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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Cannabinoids for Behavioural Symptoms in Adults with Dementia: A Review of Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Cannabinoids are psychoactive constituents found naturally in both the cannabis (marijuana) plant and in the human body as endocannabinoids.[1] Cannabinoid receptors (CB1, CB2) are mainly expressed in the central nervous system (CB1) and in immune cells (CB2).[1,2] When CB receptors are activated, a variety of neurotransmitters are inhibited such as acetylcholine, dopamine, and glutamate,[1] making the cannabinoid receptor an attractive pharmacologic target. Effects on cognition, memory, motor activity, pain perception, and energy balance have all been ascribed to CB1 activation while CB2 activation may play a neuroprotective role through reduction of inflammation.[2] Because of these pharmacologic effects, there is interest in cannabinoids as a potential treatment for dementia and its behavioural symptoms.[2,3]

To date, two oral synthetic cannabinoids have been marketed in Canada: nabilone[4] and dronabinol,[5] the latter of which was discontinued in 2012.[5,6] Dronabinol had been indicated for the treatment of AIDS-related anorexia and severe nausea and vomiting from cancer chemotherapy.[7] Nabilone is indicated for the treatment of severe nausea and vomiting from cancer chemotherapy.[8] Currently, there is no Health Canada approved indication for the use of cannabinoids in dementia.

Antipsychotics have historically been used off-label for treating dementia-related behavioural symptoms in adults residing in long-term care, but the modest benefit of treatment was found to be outweighed by the harms – including an increased risk of death – for most people.[3] Thus, the use of antipsychotics has generally been reserved for short-term treatment of the most severe cases of aggression.[9,10] Identifying safer, more effective alternatives to antipsychotics is a priority. One such potential alternative under investigation is the use of cannabinoids. The objective of this report was to review the evidence base for the use of cannabinoids in the treatment of behavioural symptoms in adults with dementia.

Research Questions

1. What is the clinical effectiveness of cannabinoids for the treatment of behavioural symptoms in adults with dementia?
2. What are the evidence-based guidelines regarding the use of cannabinoids for the treatment of behavioural symptoms in adults with dementia?

Key Findings

A total of four publications met the inclusion criteria: two systematic reviews and two randomized cross-over trials. No evidence-based guidelines were identified.

The systematic reviews collectively included eight unique studies, which primarily studied treatment with dronabinol. Nabilone treatment was limited to a single case report. Interpretation of the findings presented narratively by the systematic reviews is hampered by sparse reporting. In particular, it is difficult to discern much about the patient population studied due to a lack of reporting detail about patient characteristics, including age, sex,

severity of dementia, co-morbidities, concomitant medications, and setting (i.e., community versus long-term care). Although the studies of dronabinol treatment are consistent in reporting a reduction in behavioural symptoms, the exposure to treatment tended to be short, and almost half of the studies had no comparator. Moreover, adverse event reporting was limited to three of the eight studies, further complicating risk-benefit determinations. The two randomized cross-over trials, despite better reporting, contribute little to the evidentiary base as they were small, exploratory safety sub-studies of short-term treatment exposure to a formulation of THC unavailable in Canada. Thus, there remains a gap in the evidence on the use of cannabinoids in the treatment of dementia, which currently makes evidence-informed decision-making challenging.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2012 and November 29, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with dementia
Intervention	Cannabinoids (e.g., nabilone)
Comparator	Q1: Other cannabinoids, no treatment, placebo Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., improvement or reduction in behavioural symptoms, especially agitation and aggression), safety Q2: Evidence-based guidelines
Study Designs	HTA/systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Individual studies included in a selected systematic review were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR[11] checklist while the Downs and Black[12] instrument was used for critically appraising the included

randomized studies. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 315 citations were identified in the literature search. Following screening of titles and abstracts, 288 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 23 publications were excluded for various reasons, while 4 publications met the inclusion criteria (two systematic reviews[13,14] and two randomized controlled trials[15,16] and were included in this report. No evidence-based guidelines were identified. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Two systematic reviews and two randomized, controlled, cross-over trials were identified from the literature search. They are summarized below and detailed in Appendix 2.

Study Design

The two systematic reviews were both narrative reviews of the evidence. Lim et al.,[14] which only included randomized controlled trial (RCT) designs, broadly examined the efficacy of medical cannabinoids in neurodegenerative and psychiatric conditions, including dementia and Alzheimer's Disease (AD). Liu et al.,[13] on the other hand, included RCTs, observational studies, and case reports, and restricted their review to agitation and aggression in dementia and/or AD. Lim et al.[14] identified a total of 24 studies, four of which were relevant to this report: three in dementia and one in AD, published between 1997 and 2015, and covering approximately 90 patients. All four were cross-over in design. Liu et al.[13] identified a total of six studies in dementia and/or AD published between 1997 and 2014, and covering approximately 84 patients. There were two cross-over designs, one open-label pilot, one placebo-controlled study, one 'retrospective study', and one case report. There were two constituent studies (both cross-over designs) common to both systematic reviews. (Appendix 5). In this report, the findings from these two overlapping studies are presented with the Lim et al.[14] review.

The two primary studies[15,16] were both randomized, repeated cross-over, double-blind, placebo-controlled, 12-week Phase II safety sub-studies derived from the same main trial,[17] a constituent trial in the systematic review by Lim et al.[14] The trial by van den Elsen et al.[16] (n=18) specifically examined mobility-related safety outcomes while the trial by Ahmed et al.[15] (n=10) was a dose escalation study that investigated the pharmacokinetics, pharmacodynamics, and adverse events from two different doses of study drug. Study patients were all community-dwelling.

Country of Origin

Of the included systematic reviews, one[14] was from Singapore while the other[13] was from Canada. The two included primary studies were both[15,16] from the Netherlands.

Patient Population

Scarce information about patient characteristics was reported in the systematic reviews. Lim et al.[14] report a mean age from three of four studies that ranged from 72.7 years to 78.4 years; there was no information provided on sex distribution, severity of illness, co-morbidities, concomitant medications, or dwelling status. The information was similarly scant in Liu et al.,[13] in which mean age was not reported; however, the retrospective study included in Liu et al.[13] describes studying 'inpatients'.

