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# Cannabinoids for Behavioral Symptoms in Dementia: An Overview

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**ABSTRACT**

Dementia, with loss of memory, cognitive abilities, and independent daily functioning, is increasing worldwide, related to an aging population. Currently, there is no curative treatment for dementia. Treatment of the frequently occurring behavioral and psychological symptoms of dementia (BPSD) is partially effective and associated with significant side effects.

Cannabinoids are lipophilic molecules acting on the CB1 end CB2 receptors, essential for main biological processes such as sleep, appetite, memory, and pain. Cannabinoids might have a positive impact on amyloid formation in Alzheimer's disease, the main form of dementia, and on BPSD symptoms. Most knowledge currently concerns delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). In the context of dementia and BPSD, THC might be beneficial for associated spasticity and possible pain or lack of appetite and CBD probably works better on sleep, agitation, and anxiety.

This overview of prospective clinical studies and randomized clinical trials, published between 2005 and April 2023, using cannabinoids for BPSD suggests that older studies using low-dose oral synthetic THC showed no positive results. Still, more recent studies using THC/CBD-based oral medication at higher doses show promising results and are feasible and safe in this elderly polymedicated population. Several RCTs are ongoing and planned worldwide, and we hope other trials will follow to establish clinical efficiency and optimal dosing, as well as other outcomes such as deprescribing other medications and facilitation of care. We suggest that researchers also address the more sociological aspects of prescribing cannabinoids for dementia and BPSD in their specific context.

## Introduction

Dementia is a term for several diseases that cause a group of symptoms, including loss of memory, cognitive functioning, and the ability to perform daily activities. The impairment in cognitive functioning can be accompanied, even preceded, by changes in mood, emotional control, behavior control, and motivation. Beyond the psychological consequences, dementia has an important physical, social, and economic impact on individuals and their families [1]. Currently, dementia is affecting 55 million people, and considering the global increase and aging of the population, WHO estimates that this number will increase to 78 million in 2030.

Even if research for effective treatment is ongoing, there is currently no cure for dementia, and care focuses on slowing the disease and improving well-being and quality of life [1, 2].

The most common cause of dementia is Alzheimer's disease (60–70 %), characterized by abnormal amyloid deposits forming plaques in and around the brain cells [2]. Other forms include vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and dementia related to stroke, HIV, harmful use of alcohol, nutritional deficiencies, or repeated trauma [1]. All forms are progressive. Neuropsychiatric or behavioral and psychological symptoms of dementia (BPSD) will affect most patients in the course of the disease and include agitation, irritability, delusions, and apathy. Often, they present the most critical challenge for relatives and caregivers [3].

Cannabinoids might be of interest for the treatment of dementia and associated symptoms. In vitro and in vivo research suggests cannabinoids have neuroprotective, immunosuppressive, antioxi-

dant, and anti-inflammatory properties [3]. Almost 10 years ago, Aso and Ferrer [4] suggested cannabinoids could reduce amyloid plague formation and neurofibrillary degeneration in Alzheimer's disease. Even if this potentially curative effect of cannabinoids has not been confirmed in clinical studies, there is evidence that cannabinoids can be administered safely to patients with dementia, often elderly and polymedicated, and can have a positive impact on BPSD [3, 5].

In 2017, a specialized dementia care facility in Geneva contacted us with a severely demented female patient with BPSD. One of the most debilitating symptoms she presented was almost continuous screaming, to despair of the other patients and staff. Different psychotropic medications have been tried without sufficient effect or too many side effects (notably too heavy sedation). An exceptional authorization for the prescription of nabiximols was obtained from the Swiss Federal Office of Public Health, and quickly after the introduction, the patient stopped screaming without any apparent side-effect of the cannabinoids. The director and physician of the institution invited us to discuss the possible further use of cannabinoid-based medication for more of their patients with BPSD. Since then, we have been going through a long way of open-label feasibility studies to estimate acceptability, short-and long-term safety, best medication, and pharmacological interactions [3, 6], but also a sociological study on staff and family members [7], leading up to an RCT that recently started (September 2023) [8].

