INSTITUTO LATINO-AMERICANO DE CIÊNCIAS DA VIDA E DA NATUREZA (ILACVN)

CURSO DE MEDICINA

USO DE CANABINÓIDES NO TRATAMENTO DE DEMÊNCIAS:
REVISÃO DE LITERATURA.

MATHIAS MESQUITA RAMOS

Foz Do Iguaçu

2024

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Trabalho de Conclusão de Curso apresentado ao Instituto Latino-Americano de Ciências da Vida e da Natureza da Universidade Federal da Integração Latino-Americana, como requisito parcial à obtenção do título de Bacharel em Medicina

Orientador: Prof. Dr. Francisney Pinto do Nascimento

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ABSTRACT

Objective: This study aims to review clinical evidence on various cannabinoid interventions on dementia, as well as the adverse effects associated with these therapies.

Methodology: This study employed a literature review searching in the PubMed database, using specific terms related to cannabinoids and dementia. After title and abstract screening, six articles met the inclusion criteria focusing on randomized controlled trials, and excluding reviews and case reports.

Conclusion: Initial findings suggest promise for THC in managing cognitive decline, while Nabilone and CBD warrant further exploration for neuropsychiatric symptoms. Notably, cannabinoids may offer a safer alternative to antipsychotics for managing agitation and aggression. Overall, the favorable safety profile and emerging evidence highlight the considerable potential of cannabinoids in dementia treatment.

Keywords: Dementia; cannabinoids; cannabidiol (CBD); tetrahydrocannabinol (THC); Nabilone; Dronabinol.

RESUMEN

Objetivo: Este estudio tiene como objetivo revisar la evidencia clínica sobre diversas intervenciones con cannabinoides en la demencia, así como los efectos adversos asociados a estas terapias.

Metodología: Este estudio empleó una revisión de la literatura con búsqueda en la base de datos PubMed, utilizando términos específicos relacionados con cannabinoides y demencia. Después de la selección de títulos y resúmenes, seis artículos cumplieron con los criterios de inclusión centrándose en ensayos clínicos aleatorios y controlados, excluyendo revisiones y estudios de caso.

Conclusión: Los hallazgos iniciales sugieren una promesa para el THC en el manejo del declive cognitivo, mientras que el nabilona y el CBD justifican una mayor exploración para los síntomas neuropsiquiátricos. Cabe destacar que los cannabinoides pueden ofrecer una alternativa más segura a los antipsicóticos para el manejo de la agitación y la agresión. En general, el perfil de seguridad favorable y la evidencia emergente destacan el potencial considerable de los cannabinoides en el tratamiento de la demencia.

Palabras clave: Dementia; cannabinoids; cannabidiol (CBD); tetrahydrocannabinol (THC); Nabilone; Dronabinol.

RESUMO

Objetivo: Este estudo visa revisar as evidências clínicas sobre várias intervenções com canabinóides na demência, bem como os efeitos adversos associados a essas terapias.

Metodologia: Este estudo empregou uma revisão de literatura com busca na base de dados PubMed, utilizando termos específicos relacionados a canabinóides e demência. Após a triagem de títulos e resumos, seis artigos atenderam aos critérios de inclusão com foco em ensaios clínicos randomizados e controlados, excluindo revisões e relatos de caso.

Conclusão: Os resultados iniciais sugerem um potencial para o THC no manejo do declínio cognitivo, enquanto o Nabilone e o CBD justificam investigações adicionais para sintomas neuropsiquiátricos. Notavelmente, os canabinoides podem oferecer uma alternativa mais segura aos antipsicóticos para o manejo de agitação e agressão. De modo geral, o perfil favorável de segurança e as evidências emergentes destacam o potencial considerável dos canabinoides no tratamento da demência.

Palavras-chave: Dementia; cannabinoids; cannabidiol (CBD); tetrahydrocannabinol (THC); Nabilone; Dronabinol.