The patient populations in the sub-studies by van den Elsen et al,[16] and Ahmed et al.[15] were similar, owing to their common source population.[17] Patients were exclusively community-dwelling, predominantly white (94% and 90%) men (83% and 70%), with a mean age of 77.0 ± 6 years and 77.3 ± 5.6 years, respectively, and a diagnosis of Alzheimer's dementia (83% and 90%). Baseline mean Mini Mental State Examination (MMSE) score was 19.1 ± 6.0 and 18.5 ± 6.0, respectively, indicating moderate cognitive impairment[18] for both samples. In van den Elsen et al.,[16] cholinesterase inhibitors and psychotropic medications were taken concomitantly by 61% and 28% of patients, respectively. No information was provided on the prevalence of concomitant medications in Ahmed et al.[15].

Interventions and Comparators

In Lim et al.,[14] interventions included dronabinol 2.5 mg compared with placebo (two studies) and tetrahydrocannabinol (THC) 0.75 mg to 1.5 mg compared with placebo (two studies). In Liu et al.,[13] interventions included dronabinol 2.5 mg to 7.0 mg (five studies) compared with placebo (three studies), melatonin (one study), or no control (two studies); and nabilone 0.5 mg to 1 mg (one study) with no control comparison.

The randomized cross-over trial by van den Elsen et al.[16] compared THC 1.5 mg twice daily with placebo while that of Ahmed et al.[15] compared two doses of THC (0.75 mg, 1.5 mg twice daily) with placebo.

Outcomes

A variety of psychometric instruments were used to measure changes in behaviour. The most commonly employed instruments in Lim et al.[14] were the Cohen-Mansfield Agitation Inventory (CMAI, three studies) and the Neuropsychiatric Inventory (NPI, three studies). In Liu et al.,[13] the NPI was used in three studies along with actigraphy (two studies). Additional psychometric instruments that were used less frequently are detailed for each systematic review in Table 2 of Appendix 2.

In the randomized cross-over trial by van den Elsen et al.,[16] various mobility-related (e.g., gait, balance) assessments were conducted alongside the documentation of adverse events. Since the trial by Ahmed et al.[15] was principally an investigation of the pharmacokinetic and pharmacodynamic parameters of the study drug, this Rapid Response report presents the adverse event data that were collected during the trial.

Summary of Critical Appraisal

The critical appraisal of the two systematic reviews and two randomized, controlled, cross-over trials are summarized below and detailed in Appendix 3.

Both Lim et al.[14] and Liu et al.[13] provided a statement of their research question, conducted a comprehensive literature search – though did not pursue a supplemental grey literature search – and reported sources of funding for the systematic review. Although both teams employed at least two reviewers to conduct the review, Lim et al.[14] did not report how these

reviewers were involved in the study selection or data extraction process; rather, only described their participation in the risk of bias assessment. Liu et al.[13] included information about the study selection process, but did not describe the data extraction process; moreover, there was no risk of bias assessment performed. Both teams provided a list of included studies, but the patient characteristics for the included studies were minimally described in both cases so the overall composition of the individual study populations was unclear. Neither Lim et al.[14] nor Liu et al.[13] appear to have registered their systematic review protocol on PROSPERO.[19] There was no statement of conflict of interest provided in Lim et al.[14] A statement of conflict of interest was provided in Liu et al.,[13] in which two of the five researchers declared having received financial support, including from the pharmaceutical industry; the other three researchers declared no conflicts of interest.

The randomized, double-blind, placebo-controlled cross-over trials by van den Elsen et al.[16] and Ahmed et al.[15] were sub-studies derived from the same main trial (n=22) .[17] Although these two sub-studies shared a rigorous methodologic design, including double-blind, placebo control, randomized sequence allocation, appropriate allocation concealment and washout between study treatments, and used recognized international clinical criteria for diagnosing dementia, the sample size for each trial was small (n=18 and n=10, respectively). In the case of Ahmed et al.,[15] there was no information provided on how the 10 patients were selected for sub-study participation. However, it is likely that the 10 patients represent the initial 'hospital admission' cohort, who were originally recruited into the main trial before it was determined that patients could be safely followed on an outpatient basis.[17] In the case of van den Elsen et al.,[16] it would appear that all patients from the main trial were potentially eligible, if they were able to complete mobility-related assessments.[16,17] Patient characteristics at baseline were provided in both trials, but in the case of Ahmed et al.,[15] there was no information provided on the distribution of co-morbidities and concomitant medications; neither trial provided baseline information on severity of dementia. History of prior exposure to cannabis or cannabinoids, a potential confounder, was not reported, despite both trials taking place in The Netherlands, where cannabis is widely available.[20] Moreover, the potential harms of treatment may be underestimated in both trials if the study patients were not naïve to cannabis or cannabinoid due to the effects of tolerance from prior exposure.[21] Both trials were considered exploratory, and in the case of van den Elsen[16] there was no adjustment for multiple comparisons, thereby incurring the risk of a Type I error or false positive result.

Summary of Findings

What is the clinical effectiveness of cannabinoids for the treatment of behavioural symptoms in adults with dementia?

Two systematic reviews and two randomized cross-over trials meeting the inclusion criteria for this report were identified from the literature search to address the clinical effectiveness of cannabinoids for the treatment of behavioural symptoms in adults with dementia.

The two systematic reviews[13,14] included a total of 10 studies, two of which overlapped between the reviews, leaving eight unique studies. Neither systematic review pooled the included studies for a meta-analysis; rather, a narrative summary was provided by each review. Of these eight studies, five used dronabinol, two used THC, and one used nabilone. All five dronabinol studies, including two which had no comparator, and the nabilone case study reported improved behavioural outcomes, while the two studies on THC reported no improvement. Adverse events were reported for three of eight studies.

