Safety and effectiveness of cannabinoids for the treatment of neuropsychiatric symptoms in dementia: a systematic review

Ther Adv Drug Saf
2019, Vol. 10: 1–23
DOI: 10.1177/2042098619846993

Jodie Belinda Hillen, Natalie Soulsby, Chris Alderman and Gillian E. Caughey

Abstract

Background: Neuropsychiatric symptoms (NPS) in dementia impact profoundly on the quality of life of people living with dementia and their care givers. Evidence for the effectiveness and safety of current therapeutic options is varied. Cannabinoids have been proposed as an alternative therapy, mainly due to their activity on CB1 receptors in the central nervous system. However, little is known regarding the safety and effectiveness of cannabinoid therapy in people with dementia. A literature review was undertaken to identify, describe and critically appraise studies investigating cannabinoid use in treating NPS in dementia.

Methods: We undertook a systematic review adhering to PRISMA guidelines. Twenty-seven online resources were searched, including Medline, PsycINFO and Embase. Studies assessing the safety and or effectiveness of cannabinoids in treating NPS in dementia in people aged ⩾ 65 years were included. Study quality was assessed using the Johanna Briggs Institute and Cochrane Collaboration critical appraisal tools.

Results: Twelve studies met the inclusion criteria. There was considerable variability across the studies with respect to study design (50% randomized controlled trials), intervention [dronabinol (33%), nabilone (25%) or delta-9 tetrahydrocannabinol (THC; 42%)] and outcome measures. Dronabinol (three studies) and THC (one study) were associated with significant improvements in a range of neuropsychiatric scores. The most common adverse drug event (ADE) reported was sedation. A high risk of bias was found in eight studies. The highest-quality trial found no significant improvement in symptoms or difference in ADE rate between treatment arms. Included studies used low doses of oral cannabinoids and this may have contributed to the lack of demonstrated efficacy.

Conclusion: While the efficacy of cannabinoids was not proven in a robust randomized control trial, observational studies showed promising results, especially for patients whose symptoms were refractory. In addition, the safety profile is favourable as most of the ADEs reported were mild. Future trials may want to consider dose escalation and formulations with improved bioavailability.

Keywords: Cannabinoids, Neuropsychiatric symptoms of dementia, dementia, review

Received: 21 June 2018; revised manuscript accepted: 26 February 2019.

Correspondence to:
Jodie Belinda Hillen
Senior Research Analyst, Ward Medication Management (Ward MM), Level 21/459 Collins St, Melbourne, VIC 3000, Australia
jodie@wardmm.com.au

Natalie Soulsby
Ward Medication Management (Ward MM), Melbourne, VIC, Australia

Chris Alderman
School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia

Gillian E. Caughey
School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia School of Medicine, University of Adelaide, Adelaide, SA, Australia Department of Clinical Pharmacology, Royal Adelaide Hospital, Adelaide, SA, Australia

Introduction

Dementia is a group of diseases characterized by progressive and debilitating symptoms including cognitive decline, memory loss, changes in perception and personality.[1] In 2015, the World Alzheimer's report estimated that there were 50 million people living with dementia worldwide, with projections of this population doubling every 20 years.[2]

The most common types of dementia are Alzheimer's disease (50–70%) and vascular dementia (20–30%)

which have different aetiologies and disease course.[1,2] Common to all dementia types is the suite of neuropsychiatric symptoms (NPS) including agitation, aggression, wandering, apathy, sleep disorders, depression, anxiety, psychosis and eating disorders.[3–5] It is estimated that up to 90% of people living with dementia will experience at least one of these symptoms in their disease course.[6]

The occurrence of NPS differs across the course of dementia, with anxiety and depression reported more common in the early stages and psychosis and aggression more common in the advanced stages of dementia.[3] Regardless of the stage of dementia, occurrence of NPS impacts profoundly on the morbidity and mortality of people living with dementia, often precipitating the use of additional medications, hospitalization and institutionalized care.[3–5] It has been reported that behavioural symptoms of dementia have more significant consequences for both the patient and caregiver than cognitive decline, in part due to injury to either party through aggression and wandering.[7] Other reported impacts on carers include reduced quality of life, depression, distress and reduced employment income.[8,9] Carers of individuals living with dementia and NPS report more distress and depression than carers of individuals living with dementia with no NPS.[9] First-line treatment for NPS in dementia involves a range of nonpharmacological interventions, despite a limited and disparate evidence base.[6,7] These interventions are based upon identifying unmet physical and emotional needs that may be triggering the NPS and may include assessment for inadequately treated pain and unpleasant environmental factors.[7,10] Complementary nonpharmacological interventions include carer education and carer support.[7]

Second-line treatment of NPS involves the use of pharmacological interventions, usually in addition to the nonpharmacological strategies. Pharmacological intervention is usually warranted when a person becomes a risk to either themselves or others and nonpharmacological interventions have been unsuccessful.[6] The most common class of medications used to treat NPS of dementia is atypical antipsychotics (e.g. risperidone, olanzapine and quetiapine), although not all countries approve the use of these medications to treat NPS in dementia.[11] In Australia, risperidone is funded under the Pharmaceutical Benefits Scheme (PBS) for treating aggression and psychotic symptoms in patients with Alzheimer's disease for up to 12 weeks.[12] A similar arrangement is available in the UK.[13] Use of antipsychotics 'off label' is widespread in the aged-care setting. A retrospective cohort study of over 300,000 nursing home residents in the US, reported that 23.5% of residents were prescribed at least one antipsychotic and 86% of this prescribing was 'off label'. In addition, residents with dementia were 3.2 times more likely to use these medications 'off label' compared with residents without dementia.[14] The evidence for effectiveness of atypical antipsychotics to treat NPS of dementia is limited.[15,16] Systematic reviews have found modest improvements in agitation and psychosis in dementia.[6] There have been many studies showing an association of these medications with harmful outcomes in patients with dementia including falls, cerebrovascular events and death.[15,16] Antidepressants and antiepileptics are also used to manage NPS of dementia but are not approved for this indication. A Cochrane review undertaken in 2011, found the antidepressants sertraline and citalopram to be associated with a reduction in agitation and psychosis in dementia and were well tolerated compared with antipsychotics, however the studies were small, limiting the generalizability of these results.[17] A recent review of studies investigating the efficacy and safety of antiepileptic drugs for treating agitation and aggression in dementia found that while carbamazepine was effective at reducing symptoms, its clinical use is limited by poor tolerability and the potential for drug–drug interactions.[18] The use of valproate is not recommended due to questionable efficacy and poor tolerability and there is currently insufficient evidence to recommend the use of other antiepileptic medications in this setting.[18]

Given the limited range, questionable effectiveness and side-effect profile of current therapeutic options for treating NPS of dementia, research into alternative therapies is a priority for this growing and vulnerable population. In recent years, research has focused on developing novel therapeutic agents to treat a range of NPS in dementia. Following the identification of two main cannabinoid receptors (CB1, predominantly in the central nervous system and CB2, predominantly in the immune system), cannabinoids have been investigated for their safety and efficacy in treating NPS of dementia.[19] While little is known regarding the mechanism by which cannabinoids exert their

effects in NPS of dementia, *in vivo* studies have consistently shown a role for the endocannabinoid system in both modulating neurotransmission and exhibiting neuroprotective effects.[20,21] The endocannabinoid system has been shown to interact with several neurotransmitter systems (dopamine, norepinephrine, serotonin, GABA and acetylcholine) all of which have been implicated in the manifestations of NPS.[20] CB1 and CB2 receptors have been shown to exert neuroprotective effects through reduction of glutamate production and anti-inflammatory actions.[21]

This systematic review was undertaken to identify, describe and critically appraise all studies investigating cannabinoid use in treating NPS of dementia. The objectives of this review were to identify safety and effectiveness criteria used in the trials with a focus on the risk–benefit profile of each cannabinoid and the criteria used to measure outcomes.