LISTA DE ABREVIATURAS E SIGLAS

AD	Alzheimer's disease
CB1	Cannabinoid receptor 1
CB2	Cannabinoid receptor 2
CBC	Cannabichromene
CBD	Cannabidiol
CBG	Cannabigerol
ECS	Endocannabinoid system
FDA	Food and drug administration
ILACVN	Instituto Latino-Americano de Ciências da Vida e da Natureza
MMSE	Mini mental standard examination
mRNA	Messenger ribonucleic acid
NMDA	N-Methyl-D-Aspartic Acid
NPI	Neuropsychiatric Inventory
PET	Positron emission tomography
ROS	Reactive oxygen species
THC	Tetrahydrocannabinol
TNF-α	Tumor necrosis factor alpha
UNILA	Universidade Federal da Integração Latino-Americana

1 INTRODUCTION

1.1 DEMENTIA

Dementia is an acquired syndrome that could be described as an impairment in at least two cognitive domains, interferes with independent daily functioning and is not better explained by some other clinical conditions such, disturbances in level of consciousness or delirium (WHO, 2024)(GALE; ACAR; DAFFNER, 2018).

In 1990, there were an estimated 20.2 million cases world-wide. By 2016, this number had doubled to 43.8 million. However, comparing those two periods, there was no significant increase in the prevalence rate by age group, which was 701 cases per 100,000 in 1990 and increased to 712 cases per 100,000 in 2016. In both cases there were different prevalences between genders, with approximately 61.6% of cases occurring amongst women (NICHOLS et al., 2019).

In a literature review by Cao et al., (2020), revisiting data published from 1985 to 2019, Alzheimer's disease (AD) was the leading cause of dementia in patients older than 50 years, responding for 46,4% of cases (324 per 10.000, CI 95%); followed by Vascular dementia with 16,6% of cases of dementia (116 per 10.000, CI 95%. Other neurodegenerative causes of dementia include Lewy bodies disease, frontotemporal dementia, progressive supranuclear palsy, corticobasal syndrome and primary progressive aphasia (LJUBENKOV; GESCHWIND, 2016).

1.2 AGING, DEMENTIA AND THE ENDOCANNABINOID SYSTEM

Because of the intimate relationship between aging and various demential aetiologies, and also because of the profound influence of the endocannabinoid system (ECS) in the aging process, the potential of cannabinoid interventions in those pathologies have been proposed (BILKEI-GORZO, 2012)(ABATE; UBERTI; TAMBARO, 2021). The oxidative stress is a major factor in neuronal damage in aging and in some dementia aetiologies (BAI et al., 2022), this is specially important due to the limited potential of post-mitotic neurons to regenerate (BILKEI-GORZO, 2012). In this context, it is worth noting that *in vivo* preclinical studies show neuroprotective effects of cannabinoids. Jia et al. (2014) demonstrated a neuroprotective effect of anandamide in hippocampal mice cell line when exposed to hydrogenium peroxide, reducing the reactive oxygen species (ROS) production inside the cells; and also proved that this was a cannabinoid receptor 1 (CB1) mediated process.

Hippocampal damage is observed in various dementias (PLACHTI et al., 2020) and is believed to underlie the cognitive and psychiatric symptoms these patients experience. Supporting this notion, Terreros-Roncal et al. (2021) found that immature nerve cells in the hippocampus (dentate gyrus) had abnormal shapes in patients with Lewy body dementia and Parkinson's disease. Similarly, frontotemporal dementia patients exhibited an imbalance in cell types within the hippocampus, suggesting disrupted cellular homeostasis. While investigating the role of CB1 receptor in the aging process Bilkei-Gorzo et al. (2005) demonstrated an premature cognitive deficit in young CB1 knockout mice, similar to old mice. In a further study by Palmisano et al. (2022), CB1 receptors were blocked specifically in the hippocampus and similar social memory impairment was observed. This study also shows that locally blocked mice had doubled TNF-α mRNA expression and reduced cellular replication in the subgranular zone of the dentate gyrus.

1.3 AVAILABLE INTERVENTIONS

1.3.1 Disease-modifying drugs

In 2021 the first disease-modifying treatment to AD, Aducanumab, was approved by the Food and Drug Administration (FDA). This approval process was accelerated based on disease gravity and biomarker improvements, even though clinical evidence of benefit was controversial at that moment (TAMPI; FORESTER; AGRONIN, 2021). Further studies also could not definitively prove clinical benefits. Aducanumab is an anti-amyloid-β monoclonal antibody, imunoglobulin-1 (IgG1), able to induce the clearance of parenchymal plaques in the central nervous system. It is used in patients with mild cognitive impairment and early AD, but there is no approval to moderate-to-severe AD (SHI et al., 2022).