The systematic review by Lim et al.[14] included four studies (three in dementia and one in AD, all cross-over designs) published between 1997 and 2015, and covering 90 patients (range: 2 to 54). Limited information was provided on patient characteristics, except for age: mean age ranged between 72.7 years to 78.4 years based on three studies. No information was provided on the patients' dwelling status (i.e., independent-living versus long-term care residency). Interventions consisted of dronabinol 2.5 mg daily versus placebo (two studies) and THC 0.75 mg to 1.5 mg two to three times daily versus placebo (two studies). The findings from the four studies on the outcome of behaviour change were mixed: two studies using dronabinol found reduced 'disturbed behaviour' and nighttime agitation, respectively, while two studies using THC found no improvement in neuropsychiatric symptoms (NPS). Adverse events (AEs) were reported in two of four studies. One study of dronabinol reported common side effects of anxiety, emotional lability, tiredness, and somnolence while one study of THC reported common side effects of dizziness and somnolence. There was no information provided for either study on the number or frequency of AEs. All four studies were given an overall rating of 'unclear' for risk of bias assessment.

The systematic review by Liu et al.[13] comprised six studies, including two studies described by Lim et al.[14] All four unique studies were in AD, published between 2006 and 2014, and covered 71 patients (range: 1 to 40). Study designs included a case report, a 'retrospective study', an open-label pilot study, and a placebo-controlled study. Information about patient characteristics was limited. From one constituent study, there was a specific line description of 'inpatients' (n=40), which suggested acute hospitalization or residency in a long-term care institution as the setting. In another study of six patients, the diagnosis of 'late-stage dementia' provided a sense of disease severity. Otherwise, it was difficult to appreciate the nature of the study population from the systematic review. More detail was provided on interventions, which consisted of dronabinol in three studies and nabilone in one study (case report); one of the four studies included a comparison group (placebo, melatonin). The findings from the four studies on the outcome of behavior change were positive overall: the three dronabinol studies reported reduced motor agitation and aggressiveness (one study) and reduced nocturnal motor activity (two studies); the case report of nabilone reported reduced severity of agitation in a single patient with AD and behavioral disturbances. One of the four studies (retrospective study) reported a total of 26 AEs, which included sedation, delirium, urinary tract infection, and confusion. There was no information provided on the frequency of AEs. Unlike Lim et al.,[14] no risk of bias assessment was performed on the included studies.

The two included Phase II, randomized, double-blind, placebo-controlled, repeated cross-over trials[15,16] were sub-studies of a main trial (n=22) by van den Elsen et al.[17] The commercial formulation of THC used in the sub-studies is not available in Canada.

In the 12-week sub-study (n=18) by van den Elsen et al.,[16] THC 1.5 mg twice daily was compared with placebo on mobility-related safety outcomes. Study patients were exclusively community-dwelling, predominantly white (94%) men (83%), with a mean age of 77.0 ± 6 years, and a diagnosis of Alzheimer's dementia (83%). Baseline mean Mini Mental State Examination (MMSE) score was 19.1 ± 6.0, indicating moderate cognitive impairment.[18] Cholinesterase inhibitors and psychotropic medications were taken concomitantly by 61% and 28% of patients, respectively. Following THC administration, increased body sway was observed compared with placebo on the outcomes of static balance (eyes closed condition) and dynamic balance (during preferred speed walking). Increased stride length was observed for gait (during preferred speed walking). Notwithstanding the lack of statistical adjustment for multiplicity, the clinical meaningfulness

of these observed changes is uncertain, given the lack of information available for minimum clinically important differences for several parameters. Moreover, based on previous work by the same research group,[15] the 1.5 mg THC dose used may have been too low to produce meaningful differences in outcomes. AEs were reported for the original sample of 22 patients, four of whom did not participate in the mobility assessments. The overall incidence of AEs was similar between THC and placebo phases (91 versus 93, $P = 0.77$). Dizziness (10 versus 9 events), somnolence (2 versus 2 events), and balance disorders (1 versus 0) were recorded as mobility-related AEs. Falls were less frequent during the THC than the placebo phase (2 versus 4).

In the 12-week sub-study (n=10) by Ahmed et al.,[15] THC (0.75 mg to 1.5 mg twice daily) was compared with placebo on pharmacokinetic, pharmacodynamic, and safety outcomes. Study patients were exclusively community-dwelling, predominantly white (90%) men (70%), with a mean age of 77.3 ± 5.6 years, and a diagnosis of Alzheimer's dementia (90%). Baseline mean MMSE score was 18.5 ± 6.0, indicating moderate cognitive impairment.[18] Unlike van den Elsen et al.,[16] no information was provided on the prevalence of concomitant medications. Since pharmacokinetic and pharmacodynamic characteristics were not outcomes of interest for this report, only adverse events are presented. A total of 98 AEs were reported for the study period: 43 for the THC phase versus 55 for the placebo phase. The distribution of AEs was similar between THC and placebo phases, regardless the level of THC exposure. No THC-related severe AEs were reported. THC treatment was not associated with changes in physical, laboratory, or ECG findings. Of the 13 reported AEs that were deemed possibly or probably related to study drug, six were considered possibly related to THC: dizziness (one patient: 0.75 mg dose), fatigue (two patients: 0.75 mg dose, one patient; 1.5 mg dose, one patient), and agitation (three patients: 1.5 mg dose).

What are the evidence-based guidelines regarding the use of cannabinoids for the treatment of behavioural symptoms in adults with dementia?

No evidence-based guidelines on the use of cannabinoids for the treatment of behavioural symptoms in adults with dementia were identified from the literature search.

Limitations

This review is limited by the lack of information available on the use of cannabinoids in dementia, and on the use of nabilone, in particular. A single case report using nabilone was described within the systematic review by Liu et al.[13] The remainder of this report's evidence base resides with the use of dronabinol and THC. Although it is unclear from the systematic review reporting, in particular, it appears that the long-term care setting is understudied. No evidence-based clinical guidelines on the use of cannabinoids for the treatment of behavioural symptoms in adults with dementia were identified from the literature search.

