LITERATURE REVIEW

Risk analysis of the use of Cannabinoids compounds as therapy in Dementia:

A Systematic Literature Review

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Keywords: Cannabinoids; Dementia; Risk; Safety; Effectiveness.

ABSTRACT

Background: Nowadays dementia pharmaceutical treatment has an unfavorable risk-benefit relation. New therapeutic approaches' adoption is need due to the high prevalence of this condition.

Objectives: To evaluate the risk of using cannabinoids compounds as nonharmful therapeutic approach in dementia.

Methods: A systematic literature review based on PRISMA was performed. PubMed and Clinical Trials database were used to collect articles between 2012 and 2022. Cochrane and Consort instruments were used to evaluate the methodology quality and report quality of adverse effects.

Results: Tetrahydrocannabinol and Nabilone were associated to a moderate effectiveness in the symptomatology related with Dementia and to favorable safety and tolerability profiles.

Main Contribution to Evidence-Based Practice: Evidence obtained shows the importance of these two compounds as a new approach to dementia treatment.

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What do we already know about this topic?
Research on the use of cannabinoids, particularly compounds like tetrahydrocannabinol (THC) and cannabidiol (CBD), in the treatment of dementia is still in its early stages. But they have demonstrated: neuroprotective properties in preclinical studies; help manage certain symptoms associated with dementia, such as agitation, aggression, and sleep disturbances

What is the main contribution to Evidence-Based Practice from this article?
This review added Evidence that shows the importance of these two compounds as a new non-harmful approach to dementia treatment.

What are this research's implications towards health policy?
This work analysed several studies and concluded that it is possible to categorise therapies based on cannabinoid compounds as possible non-harmful therapies. But it also concluded that new studies are needed to better understand the impact, positive and negative of the use of cannabinoids in the type of disease.

Authors' Contributions Statement:
E.P. and P.B. contributed equally to this work.
E.P.: Research, original draft preparation, review, and editing; P.B.: Conceptualisation, research, review and editing, funding and resources, project administration; R.F.: Review and editing; C.L.: Conceptualisation, research, original draft preparation, review, and editing; All authors have read and agreed to the published version of the manuscript.

Introduction

The neurodegenerative disturbs are associated to a progressive and selective loss of vulnerable population of neurons, which is different from the selective static neuronal loss. It is related with metabolic and/or toxic disturbances and can be classify according with primary clinical characteristics (Chi et al., 2018; Kovacs, 2018).

Dementia can be defined as a cognitive and functional degenerative syndrome, normally associated with behaviour and/or personality changes (Bouchard, 2007). Alzheimer's Disease (AD) and Parkinson's Disease (PD) are two different dementia type and a worldwide concern.

Nowadays the clinical practice for AD is based on the mitigation of cognitive and behavioural symptoms associated to the disease and to minimise the general risk for the patient and promote life quality improvement (Tisher & Salardini, 2019). AD is a progressive and irreversible chronic disease, progressive and irreversible with unknown aetiology (Breijyeh & Karaman, 2020), characterised by cholinergic neuronal destruction, and manifesting mainly in memory and cognition loss, as well as changes in social behaviour, physical symptoms (e.g., forgetfulness, problems understanding and performing daily tasks) (Soria Lopez et al., 2019), and the occurrence of aggression episodes (Ballard & Corbett, 2013).

PD is an idiopathic disease of the nervous system characterised by debilitating motor impairment, including bradykinesia, rigidity, tremor, postural instability, and gait disorders. Additionally, PD patients can suffer from an array of non-motor symptoms such as sleep disorders, neuropsychiatric issues, cognitive dysfunction, and autonomic abnormalities, among others. It consists of the loss or degeneration of the nigrostriatal dopaminergic system, responsible for many of the motor symptoms observed in the disease, and the development of Lewy bodies in the central and peripheral nervous system. It is considered the second most common neurodegenerative

disease (Cabreira & Massano, 2019; Sherer et al., 2012).

AD and PD treatment options are considered palliative and aim to prevent the disease progression leading to an improvement of the patient quality of life. The pharmacological treatments for AD aim to inhibit cholinesterases (e.g., donepezil, galantimine, and rivastigmine) and increasing the bioavailability of acetylcholine and complemented with the application of non-pharmacological therapies that stimulate cognition (Direção Geral da Saúde & Ministério da Saúde, 2011). In PD therapy, levodopa associated with a peripheral dopadecarboxylase inhibitor (e.g., carbidopa or benserazide), dopaminergic agonists (e.g., bromocriptine or piribedil, ropinirol), monoamine oxidase B (MAO-B) inhibitors (e.g., selegiline), anticholinergics, among others, are used (Cabreira & Massano, 2019).