While working these years on the issue of cannabinoids and dementia, we have been struck by the fact that most reviews on medical cannabinoids combine studies with different medications used (tinctures, oil, capsules, or inhaled cannabis), synthetic or full plant medications [9]. Also, the dosages were often not mentioned. Overall conclusions, often "there is not enough evidence" for different medical indications, can be based on inadequate dosages, galenic form, or type of cannabinoids. We know now that cannabis is a complex plant with assorted cannabinoids with different effects. Most knowledge concerns now delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and a combination of the two might provide better results [10]. In the context of dementia and BPSD, THC might be beneficial for associated spasticity and possible pain or lack of appetite [8], and CBD for sleep, agitation, and anxiety [10].

In this overview, we provide a summary of published and planned clinical studies of cannabinoids for patients with severe dementia since 2005, focusing on efficacy, safety, type, and dosage of cannabinoid-based medication (CBD/THC). We will also share our experience of setting up a randomized clinical trial (RCT) with a forbidden substance in a particularly vulnerable population.

## Methods

This was a non-systematic overview of prospective clinical studies or RCTs, focusing on cannabinoids for behavioral and neuropsychiatric symptoms in dementia, published between January 2005 and April 2023. Retrospective and pre-clinical studies were excluded. We also included planned clinical trials published on clinicaltrials.gov or in peer-reviewed journals. MeSH terms used were cannabinoids, THC, cannabidiol, nabiximols, dronabinol, dementia, Alzheimer's, BPSD, humans, and RCT. Both authors independently searched PubMed, Google Scholar, Embase, Cochrane, and clinicaltrials.gov databases in March/April 2023. The research was restricted to clinical trials. The authors then confronted the search results and agreed to the complete assessments of 16 studies (▶ **Fig. 1**). A discussion on the eligibility was performed when there was no initial agreement. The authors decided to exclude the case series.

## Results

From over 1,200 initial records, we selected 16 studies using cannabinoid-based medication for dementia, focusing on behavioral symptoms that met our criteria. Of them, five were published RCTs, three published open-label studies, and eight planned trials (seven RCTs) (see ▶ **Table 1**).

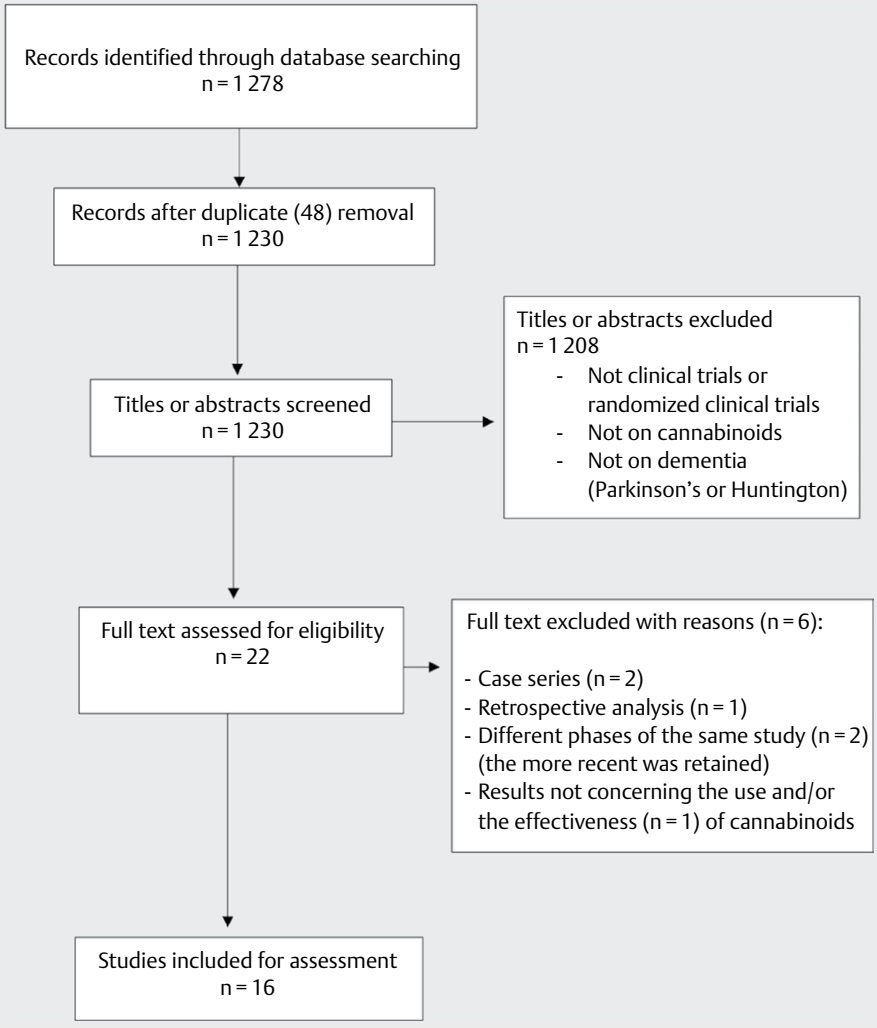
Of the five published RCTs, three showed no clinical effect, and two showed positive results. Three studies used the neuropsychiatric inventory (NPI) as a primary outcome, and two, the Cohen-Mansfield Agitation Inventory (CMAI). Other variables considered were Quality of Life scales, actigraphic nocturnal activity, and Barthel index (activities for daily living). Four trials used synthetic THC (dronabinol, nabilone, or THC oil) without CBD, in maximum dosages of 2 to 4.5 mg THC per day. In one of these THC trials [11], with only 12 patients, clinical improvement was suggested after a short (2 weeks) follow-up. The three others [12–14] showed no positive impact after 3, 6, or 12 weeks, but the THC treatment was well tolerated. In one RCT [15], 40 patients treated with CBD/THC oil (30:1) for 16 weeks showed significant clinical improvement.

