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THERAPEUTIC POTENTIAL OF CANNABINOIDS FOR STROKE: SCOPING REVIEW PROTOCOL

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Abstract

Introduction: Each year, approximately 795,000 people experience a new or recurrent stroke, ischemic or hemorrhagic. The current therapeutical approach for acute ischemic stroke includes thrombolysis and mechanical thrombectomy. However, there are no neuroprotective treatment alternatives to improve its neurological outcome. Some components of the endocannabinoid system are altered after ischemic stroke. Cannabinoids may exert neuroprotective effects, but the use of cannabinoid receptor ligands is a factor to consider due to their psychotropic properties. Regardless of the various studies describing the benefit of administering cannabinoids for experimental stroke, several questions remain unanswered since most information is about non-human species. A previous systematic review detected significant heterogeneity among studies, therefore a scoping review was performed to evaluate the feasibility of an updated systematic review and meta-analysis. This scoping review protocol aims to evaluate the therapeutic potential of modulating the endocannabinoid system for stroke. **Methods**: Published studies (all publication types) will be retrieved from Web of Science, PubMed, Scopus, Ovid, EBSCOhost, and Google Scholar. **Eligibility criteria**: Clinical or preclinical studies reporting endocannabinoid levels or their effects, or reporting administration of cannabinoid modulators (stimulating or inhibiting their synthesis or metabolism, phytocannabinoids, or synthetic cannabinoids) in patients or models of stroke will be considered for inclusion. Studies written in languages different than Spanish or English that could not be properly translated or whose full-text files could not be retrieved will be excluded. **Data charting**: Results will be summarized in tabular form. This protocol complies with PRISMA-P.

Keywords: *Artery occlusion, Endocannabinoid, Ischemia, Phytocannabinoid, Stroke*

Introduction

Overview of *Cannabis spp* use

In recent years, medical research has delved into marijuana use for the possible therapeutic effects derived from its cannabinoid (CB) content. In the United States, a total of 47 states had allowed the medical use of *Cannabis spp* by the end of 2020;[1] nevertheless, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) application are limited for some medical conditions such as end-stage cancer, amyotrophic lateral sclerosis, multiple sclerosis, seizure disorders, Crohn's disease, mitochondrial diseases, Parkinson's disease, and sickle cell disease,[1] among others.

Cannabis spp continues to be the most widely used drug worldwide. The United Nations Office on Drugs and Crime estimates that almost 4 percent of the global population aged 15–64 years consumed *Cannabis spp* at least once in 2019, almost 200 million people.[1] In addition, synthetic cannabinoids (either one of them or their mixture) are also used for recreational purposes.[2]

Stroke

Each year, about 795,000 people experience a new or recurrent stroke. Approximately 610,000 of these are first attacks, and 185,000 are recurrent attacks. Among major stroke types, about 87% are ischemic, 10% are intracranial hemorrhage (ICH), and 3% are subarachnoid hemorrhage (SAH).[3] Stroke is a leading cause of severe long-term disability in the United States. Around 3% of males and 2% of females reported being disabled because of a stroke. Moreover, total direct medical stroke-related costs are projected to increase more than 2-fold between 2015 and 2035, from $36.7 billion to $94.3 billion, with much of those costs arising from people ≥80 years of age.[4]

The current therapeutical approach for acute ischemic stroke includes thrombolysis and mechanical thrombectomy. However, no neuroprotective treatment options currently exist that improve neurological outcomes after ischemic stroke.

In addition, some patients experience a reduced quality of life after stroke, which can be related to some degree of disability, speech disturbances, cognitive impairment, and reduced mood, among other sequelae.[5]

The endocannabinoid system (ECS), integrated by endogenous ligands, cannabinoid receptors, and degrading enzymes, has been proposed as an important pharmacological target in several neurological diseases.[6]

The potential of cannabinoids for stroke therapeutics

The effect of *Cannabis spp* use on stroke incidence is unclear.[7] According to some studies,[8] its consumption is not associated with increased stroke incidence, although these results can be questionable.[9] Neither a relation has been found between its use and negative outcomes in patients with SAH. However, the incidence of some complications may be higher in endovascular-treated *Cannabis spp* users.[10]

Stroke can occur in young *Cannabis spp* users that do not show cardiovascular risk factors.[9] Also, 80% of patients with problematic *Cannabis spp* use may develop post-stroke depression.[11] By contrast, synthetic cannabinoid consumption can cause some neurological symptoms, including somnolence, paresthesia, vertigo, psychomotor retardation, seizures, aggressive behavior, and rhabdomyolysis, but is not associated with stroke.[2]

The relationship between the mechanism of action of *Cannabis spp* and its adverse effects remains unclear. Substantial evidence suggests that chronic *Cannabis spp* consumption, especially during adolescence, is associated with the later development of schizophrenia, and several other psychiatric disorders, including depression, bipolar disorder (mania), anxiety disorders, and antisocial personality disorder.[12] There are limited data regarding the safety of CBs in humans and none in the stroke population.

