Effects of cannabinoid in Amyotrophic Lateral Sclerosis (ALS) or Motor Neurone Disease (MND): A pre-clinical systematic review and meta-analysis protocol

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BACKGROUND

Amyotrophic Lateral Sclerosis (ALS), also known as Motor Neurone Disease (MND), is the third most common neurodegenerative cause of adult death (Nicholson et al., 2000). It results in the degeneration of the cortical and spinal motor neurons, and is characterised by a progressive muscular paralysis (Scotter, Abood, & Glass, 2010). It commonly affects patients between the age of 50 and 70 (Machtoub & Kasugai, 2016). ALS is mostly idiopathic, although there are strong evidences demonstrating genetic or inherited form of the disease accounting between 5 and 10% of the ALS population (Machtoub & Kasugai, 2016).

Recent discoveries of more than 20 gene mutations have been linked to ALS. Some of these are: SOD1, TARDBP (TDP-43), FUS/TLS and C9orf72 (Machtoub & Kasugai, 2016). Despite these advances, there is still a big gap in understanding its pathogenesis. Different theories have been proposed (Ludolph, Meyer & Riepe, 2000; Plaitakis & Caroscio, 1987; Robberecht, 2000; Rothstein, Martin & Kunc, 1992; Rothstein et al., 1990; Wolfram & Myers, 1973). The most popular theory in the literature is the vulnerability of motor neurons to the dysregulation of glutamate activity (Rothstein et al., 1990) resulting to excitotoxicity, oxidative damage as well as activation of inflammatory processes (Ludolph, Meyer & Riepe, 2000; Robberecht, 2000).

Endocannabinoid system (ECS) regulates the physiological functions of the nervous system, importantly, possessing neuro-protective functions. With the aforementioned theory of ALS pathogenesis, many have suggested that the activation of the endocannabinoid system can reduce excitotoxicity, oxidative cell damage as well as neuro inflammation (Carter et al., 2010) hence, a potential therapeutic agent in prolonging ALS/MND survival time.

This review aims to investigate preclinical evidences of cannabinoid in ALS/MND progression and survival time to support the conduct of a human clinical trial.

Why it is important to do this review

We are aware that there is no existing systematic review of cannabinoid in non-human animal models of ALS/MND. Strong evidence suggesting potential beneficial effects of cannabinoid in treating ALS/MND may support the need to conduct a human clinical trial.

OBJECTIVE

To evaluate the pre-clinical evidences for cannabinoid in the treatment of Amyotrophic Lateral Sclerosis (ALS) or Motor Neurone Disease (MND), determine survival effect sizes of cannabinoid in animal models and identify variables that correlate with greater effect sizes.
METHODS

Criteria for considering studies for this review

Types of studies
Any controlled comparative studies (randomised, quasi-randomised, and non-randomised) assessing the effects of cannabinoid on survival and/or disease progression in ALS/MND animal models. No language, publication date, or publication status restrictions will be imposed.

Types of participants
Any non-human animal model with known ALS/MND genetic mutations such as SOD1, TDP-43, C9ORF72, FUS, and so on.

Types of interventions
Any cannabinoid or cannabinoid based treatment (direct extract from cannabis plant or synthetic), or any endocannabinoid transport blocker, at any stage of the disease process (including prior disease onset) by any route, at any dose, for any duration.

Types of Outcome Measures

Primary Outcome
Survival time defined as time from birth to end-stage disease*.

Secondary Outcomes
1. Progression of disease:
   1.1. Motor decline assessed by any validated instrument such as rotarod, running wheel activity or motor scoring system.
   1.2. Weight decline (comparing weight at pre and post treatment)

*End-stage disease is defined as inability of an animal to right itself within <30 seconds if laid on either side, loss of 20% body weight, or first sign of leg paralysis, whichever of these signs was reached first (Acevedo-Arozena et al., 2011; Lietner, Menzies, & Lutz, 2009).

Criteria for excluding studies for this review
Narrative reviews, letters, editorials, case reports, duplicate publications or those without objective data to be evaluated will be excluded.
Search Methods for identification studies

Search strategy
We aim to find both published and unpublished pre-clinical studies. A three-step approach will be utilised in searching studies. First, an initial limited search of MEDLINE (Appendix 1) and EMBASE (Appendix 2) will be undertaken by Gold Coast Health librarian followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe article. If the review team is happy with the search results, a second search will be applied across other included databases using all the identified keywords and index terms from the initial search. Lastly, reference list of all identified relevant articles will be hand searched for additional studies. There will be no date and language restrictions.

Electronic searches
Literature search will incorporate a number of methods to identify completed or ongoing studies. This includes searching literature databases, clinical trials registry and hand searching references of relevant articles.

The databases to be searched will include:
- MEDLINE
- EMBASE
- CINAHL
- Web of science
- Scopus
- Proquest Dissertations
- PsylINFO
- CENTRAL

We will search for ongoing trials and unpublished studies via Internet searches on the following sites:
- Clinical Trials (https://clinicaltrials.gov/)
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/)

Searching other resources
We will also:
1. hand search references of the articles obtained;
2. search conference proceedings likely to contain studies relevant to the review; and
3. contact investigators and relevant study authors to seek information about unpublished or incomplete trials.
Data collection and Analysis

Selection of studies
References obtained from databases, website searches, and hand searching of reference lists will be downloaded into reference management software (Endnote) and duplicates will be removed. Papers will be screened according to the title and abstract (where available), using specific inclusion and exclusion criteria.

Two review authors (BU, MAO) will independently check the titles and abstracts identified from the literature review. The review authors will obtain the full text of all potentially relevant studies for independent assessment. Multiple publications from one particular study will be grouped together. Full text articles will also be obtained if additional information is required, to assess eligibility for inclusion. All review authors will resolve differences about inclusion of studies by discussion and grade the risk of bias of included studies.