Four trials were double-blinded [12–15] and assessed differences between treatments and/or placebo. One trial [11] aimed to determine the monitoring method to evaluate treatment activity; therefore, the study subjects and personnel were not blinded. However, it evidenced differences between different treatments and was thus included the study in our analysis.

All three open-label prospective studies showed positive clinical results (NPI, CMAI, or nocturnal motor activity). One study [16] used dronabinol (2.5 mg) for 2 weeks, one [17] used THC oil (max 15 mg) for 4 weeks, and one study [3] used full plant THC/CBD oil (1:2) with a mean of 12.4 mg THC/day and a follow-up of 13 months. This last study [3] also suggested pharmacological safety, deprescription of medications, and facilitated care.

Concerning adverse events, both RCTs and open-label studies evidenced no or few adverse events. If present, these were mainly mild, occurring at the introduction of the study treatment with no increased occurrence at higher dosages. There was no statistical difference between groups in the studies that reported adverse events. No serious adverse events related to the study treatment were reported in any of the studies (▶ **Table 1**).

Of the eight planned studies, one [18] is an open-label small trial (12 persons) using CBD-rich oil, but no other details were available. Of the seven RCTs, one [19] concerns early-stage dementia, proposing high-dose CBD (300 mg/day) for 12 weeks and investigating neuroanatomical and neuroendocrine changes. Of the six RCTs (three crossover designs) for patients with severe dementia and BPSD, one study [20] proposes dronabinol (10 mg/day). Two studies [21, 22] plan to use nabiximols (THC/CBD 1:1 mouth spray), re-




▶ **Fig. 1** Flowchart of study identification.

spectively, at 5.4 and 8.1 mg THC/day. Two studies will use full plant THC/CBD oil (one in 3:2 ratio, max 50 mg THC per day [23]) and one in 1:2 ratio, max 20 mg THC per day [8]. One study will use CBD oil caps with 90 mg CBD daily [24]. Most studies use NPI and CMAI scales, but pain scales are also included. The number of participants varies from 24 to 160, and the planned cannabinoid administration is 3 to 8 weeks.

