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Therapeutic potential of dehydroepiandrosterone for Parkinson's disease: scoping review protocol

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Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by a progressive loss of nigrostriatal dopaminergic neurons. Its treatment is symptomatic and shows limited efficacy. Dehydroepiandrosterone (DHEA) is a hormone produced in the brain. Several studies have reported beneficial effects of said steroid in experimental models of PD and various human diseases, but its potential for PD is inconclusive. Therefore, it is necessary to evaluate current evidence to determine the therapeutic potential of DHEA administration for PD since it could be an effective and low-cost treatment.

Objectives: This scoping review protocol aims to evaluate the therapeutic potential of dehydroepiandrosterone administration in patients with PD. **Inclusion criteria**: Studies describing patients with PD receiving DHEA, and reporting an outcome --on disease course, severity, or adverse effects-- compared to either placebo, an inactive treatment or a standard treatment will be included. Also, PD experimental models reporting an effect of DHEA treatment on measures of neuroprotection (cell death, motor activity, oxidative stress) will be considered. **Exclusion criteria**: Studies written in languages different than Spanish or English that could not be appropriately translated, or whose full-text files could not be retrieved will be discarded. Information sources: Studies will be retrieved from Web of Science, PubMed, Scopus, EBSCOhost, Cochrane Library, Google Scholar, and author's collections. No other sources will be considered. **Data charting**: Data will be extracted by one researcher and verified by another using a pilot-tested predefined format. Non-systematic review articles (narrative, scoping or similar) will only be considered for narrative synthesis. This protocol complies with the PRISMA 2020 statement and its main related extensions (PRISMA-A, PRISMA-P, PRISMA-Scr). It also complies with the Manual for Evidence Synthesis of the Joanna Briggs Institute.

Keywords: *Central Nervous System, Dehydroepiandrosterone, Parkinson Disease, Mechanisms, Neuroprotection*

Introduction

Parkinson's disease (PD) involves a neurodegenerative process of generally sporadic presentation. James Parkinson initially described it in 1817. PD symptoms include bradykinesia, rigidity, tremor, and postural instability; an asymmetric damage to the extremities is sufficient to suspect its diagnosis.[1] In addition, PD is characterized by marked changes in gait, such as shuffling and short steps, a low-speed walk with a small angular displacement, and alterations in posture and balance.[2] PD is the most common form of parkinsonism. Its overall incidence varies between 1.5 and 22 patients/100,000 inhabitants/year;[3] which increases in patients over 60 years old, being the male sex the most affected, this has been related to exposure to estrogens and their neuroprotective effect.

The characteristic lesion of PD occurs in the substantia nigra pars compacta (SN), which is part of the mesencephalic dopaminergic groups that innervate the basal ganglia. In PD, there is a progressive loss of the dopaminergic neurons of the nigrostriatal system –with depigmentation and gliosis– while Lewy bodies appear in the surviving neurons.

Currently, there is no cure for this disease. The treatments are symptomatic and often show limited efficacy.

Dopaminergic medications are the mainstay of symptomatic therapy for motor symptoms in PD[4], but may lead to neurological and psychiatric side-effects. Some potential treatments like noninvasive deep brain stimulation, gene therapy, immunotherapy, cell transplantation, and circuit neuromodulation have been proposed. However, as mentioned above, all therapies are symptomatic and do not seem to slow down or reverse the natural course of the disease. Furthermore, about 40% of patients experience ostensible complications after five years despite medication use, so the treatment for this condition remains a challenge for medical sciences.

Several studies have shown a neuroprotective effect of DHEA in PD models, from cell cultures to non-human primates (reviewed in [5]). Dehydroepiandrosterone (DHEA) is a hormone produced predominantly at the adrenal glands and, to a lesser extent, at the gonadal level, but it is also produced de novo in the brain.

DHEA concentrations are usually higher in the brain than in the bloodstream. DHEA is an essential precursor of androgens and estrogens; in men, 50% of androgens come from DHEA and DHEAS, and, in the case of premenopausal women, 75%. DHEA and DHEAS progressively decrease with age [6, 7], which is associated with chronic and neurodegenerative diseases.