The pharmacological treatment is complex and supported by a rigorous assessment of the evidenced symptomatology (Cabreira & Massano, 2019; Direção Geral da Saúde & Ministério da Saúde, 2011). However, the available options are limited and often exhibit unsatisfactory results (Peball et al., 2019). Additionally, they have important disadvantages regarding the risk-benefit ratio for patient due to adverse side effects (e.g., extrapyramidal effects, postural hypotension, among others and the increased difficulty of therapy implementation when comorbidities are present (e.g., depression, anxiety, among others)) (Ballard & Corbett, 2013; Schneider et al., 2005; van den Elsen et al., 2014; Vicente Forlenza et al., 2008). Finally, it is important to highlight the economic impact in health system due to the high costs of hole therapeutic process (Cotter, 2007).

The World Health Organization (WHO) reports that unsafe medication use is a leading cause of preventable harm and damage in health systems worldwide (World Health Organization, 2018). Thus, given the negative impact of this set of diseases for all those involved (e.g., patients, caregivers, care institutions, and their professionals), associated with the occurrence of adverse effects (AEs) resulting from the instituted therapies, it is important to highlight potential non-harmful pharmacotherapies (e.g., safer and more effective therapies) (Herrmann et al., 2019).

Cannabinoid compounds (CC) have been studied as a potential therapeutical option in dementia symptomatology and some studies even demonstrate improvements in agitated behaviour or nocturnal motor activity in patients with dementia (de Almeida et al., 2021; Herrmann et al., 2019; Peball et al., 2019; van den Elsen et al., 2015b; van den Elsen et al., 2015a). Others studies focusing on CC have explored relevant adverse effects, such as dizziness and sedation (Wang et al., 2008). There are also clinical trials that allow comparing advantages of using different types of CC (e.g., observing more predictable effects or causing less euphoria) (Balter & Haney, 2017; Lemberger et al., 1982). Thus, it is hypothesised that these compounds have the capacity to improve the quality of life of individuals with dementia.

For the correct risk assessment of these innovative therapies, it is essential to assess the quality of the AEs' reported in published studies associated with the analysis of the effectiveness profiles. Thus, considering the emerging field of alternative therapies, this systematic literature review was conducted with the main goals to analyse the risk of using CC as a treatment for dementia and to understand the benefit of these compounds as a non-harmful therapy for the patient.

Methods

Original articles were sought in two databases, Pubmed and Clinical Trials, by three researchers, between 1 March and 24 May 2022. Search terms were applied isolated without limits or filters (Table 1) and then through combinations using the Boolean operators AND and OR.

Table 1. MeSH terms

Cannabinoids
Safety
Adverse effects
Dementia
Efficacy

In a second step, the inclusion and exclusion criteria shown in Table 2 were applied to the articles found. In addition, and to identify relevant studies and additional literature, the Scopus database was used to check the list of references of the selected articles.

Table 1. Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
▪ Published between: January 2012 and Mars 2022; ▪ With abstract; ▪ Studies from Clinical trials (stage I to IV), randomised clinical trials and controlled clinical trials; ▪ Studies related with healthcare interventions; ▪ Discussion of therapeutic effects with mention of the incidence of adverse events through comparisons with placebos and/or synthetic drugs; ▪ Studies related with the safety of cannabinoids used in dementia or its subtypes diagnosis; ▪ Studies related with tolerance to the interventions; ▪ Studies with description of adverse effects resulting from the interventions; ▪ Studies published in English and Portuguese.	▪ Studies from laboratory procedures and protocols; ▪ Review articles and Meta-analysis articles; ▪ Studies with qualitative data only; ▪ Studies with sample size considered small (n<10).