## Discussion

Clinical studies on the use of cannabinoids in dementia mainly focus on severe dementia, BPSD, and pain but not on other symptoms. Older studies mostly used synthetic THC at relatively low dosages ( < 5 mg/day) that, in general, did not show significant improvement. More recent and planned studies opt more for THC/CBD combination in different proportions, either as an oral spray (nabiximols) or oil preparations and CBD-only preparations. Dosages of THC prescribed are, in general, higher ( > 5 up to 50 mg of THC), especially in the THC/CBD-based medications. Even if these studies show overall more positive results, we will need to wait a few more years to have the outcomes of the planned studies. Still, it is encouraging to see that research groups in different parts of the world are interested in the use of cannabinoids for dementia.

Although not always specified, cannabinoids were mainly used as add-on therapy and not as a stand-alone treatment for BPSD. One open-label study with over a year of follow-up [3] showed a deprescription of antipsychotics, tranquilizers, and opiates. It would be interesting if other studies could also address the issue of deprescription of medications that often have side effects in elderly patients. The same study also investigated pharmacokinetics and drug-drug interactions, which are essential concerns in polymedicated elderly. The study (with average doses of 12.4 mg THC/24.8 mg CBD daily) showed a slight reduction in the enzymatic activity of CYP1A2 and CYP2C19, as expected, but no significant drug-drug interactions. Still, if larger doses (e. g., 300 mg CBD daily in one planned study) are used, it seems relevant to investigate potential drug-drug interactions and the associated mechanisms.

▶ **Table 1** Clinical trials, open label and planned clinical trials with cannabinoids in dementia.

| Active principle | Dosage | Study Type | Control | Number of partici-pants | Partici-pants with cannabi-noid treatment | Study period Weeks of cannabinoids administra-tion | Primary endpoint assessment | Results | Adverse events | Author | Year (pub-lished) | Reference | NCT number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CLINICAL TRIALS** | | | | | | | | | | | | | |
| Dronabinol | 2.5 mg/ day | RCT | PLACEBO / MELA-TONIN | 24 | 7 | 2 WEEKS | Actigraphic nocturnal activity: NPI | In the verum group, actigraphic nocturnal activity (P = 0.001), NPI total score (P = 0.043), and NPI agitation subscale score (P = 0.032) showed significant reductions compared to baseline. | | Mahl-bergERG | 2007 | Mahlberg R, Walther S. Actigraphy in agitated patients with dementia. Monitoring treatment outcomes. Z Gerontol Geriatr 2007; 40: 178–184 | |
| Delta-9 THC | 1.5 mg/ day −3.0 mg/day | Repeated cross-over, RCT Double-blind | PLACEBO | 22 | 22 | 12 WEEKS | NPI | Oral THC did not reduce NPS in dementia, but was well tolerated by these vulnerable patients, supporting future higher-dosing studies. | 184 AEs of mild to moderate severity similarly distributed over the THC (91) and placebo (93). No SAEs judged to be related to study medication (4 SAE) | Van De Elsen | 2015 | van den Elsen GAH, Ahmed AIA, Verkes RJ, et al. Tetrahydrocan-nabinol in behavioral disturbances in dementia: A cross-over Randomized controlled trial. Am J Geriatr Psychiatry 2015; 23: 1214–1224. | |
| Delta-9 THC | 4.5 mg/ day | RCT (1:1) Double-blind | PLACEBO | 50 | 24 | 3 WEEKS | NPI | The difference in reduction from baseline between THC and placebo was not significant (mean difference NPI total: 3.2, 95% confidence interval [CI] −3.6 to 10.0), nor were changes in scores for agitation (CMAI Inventory 4.6, 95% CI −3.0 to 12.2), quality of life (Quality of Life-Alzheimer's Disease −0.5, 95% CI −2.6 to 1.6), or activities of daily living (Barthel Index 0.6, 95% CI −0.8 to 1.9). | 16 AEs – no SAE No significant difference between study groups. | Van De Elsen | 2015 | van den Elsen GA, Ahmed AI, Verkes RJ, et al. Tetrahydrocannabi-nol for neuropsychiatric symptoms in dementia: A randomized controlled trial. Neurology 2015; 84: 2338–2346 | |