Some components of the ECS are altered after an ischemic stroke. For example, the expression of cannabinoid CB1 and CB2 receptors is up-regulated in the rat brain after cerebral ischemia, indicating that the ECS may have an important role in the endogenous response to stroke.[13] A THC:CBD formulation is currently being tested in controlled clinical trials to improve spasticity after stroke,[14] that may also be beneficial for post-stroke pain, according to a case report.[15]

Cannabinoids may exert neuroprotective effects,[16] as some studies, mostly preclinical, have informed. It has been reported that CB receptor ligands (endocannabinoids, phytocannabinoids, or synthetic cannabinoids) reduce infarct volume after either transient or permanent ischemia in both rats and mice. However, the effect in non-human primates was non-significant.[13] It has been shown as well that CBD reduced infarct size in an ischemia/reperfusion rodent model.[17] An improved neurological outcome (but not survival) was also observed according to other studies.[13]

Some studies suggest that activation of the CB1 receptor triggers a neuroprotective effect while that of the CB2 receptor is neuromodulatory, although this conclusion might be debated. In addition, the use of CB1 receptor ligands is controversial due to their psychotropic properties.[16] It has also been reported that the deletion of the CB1 receptor increases infarct size, excitotoxicity, and neurological deficits in ischemia models.[18]

Further evidence suggests that CB2 ligands lack some CB1-mediated side effects and may be neuroprotective in models of stroke and other diseases. JWH133, a synthetic CB2 receptor agonist, reduces infarct size, infiltrating neutrophils, myeloperoxidase activity, secretion of inflammatory cytokines, inducible nitric oxide synthase expression, and motor deficits in either transient or permanent ischemia models.[16] This substance decreases glutamate release, preventing excitotoxicity. Also, it reduces brain edema and blood-brain barrier damage in models of hemorrhagic stroke.[16]

Palmitoylethanolamide, an endogenous cannabimimetic, reduces infarct size and neuron loss by diminishing the inflammatory response to anoxia after ischemia-reperfusion in experimental models.[19] In addition, blood levels of this substance correlate with neurological deficits after stroke in humans.[19] Some studies suggest that its administration improves cognition and spasticity in patients with stroke;[19] these effects may be partially mediated by the peroxisome proliferator-activated receptors,[20] which can modulate CB1 receptor activity.[21]

Some synthetic cannabinoids (e.g., HU-211) remain effective when administered several hours after stroke onset.[13] On the other hand, the effect of CB receptor antagonism in stroke is still unclear.[13]

Although many studies describe the benefits of administering cannabinoids for experimental stroke, some questions remain unanswered since most results were observed in non-human species. This scoping review aims to analyze the available evidence of the therapeutic potential of endocannabinoids, phytocannabinoids, or synthetic cannabinoids, as well as their

side effects, possible impact on financial costs and quality of life, in patients with stroke.

The rationale for the study

The neuroprotective potential of cannabinoids for stroke has been recently described in a narrative review,[16] but no systematic approach was applied. In addition, a systematic review and meta-analysis of the effect of cannabinoids in experimental stroke — based on 111 retrieved reports from four databases, excluding human studies — was published in 2015.[13] A systematic review of synthetic cannabinoids was also reported,[2] however, it did not evaluate their role in stroke. A scoping review protocol of current clinical and preclinical evidence for using both natural and synthetic CBs in stroke, utilizing a more comprehensive and updated search strategy, is valuable. A previous systematic review detected significant heterogeneity among studies,[13] therefore a scoping review is necessary to evaluate the feasibility of conducting an updated systematic review and meta-analysis.

Methods

Protocol development

This methodology is based on a preceding protocol,[22] but it is not an update of any previous review. After elaborating on the research question, we used an online tool to define the most appropriate type of review, as previously reported,[23] which was scoping review (https://whatreviewisrightforyou.knowledgetranslation.net/map/results?id=5413&code=GAkWQRoevx).

The International Prospective Register of Systematic Reviews (PROSPERO), the Clinical Online Network of Evidence for Care and Therapeutics (JBI COnNECT+), and the Open Science Framework (OSF) were consulted to identify ongoing protocols for systematic or scoping reviews related to our main research question (July 17th, 2021) but no relevant records were found.