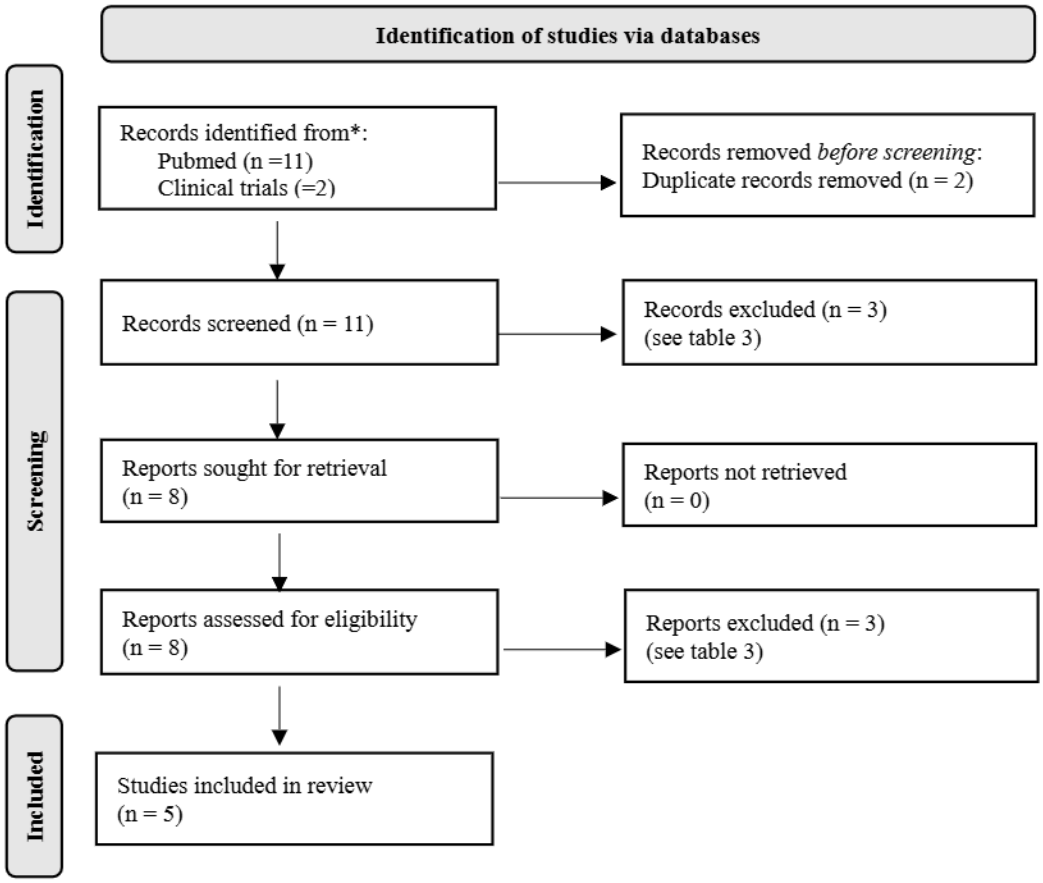
Data Extraction and Selection

For each article the following data was collected: database, title, year of publication, country, method, keywords, objective, general topic . The retrieved data is available for consultation in supplementary material, Table S1(See Appendix). The extraction was carried out by three researchers and any discrepancies were resolved by consensus between them.

A total of 13 articles were identified as relevant,

of which 2 were removed for being duplicates and 6 were excluded by applying the previous mentioned inclusion/exclusion criteria. The PRISMA selection flowchart is illustrated in Figure 1.

Figure 1. Flow diagram applied to the search.



The Table 2 presents the exclusion justification of the manuscript from the present study (de Almeida et al., 2021; de Faria et al., 2020; López-Sendón Moreno et al., 2016; Peball et al., 2019; Timler et al., 2020; van den Elsen et al., 2017).

Table 2. Excluded studies and the justification.

Study	Exclusion Justification
Timler et al., 2020 (Timler et al., 2020)	No results.
van den Elsen et al., 2017 (van den Elsen et al., 2017)	Is a part of the study from the article van den Elsen et al., 2015a.
López-Sendón et al., 2016 (López-Sendón Moreno et al., 2016)	It deals with a specific disease (Huntington's disease), an isolated article within the group of eligible articles.

de Faria et al., 2020 (de Faria et al., 2020)	The intervention takes place over a short period of time and uses a significantly different methodology when compare with other trials.
Peball et al., 2019 (Peball et al., 2019)	Prospective, open-label, single-arm study.
de Almeida et al., 2021 (de Almeida et al., 2021)	It addresses a specific behavioural disorder (RBD) resulting from Parkinson's Disease.

Legend: RBD – Rapid eye movement sleep behaviour disorder

Analysing the Quality of the Methodology

The quality of the methodology was obtained by applying the Cochrane risk of bias assessment tool (Higgins et al., 2020). This included the assessment of 6 domains: creation of the randomisation sequence; confidentiality of the allocation; blinding of patients and professionals; blinding of the results obtained; incomplete data; selective reporting. Each one was assessed as "low", "uncertain" or "high risk" of bias by consensus between the three researchers.

The selected articles were then assessed using the CONSORT - Extension for Harms guidelines (Ioannidis et al., 2004; Moher et al., 2012; Mohiuddin et al., 2020). Each article was assessed once by each of the researchers and given a "+" sign when the recommendation was met, and a "-" sign when the opposite was verified.

The quality of adverse effect reporting was categorised as: low (e.g., score ⩽ 4); medium (e.g., score between 5 - 8); high (e.g., score between 9 - 10). The articles were assessed individually by the three researchers and the final consideration was reached by consensus between them.

Results

This section shows the data collected from the selected studies regarding efficacy and safety (e.g., based on the analysis of adverse effects). First, the results of analysis of the risk of bias of adverse effect reporting in the included studies are shown in **Error! Reference source not found.** and the quality assessment in Table 4.

Table 3. Cochrane risk of bias assessment for included studies.