Methods

This study was registered in the PROSPERO database (the international prospective register of systematic reviews, registration number CRD42018086202). The study design complies with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols).[22]

Study eligibility criteria

All original peer-reviewed studies assessing the safety and or effectiveness of any cannabinoid in treating NPS in patients with a diagnosis of any type of dementia were included, regardless of publication date. Where possible, all sources and healthcare databases were searched from inception to 1 January 2018.

The inclusion criteria included studies of any design, conducted in the older population (⩾65 years) and assessing the use of any cannabinoid in treating one or more of the known NPS of dementia. Included studies needed to assess one or both of the safety or effectiveness of cannabinoids in the study population and be written in English. Exclusion criteria included studies undertaken in younger populations (<65 years), studies assessing only the delay of onset or progression of any type of dementia and studies where the full text was not available.

Identification and selection of studies

In total, 27 online resources were systematically searched as shown in Table 1. This included healthcare databases, clinical trial databases, Alzheimer's disease and dementia advocacy group websites, cannabinoid advocacy websites and Google Scholar. A reference checklist of identified studies deemed suitable for inclusion was also undertaken. The search terms used for Medline were:

> [Cannabinoid.mp. or exp Cannabinoids/cannabidiol.mp. or exp Cannabidiol/THC.mp. or exp Dronabinol/Cannabis.mp. or exp Cannabis/nabiximol.mp. or exp nabiximol/exp Dementia/ or exp Dementia, Multi-Infarct/or exp AIDS Dementia Complex/or exp Dementia, Vascular/or exp Frontotemporal Dementia/exp Alzheimer Disease/or alzheimers.mp./exp Depression/or exp Antipsychotic Agents/or BPSD.mp. or exp Behavioral Symptoms/Mental Disorders/Akathisia, Drug-Induced/or Antipsychotic Agents/or Psychomotor Agitation/or agitation.mp./aggression.mp. or exp Aggression/wandering.mp. or exp Attention/or exp Wandering Behavior/appetite.mp. or exp Appetite Depressants/or exp Appetite/or exp Appetite Stimulants/or exp Appetite Regulation/depression.mp. or Depression, Chemical/or exp Depression/or Long-Term Synaptic Depression/insomnia.mp. or exp 'Sleep Initiation and Maintenance Disorders'/exp Anti-Anxiety Agents/or exp Anxiety Disorders/or anxiety.mp. or exp Anxiety/Caregivers/or exp 'Quality of Life'/or carer burden.mp. or exp 'Feeding and Eating Disorders'/or exp Stress, Psychological/adls.mp. or exp 'Activities of Daily Living'/22. limit 21 to (English language and humans and 'all aged (65 and over)')]

One reviewer (JH) undertook the database and website searches and sifted through the titles and abstracts to identify suitable studies. Two reviewers (JH and GC) independently assessed the abstracts and full text of identified studies for inclusion. Disagreements were resolved with a third reviewer (NS). Data extraction and assessment of study quality was undertaken independently by two reviewers (JH and GC) and disagreements resolved with a third reviewer (NS).

Data collection and study appraisal

Four reviewers (JH, GC, CA and NS) developed and agreed upon the study protocol, search terms and data extraction tool. The data extraction tool

Table 1. Databases and websites searched (including search terms) from inception to 1 January 2018.

	Name of database or website	Search terms
(1)	Medline	See above.
(2)	PsycINFO	As above: limitation to older adults is not possible in PsycINFO; search retained all hits regardless of age
(3)	Embase	As above: limitation to older adults is not possible in Embase; search retained all hits regardless of age
(4)	OpenGrey Repository	Cannabinoids and limited to English language
(5)	American Chemical Society publications	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(6)	ProQuest Health and Medicine	As Medline search above
(7)	Pharmaceutical News Index	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(8)	PubChem	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(9)	ScienceDirect	As with Medline above
(10)	LILACS	As with Medline above
(11)	ALOIS	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(12)	ClinicalTrials.gov	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(13)	EU Clinical Trials	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(14)	ANZCTR	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(15)	WHO International Trials Registry	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(16)	Australian Clinical Trials Registry	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(17)	Dementia Australia	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(18)	Alzheimer's Foundation of America	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(19)	Dementia Society of America	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(20)	Alzheimer's Europe	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(21)	Alzheimer's News Today	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol
(22)	Dementia Today	Delta-9-tetrahydrocannabinol or cannabinoid or cannabidiol or dronabinol or THC or CBC or marijuana or cannabis or nabiximol

Table 1. (Continued)

	Name of database or website	Search terms
[23]	NORML	Alzheimer's disease and dementia MesH search terms
[24]	The Canadian Consortium for the Investigation of Cannabinoids	Searched each category on website for relevant documents
[25]	International Association for Cannabinoid Medicines	Alzheimer's disease and dementia MesH search terms
[26]	Google Scholar	Alzheimer's disease or dementia and cannabinoids
[27]	Cochrane Database of Systematic Reviews	Cannabinoids

CBC, cannabichromene; NORML, National Organization for the Reform of Marijuana Laws; THC, delta-9 tetrahydrocannabinol; WHO, World Health Organization.

included the following variables divided into the six categories of study description, intervention, study participant demographics, outcome measures, results and study quality.

(1) Study description: author(s), year of publication, country of origin, study design, assessment of safety, assessment of effectiveness, study setting, length of study (days) and analytic plan.
(2) Intervention: cannabinoid used, administration route, dose(s), exposure period (days) and if a comparator or placebo was used.
(3) Study participants: number of participants, mean age/median age, proportion of males, types of dementia included, criteria used to verify dementia diagnosis and history of NPS of participants and baseline cognition.
(4) Outcome measures: primary and secondary outcome measure(s) and the tools used to evaluate outcomes.
(5) Results: primary and secondary outcome measure(s) and effect size (if reported).
(6) Study quality: individual study quality was assessed using the relevant critical appraisal tool for each study design developed by The Johanna Briggs Institute (observation studies) and the Cochrane Collaboration (randomized controlled trials; RCTs).[23,24]

Synthesis of findings

For the included studies, data are presented for each study as described by the data extraction tool, including both quantitative and qualitative information. Where possible, aggregate data have been presented in proportions. Due to the expected paucity and heterogeneity of identified studies, a meta-analysis was not planned, nor undertaken.

Results

The search results are presented in the PRIMSA flowchart (Figure 1).