This protocol was drafted by the research team and revised as necessary. Supporting materials (checklists and forms) are available through the OSF (https://osf.io/8erk4/?view_only=142c7bd4f3b84f51bef04eab1baaab58) as previously reported 24 (registration date Nov. 16th, 2021; last updated Feb. 17th, 2022).

Our research team is composed of specialists with different profiles: clinical, preclinical, and socio-medical. This protocol complies with the JBI Manual for Evidence Synthesis,[25] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020[26]), complemented with the PRISMA extensions for abstracts (PRISMA-A[27]), protocols (PRISMA-P[28]), search strategies (PRISMA-S[29]), and scoping reviews (PRISMA-Scr[30]). Those guidelines were applied as much as feasible in this scoping review protocol.

Objectives

The primary objective of this study is to evaluate the therapeutic potential of modulating the ECS for stroke. The secondary objectives are as follows:

- To evaluate the therapeutic potential of either endocannabinoids, phytocannabinoids, or synthetic cannabinoids for stroke.
- To describe possible interactions between either endocannabinoids, phytocannabinoids, or synthetic cannabinoids with conventional treatments for stroke.
- To describe possible side-effects of either phytocannabinoids or synthetic cannabinoids.
- To estimate the possible financial cost of cannabinoid-based treatment for patients with stroke.
- To estimate the possible impact of either endocannabinoids, phytocannabinoids, or synthetic cannabinoids, on quality of life in patients with stroke.

Research questions[31] for this review are described in Table 1.

Search strategy

The search strategy was created by a trained investigator and was peer-reviewed using the *PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement.*[32] Published studies (all publication types) will be retrieved from Web of Science (Clarivate), Medline (PubMed), Scopus, Ovid, and EBSCOhost (Academic Search Ultimate), from the database inception to the present. Additionally, the first 100 results from Google Scholar (https://scholar.google.com/), sorted by relevance without citations, will be retrieved[24] using Publish or Perish.[33]

Databases to be consulted, their providers, and dates of coverage are listed in Appendix A (https://osf.io/8erk4/?view_only=142c7bd4f3b84f51bef04eab1baaab58). Authors will be contacted if necessary. Collections from the authors of the present manuscript will also be considered. No additional sources will be consulted. No limits or filters will be applied. Search algorithms were elaborated using an online tool and are publicly available (https://app.2dsearch.com/new-query/612a734d758bc70004e35990). These algorithms were adjusted when necessary for each database, during the line-by-line analysis described in Appendix B. (https://osf.io/8erk4/?view_only=142c7bd4f3b84f51bef04eab1baaab58).

Table 1. Research questions for this systematic scoping review.

Question type	Framework	Description
Main research question	CoCoPop Framework (Condition, Context, Population)	What is the therapeutic potential (Co) of modulating the endocannabinoid system (Co) in patients with stroke (Pop)?
Secondary research question 1	CoCoPop Framework (Condition, Context, Population)	What is the therapeutic potential (Co) of endocannabinoids, phytocannabinoids, or synthetic cannabinoids (Co) in patients with stroke (Pop)?
Secondary research question 2	CoCoPop Framework (Condition, Context, Population)	Is there any interaction between (Co) endocannabinoids, phytocannabinoids, or synthetic cannabinoids with conventional treatment (Co) for stroke patients (Pop)?
Secondary research question 3	CoCoPop Framework (Condition, Context, Population)	What are the possible side-effects (Co) of phytocannabinoids or synthetic cannabinoids (Co) in patients with stroke (Pop)?
Secondary research question 4	CoCoPop Framework (Condition, Context, Population)	What could be the financial cost (Co) of cannabinoid-based treatment (Co) in patients with stroke (Pop)?
Secondary research question 5	CoCoPop Framework (Condition, Context, Population)	What is the effect (Co) of endocannabinoids, phytocannabinoids, or synthetic cannabinoids on quality-of-life measures (Co) in patients with stroke (Pop)?

Articles written in languages other than English and Spanish will be included if adequately translated using Google Translate[34] and/or DeepL, or if appropriate translations are found.[35] Gray literature will be consulted through the Conference Proceedings Citation Index-Science (Web of Science Core Collection) and OpenDissertations (EBSCOhost).

Study selection

Retrieved references will be de-duplicated using Rayyan QCRI's default algorithm, complemented with Zotero and Endnote. Duplicates will be confirmed manually and will be eliminated.[36] Two independent researchers will assess all references for eligibility using Sysrev according to predefined criteria. A third researcher will resolve discrepancies. Inter-rater reliability will be calculated using the Sysrev concordance tool.[37] Two screening stages will be performed: Title/Abstract, and Full-text; each stage will be pilot-tested with a random sample of 25-50 studies.[25,38]

Selected studies will be retrieved using the Retraction Watch database (http://retractiondatabase.org/) to identify retracted studies, which will be eliminated. After twelve months, the search will be rerun to identify recent studies for possible inclusion. Search strategy results will be described in a PRISMA flow diagram.