Study	Creation of the randomisation sequence	Allocation confidentiality	Blinding of patients and professionals	Blinding of the results obtained	Incomplete data	Selective reporting
van den Elsen et al., 2015b (van den Elsen et al., 2015b)	Low	Low	Low	Low	Low	Low

Herrmann et al.,2019 (Herrmann et al., 2019)	Low	Uncertain	Low	Low	Uncertain	Low
van den Elsen et al., 2015a (van den Elsen et al., 2015a)	Low	Low	Low	Low	Low	Low
Peball et al., 2020 (Peball et al., 2020)	Low	Low	Low	Uncertain	Low	Low
Ahmed et al., 2015 (Ahmed et al., 2015)	Low	Low	Low	Low	Low	Low

Table 4. Assessing the quality of adverse effects (AEs) reports using CONSORT recommendations

Recommendation	Peball et al., 2020 (Peball et al., 2020)	van den Elsen et al., (van den Elsen et al., 2015b)	Herrmann et al., 2019 (Herrmann et al., 2019)	van den Elsen et al., (van den Elsen et al., 2015a)	Ahmed et al., 2015 (Ahmed et al., 2015)
Indicate in the title or abstract whether the study collected data on AEs and benefits.	+	+	+	+	+
Indicate in the introduction whether the study addresses both AEs and benefits.	+	+	+	+	+
Provide a list of the AEs addressed with definitions for each (e.g., where relevant, classification, expected versus unexpected events, reference to standardised and validated definitions and description of new definitions).	+	-	+	-	-
Clarify how information regarding AEs was collected (e.g., mode of data collection, timing, attribution methods, verification intensity and monitoring and interruption rules related to AEs, where relevant).	+	+	+	+	-
Describe the plans for presenting and analysing information on AEs (including coding, handling recurring events, specifying time problems, handling continuous measurements and any statistical analyses).	+	-	+	-	-
Describe for each arm the participants' dropouts due to AEs and the experience with the assigned treatment.	+	+	+	+	+
Provide denominators for analysing AEs.	+	-	+	+	-

Recommendation	Peball et al., 2020 (Peball et al., 2020)	van den Elsen et al., (van den Elsen et al., 2015b)	Herrmann et al., 2019 (Herrmann et al., 2019)	van den Elsen et al., (van den Elsen et al., 2015a)	Ahmed et al., 2015 (Ahmed et al., 2015)
Present the absolute risk of each AE (specifying type, grade and severity per arm), and present appropriate metrics for recurrent events, continuous variables and scale variables, where relevant.	+	-	+	-	-
Describe any subgroup analyses and exploratory analyses for AEs.	+	-	+	+	+
Provide a balanced discussion of benefits and AEs with emphasis on study limitations, generalising, and other sources of information on AEs.	+	+	+	+	-
Score	10/10	5/10	10/10	7/10	4/10

As result of the search method implemented, 5 articles were obtained and were included for the qualitative synthesis. The characteristics of the studies (e.g., authors, intervention, experimental design, duration, participants, outcomes/outcome data) are shown in Table 5.

Table 5. Characteristics of the included studies

Study	Intervention	*Design*	Time	Participants (n)	Outcomes
van den Elsen et al. (van den Elsen et al., 2015b)	THC 4.5 mg *vs.* placebo	Randomised controlled trial (RCT)	3 weeks	Dementia; n= 50 (24 on THC and 26 on placebo)	Agitation/Aggression (NPI e CMAI)
Herrmann et al. (Herrmann et al., 2019)	Nabilone 1-2 mg *vs.* placebo	Randomised controlled trial crossover	6 weeks per intervention	Alzheimer's disease or Mixed dementia; n= 38	Agitation (CMAI e NPI)
van den Elsen et al. (van den Elsen et al., 2015a)	THC 1.5 mg e THC 3 mg *vs.* placebo	Randomised controlled trial crossover	3 days per intervention with an actual duration of 12 weeks	Dementia; n= 22	Behaviour, cognition, and status behaviour (NPI, CMAI, CCGIC and sMMSE) Agitation (NPI e CMAI)
Peball et al. (Peball et al.,	Nabilone 0.50 – 2 mg *vs.* placebo	Randomised controlled trial enriched	4 weeks	Parkinson's disease; n= 38 (19 for	Non-motor aspects of daily life (MDS-UPDRS-I)

Study	Intervention	*Design*	Time	Participants (n)	Outcomes
2020)				each group)	
Ahmed et al (Ahmed et al., 2015)	THC 0,75 mg (week 1 to 6) and THC 1,5 mg (week 7 to 12) *vs.* placebo twice/day for 3 days separated by a 4-day washout period	Randomised controlled trial crossover	12 weeks	Dementia; n= 10	Safety and tolerability Pharmacokinetic changes Pharmacodynamic effects

Legend: MDS-UPDRS-I – Disorder Society - Unified Parkinson's Disease Rating Scale-I; CCGIC – Caregiver's Clinical Global Impression of Change; CMAI – Cohen-Mansfield Agitation Inventory; NPI – Neuropsychiatric Inventory; THC – Tetrahydrocannabinol; sMMSE – standardized Mini-Mental Status Examination.