Neither systematic review pooled the included studies for meta-analysis, presumably due to excessive clinical and/or methodological heterogeneity; rather, a narrative summary was provided. For each systematic review, details of the constituent studies were scant, particularly with respect to patient characteristics, limiting the interpretation of the data. Although the two included randomized cross-over trials included community-dwelling patients with dementia who were aged in their late seventies, the trials were small (n = 18, n = 10), of short duration (12 weeks), and exploratory in nature (i.e., underpowered), and only studied safety, not efficacy, outcomes. The dosing of THC (up to 1.5 mg twice daily)

used in each trial was suspected to be sub-therapeutic because of the lack of pharmacodynamic effects observed in one of the trials. Moreover, the specific formulation of THC used in the trials is not commercially available in Canada.

Conclusions and Implications for Decision or Policy Making

In this report, the clinical effectiveness of cannabinoids for the treatment of behavioural symptoms in adults with dementia was examined within an evidence base consisting of two systematic reviews of eight unique studies and two randomized cross-over trials. Dronabinol – which was discontinued from the Canadian market in 2012[5] – was the most commonly-studied drug and was associated with reductions in behavioural symptoms. However, exposure to treatment tended to be short and the study population inadequately described. Small sample size, short follow-up, and the absence of a comparator in some studies, along with a general lack of adverse event reporting further complicate any risk-benefit determination. Thus, there remains a gap in the evidence on the use of cannabinoids in the treatment of dementia, which currently makes evidence-informed decision-making challenging. Currently, nabilone is the only synthetic cannabinoid marketed in Canada,[4] but is in short supply.[22]

In addition to the evidence synthesized in this report, two citations of research in-progress were identified. One is a protocol for a Cochrane systematic review on cannabinoids for the treatment of dementia,[2] which has an estimated completion date of July 2018.[23] The other is a registered (Canadian) randomized cross-over trial studying the safety and efficacy of nabilone in Alzheimer's Disease, which has an estimated completion date of January 2018.[24]

References

1. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. JAMA [Internet]. 2015 [cited 2017 Nov 30];313(24):2474-83. Available from: https://jamanetwork.com/journals/jama/fullarticle/2338266
2. Markovic D, Bosnjak D, Brkovic T, Jeric M, Rubic Z, Vuica VA, et al. Cannabinoids for the treatment of dementia. Cochrane Database Syst Rev [Internet]. 2017 [cited 2017 Nov 30];2017(10). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012820/epdf
3. Weier M, Hall W. The use of cannabinoids in treating dementia. Curr Neurol Neurosci Rep. 2017 Aug;17(8):56, 2017.
4. Nabilone. Current status: marketed. 2014 [cited 2017 Dec 21]. In: Health Canada Drug Product Database [Internet]. Ottawa: Health Canada. Available from: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp DIN:02393581.
5. Marinol (dronabinol): cancelled from market. 2012 [cited 2017 Dec 21]. In: Health Canada Drug Product Database [Internet]. Ottawa: Health Canada. Available from: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp DIN:00611190.
6. Cannabinoids: drug comparison chart. In: RxFiles drug comparisons charts [Internet]. 11th ed. Saskatoon (SK): RxFiles Academic Detailing Program; 2017. p. 167.
7. Marinol (dronabinol (delta-9-tetrahydrocannabinol; Δ^9–THC)) 2.5 mg and 5 mg capsules [product monograph] [Internet]. Saint-Laurent (QC): Abbott Laboratories, Limited; 2011 Jan 1. [cited 2018 Jan 4]. Available from: https://pdf.hres.ca/dpd_pm/00013378.PDF
8. CPS [Internet]. Ottawa: Canadian Pharmacists Association; c2017. Cesamet® (nabilone) [product monograph]; 2009 Mar 17 [cited 2018 Jan 4]. Available from: http://www.e-therapeutics.ca
9. Panza F, Solfrizzi V, Seripa D, Imbimbo BP, Santamato A, Lozupone M, et al. Progresses in treating agitation: a major clinical challenge in Alzheimer's disease. Expert Opin Pharmacother [Internet]. 2015 [cited 2017 Nov 30];16(17):2581-8. Available from: http://www.tandfonline.com/doi/full/10.1517/14656566.2015.1092520
10. Press D, Alexander M. Management of neuropsychiatric symptoms of dementia. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2017 Oct 23 [cited 2017 Dec 20]. Available from: www.uptodate.com Subscription required.
11. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews [Internet]. BMC Med Res Methodol. 2007 Feb 15 [cited 2017 Dec 13];7:10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf
12. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun;52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf
13. Liu CS, Chau SA, Ruthirakuhan M, Lanctot KL, Herrmann N. Cannabinoids for the treatment of agitation and aggression in Alzheimer's disease. CNS Drugs. 2015;29(8):615-23.
14. Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clin [Internet]. 2017 Nov 30 [cited 2017 Nov 30];Psychopharmacol. Neurosci.. 15(4):301-12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5678490/
15. Ahmed AI, van den Elsen GA, Colbers A, Kramers C, Burger DM, Van Der Marck MA, et al. Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia. Psychopharmacology (Berl) [Internet]. 2015 Jul [cited 2017 Nov 30];232(14):2587-95. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4480847/

16. van den Elsen GA, Tobben L, Ahmed AIA, Verkes RJ, Kramers C, Marijnissen RM, et al. Effects of tetrahydrocannabinol on balance and gait in patients with dementia: a randomised controlled crossover trial. J Psychopharmacol. 2017;31(2):184-91.

17. van den Elsen GA, Ahmed AI, Verkes RJ, Feuth T, Van Der Marck MA, Olde Rikkert MG. Tetrahydrocannabinol in behavioral disturbances in dementia: a crossover randomized controlled trial. Am J Geriatr Psychiatry. 2015 Dec;23(12):1214-24.