There are studies of DHEA supplementation in older adults demonstrating beneficial effects for lupus erythematosus[8], depression[9], ulcerative colitis[10], and reduced ovarian reserve[11,12]. There is also positive evidence of its use as an adjuvant during immunization against tetanus and influenza[13], pulmonary hypertension, and chronic obstructive pulmonary disease.[14]

The neuroprotective effects of DHEA follow complex pathways of cellular genomic and nongenomic events through their conversion to testosterone and dihydrotestosterone (DHT). In turn, this effect activates androgen receptors (AR), its conversion into estradiol, and the subsequent activation of estrogen receptors (ER). A study on cortical and hypothalamic astrocytes isolated from neonatal rats showed its capacity to synthesize both testosterone and estrogen from exogenous DHEA. On the other hand, DHEA itself can bind and modulate some receptors.

Injury with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) provides a model of PD that allows studying the neuroprotective effects of hormones. Sex differences in sensitivity to MPTP have been reported, with a more significant neurotoxic effect observed in male rodents than females[15–17]. Animal studies have shown that DHEA administration is as effective as 17β-estradiol to produce a neuroprotective effect against MPTP toxicity.[18] This treatment modulates the dopaminergic system at different levels.

Nowadays, PD treatment can be expensive in contrast with other neurological disorders. Moreover, with the epidemiological and demographic transition underway, it can become a public health problem that will put enormous pressure on governmental health systems.

Study rationale

As the disease progresses, the treatment alternatives for PD lose efficacy, which leads to a worse quality of life, primarily due to motor and non-motor complications. This reinforces the necessity to evaluate current evidence and determine the therapeutic potential of DHEA administration in the PD treatment since it could be an effective and low-cost option for patients.

Registration or publication of systematic review protocols is important for several reasons: "planning and documentation of review methods, act as a guard against arbitrary decision

making during review conduct, enable readers to assess for the presence of selective reporting against completed reviews, and, when made publicly available, reduce duplication of efforts and potentially prompt collaboration"[19]. However, this is not performed in most cases. According to some studies, only 20% of systematic reviews have a registered or published protocol.[20]

Methods

Research questions

Research questions for this review are described in Table 1. In addition, secondary research question three –related to the financial impact of the treatment– was included as recommended by the Cochrane Handbook for Systematic Reviews of Interventions.[21]

Table 1. Research questions for the scoping review protocol

Question type	Framework	Description
Main research question	CoCoPop (Condition, Context, Population)[38]	What is the therapeutic potential (Co) of dehydroepiandrosterone administration (Co) in patients with Parkinson´s Disease (Pop)?
Secondary research question 1	PICOC (Population, Intervention, Comparison, Outcome, Context) [39]	In Parkinson's disease (**P**), could dehydroepiandrosterone administration (**I**), compared to an inactive treatment (**C**), decrease symptomatology (**O**) according to clinical and preclinical studies (**C**)?
Secondary research question 2	CoCoPop (Condition, Context, Population)[38]	What are the possible side-effects (**Co**) of dehydroepiandrosterone administration (**Co**) in patients with Parkinson's disease (**Pop**)?
Secondary research question 3	MIP (Methodology, Issues, Participants) (40)	Which could be the financial cost (**M**) of dehydroepiandrosterone administration (**I**) in patients with Parkinson disease (**P**)?
Secondary research question 4	CIMO (Context, Intervention, Mechanisms, Outcomes)[41]	According to published studies (**C**) regarding dehydroepiandrosterone administration (**I**), which mechanisms of action (**M**) may be beneficial for Parkinson disease (**O**)?
Secondary research question 5	MIP (Methodology, Issues, Participants) [40]	Does dehydroepiandrosterone administration (**M**) modify quality-of-life measures (I) in patients with Parkinson disease (**P**)?