Four randomised placebo-controlled trials (RCTs) were identified. Three of them are crossover RCTs (Ahmed et al., 2015; Herrmann et al., 2019; van den Elsen et al., 2015a), one is an enriched RCT (Peball et al., 2020) and the last is a randomised controlled trial (van den Elsen et al., 2015b). Two studies compared THC 1.5 - 4.5 mg and placebo (van den Elsen et al., 2015b; van den Elsen et al., 2015a) in samples of individuals diagnosed with dementia. The remaining two studies compared nabilone 0.5 - 2 mg, a THC analogue with placebo (Herrmann et al., 2019; Peball et al., 2020) in samples of individuals with AD or mixed dementia (Herrmann et al., 2019) and individuals with PD (Peball et al., 2020). The latter evaluated the safety and tolerability of THC 0.75 mg and THC 1.5 mg in individuals also diagnosed with dementia (Ahmed et al., 2015). The latter also investigated its pharmacodynamic and pharmacokinetic effects, which will not be explored in this study.

Three of the studies assessed agitation and aggression symptoms as the main objective, using the NPI and CMAI as measures (Herrmann et al., 2019; van den Elsen et al., 2015b; van den Elsen et al., 2015a). One study investigated non-motor aspects of daily life (Peball et al., 2020) using the MDS-UPDRS-I. The last study looked at psychedelic effects, body sway and vital signs in favour of assessing the safety and tolerability of interventions and pharmacokinetic and pharmacodynamic parameters (Ahmed et al., 2015).

Efficacy

The results on the efficacy parameter obtained from the interventions in each study are shown in Table 6. The results of the study by Ahmed et al. (Ahmed et al., 2015) are only presented in table 8, as they mainly refer to adverse effects.

Table 6. Results of the effectiveness of cannabinoid compounds

Study	Results	Considerations
Cognitive Function and/or Non-motor Symptoms		
Peball et al.	Primary Outcomes	

Study	Results	Considerations
Cognitive Function and/or Non-motor Symptoms		
(Peball et al., 2020)	MDS-UPDRS-I: MD(DP) = 1.63 (0.09 to 3.18), p = 0.030, Cohen's d = 0.66	- Significant difference between groups with a disadvantage for placebo.
	<u>Secondary and Exploratory Outcomes</u> NMSS: $M(DP)_{NG}$ = 4.05 (-0.65 to 8.75), p = 0.096, Cohen's d = 0.42 $M(DP)_{PG}$ =11 (4.68 to 16.32), p = 0.004, Cohen's d = 0.84[1] MD(DP) = 6.95 (0.66 to 14.55), p = 0.147, Cohen's d = 0.58	- Change was not significant in the nabilone group, however, the placebo group worsened significantly with a large effect size. - Between groups effect size with a disadvantage for placebo.
	Anxious mood: MD(DP) = 0.37 (-0.07 to 0.80), p = 0.044, $r_{contrast}$ = 0.33 Night-time sleeping problems: MD(DP) = 1.74 (0.95 to 2.53), p < 0.001, $r_{contrast}$ = 0.61	- Significant between-group changes to the advantage of the nabilone group.
	CGI-I: MD(DP) = 0.53 (0.09 to 0.96),0.53, p = 0.019, φ coefficient = 0.37	- Significant deterioration with a medium effect size to the disadvantage of the placebo group.
Herrmann et al. (Herrmann et al., 2019)	<u>Primary Outcomes</u> Agitation (CMAI): b = -4.0 (-6.5 to -1.5), t(30.2) = -3.3, p = 0.003, Cohen's d = 0.52	- Favouring nabilone over placebo (negative differences favour nabilone)