18. Guidelines & Protocol Advisory Committee. Standardized Mini-Mental State Examination (SMMSE). In: BC guidelines.ca [Internet]. Victoria (BC): Government of British Columbia; 2014 [cited 2017 Dec 21]. Available from: https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/cogimp-smmse.pdf

19. PROSPERO: international prospective register of systematic reviews [Internet]. York (GB): University of York. 2017 [cited 2017 Dec 20]. Available from: https://www.crd.york.ac.uk/prospero/

20. Toleration policy regarding soft drugs and coffee shops [Internet]. The Hague (NL): Government of the Netherlands; 2017. [cited 2017 Dec 20]. Available from: https://www.government.nl/topics/drugs/toleration-policy-regarding-soft-drugs-and-coffee-shops

21. Wilkinson ST, Radhakrishnan R, D'souza DC. A systematic review of the evidence for medical marijuana in psychiatric indications. J Clin Psychiatry. 2016 Aug;77(8):1050-64.

22. Reports for Nabilone [Internet]. Ottawa: Drug Shortages Canada; 2017. [cited 2017 Dec 21]. Available from: https://www.drugshortagescanada.ca/ingredient/2350

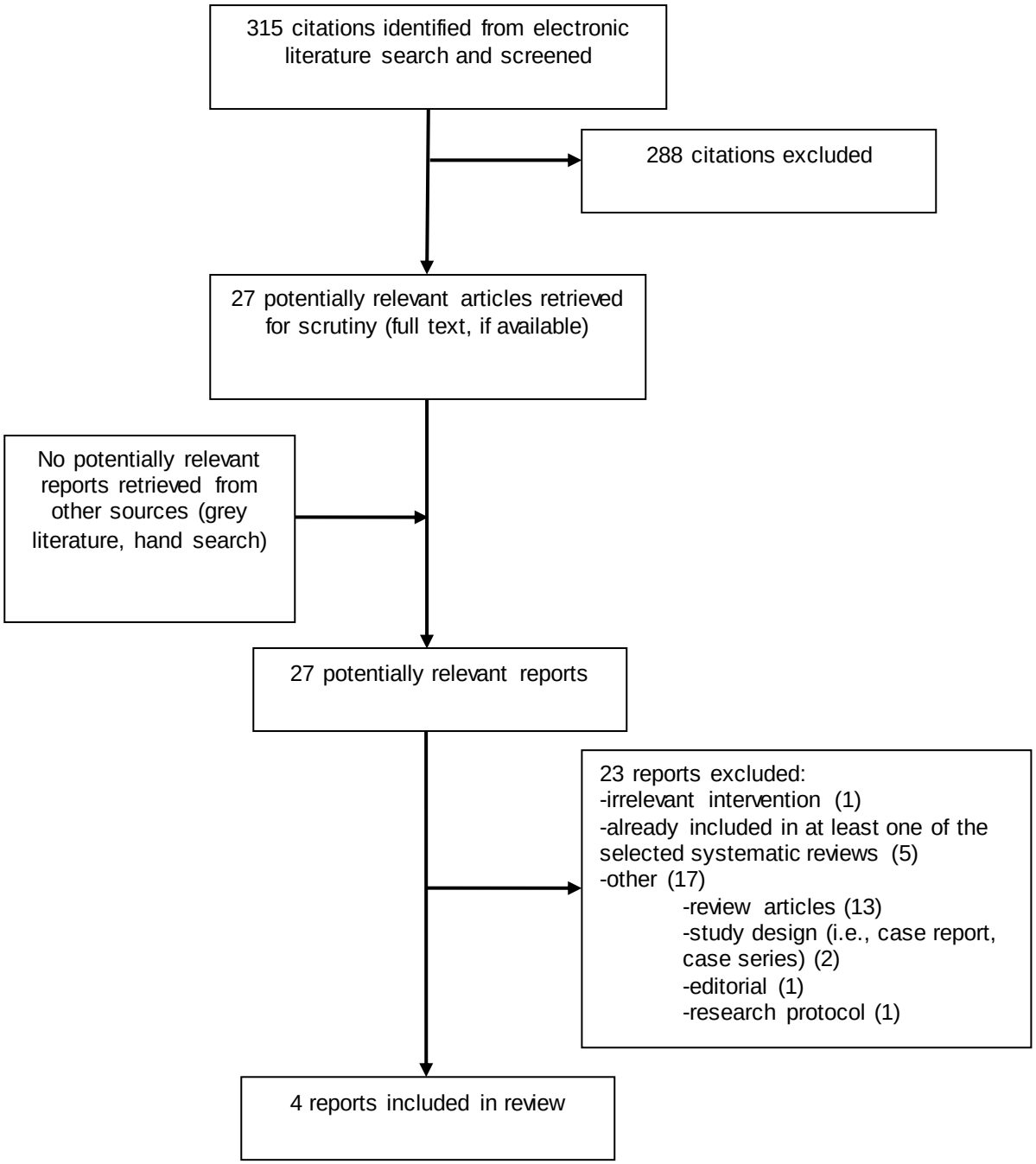
23. Markovic D, Bosnjak D, Brkovic T, Jeric M, Rubic Z. Cannabinoids for the treatment of dementia [Cochrane protocol]. In: PROSPERO: international prospective register of systematic reviews [Internet]. York (GB): University of York; 2018 [cited 2018 Jan 3]. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=83364

24. Sunnybrook Health Sciences Centre. Safety and efficacy of Nabilone in Alzheimer's disease: a pilot study. 2015 Jan 30 [cited 2017 Dec 20; Last updae posted: 2017 Oct 5]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02351882 Identifier: NCT02351882.