Objectives

The primary objective of this scoping review will be to evaluate the therapeutic potential of DHEA administration in patients with PD. Secondary objectives are as follows:

- To evaluate if DHEA administration, compared to an inactive or standard treatment, could decrease symptomatology in PD according to clinical and preclinical studies.
- To evaluate what are the possible side-effects of DHEA administration in patients with PD.
- To estimate which could be the financial cost of DHEA administration in patients with PD.
- To determine which DHEA's mechanisms of action may be beneficial for PD.
- To estimate if DHEA administration could modify quality-of-life measures in patients with PD.

Protocol development

We determined the appropriate type of review article according our research questions and objectives using an online tool, as previously reported.[22] The result was "scoping review" and is available https://whatreviewisrightforyou.knowledgetranslation.net/map/results?id=5413&code=GAkWQRoevx.

We consulted the International Prospective Register of Systematic Reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/), the JBI Clinical On-line Network of Evidence for Care and Therapeutics (JBI COnNECT+, https://connect.jbiconnectplus.org/), and the Open Science Framework (OSF, https://osf.io/), to search ongoing protocols for systematic or scoping reviews related to our research questions. However, no relevant records were retrieved (July 2nd, 2021). Our protocol was drafted by the research team and revised as necessary. Supporting materials [appendix A (see below) and guideline checklists] are available through the Open Science Framework (https://osf.io/np2jr/?view_only=ffe214c3396a4c06b21b60e8a3b9188e), as previously reported[23] (registration date Sept.14th, 2021; last updated Oct. 2nd, 2021).

Our investigation team comprises different profiles: clinical, preclinical, and socio-medical science research specialists. The protocol for this scoping review complies with the JBI Manual for Evidence Synthesis[24], complemented with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020[25]), and the PRISMA extensions for abstracts (PRISMA-A[26]), protocols (PRISMA-P[19]), and scoping reviews (PRISMA-Scr [27]). We applied these guidelines to the most possible extent for a scoping review protocol.

Search strategy

A trained researcher elaborated our search strategy, which was peer-reviewed by another specialist using the Peer Review of Electronic Search Strategies (PRESS [28]), – this strategy was not adapted from any previous protocol and is reported according to PRISMA-S.[29]

Published studies (all publication types) will be retrieved from Web of Science (Clarivate), MEDLINE (PubMed), Scopus, EBSCOhost (Academic Search Ultimate), Cochrane Library, from database inception to the date of the research.

Sources or grey literature will be: the Conference Proceedings Citation Index- Science (Web of Science Core Collection), OpenDissertations (EBSCOhost), and Scopus (which includes conference proceedings). In addition, the first 100 results from Google Scholar (https://scholar.google.com/, accessed from Mexico City in incognito mode) sorted by relevance without citations, will be retrieved.[23] Finally, the author's collections will also be consulted. No other sources will be considered.

Search algorithms were elaborated using an online tool and are publicly available (https://app.2dsearch.com/new-query/6128c7e22bde1000048c6380). Those algorithms were adjusted, if necessary, according each database during line-by-line analysis. Databases to be consulted, their providers, and coverage dates (if available) are listed in Table 2. Line-by-line evaluation of all search algorithms is described in Appendix A (available at https://osf.io/np2jr/?view_only=ffe214c3396a4c06b21b60e8a3b9188e). No search filters or limits will be applied.