Study	Results	Considerations
Cognitive Function and/or Non-motor Symptoms		
Herrmann et al. (Herrmann et al., 2019)	Secondary Outcomes Behaviour (NPS): b = -4.6 (-7.5 to -1.6), t(32.9) = -3.1, p = 0.004 Behaviour (NPI-agitation/aggression): b = -1.5 (-2.3 to -0.62), t(33.2) = -3.6, p = 0.001 Cognition (sMMSE): b = 1.1 (0.1 to 2.0), t(22.6) = 2.4, p = 0.026	- Both favored nabilone. - Significant difference in cognition in favour of nabilone.
van den Elsen et al. (van den Elsen et al., 2015b)	NPI_{14}: THC, p = 0.002; placebo, p = 0.002 NPI_{21}: THC, p = 0.003; placebo, p = 0.001 $MD(DP)_{21}$ = 3.2(-3.6 to 10) $NPI_{agitation}$: 20.1(22.0 to 1.9) $NPI_{aberrant\ motor\ behaviour}$: 0.3(21.0 to 1.7)	- Total NPI scores decreased in both groups after 14 and 21 days of intervention. - No significant difference between groups after 21 days of treatment. - No significant difference in agitation or aberrant motor behaviour.
van den Elsen et al. (van den Elsen et al., 2015a)	Primary Outcomes THC *vs* placebo: NPI_{Total}: -0.5 (-3.1 to 2.2) $NPI_{Agitation/aggression}$: -0.3 (-0.9 to 0.2) THC low dose *vs* placebo*: NPI_{Total}: 1.8 (-2.1 to 5.8) $NPI_{Agitation/aggression}$: 0.0 (-0.8 to 0.8) THC high dose *vs* placebo*: NPI_{Total}: -2.8 (-7.4 to 1.8) $NPI_{Agitation/aggression}$[1]: -0.7 (-1.6 to 0.3) THC low dose *vs* THC high dose *vs* placebo*: NPI_{Total}: p = 0.22 $NPI_{Agitation/aggression}$: p = 0.29	- 7 missing values (3 on THC, 4 on placebo). *For p value, significance level was set at $p \leq 0.025$. - There was no effect of THC treatment compared to placebo on NPI. - No differences were found between low dose THC and placebo and between high dose THC and placebo. - Analysis per group did not show significant differences between the interventions.
	Secondary Outcomes $CMAI_{THC\ vs\ placebo}$: -1.5 (-4.0 to 1.0) $CMAI_{THC\ low\ dose\ vs\ placebo}$: -1.2 (-5.0 to 2.7) $CMAI_{THC\ high\ dose\ vs\ placebo}$: -1.8 (-5.5 to 1.9) $CMAI_{THC\ low\ dose\ vs\ THC\ high\ dose\ vs\ placebo}$: p = 0.51*	*For p value, significance level was set at $p \leq 0.025$. - 16 missing values (7 on THC, 9 on placebo). - No significant differences were found between THC and placebo on CMAI domains.
Motor Symptoms		
Peball et al. (Peball et al., 2020)	MDS-UPDRS-III score: mean of effect sizes = 0.39 Total motor score: mean of effect sizes = 0.44	- Scores worsened in the placebo group, between-group differences were not significant.

Herrmann et al. (Herrmann et al., 2019)	Pain (PAINAD): b = 0.03(0.22 - 0.27), t(19.9) = 0.2, p = 0.82	- No treatment differences.

Legend: For all p values, significance level was set at $p \leq 0.05$, except for van den Elsen et al., 2015a indicated outcomes.
Effect size measured by Cohen's d; 0.2, 0.5 and 0.8 considered to be "small", "medium" and "large", respectively.
Effect size measured by $r_{contrast}$ and φ coefficient = 0.1, 0.3 and 0.5 considered to be "small", "medium" and "large".
MDS-UPDRS-I/III – Disorder Society - Unified Parkinson's Disease Rating Scale-I/III; GIC – Caregiver's Clinical Global Impression of Change; CMAI – Cohen-Mansfield Agitation Inventory; NPI – Neuropsychiatric Inventory; THC – Tetrahydrocannabinol; CGI – Clinical Global Impression; sMMSE – standardized Mini-Mental Status Examination; NMSS – Non-motor Symptoms Scale.

Safety and Tolerability are shown in

The adverse effects recorded in the studies

Table 7.

Table 7. Results regarding the safety and tolerability of cannabinoid compounds through adverse effects (AEs)

Study	Adverse Effects	Authors conclusions	Considerations
van den Elsen et al. (van den Elsen et al., 2015b)	- The occurrence of AEs was similar between groups. - Patients with at least 1 AE: 16 on THC (66.7%) , 14 on placebo (53.8%), $p = 0.36$ - Occurrence of 1 serious AE not related to treatment. - No significant differences in the occurrence of drowsiness, euphoria, dizziness or falls between groups.	"THC was safe and well tolerated. "The low observation of biological signs of AEs indicates that very low doses were used, and psychoactive drugs are rarely effective when there are no occurrences of AEs. These data warrant the need for further studies with higher doses of THC".	- Three withdrawals, pneumonia (n=1) from the THC group, persistent nausea (n=1) from the placebo group) and informed consent (n=1). - No changes in other safety parameters between groups (e.g., weight, heart rate and blood pressure).
Herrmann et al. (Herrmann et al., 2019)	- The most common AE was sedation (McNemar's test, p= 0.09) on nabilone group (n=17[a]) and falls (n=15) with no significant difference between groups. - 31 AEs on nabilone group and 14 AEs on placebo group. - 9 occurrences of SAEs and 2 deaths[b].	"Cannabinoids have a distinct pharmacological profile and may offer an alternative mechanism for treating agitation, with modest efficacy and safety compared to previous pharmacological therapies."	[a] Dose reduction improved AEs in 12 individuals, with a difference in CMAI (p<0.001) favouring nabilone. [b] Sudden death in the placebo group and stroke suspected to be caused by nabilone administration.
van den Elsen et al (van den Elsen et al., 2015a)	- Total of 184 occurrences of mild to moderate AEs, 91 on THC and 93 on placebo group. - 4 SAEs occurred, requiring (prolongation of) hospitalisation, no SAE related to the intervention.	"Reports of AEs, vital signs and mobility showed that the intervention was well tolerated by the group. This may suggest future research using higher doses to treat behavioural disorders in dementia."	- There was no increase in occurrence after high dose of THC. - Two dropouts, occurrence of malignant symptoms (n=1) and due to extensive use of psychotropic medication (n=1).