We identified a total of 4951 studies of which 12 met the inclusion criteria (Figure 1). Study descriptions and participant baseline characteristics are summarized in Table 2. Included studies were published over a 20-year period (1997–2017). Six studies were RCTs, two were cohort studies and four were case series or studies. Four studies were from the Netherlands, two from the UK and USA, respectively, and one each from Germany, Israel, Switzerland and Canada. Seven studies were undertaken in hospital (psychogeriatric units), two studies in the community, two were in both the community and hospital, and one study was undertaken in the community and nursing home settings. Five studies included participants with any type of dementia (Alzheimer's disease, vascular dementia, frontotemporal dementia and mixed dementia), four studies included participants with Alzheimer's disease only and three studies included one or two of a selection of dementia types. The cannabinoids used in the included studies were dronabinol (dose range = 2.5–7.03 mg/day), delta-9 tetrahydrocannabinol (THC; Namisol®;

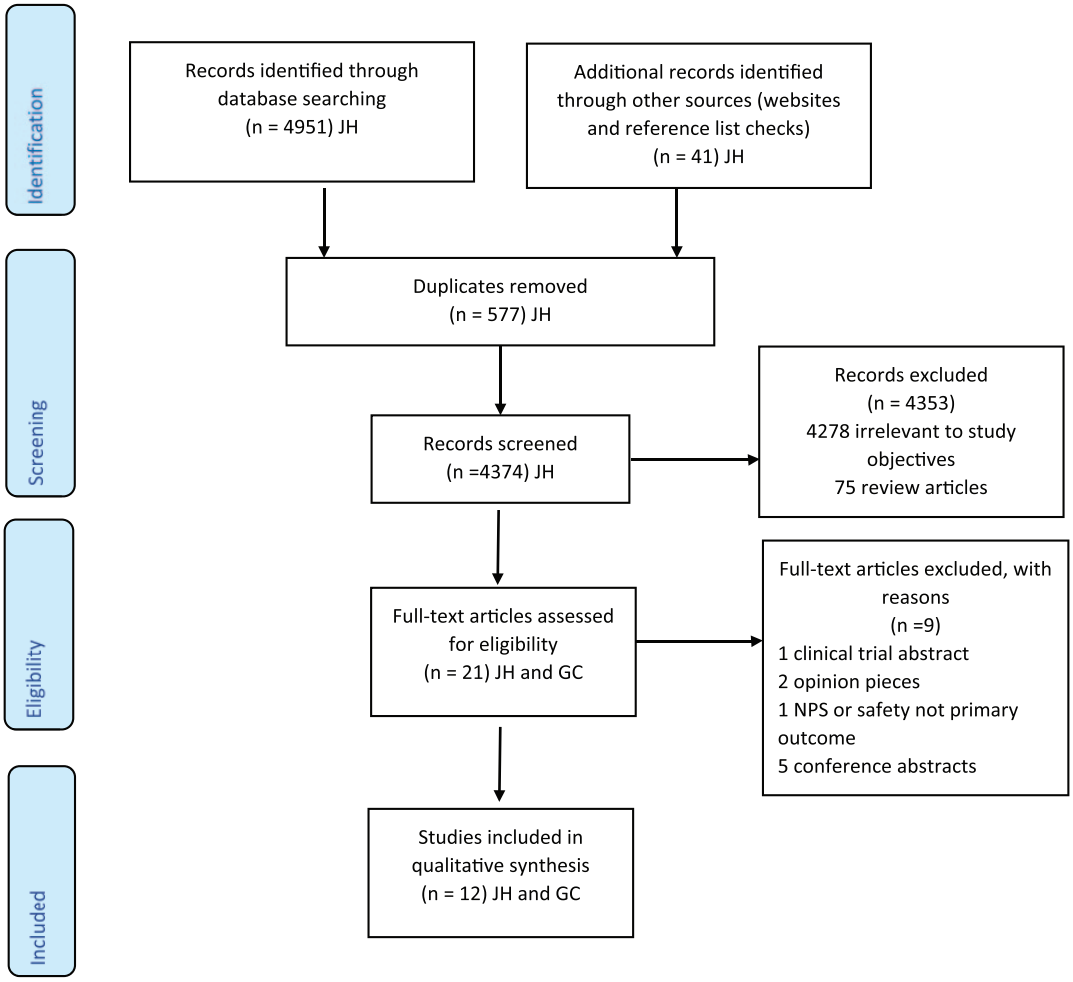

Figure 1. PRISMA flow diagram[22] of systematic review search results.
NA, not applicable; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols.

dose range = 1.5–15 mg/day) or nabilone (dose range = 0.5–2.0 mg/day) and were all administered orally.

The number of participants in the studies ranged from 2 to 50. The mean age ranged from 72.7 to 81.5 years, with the proportion of males included ranging from 30 to 100%. Baseline cognition (assessed using the Mini-Mental State Examination or MMSE) was reported in nine studies and scores ranged from 4 (severe cognitive impairment) to 22 (mild cognitive impairment). In four studies (all RCTs), participants had to score ⩾ 10 on the Neuropsychiatric Inventory Index (NPI) to be included. Reporting of prior treatment for NPS varied across the included studies but overall, was limited. Studies reporting concomitant medication use at the time of the trial recorded multiple medication use, including antipsychotics, antidepressants and neuromodulators; however, it was often unclear which medications were indicated for treating NPS of dementia.

Outcomes reported in the included trials varied substantially with heterogeneity of cannabinoid type used and evaluation of effectiveness criteria (Table 3). Half the identified studies used more than one set of criteria to evaluate effectiveness. The most common tool for assessing effectiveness of cannabinoid therapy for treating NPS of dementia was the NPI, which was used in five studies. Of these five studies, two RCTs reported no significant improvement in NPI,[26,27] one case series reported significant improvement in overall NPI score and three subscales (aberrant motor

Table 2. Included studies: study description and participant baseline characteristics.

Randomized controlled trials $n = 6$										
Citation	**Year and country of origin**	**Study design description**	**Study setting**	**Intervention**	**Types of dementia included**	**Participants *n***	**Male % and age(s)**	**MMSE baseline score (SD)**	**NPS history of participants**	**Prior treatment for NPS**
Walther et al.[25]	Switzerland, 2011	Randomized PC DB crossover trial	Hospital	Dronabinol capsules 2.5 mg orally nocte for 14 days	Alzheimer's disease	2	100% (75 and 81 years)	22 and 17	Circadian rhythm disturbances, verbal aggression, delusions and apathy	Not reported. No psychotropics listed in regular medications
Van den Elsen et al.[26]	The Netherlands, 2015	Randomized DB PC multicentre phase II trial	Community and nursing home	THC (Namisol®) 1.5 mg orally t.d.s for 3 weeks	Alzheimer's disease, vascular and mixed	50	50%, mean age 78.4 (SD 7.4)	THC arm 15.9(6.7) Placebo arm14.0 (6.8)	Agitation, aggression or aberrant motor behaviour for at least one month prior and NPI $\geqslant 10$	Not explicitly stated, however, participants were on a range of antipsychotics, antidepressants, benzodiazepines and anticonvulsants (dose and frequency stable for 2 weeks prior and throughout trial)
Van den Elsen et al.[27]	The Netherlands, 2015	Randomized DB PC repeated crossover trial	Hospital and community	THC (Namisol®) 0.75 mg orally b.d. for 3 days (weeks 1–3) and 1.5 mg orally b.d. for 3 days (weeks 4–6)	Alzheimer's Disease, vascular and mixed	22	68%, mean age 76.4 (SD 5.3)	16.9 (7.8)	Agitation and aggression and NPI $\geqslant 10$	18 (81%) of participants were on psychotropic medications (antipsychotic, antidepressant, anxiolytic, anticonvulsant or antidementia) These medications continued throughout trial (no information on doses or changes)
Volicer et al.[28]	USA, 1997	Randomized DB PC crossover trial	Hospital dementia study unit	Dronabinol oil 2.5 mg orally b.d. for 6 weeks then crossover	Alzheimer's disease	15 (3 dropouts)	91.7%, mean age 72.7 (SD 4.9)	4.0 (7.4)	Food refusal	Not reported
Van den Elsen et al.[29]	The Netherlands, 2017	Randomized DB PC crossover trial	Community	THC (Namisol®) 1.5 mg orally b.d. for 1 week	Alzheimer's disease, mixed and vascular	18	83%, mean age 77 years (SD = 6)	19.1 (SD 6)	NPS $\geqslant 10$ and clinically stable	Not explicitly stated, however, 28% of participants were on psychotropic medications (antidepressants, benzodiazepines, antipsychotics and antiepileptics)
Ahmed et al.[30]	The Netherlands, 2015	Randomized DB PC multiple dose phase II trial	Community	THC 0.75 mg orally b.d. or placebo for 3 days each week (weeks 1–6) then 1.5 mg b.d. of placebo for 3 days each week (weeks 7–12)	Alzheimer's disease, vascular and mixed	10	70%, mean age 77.3 years (SD 5.6)	18.5 (SD = 6)	Clinically relevant NPS in past 30 days (NPI $\geqslant 10$)	Not reported

