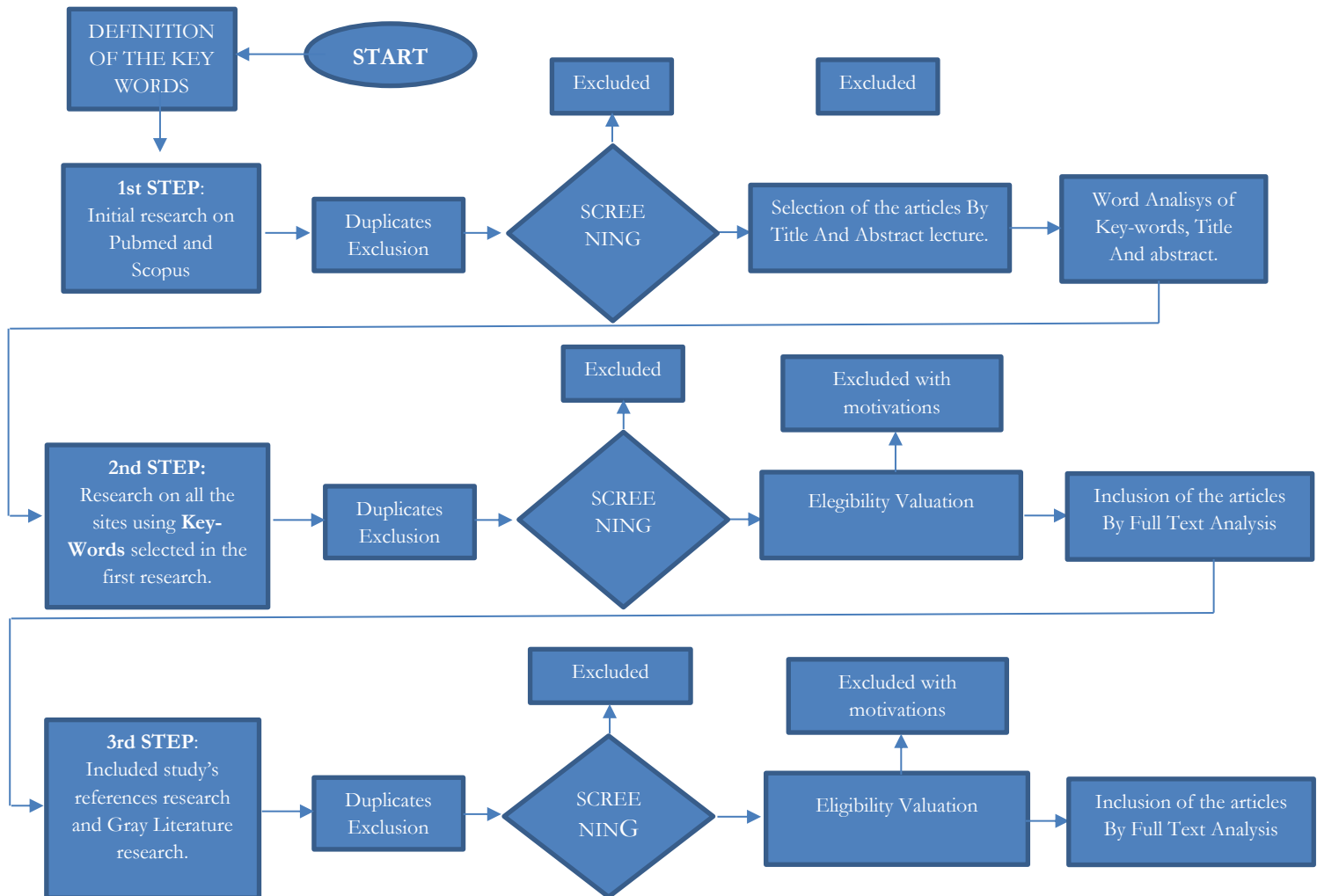
Image 1: Research Strategy

REFERENCES	COUNTRY	STUDY TYPE		SAMPLE					TREATMENT TYPE				TYPE OF ADMINISTRATION			
		Quasi-experimental study design	Randomized controlled Trial	Previous use of Cannabis	Previous drugs or alchool abuse	Previous drug therapy	Previous psychotherapy	Both drug and psychotherapy	THC	CBD	NABILONE	Other	Inhalation	Essential oils	Tablets	Other
Example, 2022	Italy		X		X		X		X				X			
[…]																

Table 2: results presentation

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REFERENCES

1. Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, et al. Trauma and PTSD in the WHO World Mental Health Surveys. Eur J Psychotraumatol [Internet]. 2017 Oct 27;8(sup5):1353383. Available from: https://www.tandfonline.com/doi/full/10.1080/20008198.2017.1353383

2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. American Psychiatric Association; 2013. Available from: https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596

3. National Institute of Mental Health. Post-Traumatic Stress Disorder [Internet]. 2019 [cited 2021 Nov 18]. Available from: https://www.nimh.nih.gov/health/topics/post-traumatic-stress-disorder-ptsd

4. Portnov A. Disturbo da stress post-traumatico: trattamento [Internet]. 2021 [cited 2021 Dec 14]. Available from: https://it.iliveok.com/health/disturbo-da-stress-post-traumatico-trattamento_86885i15946.html

5. Orsolini L, Chiappini S, Volpe U, De Berardis D, Latini R, Papanti G, et al. Use of Medicinal Cannabis and Synthetic Cannabinoids in Post-Traumatic Stress Disorder (PTSD): A Systematic Review. Medicina (B Aires) [Internet]. 2019 Aug 23;55(9):525. Available from: https://www.mdpi.com/1648-9144/55/9/525

6. Stanciu CN, Brunette MF, Teja N, Budney AJ. Evidence for Use of Cannabinoids in Mood Disorders, Anxiety Disorders, and PTSD: A Systematic Review. Psychiatr Serv [Internet]. 2021 Apr 1;72(4):429–36. Available from: https://psychiatryonline.org/doi/10.1176/appi.ps.202000189

7. Hindocha C, Cousijn J, Rall M, Bloomfield MAP. The Effectiveness of Cannabinoids in the Treatment of Posttraumatic Stress Disorder (PTSD): A Systematic Review. J Dual Diagn [Internet]. 2020 Jan 2;16(1):120–39. Available from: https://www.tandfonline.com/doi/full/10.1080/15504263.2019.1652380

8. Rehman Y, Saini A, Huang S, Sood E, Gill R, Yanikomeroglu S. Cannabis in the management of PTSD: a systematic review. AIMS Neurosci [Internet]. 2021;8(3):414–34. Available from: http://www.aimspress.com/article/doi/10.3934/Neuroscience.2021022

9. Salmond S, Bennett MJ. Systematic review of qualitative evidence. Comprehensive Systematic Review for Advanced Practice Nursing, Third Edition. 2021. 295–349 p.

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