Study	Adverse Effects	Authors conclusions	Considerations
Peball et al. (Peball et al., 2020)	- No serious AEs. - AEs noted: insomnia, respiratory tract infections, pain, falls and syncope. - Occurrence of 1 case of transient panic attack in the nabilone group. - No significant changes in other safety parameters.	"Treatment with nabilone was well tolerated. This adds to the evidence of safety and efficacy of cannabinoid-based treatments."	- Safety MDS-UPDRS parameters not altered. - Change in domain 1 of the NMSS (e.g., cardiovascular) with a disadvantage for the nabilone group (mean effect size of 0.51)
Ahmed et al. (Ahmed et al., 2015)	- Total of 98 AEs, 55 on placebo and 43 on THC group. - 21 AE on THC 0.75 mg *vs* 30 AEs on placebo group, p = 0.290.	"Low doses of THC were well tolerated by elderly people with dementia. Possible THC-related AEs were mild and transient. There were no serious THC-related AEs."	- All participants completed the study. - All verified AEs were mild and resolved spontaneously without the need for intervention.

Legend: AE – Adverse Effect; SAEs – Severe Adverse Effects; THC – Tetrahydrocannabinol; CMAI – Cohen-Mansfield Agitation Inventory; MDS-UPDRS – Disorder Society - Unified Parkinson's Disease Rating Scale; NMSS – Non-motor Symptoms Scale.

Table 8 shows the description of the AEs that were mutually verified and occurred most frequently in the analysed studies.

Table 8. Description of adverse effects(AEs) found in the studies.

Study (n)	Adverse Effects	Total occurrences/ adverse effect (n)	Study group (n)	Control group (n)	Comments
Peball et al. (Peball et al., 2020) (n = 48)	Insomnia	4	2	2	The authors differentiated the severity of the adverse events observed: Nabilone group: n=3 mild AEs and n=1 moderate AE;
	Respiratory disorders	3	0	3	
	Pain	3	1	1	
	Falls	2	1	1	
	Syncope	2	0	2	
van den Elsen et al. (van den Elsen et al., 2015b) (n = 50)	Dizziness	8	4	4	Pain e.g., headache, stomach, muscle, abdominal, among others.
	Drowsiness	6	2	4	
	Cognitive impairment	4	3	1	
	Insomnia	3	2	1	
	Fatigue	4	2	2	
	Respiratory	5	5	0	

Study (n)	Adverse Effects	Total occurrences/ adverse effect (n)	Study group (n)	Control group (n)	Comments
	disorders				
	Falls	4	1	3	
	Pain	6	5	1	
Herrmann et al. (Herrmann et al., 2019) (n=38)	Sedation	29	22	7	Severe AEs included lethargy (n=2), a critical increase in the INR (n=1), myocardial infarction (n=1), pneumothorax (n=1) and urinary tract infection (n=1).
	Falls	15	8	7	
	Deaths	2	1	1	
van den Elsen et al. (van den Elsen et al., 2015a) (n=20)	Psychiatric disorders	47	21	25	Authors have quantified AEs using MedDRA.
	Nervous system disorders	34	15	19	
	General disorders	20	11	9	
	Cardiac disorders	11	5	6	
	Gastrointestinal disorders	8	7	4	
	Respiratory disorders	9	8	1	
Ahmed et al. (van den Elsen et al., 2017) (n=10)	No indication of occurred AEs.	98	43	5	-

Legend: AEs – Adverse effects; INR – International Normalised Ratio; MedDRA – Medical Dictionary for Regulatory Activities.

Discussion

Efficacy

In the study by van den Elsen et al. (van den Elsen et al., 2015b), the administration of THC 4.5 mg/day did not show a significant reduction in agitation/aggression compared to the placebo group, the same as in van den Elsen et al. (van den Elsen et al., 2015a) with the administration of THC 1.5 and 3 mg/day (both with NPI and CMAI measurements). However, Herrmann et al. (Herrmann et al., 2019) found an improvement in agitation/aggression with the administration of 1 to 2 mg of nabilone, observed by the mean difference in CMAI and NPI measurements ($p = 0.003$ and $p = 0.004$, respectively). The study that measured the effect of nabilone on cognitive function indicates a general improvement in NMSS, as evidenced by the positive mean effects relates to sleep and

anxiety ($p < 0.001$ and $p = 0.004$) (Peball et al., 2020). Herrmann et al. (Herrmann et al., 2019) found improvements in mental state in the sample intervened with nabilone ($p = 0.026$). When assessing the risk of bias, two studies showed a low/uncertain risk of bias (Herrmann et al., 2019; Peball et al., 2020) and the remaining three a low risk (Ahmed et al., 2015; van den Elsen et al., 2015b; van den Elsen et al., 2015a). Thus, it is believed that the results obtained by the interventions add evidence of satisfactory quality regarding the efficacy of the cannabinoid compounds THC and nabilone in the treatment of dementia.