▶ **Table 1** Continued

| Active principle | Dosage | Study Type | Control | Number of partici-pants | Partici-pants with cannabi-noid treatment | Study period Weeks of cannabinoids administra-tion | Primary endpoint assessment | Results | Adverse events | Author | Year (pub-lished) | Reference | NCT number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nabilone | 1.0–2.0 mg | RCT; double-blind, cross-over | PLACEBO | 39 | 39 | 6 WEEKS | CMAI | CGIC improvement during nabilone (47 %) and placebo (23 %) was not significantly different (McNemar's test, exact p = 0.09). | 31 AE – no significative difference in AE treatment or placebo apart from lethargy, which was higher in the treatment group. No SAEs related to study treatment (1 in placebo and 1 in treatment group) | Her-rmann | 2019 | Herrmann N, Ruthirakuhan M, Gallagher D et al. Randomized placebo-controlled trial of nabilone for agitation in Alzheimer's disease. Am J Geriatr Psychiatry 2019; 27: 1161–1173 | |
| Medical cannabis oil 30 %CBD-1 %THC – AVIDEKEL | Start at 35.4 mg CBD/1.5 mg THC – up to mean 527.5 mg and 22.3 mg per day | RCT (2:1) Double-blind | PLACEBO | 60 | 40 | 16 weeks | CMAI | There was a statistically significant difference in the proportion of subjects who had a CMAI Inventory score reduction of ≥ 8 points at week 16: 20/40 (50 %) and 3/20 (15 %), respectively ($\chi 2 = 6.42$, $P = 0.011$). | No significant difference in AE between groups. Higher sleepiness and hallucinations in the intervention group. No SAEs related to study treatment. | Hermush | 2022 | Hermush V, Ore L, Stern N et al. Effects of rich cannabidiol oil on behavioral disturbances in patients with demen-tia: A placebo-con-trolled randomized clinical trial. Front Med 2022; 9: 951889. doi: 10.3389/ | |
| **OPEN-LABEL STUDIES** | | | | | | | | | | | | | |
| Dronabiol | 2.5 mg/day | open-label pilot | / | 6 | 6 | 2 WEEKS | Nocturnal motor activity | Compared to baseline, dronabinol led to a reduction in nocturnal motor activity (P = 0.028). These findings were corroborated by improvements in NPI score (P = 0.027) as well as in subscores for agitation, aberrant motor, and nighttime behaviors (P < 0.05). No side effects were observed. | No adverse events occurred during the study | Walther | 2006 | Walther S, Mahlberg R, Eichmann U et al.. Delta-9-tetrahydrocan-nabinol for nighttime agitation in severe dementia. Psychophar-macology (Berl) 2006; 185: 524–528 | |

▶ **Table 1** Continued

| Active principle | Dosage | Study Type | Control | Number of partici-pants | Partici-pants with cannabi-noid treatment | Study period Weeks of cannabinoids administra-tion | Primary endpoint assessment | Results | Adverse events | Author | Year (pub-lished) | Reference | NCT number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical Cannabis Oil (THC rich – No CBD) | 5.0 mg THC/day up to 15 mg/day | open-label prospective | / | 11 | 11 | 4 WEEKS | CGI; NPI | Ten patients completed the trial. Significant reduction in CGI severity score (6.5 to 5.7; $p < 0.01$) and NPI score were recorded (44.4 to 12.8; $p < 0.01$). | | Shelef | 2015 | Shelef A, Barak Y, Berger U et al. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: An-open label, add-on, pilot study. J Alzheimers Dis 2016; 51: 15–19 | |
| THC/CBD Cannabis Oil | 7.5 mg THC/15 mg CBD-day up to 19.2 MG THC/38.4 mg CBD -day – mean 12.4mgTHC/ 24.8 mg CBD – day | open-label prospective | / | 19 | 19 | 13 MONTHS | CMAI | Clinical scores showed a marked improvement that was stable over time, deprescription of other medications, and care facilitated. | 117 AE – mild – only few related to study treatment. No SAEs related to study treatment. (3 SAE) | Pautex | 2022 | Pautex S, Bianchi F, Daali Y et al. Cannabinoids for behavioral symptoms in severe dementia: Safety and feasibility in a long-term pilot observational study in nineteen patients. Front Aging Neurosci 2022; 14: 957665 | |
| **PLANNED AND ONGOING CLINICAL TRIALS** | | | | | | | | | | | | | |
| HIghCBD/ lowTHC | | OPEN-LABEL | / | 12 | | 8weeks | NPI and GAD-7 | | | McManus /Gruber | 2021 | McManus K, Ash E, Harper D et al. Caring for behavioral symptoms of dementia (CBD): A new investigation into cannabidiol for the treatment of anxiety and agitation in Alzheimer's dementia; https://doi.org/10.1016/j.jagp.2021.01.107 | NCT040 75435 |
| Medical Cannabis oil THC/CBD 3:2 | 2.5 mg THC/day up to 50 mg THC/ day | RCT/ cross-over | placebo | 50 | | 6 weeks | NPI and CMAI | | | Timler | 2020 | Timler A, Bulsara C, Bulsara M et al. Use of cannabinoid-based medi-cine among older residential care recipients diagnosed with dementia: study protocol for a double-blind randomised cross-over trial. Trials. 2020; 21: 188 | AC-TRN1261 900047 4156 |