Eligibility criteria

Inclusion criteria

- Clinical or preclinical studies reporting endocannabinoid levels in any biological sample , assessed by any imaging or biochemical method, in stroke patients or experimental models.
- Clinical or preclinical studies reporting the administration of endocannabinoid modulators (stimulating or inhibiting their synthesis or metabolism, any pharmacological treatment) in stroke patients or experimental models.
- Clinical or preclinical studies reporting the effect of either phytocannabinoid or synthetic cannabinoids (any pharmacological treatment) in stroke patients or experimental models.
- Clinical or preclinical studies showing an effect of stroke on endocannabinoid levels in the blood and/or the brain of patients or experimental animals.
- As previously reported,[39] no specific diagnostic criteria for stroke will be required if the studies describe their population as presenting the condition.
- Analysis will not be limited to a clinical setting. All quantitative, qualitative, or mixed-method studies will be considered.

Exclusion criteria

- Studies written in languages other than Spanish or English that could not be appropriately translated using Google Translate and/or DeepL.
- Studies whose full-text files could not be retrieved.

Eligibility criteria may be adjusted during the screening process, as previously reported.[24] Adjustments will be applied to all studies and reported accordingly.

Data charting

Charting variables include age [years (humans), bodyweight or months (experimental animals)], gender (male/female), cannabinoid class (phyto-, endo-, synthetic), dose, duration of treatment, study type (clinical study, experimental model or theoretical study), species analyzed and their respective strains and/or genetic modifications (cell culture, rodents, non-human primates), type of stroke (ischemic, hemorrhagic, other), disease stage, therapeutic effect (survival, neurological

deficit, infarct size), pathophysiological mechanisms (oxidative stress, cell death, excitotoxicity), interaction with conventional treatment (present, absent), cannabinoids' side-effects, patients' comorbidities, quality-of-life measures. Only original research studies are eligible for these charting methods. Therapeutic effects are the main objective of this review. No data will be extracted from the figures.

Data will be reported in the units of their original report; no conversions will be applied. Unclear information will not be considered. Two independent researchers will extract data using Sysrev; a third researcher will resolve discrepancies. Inter-rater reliability will be calculated using the Sysrev concordance tool.[37] This process will be pilot-tested with a random 25-50 studies sample.[25,38]

Data synthesis

All studies are eligible for narrative synthesis. Results will be summarized in tables. Clinical and preclinical studies will be analyzed separately but may be discussed together. Preclinical studies will be discussed by study type (cell culture, rodent models, non-human primates).No statistical synthesis will be applied.

Strengths and limitations

This scoping review will provide an integrative perspective of the therapeutic potential of cannabinoids for stroke based on both clinical and preclinical studies. Also, possible side effects of this treatment were included to determine an objective recommendation for its use. Finally, the costs of current treatments for this disease will be included — when possible — to evaluate its possible general application.

In contrast to other protocols,[24] our research question complies with a systematic framework that also supports our search strategy, which was peer-reviewed. An effort will be made to include articles written in any language. The multidisciplinary research group provides complementary perspectives. This protocol complies with several guidelines, not only for scoping reviews (PRISMA-Scr, JBI Manual for Evidence Synthesis) but also for systematic reviews (PRISMA 2020, PRISMA-P, PRISMA-S, PRISMA-A).

Only a narrative analysis of the evidence will be presented. No risk-of-bias analysis or certainty of evidence assessment will be considered. The heterogeneity of the included studies allows an exhaustive analysis of the research topic. However, this could be a limitation since it might preclude performing a systematic review of intervention or meta-analysis.

Authors' contributions

I.P.N. provided methodological expertise, contributed to the design of the protocol's methodology (including search strategy), coordinated the co-author's contributions, corrected and approved the final draft, will implement protocol amendments if necessary, and is the guarantor of the review. R.M. and M.D.E. contributed with topic expertise, the design of the protocol's methodology (including search strategy), and corrected and approved the final draft. H.S. provided methodological expertise, contributed to the design of the protocol's methodology (including search strategy peer-review), and corrected and approved the final draft. M.Z. provided topic expertise, contributed to the design of the protocol's methodology, and reviewed and approved the final draft. C.R. provided topic expertise, contributed to supervising the review team, and approved the protocol's methodology and the final draft.

Conflicts of interest

I.P.N. is an Editor for *Archivos de Neurociencias*.

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