25. Klumpers LE, Beumer TL, van Hasselt JG, Lipplaa A, Karger LB, Kleinloog HD, et al. Novel Delta(9) -tetrahydrocannabinol formulation Namisol(R) has beneficial pharmacokinetics and promising pharmacodynamic effects. Br J Clin Pharmacol [Internet]. 2012 Jul [cited 2017 Dec 20];74(1):42-53. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394127

26. van den Elsen GA, Ahmed AI, Lammers M, Kramers C, Verkes RJ, Van Der Marck MA, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing Res Rev. 2014 Mar;14:56-64.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included, Objective, Sample size, Duration, Setting	Eligibility criteria	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Lim,[14] 2017, Singapore	4/24 relevant studies (all 4 cross-over design, 3 DB; AD = 1, dementia = 3; n=90* [range: 2 to 54]); of the 4 relevant studies, 2 were also included in the review by Liu et al.[13] Objective: To evaluate the efficacy of medical cannabinoids across a range of neurodegenerative disorders and psychiatric conditions Duration and setting of included studies not reported.	RCTs comparing cannabis (any form, any route of administration, for medical use) with placebo or other active treatments; any age; male or female; with either a movement disorder, or neurological (e.g., AD, dementia) or psychiatric condition	Limited narrative synthesis on patient characteristics: Mean age = 72.7 to 78.4 years**	Dronabinol 2.5 mg twice daily versus placebo (2 studies); THC 0.75 to 1.5 mg two to three times daily versus placebo (2 studies)	Change in: CMAI; NPI; Barthel index; QoL-AD; CCGIC; ZBI; Nonparametric circadian rhythm analysis; Lawton observed affect scale
Liu,[13] 2015, Canada	6 studies total (2 cross-over, 1 DB; 1 open-label pilot; 1 placebo-controlled; 1 retrospective; 1 case report); n=84* [range: 1 to 40]; of the 6 studies, 2 were also included in the review by Lim et al.[14] Objective: To evaluate the evidence for cannabinoids in the	RCTs, observational studies, or case studies evaluating cannabinoids for the treatment of agitation and/or aggression in dementia or AD	Limited narrative synthesis on patient characteristics: "A significant portion of all patients had used or were using psychoactive medication to manage their symptoms." (p.616) Two of the six studies included patients with 'probable' AD	Dronabinol 2.5 mg to 7.0 mg daily (5 studies); versus placebo (3 studies), melatonin (1 study), or no control (2 studies) Nabilone 0.5 to 1 mg daily (1 study); no control	Change in: CMAI, NPI, PAS, actigraphy

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included, Objective, Sample size, Duration, Setting	Eligibility criteria	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
	treatment of agitation and aggression in dementia and/or AD Total sample size could not be determined from the data; study duration and setting not reported.		dementia or AD. No information provided on age, sex distribution, or co-morbidities.		

AD = Alzheimer's disease; CCGIC = Caregiver Clinical Global Impression of Change; CMAI = Cohen-Mansfield Agitation Inventory; DB = double blind; NLD = The Netherlands; NPI = Neuropsychiatric Inventory; PAS = Pittsburgh Agitation Scale; QoL-AD = Quality of Life in Alzheimer's Disease scale; RCT = randomized controlled trial; THC = tetrahydrocannabinol; ZBI = Zarit Burden Interview

***It is unclear whether the reported sample size represents all enrolled patients or the subset of those who received study drug or successfully completed the protocol.**

**Based on reporting by three studies. (Sex distribution was not reported in three studies.)

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design, Objective, Sample Size, Duration, Setting	Eligibility criteria	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
van den Elsen,[16] 2017, NLD	RCT (sub-study from same main trial[17] as Ahmed et al.[15] sub-study); repeated cross-over, DB, placebo-controlled, Phase II; two sites Objective: To evaluate mobility-related safety outcomes of low-dose oral THC in patients with dementia N=18* 12 weeks Tertiary care; geriatric specialty outpatient clinics	Community-dwelling adults aged ≥ 18 years;[17] diagnosis of Alzheimer's, vascular, or mixed dementia per NINCDS-ADRDA or NINDS-AIREN criteria; NPI score ≥ 10; able to walk ≥ 10 m and understand simple instructions;[16] informal caregiver at least once weekly[15] *Exclusions*: current major psychiatric disorder; any severe or unstable concomitant illness; frequent falls due to orthostatic hypotension; history of alcohol or drug abuse; current use of tricyclic antidepressants, opioids, or CYP 2C9, 2C19, or 3A4 inhibitors	Mean age = 77.0 ± 6 years; 83% male; 94% Caucasian; dementia type: Alzheimer's (83%), vascular (6%), mixed (11%); mean MMSE score = 19.1 ± 6.0; concurrent medications: cholinesterase inhibitors (61%), psychotropic (28%: antidepressant [17%], benzodiazepine [17%], antipsychotic [11%]); baseline mean gait velocity: 91.8 ± 20.4 cm/s	THC 1.5 mg twice daily versus placebo	Changes in: static and dynamic balance (body sway); gait (velocity, stride length, double support time, base of support); mobility tasks (stance, gait) Adverse events
Ahmed,[15] 2015, NLD	RCT (sub-study from same main trial[17] as van den Elsen et al.[16] sub-study); dose escalation study; repeated cross-over, DB, placebo-controlled, Phase II; two sites Objective: To evaluate safety, PD, PK of multiple low doses of THC in older persons with dementia N=10 12 weeks Tertiary care; geriatric specialty		Mean age = 77.3 ± 5.6 years; 70% male; 90% Caucasian; dementia type: Alzheimer's (90%), mixed (10%); mean MMSE score = 18.5 ± 6.0	THC 0.75 mg twice daily, 1.5 mg twice daily versus placebo	Adverse events

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design, Objective, Sample Size, Duration, Setting	Eligibility criteria	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
	outpatient clinics; in addition, 4 x 3-day hospital admissions to facilitate blood sampling				

DB = double blind; cm/s = centimetres per second; MMSE = Mini Mental State Examination; NINCDS-ADRA = National Institute of Neurological Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; NINDS-AIREN = National Institute of Neurological Disorders and Stroke – Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NLD = The Netherlands; NPI = Neuropsychiatric Inventory; PD = pharmacodynamics; PK = pharmacokinetics; RCT = randomized controlled trial; THC = tetrahydrocannabinol

Mean ± standard deviation

*Main trial enrolled 22 patients;[17] four patients were excluded from van den Elsen et al.[16] due to either inability to understand instructions (n=2) or complete mobility assessments (n=2).