Table 2. Databases to be consulted, along with providers and dates of coverage

Database	Interface
Science Citation Index Expanded (1900-present)	Web of Science
Social Sciences Citation Index (1900-present)	
Arts & Humanities Citation Index (1975-present)	
Conference Proceedings Citation Index- Science (1990-present)	
Conference Proceedings Citation Index- Social Science & Humanities (1990-present)	
Book Citation Index– Science (2005-present)	
Book Citation Index– Social Sciences & Humanities (2005-present)	
Emerging Sources Citation Index (2015-present)	
Biological Abstracts (1993-present)	
Current Contents Connect (1998-present)	
Derwent Innovations Index (1963-2019)	
KCI - Korean Journal Database (1980-present)	
Russian Science Citation Index (2005-present)	
SciELO Citation Index (2002-present)	
Zoological Record (1976-present)	
Academic Search Ultimate	EBSCOhost
Applied Science & Technology Source Ultimate	
Art & Architecture Source	
Audiobook Collection (EBSCOhost)	
Business Source Ultimate	
CINAHL with Full Text	
Communication & Mass Media Complete	
Dentistry & Oral Sciences Source	
eBook Collection (EBSCOhost)	
EconLit with Full Text	
E-Journals	
Environment Complete	
ERIC	
Family & Society Studies Worldwide	
Food Science Source	
FSTA - Food Science and Technology Abstracts	
Gender Studies Database	
Historical Abstracts with Full Text	
Humanities Source	
Inspec	
Inspec Archive - Science Abstracts 1898-1968	
Left Index	
Library & Information Science Source	
MathSciNet via EBSCOhost	
MedicLatina	
MLA Directory of Periodicals	
MLA International Bibliography	
Newspaper Source Plus	
Newswires	
OpenDissertations	
Philosophers Index with Full Text	
Regional Business News	
Research Starters - Business	
Research Starters - Education	
Research Starters - Sociology	
RILM Abstracts of Music Literature	
Textile Technology Complete	
Web News	
World Textiles	
MEDLINE	**Pubmed**
Scopus	**Scopus**
Cochrane Library	**Cochrane Library**
Google Scholar	**Google Scholar**
Authors' collections	**Authors' collections**

Articles written in languages different from English and Spanish will be included if they can adequately translated using Google Translate[30] or if English or Spanish translations are available [31], as previously reported.

We will de-duplicate retrieved references using the default algorithm of Rayyan QCRI.[32] Identified duplicates will be manually revised to confirm duplicated publications to be eliminated[32]. Both reference and study duplicates (i.e., articles published more than once) will be identified through Rayyan, followed by their visual inspection; only the earliest publications will be included.

The screening process (title/abstract stage) will be performed using an online tool (Sysrev[33]) and will be pilot-tested with a random sample of 25 studies.[24] Two screening stages will be performed: title/abstract and full-text.[24] The second screening process will be performed in those studies whose inclusion/exclusion could not be decided by title/abstract screening. Full-text will be retrieved for all studies selected for inclusion or left undecided after the first screening stage. Besides the screening process, further studies could be excluded if their full-text is not available. Eligibility will be assessed by two independent researchers using Sysrev [33] according to predefined criteria. As previously reported, one decision will be considered sufficient for inclusion, while two decisions will be required for exclusion.[23] A third researcher will re-assess all excluded studies, and this decision will be considered final.

Agreement between reviewers will be assessed using Sysrev tools.[33] We will retrieve all studies selected for inclusion using Scite[34], in order to identify retracted studies, which will be eliminated. After six months of initial searches, and before the final analysis, we will re-run the search strategy to identify more recent studies for possible inclusion. A PRISMA flow diagram will be used to describe search results.[35] Also, the number of included/retrieved references (precision of literature retrieval), will be reported.

Eligibility criteria

Inclusion criteria

- Studies describing patients with PD (or Parkinsonism) receiving DHEA (or its sulfated ester DHEAS, any treatment regime) independently of their age, race, sex/gender, current treatment, or any other PROGRESS equity characteristic.[36]
- No specific diagnostic criteria for PD (or Parkinsonism) will be considered if the studies describe their population as presenting the condition, as previously reported.[37] The analysis will not be limited to any clinical setting. All types of quantitative, qualitative, or mixed-method studies will be considered.
- Any experimental model of PD reporting and effect of DHEA (or DHEAS) treatment (any pharmacological regime). Studies will be analyzed separately by type of experimental model (cell cultures, rodents, or non-human primates).
- Any theoretical study discussing the effects, advantages, disadvantages, side-effects, or therapeutic implications of administering DHEA (or DHEAS) to PD (or Parkinsonism) patients.