A similar recombinant anti-amyloid-β monoclonal antibody, Lecanemab, targets soluble protofibrils, and has been approved by the FDA in 2023 for early AD (VARADHARAJAN et al., 2023)(HARRIS, 2023). In a double-blinded, placebo controlled, randomized trial by McDade *et al*. (2022) different doses of Lecanemab were compared to placebo through 18 months of trial. A reduction in the rate of disease progression was determined using a linear model which correlates the presence of amyloid-β observed in the positron emission tomography (PET) scan and clinical effects. Further studies confirmed the statistical efficacy and relative security of the treatment (ABDELAZIM et al., 2024). Issues are raised concerning the clinical relevance of Lecanemab's benefits , and also its cost-effectivity. According to Nguyen *et al*. (2024) this monoclonal therapy can be considered a favorable alternative to the standard treatment if its annual cost falls below five thousand one hundred United States dollars.

1.3.2 Cognitive symptoms

The medications that are currently approved by the FDA for treatment of cognitive symptoms in AD are memantine and cholinesterase inhibitors. Cholinesterase inhibitors and memantine are also frequently used to reduce cognitive symptoms in dementia with Lewy bodies, Parkinson's disease dementia and vascular dementia (HAFIZ et al., 2023).

Memantine antagonizes the N-methyl-D-aspartate receptor (NMDAr) and some cholinergic receptors; it also has an agonistic effect at D2 dopamine receptors in the striatum. It is thought that the predominant mechanism of action is the NMDAr blocking (KARIMI TARI et al., 2024). Cholinesterase inhibitors prevent the acetyl-choline breakdown in the neuronal cleft, increasing cholinergic effects (COLOVIC et al., 2013). Within this drug class three medications are available: donepezil, rivastigmine and galantamine. Cognitive interventions as cognitive enrichment have also shown evidence of improvement in cognition, mood and quality of life (TISHER; SALARDINI, 2019).

1.3.2 Noncognitive symptoms

Brexpiprazole is an atypical antipsychotic drug approved by the FDA for agitation in patients with AD. It antagonizes 5-HT2A, 5-HT2B, 5-HT7, α1A, α1B, α1D, and α2C receptors, and partially agonizes 5-HT1A, D2, and D3 receptors. Those pharmacological characteristics are less associated with sedation or extrapyramidal symptoms than typical antipsychotics (VARADHARAJAN et al., 2023). Antipsychotics are associated with increased risk of overall mortality in demented patients, but there is a lack of evidence if Brexpiprazole is also associated with these effects (ROGOWSKA et al., 2023).

Suvorexant was approved by the FDA to treat sleep disturbances in mild to moderate AD. This drug antagonizes receptors OX1R and OX2R, respectively competing with neuropeptides orexin A and B. Various clinical trials demonstrated its effectiveness in prolonging sleep time and reducing sleep latency. Although, its effectiveness is reduced in patients suffering from insomnia for more than a year (HAN et al., 2023).

2 METHODOLOGY

The source material was obtained from the PubMed database by searching for the terms "(cannabinoids)AND(dementia)", "(dronabinol)AND(dementia)", "(nabilone)AND(dementia)", "(THC)AND(dementia)" and "(cannabidiol)AND(dementia)" yielding a total of 826 results, from which 308 repeated titles were excluded. After reviewing the titles, 466 articles were excluded as they did not align with the review's scope, leaving 52

articles. Further examination of the abstracts led to the selection of six articles for comprehensive text evaluation and review synthesis. Case reports, case series, preclinical studies and reviews, were not included. A seventh study by Bar-Lev Schleider *et al*. (2022) has been added to the discussion section on adverse effects to compare demented and non-demented patients treated with cannabinoids.

3 DISCUSSION

3.1 COGNITIVE SYMPTOMS

In a randomized, double-blind crossover trial, Herrmann et al., (2019) observed a minimal, yet statistically significant, reduction in Standard Mini-Mental State Examination (sMMSE) scores. This study included 38 patients, and compared placebo to Nabilone in a mean daily dose of 1,6 ± 0,5 mg, throughout a six week exposition period.

On the other hand, Hermush et al. (2022) in a double-blind trial with 60 patients through a sixteen week period, found no statistical benefit of a high Cannabidiol (CBD) chemovar oil (Avidekel®) on MMSE in comparison to placebo ($p = 0,21$). In this study the mean daily dose was 527.5mg CBD and 22.3mg Tetrahydrocannabinol (THC).

This study with Avidekel® minimizes the expectancy of cognitive benefits with high CBD compounds. In contrast, nabilone, as a THC analogue, points to more promising investigation on THC based interventions. The limited size of Herrmann's study opens space for future larger studies.