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[11]

Strengths	Limitations
Lim et al. 2017[14]	
• A description of the research question and inclusion criteria was provided. • Two reviewers assessed each included study for methodological quality; however, discrepancies were not resolved by a third reviewer, rather by discussion amongst the two reviewers. • A fairly comprehensive literature search was performed including a hand search of references lists from retrieved articles. • Internal validity was assessed and documented using the Cochrane risk of bias tool. • The results of the quality assessment were appropriately applied both in the (narrative) analysis and conclusions. • Sources of funding were reported for the systematic review, but not for the constituent studies.	• There is no indication that the systematic review protocol was registered on PROSPERO. • There was no information provided on how studies were selected or how discrepancies in study selection were resolved. There is no information provided on the personnel involved in data extraction. • A list of included studies was provided, but the accompanying description of study characteristics was so minimal as to be unhelpful for appreciating the study population. • There does not appear to have been any supplemental grey literature search conducted. A language filter was applied to select English language publications. • A list of excluded studies was not provided. • Due to presumed clinical and/or methodological heterogeneity, the authors did not pool the studies for meta-analysis; instead, a narrative summary was presented. • Publication bias was not assessed.
Liu et al. 2015[13]	
• A statement of the research question was provided. • Three reviewers participated in study selection; however, there was no information provided on how consensus was achieved. • A fairly comprehensive literature search was performed. • Sources of funding were reported for the systematic review but not for the constituent studies. Two researchers disclosed prior funding from various pharmaceutical industry companies, foundations, and government agency sponsors.	• There is no indication that the systematic review protocol was registered on PROSPERO. • Inclusion criteria were minimal in detail. • A list of included studies was provided, but the accompanying description of study characteristics was so minimal as to be unhelpful for appreciating the study population. • It is unclear whether the three reviewers involved in study selection likewise participated in data extraction. There was no information provided on how discrepancies were resolved. • There does not appear to have been any supplemental grey literature search conducted. No hand-search was performed. A language filter was applied to select English language publications. • A list of excluded studies was not provided. • There was no internal validity (i.e., risk of bias) assessment performed. • Due to presumed clinical and/or methodological heterogeneity, the authors did not pool the studies for meta-analysis; instead, a narrative summary was presented. • Publication bias was not assessed.

Table 5: Strengths and Limitations of Randomized Controlled Trials using Downs & Black[12]

Strengths	Limitations
van den Elsen et al. 2017[16]	

• Double-blind, quadruple-masked (i.e., patient, care provider, investigator, outcomes assessor),[17] placebo-controlled, cross-over (patients served as their own control) RCT design, in which the sequence of treatment was randomized; allocation concealment was adequate.
• A washout period of 4 days was included in the protocol. Based on the prior PK study of oral THC,[25] the length of this washout period appears adequate.
• Outcomes were adequately described.
• Use of objective instruments, supported by some validity data, for assessing balance and gait (i.e., accelerometry, electronic walkway with sensors)
• Internationally recognized clinical criteria specified for diagnosis of dementia type
• Intervention (THC 1.5 mg) and comparator (placebo) adequately described.
• Adverse events were collected for all patients (n=22), regardless of whether they underwent mobility assessments (n=18)
• Protocol for main trial registered on ClinicalTrials.gov[17]
	• Small sample size (n=18); 4 patients from the original sample (n=22) were excluded from mobility assessments due to comprehension or logistical issues. By reason of exclusion and in the absence of data, it is possible that these 4 patients may be at higher risk for falls compared with the remaining 18 patients.
	• Patients were all community-dwelling, so findings cannot be viewed in the context of the long-term care setting.
	• No information provided on the following patient characteristics:
	  ○ Baseline severity of neuropsychiatric symptoms, such as agitation (e.g., NPI score)
	  ○ Prior exposure to cannabis or cannabinoids.
	• Exploratory safety analysis, which did not adjust for multiple comparisons, thereby incurring risk of Type I error (i.e., false positive result)

Ahmed et al. 2015[15]	

• Double-blind, quadruple-masked (i.e., patient, care provider, investigator, outcomes assessor),[17] placebo-controlled, cross-over (patients served as their own control) RCT design, in which the sequence of treatment was randomized; allocation concealment was adequate.
• A washout period of 4 days was included in the protocol. Based on the prior PK study of oral THC,[25] the length of this washout period appears adequate.
• Outcomes were adequately described.
• Internationally recognized clinical criteria specified for diagnosis of dementia type
• Interventions (THC 0.75 mg, 1.5 mg) and comparator (placebo) adequately described. Helpful schematic of cross-over protocol included.
• All patients completed the study.
• Protocol for main trial registered on ClinicalTrials.gov[17]
	• Small sample size (n=10) and no information provided on how these patients were selected from the main trial[17] (n=22).
	• No information provided on the following patient characteristics:
	  ○ Baseline severity of neuropsychiatric symptoms, such as agitation (e.g., NPI score)
	  ○ Distribution of co-morbidities and concomitant medications
	  ○ Prior exposure to cannabis or cannabinoids
	• Patients were all community-dwelling, so the findings cannot be viewed in the context of the long-term care setting.
	• Possibility that the dosing studied (TDD = 1.5 mg, 3.0 mg) was sub-therapeutic, given the greater number of adverse events in the placebo versus THC phases and the smaller than expected pharmacodynamic effects observed, per the investigators.
	• The THC formulation studied is not commercially available in Canada.
	• Exploratory safety analysis, which limits interpretation of findings.

NPI = Neuropsychiatric Inventory; PK = pharmacokinetic; TDD = total daily dose; THC = tetrahydrocannabinol