(Continued)

Table 2. (Continued)

Randomized controlled trials $n = 6$										
Citation	**Year and country of origin**	**Study design description**	**Study setting**	**Intervention**	**Types of dementia included**	**Participants *n***	**Male % and age(s)**	**MMSE baseline score (SD)**	**NPS history of participants**	**Prior treatment for NPS**
Cohort studies $n = 2$										
Shelef et al.[31]	Israel, 2016	Open-label prospective cohort study	Hospital	MCO-THC 2.5–7.5 mg b.d. depending on response and adverse effects for 28 days	Alzheimer's disease	11	46%, mean age 73.2 (SD8.59 years)	10.3 (SD 9.4)	Severe agitation and aggressive behaviour resulting in hospitalization	Reported for eight participants: risperidone, olanzapine and clozapine
Woodward et al.[32]	US, 2014	Retrospective systematic chart review (pre–postintervention)	Hospital	Dronabinol mean dose = 7.03 mg/day for 4–50 days (average = 16.9 days)	Alzheimer's disease, vascular, mixed and frontotemporal	40	30%, age not reported	Mean = 7	Agitation, aggression or resistance to care	Not explicitly stated; 92.5% had at least one psychotropic medication (average of 3.25 at baseline)
Case study/series $n = 4$										
Walther et al.[33]	Germany, 2006	Open-label pilot study of six consecutive inpatients	Hospital	Dronabinol 2.5 mg orally nocte for 14 days	Alzheimer's disease and vascular	6	66.6%, mean age 81.5 (SD6.1)	10.33 (SD 6.28)	Night-time agitation, daytime rhythm disturbances or sundowning	Not explicitly stated; four patients taking psychotropic medications (risperidone, carbamazepine, donepezil, galantamine, mirtazapine or chloral hydrate); these continued throughout trial
Zajac et al.[34]	UK, 2015	Case study: refractory to treatment	Hospital	Nabilone 0.5 mg b.d., t.d.s. and 1 mg b.d.	Mixed	1	100%, 71	Not reported	Sexual disinhibition refractory to treatment	Nonpharmacological treatment, sertraline, divalproex, trazodone, risperidone, aripiprazole and lorazepam
Amanullah et al.[21]	UK, 2013	Case series	Hospital	Nabilone 0.5 mg b.d. to 0.5 mg t.d.s.	Alzheimer's disease and frontotemporal	2	100%, 79 and 60 years	Not reported	Aggressive behaviour	Both participants had trialled antipsychotics, antidepressants, anticonvulsants and memantine
Passmore[35]	Canada, 2008	Case study	Hospital	Nabilone 0.5 mg orally daily then increased to b.d.	Alzheimer's disease	1	100%, 72 years	Not reported	Agitation, aggression and disinhibition	Gabapentin, trazodone, quetiapine, olanzapine, lorazepam and citalopram

MMSE subscales of range 0–30 points: 30–25 = no cognitive impairment; 24–21 = mild cognitive impairment; 21–10 = moderate cognitive impairment; and 9–0 = severe cognitive impairment.[36]
b. d., twice daily; DB, double blind; MCO, medical cannabis oil; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory Index; NPS, neuropsychiatric symptoms; PC, placebo controlled; t.d.s., thrice daily; SD, standard deviation; THC, delta-9 tetrahydrocannabinol.

Table 3. Summary of study outcomes and quality.

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Walther[25]	RCT	Dronabinol oral 2.5 mg nocte 28 days (2-week crossover) Placebo	Nocturnal motor activity (Actiwatch, counts of movement) Circadian rhythm analysis (using sleep-analysis software)	(1) NPS (NPI scores) (2) ADEs (clinical observation)	Patient A: decreased nocturnal activity until third week (67% reduction in movement counts), fourth week returned to baseline (dronabinol first 2 weeks) Patient B: decreased nocturnal activity in third week, increased in fourth week (dronabinol in weeks 3 and 4)	(1) NPS improved for both patients from baseline (patient A: 18 *versus* 8; patient B: 44 *versus* 32) (2) There were no ADEs reported	High	This RCT included only two patients; allocation sequence generation, randomization and blinding methods unclear; there was use of rescue medication throughout the trial; ADE ascertainment methods unclear; there was selective reporting of results
Van den Elsen[26]	RCT	THC (Namisol®) oral 1.5 mg t.d.s 21 days Placebo	(1) Change in NPS (NPI)	(1) Agitation (CMAI) (2) Quality of life in Alzheimer's disease (QuOL-AD) (3) ADL (Barthel index) (4) CCGIC (caregiver observation) (5) BP (6) Weight (7) HR (8) ADEs (self or carer report from a predetermined list) (9) ECG (10) Biochemistry and bloods (11) Episodic memory (PAL-WMSR)	No significant difference between groups from baseline (1) Change in NPI = 3.2 (95% CI = −3.6 to 10)	No significant differences between groups on all parameters (1) CMAI = 4.6 (95% CI = −3.0 to 12.2) (2) QuOL-AD = −0.5 (95% CI = −2.6 to 1.6) (3) Barthel index = 0.6 (95% CI = −0.8 to 1.9) (4) CCGIC = −0.2 (95% CI = −0.5 to 0.9) (5) Systolic = −3.4 (95% CI = −6.5 to 12.2) and diastolic = −1.8 (95% CI = −6.6 to 3.1) (6) Weight = −0.1 (95% CI = −0.8 to 0.7) (7) HR = −3.3 (−7.5 to 0.9) (8) 16 ADEs reported in THC group and 14 in placebo group ($p = 0.36$); two dropouts (pneumonia and nausea) (9) Not reported (10) No significant differences (11) PAL-WMSR decreased by 1.4 points in THC group and 1.2 in placebo ($p = 1.0$)	Low	Recruited from outpatients, NH, GPs and advertisement in local papers CONSORT flow chart included There were missing MMSE data at baseline However, ITT analysis used Authors acknowledge a large placebo effect (may be due to study design which included education and support of carers and NH staff; the Hawthorne effect)

(Continued)

Table 3. (Continued)