▶ **Table 1** Continued

| Active principle | Dosage | Study Type | Control | Number of partici-pants | Partici-pants with cannabi-noid treatment | Study period Weeks of cannabinoids administra-tion | Primary endpoint assessment | Results | Adverse events | Author | Year (pub-lished) | Reference | NCT number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical Cannabis Oil THC/CBD1:2 | | RCT/ cross-over | | 24 | | 8 weeks | CMAI | | | Bianchi | 2023 | Bianchi F, Pautex S, Wampfler J et al. Medical cannabinoids for painful symptoms in patients with severe dementia: A randomized, double-blind cross-over placebo-controlled trial protocol. Front Pain Res 2023; 4: 1108832 | NCT054 32206 |
| Nabiximols | 2.7 mg THC/2.5 mg CBD day and 5.2 mg THC/ 5.0 mg day | RCT (1:1) | placebo | 40 | | 4 weeks | CMAI and Mobilization-Observation-Behavior-Intensity-Dementia | | | Scuteri | 2022 | Scuteri D, Guida F, Boccella S et al. NAbiximols clinical translation to the treatment of pain and agitation in severe dementia (NAC-TOPAISD): Clinical trial protocol. Biomed Pharmacother 2022; 153: 113488 | Italian authoriza-tion – not found on the registry |
| Sativex | 2.7 mg THC/2.5 mg CBD day up to 10.4 mg THC/10 mg CBD day | RCT (1:1) | placebo | *60* | | 4 weeks | CMAI; feasibility | | | Albertyn | 2023 | ISRCTN registry | ISRCTN 97163562. |
| Dronabiol | 10 mg | RCT (1:1) | placebo | 160 | | 3 weeks | Pittsburgh agitation scale; NPI | | | Rosen-berg/ Forester | recruiting /finish preview 2024 | Cohen LM, Ash E, Outen JD et al. Study rationale and baseline data for pilot trial of dronabinol adjunctive treatment of agitation in Alzheimer's dementia (THC-AD). Int Psychogeriatr 202111: 1–6 | NCT027 92257 |
| CBD | 90 mg/day | RCT/ cross-over | placebo | 40 | | 6 weeks | CMAI | | | Ockravi | recruiting /finish preview 2024 | clinicaltrials.gov | NCT044 36081 |

▲ **Table 1** Continued

| Active principle | Dosage | Study Type | Control | Number of participants | Participants with cannabinoid treatment | Study period Weeks of cannabinoids administration | Primary endpoint assessment | Results | Adverse events | Author | Year (published) | Reference | NCT number |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CBD | 300 mg/day | RCT | placebo | 60 | | 12 weeks | Neuroanatomical changes: neuroendocrine changes; psychological symptoms | | | Bartschi | 2023 | Bartschi JG, Greenwood LM, Montgomery A et al. Cannabidiol as a treatment for neurobiological, behavioral, and psychological symptoms in early-stage dementia: A double-blind, placebo-controlled clinical trial protocol. Cannabis Cannabinoid Res 2023; 8: 348–359 | ACTRN12621001364864 |

**Abbreviations:** AE: adverse event, CBD: Cannabidiol, CGI-CGIC: Clinical Global Impression of change, CMAI: Cohen-Mansfield Agitation Inventory, GAD-7: Generalized Anxiety Disorder 7 Item, NPI: Neuropsychiatric Inventory, RCT: Randomised Clinical Trial, SAE: serious adverse event, THC (delta-9-THC): delta-9- Tetrahydrocannabinol.