Exclusion criteria

- Studies written in languages different than Spanish or English that can not be appropriately translated
- Duplicated references or studies
- Studies whose full-text files can not be retrieved

No restrictions regarding follow-up time, year of dissemination, language, or publication status will be considered. These criteria may be adjusted during the screening process, as in previous studies.[23]. At least 75% agreement among reviewer team members will be required to introduce changes in these criteria.[24] Adjustments will be applied to all studies and reported accordingly.

Data charting

Data will be extracted by one researcher and verified by another using Sysrev [33] and predefined criteria [19]. Discrepancies will be solved through discussion. Although we will pilot-test the extraction format with a random sample of 25 studies [24], the format may be adjusted as necessary.

Either clinical or preclinical studies will be analyzed separately (for summary tables), even though they might be discussed jointly in the narrative synthesis. The results will be presented in the order established in the research questions.

The main outcomes of interest are the following:

- For clinical studies: clinical scales scores (any) for PD, quality-of-life scales (any), incidence of side-effects (any), interaction with conventional treatments (changing dose regimens, modifying incidence or severity of side-effects for conventional treatments).
- For preclinical studies: brain dopamine content (either in specific brain regions or the whole brain), motor activity (measured in an activity chamber), biochemical/histological/histochemical evidence of neuronal death

(caspase activity or expression, markers of necrosis/apoptosis/autophagy, markers of free radicals/oxidative stress/antioxidant mechanisms).

Additional variables to be extracted include sample size (per treatment group), type of study (clinical/preclinical, randomized/quasi-randomized/non-randomized, trial/observational), clinical setting, treatment comparator (placebo/inactive treatment, active treatment), concomitant conventional treatments, age (years for humans, or months/bodyweight for experimental animals), sex/gender (male, female, other), animal species, DHEA dose (mg, mg/day, or mg/kg), administration route, duration of treatment if more than a single administration (hours or days).

Data synthesis

Data summaries from original studies and systematic intervention reviews will be presented in graphs, figures, tables, and narrative synthesis. Other types of review articles (scoping, narrative) will only be considered for narrative synthesis. Results will be presented as originally reported, no conversions will be applied if different units are involved.

Conclusions

This protocol has some strengths and limitations, it is intended to provide an integrative perspective of the therapeutic potential of dehydroepiandrosterone for PD based on both clinical and preclinical studies. Also, possible side-effects of this treatment are considered to suggest an objective recommendation of its use. Finally, the costs of current treatment for this disease are included to estimate the generalizability of its application.

In contrast to other protocols[23], our research questions comply with systematic frameworks supporting our search strategy, which was peer-reviewed. Efforts will be made to include articles written in any language. The multidisciplinary research group provides complementary perspectives from several profiles.

This protocol complies to the most possible extent with several guidelines, including several for systematic reviews (PRISMA 2020, PRISMA-A, PRISMA-P, PRISMA-S, PRESS) besides those for scoping reviews (PRISMA-Scr, JBI Manual for Evidence Synthesis).

Only a narrative analysis of the evidence will be presented. No risk-of-bias analysis or certainty of evidence assessment will be applied. We consider the heterogeneity of the included studies to be an asset, since it allows an exhaustive analysis of the research topic. However, it is also a limitation, considering it precluded us from performing a systematic review of intervention or meta-analysis.

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Authors' contributions

- I.P.N. provided methodological expertise, topic expertise, original idea; and contributed developing the protocol's methodology (including search strategy), coordinating co-author's participation and activities; drafting, correcting, and approving the protocol; documenting and implementing protocol amendments, and is the guarantor of the review.
- C.E.D.C. provided topic expertise, original idea; contributed with the drafting, correcting, and approval the protocol.
- H.S. provided methodological expertise; contributed to the protocol's methodology; drafted the manuscript; revised, corrected, and approved the protocol, and participated in the peer-reviewing of the search strategy.
- V.A.C.P. contributed with the protocol's methodology, and the drafting, revising, and approval the protocol.
- E.C.M. provided topic expertise, and contributed to revising, correcting, and approving the protocol.
- C.R. provided topic expertise; contributed by supervising the reviewer team, and revising, correcting, and approving the protocol.

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Artículo sin conflicto de interés