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Van den Elsen[27]	RCT	THC (Namisol®) oral: 0.75 mg b.d. for 3/7, 4/7 washout then 3/7 placebo and repeat three times then increase dose to 1.5 mg b.d. 84 days Placebo	(1) Change in NPS (NPI)	(1) Agitation (CMAI) (2) Caregiver burden (ZBI) (3) ADEs (patient or caregiver report) (4) Mobility (Tinetti–POMA, TUG, GAITRite and SwayStar) (5) Perception (VAS) (6) Vital signs (7) Observation and physical examination (8) Weight (9) Laboratory tests (10) ECG (11) Delirium Observation Scale	No significant difference between groups with respect to NPI; *Post hoc* analysis found a clinically relevant and significant decrease in NPI scores in 38.9% of treatment blocks ($p = 0.074$) and a clinically relevant and significant increase in NPI scores in 31.5% of treatment blocks ($p = 0.09$; author interpretation)	(1) and (2) no significant differences on CMAI and ZBI between groups was observed for either dose of THC (*t* test values given, no *p* values) (3) 91 ADEs reported for THC *versus* 93 for placebo ($p = 0.77$); ADEs classified as 'psychiatric disorders' the most frequently reported; there were four serious ADEs (gastroenteritis, worsening of NPS, exacerbation of vestibular disorder and malignancy; none thought to be associated with THC) (4) No significant effect on Tinnetti–POMA or TUG scores (no *p* values); significant increase in body sway (SwayStar pitch angle degree 3.45 *versus* 2.38 for placebo, $p = 0.01$ and pitch velocity degree/second 6.70 *versus* 4.67, $p = 0.02$ and GAITRite stride velocity (cm/s) 93.1 *versus* 91.7, $p = 0.06$) (5) THC significantly affected on internal perception mean difference THC *versus* placebo = 0.0325 (95% CI = 0.01–0.04, $p = 0.0014$) (6) THC increased systolic blood pressure by 2.6 mmHg 4 h after dose; no changes in BP or HR observed (no values given); no other results reported	Moderate	This study used a robust design to determine efficacy and safety of THC including an intention-to-treat analysis; there were two dropouts in this study Not all results are reported; there are numerous missing values for participants There are two groups in this study (ambulatory and hospitalized) which differ substantially at baseline cognitive scores; it is unclear how these two groups were randomized; results not stratified by setting

Table 3. (Continued)

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Volicer et al.[28]	RCT	Dronabinol (oil) oral 2.5 mg b.d. 84 days (6-week crossover) Placebo	(1) Weight gain [BMI% change, weight gain (lbs)] (2) Behaviour changes (CMAI and Lawton observed effect scale)	(1) ADEs (carer observation from a predetermined list)	Body weight increased significantly in the 12-week period regardless of the order of treatments (BMI% change over time = 3.65, $p < 0.01$); there was more weight gain in the group receiving dronabinol first (7.0 ± 1.5 lb *versus* 2.3 ± 1 lb There was no difference in disturbed behaviour between periods (% change in CMAI, $p = 0.12$) Negative-effect score significantly decreased over the study period (% change = 2.46, $p = 0.045$) and more significantly during dronabinol treatment (% change = 5.45, $p < 0.01$)	There were three dropouts [seizure (1) and serious infection (2)] More patients reported ADEs when in the dronabinol arm than placebo (66 ADEs reported *versus* 59 ADEs) More patients experienced tiredness, somnolence and euphoria during dronabinol treatment[24] compared with placebo[14]	High	This study had a small sample size with three dropouts; dropouts were not included in the final analysis; selection, randomization and blinding methods were unclear; there was selective reporting of results; there was use of multiple rescue medications throughout the trial
Van den Elsen[29]	RCT	THC (Namisol®) Oral 1.5 mg b.d. or placebo for 3/7 followed by washout of 4/7 14 days (7-day crossover) Placebo	(1) Static and dynamic balance (SwayStar) (2) Gait (GAITRite system) and (3) Mobility tasks (GAITRite system)	(1) ADEs (open questions and clinical observation)	(1) No difference in static balance with eyes open ($p > 0.05$) Static balance decreased with eyes closed ($p < 0.05$) Decrease in dynamic balance ($p < 0.05$) (2) THC ingestion significantly increased stride length ($p < 0.05$) (3) No changes to dynamic balance and gait when undertaking a task ($p > 0.05$)	(1) This is a study within a study Authors reported the same ADE profile as above (Van den Elsen[26])	N/A	The authors questioned the clinical significance of these findings as the changes in balance and gait were very small

(Continued)

Table 3. (Continued)

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Ahmed[30]	RCT	THC (Namisol®) oral 0.75 or 1.5 mg b.d. 3 days of exposure followed by a 4-day washout period 14 days (7-day crossover) Placebo	(1) Safety (incidence and severity of ADEs observed by researchers using reporting) and physical parameters (BP, HR, ECG, VAS and body sway)	(1) Causality of THC to ADEs rated by a research physician blinded to treatment allocation	(1) 98 ADEs in total reported: 0.75 mg block (THC $n = 21$ *versus* placebo $n = 30$, $p = 0.290$) and 1.5 mg block (THC $n = 22$ *versus* placebo $n = 25$, $p = 0.435$); no serious ADEs reported (2) No differences in laboratory tests or ECG reported; VAS: significant changes in internal perception with 0.75 mg dose [0.025 U (95% CI = 0.01–0.04), $p = 0.001$]; body sway eyes closed significantly increased with 1.5 mg dose [0.59°/sec (95% CI = 0.13–1.06, $p < 0.05$)] (3) 0.75 mg dose significantly decreased blood pressure [−7.2 mmHg (95% CI = −11.4 to −3.0, $p < 0.001$)] and 1.5 mg dose significantly increased systolic blood pressure [5.1 mmHg (95% CI = 1.0–9.2, $p < 0.05$)] (4) 0.75 mg dose significantly increased HR [2.1 beats/min (95% CI = 0.4–3.8, $p < 0.05$)]	13 ADEs deemed possible or probably related to treatment, of which 6 were related to THC 0.75 mg block, two ADEs (dizziness and fatigue) associated with THC and 1.5 mg block, 4 ADEs [agitation (3) and fatigue] associated with THC	High	This study used a robust design to determine ADEs associated with TCH; however, the sample size was small, there were missing data and the rating of ADEs associated with THC was objective

Table 3. (Continued)

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Shelef[31]	Cohort	Medical cannabis oil containing THC oral 2.5 mg b.d. titrated up to 7.5 mg b.d. if tolerated 28 days No	(1) Physical parameters: weight (kg); glucose (%mg); and BP (2) Cognitive parameters (NPI, MMSE, CGI and CGI-S) (3) ADEs (clinical observation)	n/a	(1) No significant changes from baseline in physical parameters assessed: weight (66.57 *versus* 67.64, $p > 0.05$); glucose (114.9 *versus* 117.8, $p > 0.05$); systolic BP (151.6 *versus*139.4, $p > 0.05$); diastolic BP (82.9 *versus* 75.1, $p > 0.05$) (2) There were statistically significant improvements in CGI-S (6.52 *versus* 5.7, $p < 0.05$) and overall NPI scores (44.4 *versus* 12.8, $p < 0.01$) and MMSE (10.0 *versus* 11.0, $p < 0.05$); there were significant improvements in 6/13 NPI subscales assessed: agitation/aggression (8.2 *versus* 2.1, $p < 0.05$), disinhibition (5.3 *versus* 1.6, $p < 0.05$), irritability/lability (5.9 *versus* 1.7, $p < 0.05$), aberrant motor behaviour (4.6 *versus* 1.9, $p < 0.05$), nocturnal behaviour disorders (3.8 *versus* 0.9, $p < 0.05$) and caregiver burden (20.7 *versus* 9.4, $p < 0.05$) (3) Three ADEs were reported for three patients respectively (dysphagia, fall and confusion) Confusion was observed at the higher dose	n/a	Moderate	This study had a small sample size (11 including 1 dropout); there was inadequate identification and analysis of confounding factors; it was unclear how ADEs were identified

(Continued)

Table 3. (Continued)