Those who have experience with or plan to do clinical research on cannabinoids in patients with dementia probably know how difficult it is to do a study in a highly vulnerable polymedicated population with a medication that is considered a forbidden substance. We called this once a "marathon full of pitfalls and barriers" [25]. Beyond those mentioned, difficulties also include the lack of other studies and recognized medications, as well as the cost, be it for the expensive medications, data management, and liability insurance. We also realized the risk of conflicts of interest since there is a lot of pressure from the pharmaceutical cannabinoids industries for the indication of dementia, considering the potential market. Practical constraints include the amount of paperwork for the ethical committee, different partners, different study sites, and the national medication registry.

Beyond the "medication" and pharmacological aspects of studying cannabinoids in demented patients, according to the local context, it can be recommended and interesting to explore the more sociological aspects of such studies. Staff of the health care settings and family members might have stereotyped ideas about cannabis and cannabinoids. One sociologist accompanied our project in Geneva from the beginning, and conducted semi-structured interviews of staff and family caregivers who had to give consent for the study participation of their parent or patient [7]. She found that the staff was initially reluctant to introduce cannabinoids to the patients, but this quickly turned into over-enthusiasm when they discovered how the cannabinoids improved the contact with the patients and facilitated daily care, especially for those with spasticity and when opioids could be deprescribed, resulting in less constipation and fewer enemas. Unexpectedly, family members were extremely satisfied with the study proposal overall and grateful that efforts were made to improve the situation for their parents or partners. So, we had no refusals to participate in the open-label study and hope for the same for the planned RCT.

Our review on cannabinoids in dementia is, of course, non-exhaustive due to the non-systematic approach, but we think it is relatively complete for the most important studies in the field. Negative publication bias does not really seem to be an issue since several negative studies were included, but we cannot exclude its presence. Still, we believe that more studies are needed, with a higher number of patients, to be able to provide a comprehensive perspective of the use of cannabinoids (dosages, type of cannabinoid, patient characteristics). This overview is intended as a guide for future research more than a guide on the use of cannabinoids.

## Perspectives

With the foreseen worldwide increase in the prevalence of dementia and related symptoms, combined with the lack of curative treatment and/or medications with acceptable side effects, we think there is genuine interest in the use of cannabinoids, especially for BPSD.

Currently, sufficient evidence is lacking to recommend its use, but this is probably because past trials used pure THC in insufficient dosages. Ongoing trials use THC/CBD combinations in higher dosages or pure CBD medications. We recommend physicians working in the field of dementia to actively search for upcoming publications and contact researchers working in the field to exchange information on the practical aspects of cannabinoid treatment and,

of course, consider setting up much-needed clinical trials. We also suggest studying, beyond behavioral aspects, other outcomes, such as the deprescription of other medications and facilitation of care, as well as sociological aspects of prescribing cannabinoids for dementia and BPSD in their specific context.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## References

[1] WHO fact sheet on dementia. 2023; https://www.who.int/news-room/fact-sheets/detail/dementia; Accessed July 2023

[2] NHS guidelines. https://www.nhs.uk/conditions/alzheimers-disease/; Accessed July 2023

[3] Pautex S, Bianchi F, Daali Y et al. Cannabinoids for behavioral symptoms in severe dementia: safety and feasibility in a long-term pilot observational study in nineteen patients. Front Aging Neurosci 2022; 14: 957665

[4] Aso E, Ferrer I. Cannabinoids for treatment of Alzheimer's disease: Moving toward the clinic. Front Pharmacol 2014; 5: 37