3.2 GENERAL NEUROPSYCHIATRIC SYMPTOMS

The Neuropsychiatric Inventory (NPI) seeks to characterize neuropsychiatric and psychopathological symptoms in patients with AD or other dementias. The inventory assesses the frequency, severity, and distress of ten behavioral and two neurovegetative areas. The final score is derived by adding the product of the frequency and severity scores of the behavioral items for each domain. Neurovegetative domains and distress scores are summed separately (CUMMINGS, [s.d.]). The Neuropsychiatric Inventory – Nursing Home Version (NPI-NH) derives from the NPI, but it relies on the observations of a professional caregiver in daily contact with the patient. It evaluates the same elements, except from distress which was replaced by occupational disruptiveness (CUMMINGS, 2009).

In a double-blinded, randomized, placebo controlled trial with 50 patients, Van Den Elsen et al. (2015) investigated the use of daily 4,5mg THC over three weeks. The research shows no statistical difference between placebo and treatment in total NPI scores (mean difference NPI total: 3.2, 95% confidence interval [CI] 23.6 to 10.0). Similar results were found

by Timler et al. (2023) in a double-blinded, randomized, cross-over trial, comparing placebo to a mean daily dose of 30.1mg THC/20.5 mg CBD. The study was conducted with 21 patients evaluated over eighteen weeks (six weeks of exposition period), and the Nursing Home version was applied (NPI-NH). The study of Herrmann et al. (2019) with Nabilone also evaluated the changes in NPI-NH scores, however an statistically significant reduction in treatment scores was observed (b = -4.6 [-7.5 to -1.6], t (32.9) = 3.1 p = 0.004). A prospective observational research with 19 patients, by Pautex et al. (2022), presents a mean reduction on NPI scores from 71.6 (± 36.5; 24–132) to 33.7 (± 19.2; 4–60) over 13 months of treatment with mean daily doses of 12,4mg THC/24,48mg CBD.

A number of reasons for these mixed results could be suggested. In light of negative results achieved by Timler et al. (2023), and considering its superior design, the positive outcome observed by Pautex et al. (2022) may be questioned. Nonetheless, in opposition to the former study, the latter employed a CBD predominant compound, and a regulatory effect of CBD over THC may also explain the different outcomes. This interaction was pointed out in other pathological contexts (KIRKLAND et al., 2022)(FREEMAN et al., 2019). Herrmann's positive results with Nabilone in AD patients is unprecedented, even contradicting with the negative results of THC predominant compounds of Van Den Elsen et al. (2015) and Timler et al. (2023). The difference between Herrmann's and Van den Elsen' studies may rest in the longer period of exposition of the former (six weeks) in comparison to the latter. Another explanation is that in the THC trial patients with vascular or mixed dementia were also included.

Because of the higher mortality risk associated with atypical antipsychotics in demented patients (MÜHLBAUER et al., 2021), and the relatively safe profile of cannabinoids (HILLEN et al., 2019), further studies should be made to ascertain these positive results with Nabilone and high CBD compounds.

3.3 AGITATION AND AGGRESSION

One of twelve subscales of NPI-NH is "Agitation/Aggression", and is commonly used alone to evaluate changes in this behavior over a determined period of time. In the study of Van Den Elsen et al. (2015) no statistical benefit was found by low dose THC compared to placebo (ΔNPI agitation: 20.1, 95% CI 22.0 to 1.9).

While comparing Avidekel® to placebo, Hermush et al. (2022) reported a reduction of 29.4% in the NPI-NH agitation/aggression subscale ($\chi 2 = 5.98$, P = 0.01). Statistic significant reduction on NPH-NH agitation/aggression score was also presented in a randomized, double-blinded, crossover trial with 21 demented patients comparing an oral spray composed

of 3:2 THC/CBD to placebo. The interventional period lasted for six weeks, and the daily doses varied from 2,5 mg THC/1,7 mg CBD to 50mg THC/34 mg CBD (TIMLER et al., 2023).

The Cohen-Mansfield Agitation Inventory (CMAI) was developed to assess the frequency of agitated behavior in elderly patients. It consists of 29 behaviors, each rated on a 7-point scale, depending on the number of occurrences in the past two weeks. Scores can be examined individually or aggregated into groups (COHEN-MANSFIELD, 1991).