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Woodward[32]	Cohort	Dronabinol oral Mean dose of 7.3 mg/day Mean duration of use was 16.88 days (range from 4 to 50 days) No	NPS: (a) PAS; (b) CGI; and (c) GAF	(1) ADEs (frequency recorded in medical notes) (2) Weight (lb) (3) Comorbidity burden (CIBRS) (4) Sleep patterns (night-time wakening and hours of sleep) (5) Food consumption (% food consumed at meal-times) (6) Number of rescue medications	(1) Significant improvements in overall PAS from baseline [9.68 (SD 3.91) *versus* 5.25 (SD 4.17), $p < 0.05$] and significant improvements in each PAS domain from baseline: aberrant vocalization [2.50 (SD 1.06) *versus* 1.15 (SD 1.09), $p < 0.05$]; motor agitation [2.02 (SD 1.0) *versus* 1.18 (SD 0.98), $p < 0.05$]; aggressiveness [2.25 (SD 1.71) *versus* 1.08 (SD 1.49), $p < 0.05$]; and resting care [2.80 (SD 1.86) *versus* 1.80 (SD 1.62), $p < 0.05$] (2) Significant improvements in CGI from baseline [5.15 (SD 0.92) *versus* 3.75 (SD 1.28), $p < 0.05$] (3) No significant change in GAF from baseline [23.1 (SD 7.01) *versus* 25.22 (SD 8.66), $p = 0.09$]	(1) 26 ADEs reported [sedation (9), delirium (4), UTI (3)] and confusion most frequently reported (2) No significant change in weight from baseline (mean weight = 137.1 *versus* 133.6, $p = 0.64$), (3) Comorbidity not reported (4) No changes in number of hours slept (6.5 *versus* 6.8 h) or night-time waking episodes (no values given; $p > 0.05$) (5) Significant increase in % food consumed (no values reported, $p < 0.01$) (6) No difference in number of rescue medications from baseline (no values given, $p > 0.05$)	High	In this study, there was variation in the amount and time of medication exposure; confounding factors were inadequately identified and addressed; it is unclear if follow up was complete or if there were missing data; full results values not given

Table 3. (Continued)

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Walther[33]	Case series	Dronabinol oral 2.5 mg nocte 14 days No	Nocturnal motor activity, daytime rhythm disturbances and sundowning (Actometer wrist band)	(1) NPS (NPI scores and number of rescue mediations used) (2) ADEs (clinical observation)	Nocturnal activity significantly decreased after treatment (actography median activity counts = 34.26 *versus* 10.79, $p < 0.05$). There was no change in diurnal or evening activity	(1) Rate of rescue medications use did not change compared to baseline (mean medication units/day at baseline = 1.04 (SD = 0.66) *versus* 0.92 (SD = 0.77) at end of trial, $p = 0.41$) Total NPI score and subscores of aberrant motor behaviour, agitation and night-time behaviours all significantly lower at end of trial compared with baseline (no values given, $p < 0.05$) (2) There were no ADEs reported	High to moderate	This study had a small sample size; there was insufficient demographic and clinical information of participants; there was incomplete reporting of results; ADE ascertainment method was unclear
Zajac[34]	Case study	Nabilone presumed oral 0.5 mg b.d., t.d.s. and 1 mg b.d. Months No	Change in behaviours	ADEs (clinical observation)	Some improvement and return to NH	Sedation: withheld nabilone on two occasions	High	No formal cognitive or NPS testing; no formal assessment of ADEs Risperidone and lorazepam p.r.n. started at same time and did not state how many doses given
Amanullah[21]	Case series	Nabilone oral (1) 0.5 mg b.d. (2) 0.5 mg t.d.s. (1) 78 days observation and ongoing (1) 63 days observation and ongoing No	(1) NPS (KSBA) (2) Effectiveness in decreasing aggression and caregiver time (family observations)	n/a	(1) No improvements in overall KSBA from baseline (patient A: 44–43 and patient B: 39–37; scores fluctuated over the study period) (2) Families reported the treatment to be effective in reducing their emotional distress and burden. Families also reported the patients to be more communicative	n/a	High	Difficult to deduct any findings from this study, as patients on multiple psychotropics with multiple interventions throughout the observed period; the authors interpret a change of 1 in a score as significant for aggression but not for other variables recorded in the KSBA

(Continued)

Table 3. (Continued)

Study		Intervention	Outcome measures		Results		Quality of study	
Author and date	**Study design**	**Cannabinoid administration route, dose-exposure period (days), comparator or control**	**Primary outcome (s)**	**Secondary outcome(s)**	**Primary outcomes**	**Secondary outcomes**	**Risk of bias**	**Potential for bias**
Passmore[35]	Case study	Nabilone oral 0.5 mg/d titrated up to b.d. 168 days No	Observed response to nabilone	n/a	Behaviour resolved sufficiently to return to nursing home	n/a	High	There were no formal cognitive and NPS assessments; author mentioned 'no emergent' effects of nabilone but ADEs/safety not formally addressed; this case is the longest duration of use reported for a cannabinoid and shows persistent effects, although we do not know if other medications were changed or introduced in the 3-month period, or what other clinical changes may have occurred

ADEs, adverse drug events; ADL, activities of daily living; b.d., twice daily; BMI, body mass index; BP, blood pressure; CGI, Clinical Global Impression (-S, severity); CCGIC, Caregiver Clinical Global Impression of Change; CI, confidence interval; CIBRS, CONSORT, Consolidated Standards of Reporting Trials; Cumulative Illness Burden Rating Scale; CMAI, Cohen–Mansfield Agitation Inventory; ECG, electrocardiogram; GAF, Global Assessment of Functioning; GP, general practitioner; HR, heart rate; ITT, intention to treat; KSBA, Kensington Standardized Behaviour Assessment tool; MMSE, Mini-Mental State Exam; n/a, not applicable; NPI, Neuropsychiatric Inventory; NH, National Health; NPS, neuropsychiatric symptoms; PAL-WMSR, Paired Associate Learning Wechsler Memory Scale Revised; PAS, Pittsburg Agitation Scale; Tinetti–POMA, p.r.n., as required; RCT, randomized controlled trial; t.d.s., thrice daily; Tiinetti–Performance-Oriented Mobility Assessment; TUG, Timed Up and Go; UTI, urinary tract infection; VAS, Visual Analogue Scale; ZBI, Zarit Burden Index.

behaviour, agitation and night-time behaviours),[33] one cohort study reported significant improvement in 6 of the 13 NPI subscales (agitation, disinhibition, irritability, aberrant motor behaviour, night-time behaviour and caregiver burden).[31] The fifth study, an RCT with two participants, reported improvement in overall NPI score.[25] The Cohen–Mansfield Agitation Inventory (CMAI) was used in three RCTs with no significant changes reported.[26–28]

Reporting of adverse drug events (ADEs) was the most frequently used method for assessing safety in the included trials, used in 10 studies (one case series and one case study did not report ADEs; Table 3). Methods for ascertaining ADEs included participant and carer reports, predetermined lists of ADEs to aid in identification, medical notes or clinical observation or a combination of these. Four RCTs reported no significant difference in ADEs between treatment arms[26,27,29,30] and two studies (one RCT and one case series) reported no ADEs during the trial.[25,33] One RCT used a blinded independent physician to rate causality of an ADE to treatment with a cannabinoid. In this study, dizziness, fatigue and agitation were all considered related to Namisol® administration and were dose related (Table 3).[30] Serious ADEs were reported in three trials. One RCT reported three serious ADEs (one seizure and two serious infections).[28] Another RCT reported four serious ADEs (gastroenteritis, worsening of NPS, exacerbation of vestibular disorder and malignancy).[27] One cohort reported three serious ADEs (dysphagia, fall and confusion).[31] Overall, the most common ADE reported was sedation.