Safety

All studies reported the occurrence of AEs in both experimental groups. The two THC vs. placebo studies conducted by van den Elsen and colleagues (van den Elsen et al., 2015b; van den Elsen et al., 2015a) showed no significant differences between groups in the occurrence of drowsiness, euphoria, dizziness or falls. In the first study, there were no significant changes in blood pressure and heart rate. In the nabilone trial by Herrmann et al. (Herrmann et al., 2019), the most common AE was sedation ($p = 0.009$), with a statistical significance of 44.7% in the nabilone group vs. 15.8% in the placebo group. There was no significant difference in the incidence of falls or other AEs. The same was seen in Peball et al. (Peball et al., 2020), in which no serious AEs were recorded. However, there were occurrences of reduced severity in both groups in a similar proportion (42% in the placebo group and 32% in the nabilone group), with a disadvantage for the placebo group in the severity and number of occurrences. Ahmed et al. (Ahmed et al., 2015) recorded 98 AEs, 6 of which were possibly related to THC administration.

The effects recorded were agitation, fatigue, and dizziness. There was a higher incidence of AEs such as insomnia, sedation, cognitive and psychiatric disorders, and general disorders such as pain, dizziness, fatigue, and falls. Based on the scores obtained after applying the CONSORT instrument, two studies (Herrmann et al., 2019; Peball et al., 2020) showed high quality in the reporting of AEs and two others medium quality (van den Elsen et al., 2015b; van den Elsen et al., 2015a). The study by Ahmed et al. (Ahmed et al., 2015) revealed low quality reporting. The overall assessment of AE reporting is assumed to be average.

Non-harmful therapy

The association between the efficacy parameter and the safety and tolerability profile obtained from the analysis of the articles, corroborated by the subsequent evaluation, makes it possible to categorise therapies based on cannabinoid compounds as possible non-harmful therapies. This finding is supported by the evidence of efficacy obtained from the use of low doses of CC and of safety, in this parameter, acquired by extrapolating the occurrences of AEs verified. It should be noted that the AEs observed in the interventions were considered to have less of a negative impact than those caused by conventional medication. In view of the WHO (World Health Organization, 2018) initiative mentioned above, therapy using these compounds will make it possible to reduce the harm related to conventional medication (e.g., reduce the adverse effects and complications it brings to patients) and, consequently, increase its safety. Continued exploration of these compounds will make it possible to ensure the quality of the product administered to the patient and prove its efficacy as a therapy. To this end, a continuous increase in the number of studies on the subject and in the quality of

the reports made by researchers (e.g., through the act of reporting incidents arising from the interventions, duly associated with proven efficacy profiles) is necessary.

Conclusion

In this study was possible to associate THC and nabilone with moderate efficacy in dementia symptoms (depending on the time and doses administered) and favourable safety and tolerability profiles (e.g., no serious adverse effects at the doses used in the study). We therefore believe that the main goal of this review has been achieved, as it is possible to propose the exploration of these compounds for use in dementia and as a possible non-harmful therapy, meeting the objective proposed by WHO.

Nevertheless, the study has some limitations. Firstly, the small number of studies included in the review which, despite having allowed a detailed analysis of all the documents, does not allow conclusions to be generalised for certain compounds or their association with a certain type of dementia. The evidence gathered comes from studies with a heterogeneous methodology and whose interventions involve administering THC or nabilone to samples made up of individuals diagnosed with PD or AD. It is therefore not possible to establish a relationship between compounds (suitable) for a given situation. In addition, analysing the risk of bias to assess the quality of the methodology of these studies using the Cochrane Risk of Bias Assessment Tool carries some subjectivity due to different experience level of the researchers.

The safety assessment of the compounds was based on the occurrences of AEs found in all the studies analysed and then the CONSORT instrument was applied to assess the quality of these reports. This methodology lacks power, as there were several terminologies indicating the same AEs and some of the studies did not explicitly reveal their severity. It is also worth mentioning the subjectivity of this assessment due to the different experience of the researchers.

For a more reliable analysis of the risk-benefit ratio of cannabinoid compounds as a dementia therapy, it is also necessary to analyse the efficacy and safety profiles of conventional drugs, which was not explored in depth in this study.

New studies should therefore tend towards a rigorous and in-depth assessment of the risk of these new therapies for the patient (e.g., providing concrete information that allows risk management). That said, we believe that in the future it will be important to combine the efficacy and safety profiles of these compounds to unequivocally assess the quality of the therapy and its application as a non-harmful therapy.

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