Heterogeneous results were obtained in this score with cannabinoid interventions. In the study of Timler *et.al.* (2023) no statistical difference between the placebo and THC/CBD groups were found on CMAI scores. Similar results were found by Van Den Elsen *et.al.* (2015). However, Hermush *et.al.* (2022) found higher proportions of ≥ 4 point reduction on CMAI scores in the Avidekel® group (60,0%), in comparison to the placebo group (30,0%)($\chi 2$ = 4.80, p = 0.03) Likewise, Herrmann *et.al.* (2019) report a significant effect of Nabilone on CMAI scores (b = -4.0 (-6.5 to -1.5], t(30.2) = -3.3, p = 0.003), with a Cohen's d effect size of 0,52. Similarly, Pautex *et al.* (2022) also suggests a potential benefit from daily doses of (1:2) THC/CBD in reducing CMAI scores.

The THC exclusive trial, by Van Den Elsen et al. (2015), did not achieve a positive result. Although, because of the positive results found by nabilone six weeks trial, the shorter period of exposition to THC may be pointed out as the reason to unsuccess. The contradictory results found by Timler *et.al.* (2023) could be secondary to differences in the tests applied. NPI subscale agitation/aggression takes the severity of the behavior in account, but the CMAI scores only measures the frequency. If this inference is right, the THC/CBD treatment reduced the intensity of the events.

3.4 QUALITY OF LIFE

There is a very limited number of studies evaluating the effect of cannabinoids on the quality of life in demented patients. The trial conducted by Van Den Elsen et al. (2015) revealed no statistically significant difference between THC treatment and placebo in the Quality of Life–Alzheimer’s Disease scale (-0.5, 95% CI -2.6 to 1.6). Timler et al. (2023) likewise reported unpromising findings, observing no differences when comparing THC/CBD to placebo using the same tool. However, both these studies showed design problems, as already mentioned, which reaffirm the necessity of further studies to define cannabinoid effect on quality of life of demented patients.

3.5 GENERAL IMPROVEMENT IN DISEASE

In the study of (VAN DEN ELSEN et al., 2015) the Caregiver Clinical Global Impression of Change scale was applied to the patients at the third week of treatment, and no statistical differences, in the proportion of minimal to marked improvement, were found between THC (36%) and placebo (50%) groups (χ^2, p = 0,35).

Herrmann et al. (2019) applied the Clinician's Global Impression of Change, a similar scale of the one used in the latter research. Although the differences in the groups were prominent, no statistical differences were found. "Minimal" to "marked" change was present in 47% of the treatment group and in 23% of the placebo group (McNemar'stest, exact p = 0.09).

Woodward et al. (2014) in a retrospective study with 40 patients, evaluating Dronabinol use for agitation and aggressive behavior, found a significant decrease in the Clinical Global Impression scores (z = -5.0281, p <0.0001). However, due to the uncontrolled nature of the study, the findings have limited external validity.

3.6 ADVERSE EVENTS

3.6.1 Total adverse events

In Herrmann et al. (2019) work, the total number of adverse effects were higher in the Nabilone group in comparison to the placebo group (McNemar's test, exact p = 0,05). Similar results were seen in the clinical trial conducted by Timler et al. (2023); the total number of adverse effects was significantly greater in the treatment group in comparison to the placebo group (57%, χ^2= 17.5, p < 0,001). But any of the sixteen types of adverse effects evaluated were statistically more incident in the treatment group.