In addition to reporting ADEs, a variety of physical parameters related to safety were monitored in seven studies and included blood pressure, heart rate, electrocardiogram and weight. One RCT and two cohort studies reported no significant change in parameters.[26,31,32] One RCT reported significant increases in body sway, stride and change in internal perception.[27] Another RCT reported a significant increase in weight.[28] One RCT reported significant decrease in balance and increase in stride.[29] Lastly, an RCT reported significant changes in perception, increase in body sway, increase and decrease in systolic blood pressure (dose dependent) and increase in heart rate.[30] Two RCTs formally assessed caregiver burden using the Zarit Burden Interview[27] and Caregiver Clinical Global Impression of Change (CCGIC)[26] with no significant differences reported between treatment and placebo arms, respectively. A case series reported families felt the treatment to be effective and with a reduction in their emotional burden.[21]

Overall, the quality of included trials was low with a high risk of bias assessed for 8 of the 12 studies (66.7%; Table 3). Half (3/6) of the RCTs were assessed as low quality mainly due to small sample size, unclear methods of randomization and blinding, and selective reporting of results. The two cohort studies were of moderate and low quality, with both inadequately identifying confounding factors. In addition to the inadequacies identified above, the cohort study rated lowest quality had time-varying exposure to dronabinol and incomplete reporting of results.[32] The four included case series/studies were all assessed as low quality, as there was insufficient clinical and demographic information reported. The highest-quality trial was a randomized placebo-controlled crossover trial, which had a low risk of bias and was sufficiently powered to find a clinically significant change in NPI.[26] This study found no significant improvement in NPI compared with baseline between placebo and THC 1.5 mg three times daily for 21 days. Similarly, this study found no significant differences between placebo and treatment arm for ADEs or other physical parameters.

Table 4 provides a summary of the overall risk–benefit profile of each type of cannabinoid used in the included studies. Dronabinol was used in four studies with a daily dose range of 2.5–7.03 mg. The use of dronabinol was associated with significant improvements in several NPS scores [Pittsburg Agitation Scale, negative affect, Clinical Global Impression (CGI) and NPI], increase in weight, reduction in nocturnal activity and increase in percentage of food consumed. Dronabinol was not significantly associated with any ADEs; however, at a dose of 2.5 mg twice daily, dronabinol was associated with three serious ADEs (one seizure and two serious infections). Nabilone was used in three studies with a daily dose range of 0.5–2.0 mg. Nabilone was not significantly associated with an improvement in NPS of dementia or any ADEs; however, at a dose of 1.5 mg twice daily, nabilone caused severe sedation which required withholding of the

Table 4. Summary of effectiveness and safety outcomes by cannabinoid.

Cannabinoid (number and type of studies)	Dose range (total daily dose)	Duration of use (days)	Reported efficacy	Reported safety (ADEs and physical parameters)
Dronabinol (Four: two RCTs, one cohort and one case series)	2.5–7.03 mg	14–50	(1) RCT: reduction in nocturnal motor activity and improvement in NPI scores (2) RCT: increase in body weight and negative-effect score decreased*; no change in CMAI* (3) Cohort: decrease in overall PAS scores and the domains of aberrant vocalization, motor agitation, aggressiveness, and resting care*; decrease in CGI scores*; no change in GAF*; percentage of food consumed increased; however, no change in weight*; no change in number of hours slept or night-time wakening*; no difference in the number of rescue medications before and during treatment* (4) Case series: nocturnal activity decreased*; significant decreases in overall NPI score and domains of aberrant motor behaviour, agitation and night-time behaviours*; no change in the number of rescue medications from baseline*	(1) RCT: no ADEs reported (2) RCT: three dropouts (seizure and infections); somnolence (8 *versus* 4 patients); tiredness (9 *versus* 5 patients); and euphoria (7 *versus* 5 patients) were reported more often in the dronabinol arm compared with placebo (3) Cohort: 26 ADEs reported [sedation (9), delirium (4) and confusion (3)] most common (4) Case series: no ADEs reported
Nabilone (three case studies/ series)	0.5 mg–2.0 mg	63–ongoing	(1) Case study: improved behavioural symptoms (aggression and agitation) in one refractory patient (2) Case series: no change in KSBA*; families reported patients to be calmer and more alert (3) Case study: behaviour improved to return to nursing home	(1) Case study: sedation (nabilone withheld on two occasions) (2) Case series: not reported (3) Case study: not reported
THC (Five: four RCTs and one cohort)	1.5 mg–15 mg	7–28	(1) RCT: no improvement in NPI, CMAI, QuOL-AD, CCGIC and Barthel scores*; no change in episodic memory* (2) RCT: no change in NPI, CMAI and ZBI* (3) Cohort: significant improvements in CGI, overall NPI scores and NPI domains of agitation/aggression, disinhibition, irritability/lability, aberrant motor behaviour, nocturnal behaviours and carer burden* Two RCTs assessed safety only	(1) RCT: no difference in ADEs, weight, BP or HR between treatment arms*; two dropouts due to pneumonia and nausea (2) RCT: no difference in ADEs between treatment arms*; four serious ADEs (gastroenteritis, worsening of NPS, exacerbation of vestibular disorder and malignancy); significant decrease in balance and increase in stride*; increase and decrease in systolic blood pressure*; increase in HR* but not diastolic blood pressure; changes in internal perception* (3) RCT: significant increase in stride length and decrease in balance* (4) RCT: six ADEs related to THC [dizziness (1), agitation (3) and fatigue (2)] (5) Cohort: three ADEs reported (dysphagia, falls and confusion)

*Indicates statistical significance.
ADEs, adverse drug events; BP, blood pressure; CGI, Clinical Global Impression; CCGIC, Caregiver Clinical Global Impression of Change; CMAI, Cohen–Mansfield Agitation Inventory; GAF, Global Assessment of Functioning; HR, heart rate; KSBA, Kensington Standardized Behaviour Assessment tool; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; QuOL-AD, quality of life in Alzheimer's disease; PAS, Pittsburg Agitation Scale; RCT, randomized controlled trial; ZBI, Zarit Burden Index.

medication. THC was used in six studies with a daily dose range of 1.5 to 15 mg. THC was associated with significant improvement in NPS of dementia in one trial (improvement in CGI and NPI).[31] THC was the only cannabinoid to be significantly associated with ADEs, including increase in body sway, increase and decrease in systolic blood pressure and increase in heart rate and in one trial, there were two dropouts due to pneumonia and nausea.

Discussion

To our knowledge, this systematic review is the most comprehensive presentation of the effectiveness and safety of cannabinoids in treating NPS of dementia. Overall, it was difficult to make generalizations about the safety and effectiveness of cannabinoids in treating NPS of dementia due to the heterogeneity of the included studies (even within study design), the range of assessment tools used and the poor quality of identified studies. While the efficacy of cannabinoids was not proven in a robust RCT, observational studies showed promising responses, especially for refractory patients. In addition, the safety profile presented was favourable, as the majority of ADEs reported were mild.

Within the RCT group of included trials, inclusion criteria differed substantially with respect to baseline MMSE, prior treatment for, and severity of, NPS. In addition, these trials used a variety of tools to measure change in NPS of dementia. Evidence of effectiveness and safety was limited by the power of the RCTs to detect a statistically significant change: only one trial predetermined a clinically relevant change and powered the study to detect such a change.[26] Five of the six RCTs were therefore underpowered to detect true effectiveness of cannabinoids in treating NPS of dementia.