[5] Bahji A, Meyyappan AC, Hawken ER. Cannabinoids for the neuropsychiatric symptoms of dementia: A systematic review and meta-analysis. Can J Psychiatry 2020; 65: 365–376

[6] Broers B, Patà Z, Mina A et al. Prescription of a THC/CBD-based medication to patients with dementia: A pilot study in Geneva. Med Cannabis Cannabinoids 2019; 2: 56–59

[7] Revol A. Prescription de cannabis à usage thérapeutique pour les personnes âgées atteintes de démence: L'engouement des proches aidants. Psychotropes 2019; 25: 129–149

[8] Bianchi F, Pautex S, Wampfler J et al. Medical cannabinoids for painful symptoms in patients with severe dementia: A randomized, double-blind crossover placebo-controlled trial protocol. Front Pain Res 2023; 4: 1108832

[9] Whiting PF, Wolff RF, Deshpande S et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015; 313: 2456–2473

[10] Russo E, Guy GW. A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses 2006; 66: 234–246

[11] Mahlberg R, Walther S. Actigraphy in agitated patients with dementia. Monitoring treatment outcomes. Z Gerontol Geriatr 2007; 40: 178–184

[12] van den Elsen GAH, Ahmed AIA, Verkes RJ et al. Tetrahydrocannabinol in behavioral disturbances in dementia: A crossover randomized controlled trial. Am J Geriatr Psychiatry 2015; 23: 1214–1224

[13] van den Elsen GA, Ahmed AI, Verkes RJ et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: A randomized controlled trial. Neurology 2015; 84: 2338–2346

[14] Herrmann N, Ruthirakuhan M, Gallagher D et al. Randomized placebo-controlled trial of nabilone for agitation in Alzheimer's disease. Am J Geriatr Psychiatry 2019; 27: 1161–1173

[15] Hermush V, Ore L, Stern N et al. Effects of rich cannabidiol oil on behavioral disturbances in patients with dementia: A placebo controlled randomized clinical trial. Front Med 2022; 9: 951889

[16] Walther S, Mahlberg R, Eichmann U et al. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. Psychopharmacology 2006; 185: 524–528

[17] Shelef A, Barak Y, Berger U et al. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: An-open label, add-on, pilot study. J Alzheimers Dis 2016; 51: 15–19

[18] McManus K, Ash E, Harper D et al. Caring for behavioral symptoms of dementia (CBD): A new investigation into cannabidiol for the treatment of anxiety and agitation in Alzheimer's dementia. Am J Geriatr Psychiatry 2021; 29: S110–S111

[19] Bartschi JG, Greenwood LM, Montgomery A et al. Cannabidiol as a treatment for neurobiological, behavioral, and psychological symptoms in early-stage dementia: A double-blind, placebo-controlled clinical trial protocol. Cannabis Cannabinoid Res 2023; 8: 348–359

[20] Cohen LM, Ash E, Outen JD et al. Study rationale and baseline data for pilot trial of dronabinol adjunctive treatment of agitation in Alzheimer's dementia (THC-AD). Int Psychogeriatr 2021; 11: 1–6

[21] Scuteri D, Guida F, Boccella S et al. NAbiximols Clinical Translation To the treatment of Pain and Agitation In Severe Dementia (NACTOPAISD): Clinical trial protocol. Biomed Pharmacother 2022; 153: 113488

[22] Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London and South London and Maudsley NHS STAND Trial. Exploring the feasibility of a cannabinoid oral spray for the treatment of behavioural symptoms in dementia in UK care homes. ISRCTN registry

[23] Timler A, Bulsara C, Bulsara M et al. Use of cannabinoid-based medicine among older residential care recipients diagnosed with dementia: Study protocol for a double-blind randomised crossover trial. Trials 2020; 21: 188

[24] Eastern Virginia Medical School. Effects of THC-Free CBD Oil on Agitation in Patients With Alzheimer's Disease; clinicaltrials.gov

[25] Bianchi F, Pautex S, Wampfler J et al. Preparation of a placebo-controlled trial of THC-CBD medication for severely demented patients with behavioral symptoms: A marathon full of barriers and pitfalls. Med Cannabis Cannabinoids 2022; 5: 159–198