Data extraction and management
Quantitative data will be extracted from papers included in the review using a data extraction and assessment tool adapted from The Cochrane Public Health Group by two independent reviewers (BU, AO). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. We will contact study authors for any necessary clarifications.

Disagreements around data extraction between the two authors will be resolved by discussion, or by a third author (MK) if a consensus cannot be reached by discussion alone. Where there are multiple reports from the same study, one data collection form will be completed for the study collated from all of the reports.

Assessment of risk of bias
The independent authors (BU, MAO) will assess risk of bias for each pre-clinical study to be reviewed using criteria outlined in the SYRCLE’s risk of bias took for experimental animal models (Hooijmans et al., 2014). These are: selection bias (sequence generation, baseline characteristics, allocation concealment), performance bias (random housing, blinding), detection bias (random outcome assessment, blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), other (other sources of bias).

We will assess the risk of bias in each domain and overall, using categories of high, low or unclear risk of bias and provide a justification for our judgment in the ‘Risk of bias’ table, including a quote from the study, if necessary. High risk of bias means there is a plausible bias that seriously weakens confidence in the results, low risk bias of bias means plausible bias unlikely to seriously alter results,
whilst unclear risk of bias means plausible bias that raises some doubt about the results.

We will consider blinding of outcome assessor(s) and personnel for each objective outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias maybe different in assessing end stage disease versus weight-taking). When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

In cases of disagreements, all other review authors will determine final assessment by consensus. If there are inadequate details in the article needed to review risk of bias, we will contact study authors to obtain further information. We will consider incomplete outcome data for all outcomes.

Assessment of bias in conducting the systematic review
We will conduct the review according to this published protocol. Any deviations will be reported in the ‘Differences between protocol and review’ section of the systematic review.

Measures of treatment effect
We will use weighted mean differences (WMD) between groups for evaluating continuous outcomes. In each study, we will compare the mean score differences from baseline to the end of treatment of each group. We will also use standardised mean differences (SMDs) for outcomes that are the same but are measured using different instruments or scales (e.g. motor decline measured by rotarod or running wheel activity). 95% confidence interval (CI) will be calculated to measure treatment effect.

Meta-analysis will be undertaken if outcomes of the underlying question(s) are similar enough and deemed appropriate to be pooled for analysis.

Dealing with missing data
We will contact study authors to request missing data, whenever possible. If missing data cannot be obtained and are thought to introduce bias, we will evaluate the influence of including missing data in the overall outcome by performing sensitivity analysis.

Assessment of heterogeneity
To measure heterogeneity amongst trials, we will use $I^2$ statistic. If there is substantial heterogeneity detected, this will be reported and possible explanations for the heterogeneity will be explored by pre-specified subgroup analyses.

Assessment of reporting biases
We will use funnel plot to determine any potential publication bias of pre-clinical studies to be reviewed. Funnel plot is a scattered plot of the effect estimate from each pre-clinical study against its sample size or effect standard error.
Appendix 1. MEDLINE (Ovid SP) search strategy

Database: Ovid MEDLINE(R) ALL <1946 to November 08, 2017>

Search Strategy:

--------------------------------------------------------------------------------
1 exp Motor Neuron Disease/ (26263)
2 motor neuron* disease*.tw. (5801)
3 amyotrophic lateral scleros*.tw. (20719)
4 lou gehrig* disease*.tw. (124)
5 (als or mnd).tw. (25373)
6 or/1-5 (43952)
7 exp Cannabaceae/ (8784)
8 Medical Marijuana/ (580)
9 cannabis.tw,nm. (13164)
10 marijuana.tw,nm. (11753)
11 cannabin*.tw,nm. (20880)
12 cannabinid*.tw,nm. (2057)
13 phylocannabin*.tw,nm. (341)
14 endocannabin*.tw,nm. (8975)
15 tetrahydrocannabin*.tw,nm. (6639)
16 thc.tw,nm. (6262)
17 cbd.tw,nm. (5795)
18 or/7-17 (53009)
19 6 and 18 (135)
20 remove duplicates from 19 (118)
21 limit 20 to english language (111)
22 20 not 21 (7)
### Appendix 2. EMBASE (Ovid SP) search strategy

Database: EMBASE

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<td>#6 AND #13 AND [english]/lim</td>
</tr>
<tr>
<td>#14</td>
<td>#6 AND #13</td>
</tr>
<tr>
<td>#13</td>
<td>#7 OR #8 OR #9 OR #10 OR #11</td>
</tr>
<tr>
<td>#12</td>
<td>#7 OR #8 OR #9 OR #10 OR #11</td>
</tr>
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<td>#11</td>
<td>thc:ti,ab OR cbd:ti,ab</td>
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<tr>
<td>#10</td>
<td>cannabis:ti,ab OR marijuana:ti,ab OR cannabin*:ti,ab OR cannabid*:ti,ab OR phytocannabin*:ti,ab OR endocannabin*:ti,ab OR tetrahydrocannabin*:ti,ab</td>
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CONTRIBUTIONS OF AUTHORS

BU conceived of the review.

All authors assisted in designing the review and the search strategies detailed in this protocol.

All authors assisted in drafting and providing critical appraisal of this protocol.

DECLARATIONS OF INTEREST

BU and AS are both investigators of a clinical trial investigating the efficacy of medicinal cannabis in treating Amyotrophic Lateral Sclerosis or Motor Neuron Disease patients.

Other authors: None known.

SOURCES OF SUPPORT

Internal Sources

• No sources of support supplied

External Sources

• No sources of support supplied

REFERENCES