Table 1: Clinical trials

Substance	Prescription	Pathology	Study design	Exposition time	Study size	Improvement	No improvement	Agravation	Side effects	Author
Nabilone	1,6 mg ± 0,5 (daily)	Alzheimer's disease	Double-blind randomized controlled trial	6 weeks	38 (crossover)	CMAI, NPI-NH, NPI-NH caregiver distress, sMMSE	CGIC	SIB	sedation	Herrmann et. al. (2019)
Avidekel	527.5mg CBD + 22.3mg THC (divided in 3 doses per day)	Major neurocognitive disorder (DSM-V) with neuropsychiatric symptoms	Double-blind, randomized, controlled, single-center trial	16 weeks	60 (40T + 20C)	CMAI, NPI-NH agitation/agression, NPI-NH sleep	MMSE	-	-	Hermush et. al. (2022)
THC	4,5 mg THC (divided in 3 doses per day)	Alzheimer's disease, vascular dementia or mixed dementia, with neuropsychiatric symptoms.	Double-blind, randomized, controlled, multicenter, phase II trial	3 weeks	50 (24T + 26P)	-	CMAI, NPI, Bathel index, QoL-AD, CCGI, PAL-WMSR,	-	-	Van Den Elsen et al. (2015)
THC/CBD (3:2)	mean 30.1 mg THC + 20.5 mg CBD (daily)	Dementia (excluded patients with Lewy body dementia, frontotemporal dementia, Parkinson's disease, epilepsy, comorbid psychiatric disaease and anorexia nervosa)	Double-blind, randomised, controlled, crossover, phase IIa trial	6 weeks	21 (crossover)	NPI-NH agitation/agression	CMAI, NPI-NH, QoL-AD, APAS	-	Higher incidense of general adverse effects, but none specifically	Timler et al. (2023)
THC/CBD (1:2)	mean 12,4 mg 9THC + 24,48 mg CBD (divided in 3 doses per day)	Severe dementia	Single-center, prospective observational study	mean 40 (20 to 58 weeks)	19 (19T)	CMAI*, NPI*, MIDA*, MIBT*, UPDRS*	-	-	was not registered	Pautex et al. (2022)
Dronabinol	mean 7,03 mg (daily)	Alzheimer's disease, vascular dementia, mixed etiology dementia, frontotemporal dementia and unspecified dementia.	Single-center, retrospective systematic chart review	mean 2,4 weeks (0,57 - 7,14 weeks)	40 (40T)	PAS, CGI, Higher percentage of food consumed	GAF, Body weight, Night time awakenings, Hours of sleep		sedation*, delirium*	Woodward et al. (2014)

* no statistical evaluation; T: Treatment group; C: Control group; CBC: Cannabichromene; CBD: Canabidiol; CBG: Cannabigerol; CBDV: Cannabidivarin; THC: Δ9-tetrahydrocannabinol; PAL-WMSR: Paired Associate Learning subtest of Wechsler Memory Scale–Revised; APAS: Abbey Pain Assessment Scale; PAS: Pittsburgh Agitation Scale; CGI: Clinical Global Impression; GAF: Global Assessment of Functioning.

Reference: Author

Although, in evaluating adverse effects, because of its reduced incidence in the population, the studies frequently require a higher number of patients to achieve statistical power to identify differences between populations. In most of the studies reporting adverse effects no statistical power is demonstrated, in consequence of that the most of them show no statistical relevant differences, which is not necessarily true.

3.6.2 Sedation or lethargy

Revisited in a meta-analysis by Bosnjak et al. (2021), Herrmann et al. (2019) observed statistical difference in the incidence of sedation while using Nabilone (17) in comparison to placebo (6)(McNemar's test, exact p = 0,02). However, no statistical difference was seen in "treatment-limiting" sedation (McNemar's test, exact p = 0,22).

Drowsiness was among the sixteen types of adverse effects evaluated by Timler et al. (2023), and its incidence throughout the study were 13 events in the THC/CBD group against six events in the placebo group. Nevertheless, as above mentioned, no statistical difference between groups was detected.

In the retrospective study by Woodward et al. (2014), nine of the 40 patients (22,5%) using Dronabinol reported at least one episode of sedation. However, the absence of a control group hinders the causation link to be established.

This adverse effect was also seen in different populations submitted to cannabinoid treatments. An observational prospective study by Bar-Lev Schleider et al. (2022) investigating effectiveness, safety and adherence of a variety of cannabinoid treatments in a plethora of pathologies (predominantly cancer and non-specific pain), 217 of the 4.891 patients (4,4%) answered that they have experienced sleepiness "due to use of cannabis".

3.6.3 Psychoactive e psychiatric disorders

In the same research by Bar-Lev Schleider et al. (2022), 208 patients (4,3%) reported psycho-active effects ("feeling high"), although some patients evaluated used smoked marijuana as a method of treatment. Delirious symptoms were reported by Woodward et al. (2014), however, six patients of the group had previous diagnosis of delirium. These data alone do not establish a solid link between non smoked cannabinoid treatments and psychoactive events.

4 CONCLUSION

The increasing number of clinical trials examining different cannabinoid treatments for dementia is revealing more specific details about the effectiveness and safety of particular

compounds and dosages. The available evidence encourages further investigation on THC based therapies for cognitive symptoms, as also stimulates Nabilone and CBD based interventions on general neuropsychiatric symptoms. Also, a modest number of trials showed evidence of benefit of Nabilone and CBD/THC compounds on agitation and aggression in demented patients, which could be a safer alternative to the current treatment with antipsychotics. The adverse effects prove to be uncommon and of low severity. This overall profile reassures the great potential of cannabinoids in treatment of demented patients.

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