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Systematic reviews	
Lim et al. 2017[14]	
This narrative review covered 4 trials, including 2, which were also covered by Liu et al.[13] and are presented here: ***Alzheimer's Disease:*** One small DB, placebo-controlled, cross-over RCT (n=12,* 92% male) of dronabinol in patients aged 65 to 82 years reported decreased severity of 'disturbed behaviour' (CMAI, *P* = 0.05) and decreased negative affect (*P* = 0.045). However, this trial had an 'unclear' rating for risk of bias and has been criticized by others[13,26] for methodologic flaws such as not including a washout period in its study, which likely led to the observed time by treatment ('carry-over') effect.[13] Moreover, 'disturbed behaviour' was not the primary outcome measure of this trial.[13] **Dementia:** The results of three small trials (n=78*), each with a rating of 'unclear' for risk of bias, were mixed on the outcomes of nighttime agitation (improved with dronabinol in one trial) and NPS (no improvement with THC capsules in two other trials). Two of four studies did not report adverse events. The single trial of dronabinol in AD reported common side effects of anxiety, emotional lability, tiredness, and somnolence; however, frequency distribution was not reported. Similarly, one of the two THC trials reported common side effects of dizziness and somnolence but without frequency distribution.	"Although results were inconsistent, there appears to be some low quality evidence for cannabinoids for… agitation in Alzheimer's disease and dementia… However, concrete conclusions of its efficacy could not be made due to the unclear risk of bias presented in these trials… Methodological issues such as inadequate description of allocation concealment and blinding, varying cannabinoid formulations and doses, and small sample sizes limit its potential clinical utility" (p.310)
Liu et al. 2015[13]	
This narrative review covered 6 studies; however, 2 were also covered by Lim et al.[14] including the single (positive) trial in AD and the (positive) dronabinol trial in dementia. These two overlapping trials are presented above. The results from the remaining 4 studies (n=71*) in AD, which included a case report, a 'retrospective study', an open-label pilot study, and a placebo-controlled study are presented here: The case report described reduced severity of agitation with nabilone. The retrospective study reported reduced motor agitation ($z = -4.4423$, $P < 0.0001$) and aggressiveness ($z = -3.9102$, $P < 0.0001$) with dronabinol. The open-label pilot study of late-stage dementia reported reduced nocturnal motor activity (*P* = 0.028), with an average decrease of 59% (range: 13% to 85%) compared with baseline during the first two days of dronabinol treatment. The placebo-controlled study in patients	"The small number of studies in this review highlights the need for further randomized controlled trials to evaluate the safety and efficacy, including the habituation and potential for abuse, of cannabinoids for the treatment of agitation and aggression in severe dementia and AD." (p. 621)

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
with 'probable' AD dementia reported a 16% reduction in nocturnal motor activity (statistical significance not reported) with dronabinol compared with baseline. Three of four studies did not report adverse events. The retrospective study recorded 26 AEs during dronabinol treatment including sedation, delirium, urinary tract infection, and confusion. No data on frequency were reported.	
Randomized Controlled Trials	
van den Elsen et al. 2017[16]	
This trial is a substudy (along with the substudy by Ahmed et al.[15]) of the main trial by van den Elsen et al.[17] Results presented for the subset of 18 patients who underwent mobility assessments: *Static balance (standing, eyes open or closed condition)* • Eyes open: No differences in body sway between THC and placebo • Eyes closed: Increased roll angle, pitch angle, pitch velocity after THC versus placebo (0.32 [0.6]°/s, *P* = 0.05; 1.04 [1.5]°/s, *P* = 0.009; and 1.96 [3.3]°/s, *P* = 0.02, respectively) *Dynamic balance (assessed during preferred speed walking)* • PSW alone: Increased pitch angle displacement after THC versus placebo (1.18 [1.6]°, *P* = 0.005) • PSW + cognitive dual task: No effect of THC on dynamic balance *Gait (assessed during preferred speed walking)* • PSW alone: Increased stride length (4.3 [5.4] cm, *P* = 0.005) after THC versus placebo • PSW + cognitive dual task: No effect of THC on gait *Adverse events* AEs were reported for the original sample of 22 patients (including the 4 patients who did not participate in mobility assessments). There was no difference between the THC and placebo phases in the overall incidence of AEs (91 versus 93, *P* = 0.77). Dizziness (10 versus 9 events), somnolence (2 versus 2 events), and balance disorders (1 versus 0) were recorded as mobility-related AEs. Falls were less frequent during the THC than the placebo phase (2 versus 4).	"These first results suggest that low-dose oral THC is well tolerated by community-dwelling dementia patients concerning mobility and risk of falling. This dose [1.5 mg twice daily] did not show benefit** in the treatment of dementia-related NPS compared to placebo." (p.189)
Ahmed et al. 2015[15]	
This trial is a substudy (along with the substudy by van den Elsen et al.[16]) of the main trial by van den Elsen et al.[17] Safety results presented for the subset of 10 patients, all of whom completed the substudy.	"Our data demonstrate that THC doses of 0.75 and 1.5 mg twice daily are safe and well tolerated by older individuals with dementia [based upon short-term use]." (p.2592)

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Adverse events A total of 98 AEs were reported for the study period: 43 for the THC phase versus 55 for the placebo phase. The distribution of AEs was similar between THC and placebo phases, whether THC exposure was 0.75 mg (21 versus 30, *P* = 0.290) or 1.5 mg (22 versus 25, *P* = 0.435) THC twice daily. No THC-related SAEs were reported. THC treatment was not associated with changes in physical, laboratory, or ECG findings. Of the 13 reported AEs that were deemed possibly or probably related to study drug, 6 were considered possibly related to THC: dizziness (1 patient: 0.75 mg dose), fatigue (2 patients: 0.75 mg dose, 1 patient; 1.5 mg dose, 1 patient), agitation (3 patients: 1.5 mg dose).	

AD = Alzheimer's Disease; AE = adverse event; CMAI = Cohen-Mansfield Agitation Inventory; DB = double-blind; ECG = electrocardiography; NPS = neuropsychiatric symptoms; PSW = preferred speed walking; RCT = randomized controlled trial; s = second; SAE = serious adverse event; THC = tetrahydrocannabinol

*It is unclear whether the reported sample size represents all enrolled patients or the subset of those who received study drug or successfully completed the protocol.

**Efficacy results from the main trial cited within this sub-study were published separately and were included in the systematic review by Lim et al.[14] summarized in this report.

Appendix 5: Overlap between Included Systematic Reviews

Table 7: Overlap in Studies on Dementia or Alzheimer's Disease between the Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Lim et al. 2017[14]	Liu et al. 2015[13]
Volicer et al. 1997	■	■
Walther et al. 2011	■	■
van den Elsen et al. 2015[a]	■	
van den Elsen et al. 2015[b]	■	
Walther et al. 2006		■
Mahlberg & Walther 2007		■
Passmore 2008		■
Woodward et al. 2014		■