The quality of the observational studies was limited by inadequately described comorbidities and medication use making it difficult to determine if cannabinoids were the only contributing factor to improvement in NPS of dementia. More robust cohort studies adjusting for concomitant medications and comorbidities may give insight into the true effectiveness of cannabinoids in refractory patients.

The NPI was the most frequently used tool to assess NPS in dementia response to cannabinoid treatment. This tool uses an informant to report on the severity and frequency of a broad range of symptoms (depression, anxiety, apathy, hallucinations, delirium, agitation, sleep, irritability and elation).[37] The CMAI was the second most frequently used tool to measure effectiveness of cannabinoids in treating NPS of dementia. This tool is specific to agitation with information gained through observation and informant reporting.[38] Two RCTs used both the NPI and CMAI and both did not find significant differences in NPS between treatment arms on either scale. Improvement in NPS in dementia as measured by the NPI was reported for one RCT (two patients), one cohort and one case series. This may be due to observational study design characteristics such as closer and prolonged observation of patients, more in-depth knowledge of patients and nonblinding of the assessor. Several studies used multiple tools to assess response to treatment which covered a range of NPS and global functioning. There was minimal discussion in the included studies regarding the selection criteria for assessment tool(s) and who administered the test(s). Clear description of why each tool was chosen, how it was administered and how the tools relate to one another would assist with interpreting the results.

The use of caregiver reporting of response to therapy provides additional insights. Although highly subjective in nature, these reports can represent a change in physical and emotional burden for caregivers. In one case series, caregivers reported improvement in NPS and carer burden post-treatment. However, this was not supported by the formal assessment of caregiver burden in two RCTs.

The safety profile of the cannabinoids used in the identified studies appears to be reasonable. Studies reported mostly mild adverse effects such as sedation, somnolence and fatigue. Changes in blood pressure, balance and infections were reported from several studies and are worth a more in-depth surveillance in future studies, as these effects may have serious outcomes in an older, frailer population. Long-term safety was not established in the studies due to short exposure times.

Conducting clinical trials for treating NPS in dementia has many obstacles. As demonstrated

Table 5. Clinical trial criteria for assessing NPS of dementia response to cannabinoids.

Criteria	Quality of evidence
RCT DB PC crossover	Minimize bias: allocation, observation and ascertainment Confounding: using participant as own control will assist with adjustment for clinical characteristics; however, will not adjust for change in NPS over time
Baseline cognition	Minimize bias: include participants from one category of baseline MMSE (mild, moderate or severe) **or** stratify by MMSE category (if sample size allows)
Baseline medication use and rescue medications	Clearly describe all medications participants are taking at baseline; keep doses of regular medication stable prior to and during clinical trial; report use of rescue medications (dose and frequency)
Effect size and study power	Predetermine a clinically relevant change in NPS of dementia and adequately power study to detect true change
Evaluation tool	Select a validated and reliable tool relevant to the setting of the clinical trial; clearly describe why the tool was chosen and how the tool was used
ITT and reporting of results	Report all results (test scores, statistical test results and significance); use an ITT analysis; clearly report and follow up trial dropouts

DB, double blind; ITT, intention to treat; MMSE, Mini-Mental State Examination; NPS, neuropsychiatric symptoms; PC, placebo controlled; RCT, randomized controlled trial.

by the included studies, this cohort is frail with multiple comorbidities and multiple chronic medications making it difficult to conduct trials where there is only one variable of change. In addition, severity of a person's NPS in dementia can vary over time. Several of the included RCTs used a crossover design which can assist with adjusting for confounders, however, will not adjust for within-person changes over time. The main deficits in the identified studies were incomplete reporting of study design, patient clinical characteristics and outcomes. Future studies should focus on improving the quality of study design and reporting as outlined in Table 5, which includes appropriate study design, accurate assessment and reporting of baseline cognition, medication use and rescue medications, calculation of effect size and study power *a priori*, use of a validated and reliable assessment tool to evaluate change and the thorough and accurate reporting of all study results.

Despite the paucity of evidence for safety and effectiveness of cannabinoids in treating NPS of dementia, it is important to recognize the identified trials' contribution to knowledge in this field. Identified observational studies have shown potential for cannabinoid use in treating refractory NPS of dementia with minimal side effects. While larger RCTs did not show effectiveness of cannabinoids, the reported safety profile was acceptable. However, doses used in these studies may be a key issue in terms of safety and effectiveness of cannabinoids.

The included studies used low doses of oral cannabinoids relative to studies treating other indications, and this may have contributed to the lack of demonstrated efficacy. A systematic review of RCTs investigating the use of cannabinoids for treating chemotherapy-induced nausea and vomiting found that doses of oral nabilone 2 mg twice daily and oral dronabinol 10–15 mg/m^2 up to six times daily were effective in reducing nausea and vomiting by up to 50%; however, adverse effects were commonly reported with fatigue significantly associated with treatment.[39] Therefore, dose escalation may be warranted in future studies investigating the efficacy and safety of cannabinoids in treating NPS in dementia.

Furthermore, orally administered cannabinoids have poor oral bioavailability due to high first-pass hepatic metabolism.[40] For example, a 10 mg oral dose of dronabinol has a bioavailability of approximately 6–7%.[40] Namisol® is a THC formulation with reported enhanced bioavailability (up to 30%) due to Alitra®, a lipophilic delivery technology.[41]

Future studies investigating the efficacy and safety of cannabinoids in treating NPS of dementia should trial innovative administration modalities to improve bioavailability.

This study was a systematic review registered with PROSPERO and followed the PRISMA guidelines. However, we cannot confirm that we have correctly identified all relevant studies. The inclusion criteria of studies in the older population may have reduced the likelihood of including executive and frontal variants of dementia, which are more common in the younger dementia population. However, the symptoms of NPS are more likely in the older population. Two reviewers independently selected studies for inclusion and extracted the relevant information. The studies identified in our study are similar to those reported in the Cochrane systematic review of RCTs[42] and a recently published review.[43] Our systematic review identified two more RCTs than a review published in 2017 which assessed effectiveness of cannabinoids.[44] The 2017 systematic review assessed the quality of the included RCTs as 'unclear'. In addition, we have graded the quality of each study and identified areas of bias in each study.

Conclusion

This systematic review has found that the quality of studies examining the use of cannabinoids to treat NPS of dementia is poor. While the efficacy of cannabinoids was not proven in a robust RCT, observational studies showed promising responses, especially for refractory patients. In addition, the safety profile appears favourable, as most ADEs reported were mild. However, formulations and doses of the cannabinoids used in the identified studies may have limited the ability to demonstrate cannabinoid efficacy and safety for this indication. A large, well-controlled trial is warranted given the current limited treatment options available for NPS in dementia patients.

Acknowledgements

We would like to thank Dr Rocco Iannello, Head of Research and Development (WardMM) and Dr Ric De Garis, Head of Clinical Trials (WardMM).

Funding

WardMM received support for this study from LeafCann Pty Ltd. LeafCann and its employees were not involved in the undertaking of this systematic review, nor the interpretation of the results.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Australian Institute of Health and Welfare 2012. *Dementia in Australia.* Cat. no. AGE 70. Canberra: AIHW.
2. Prince M, Wimo A, Guerchet M, *et al. The World Alzheimer Report 2015. The Global Impact of Dementia. An analysis of prevalence, incidence, costs and trends*. London: Alzheimer's Disease International; 2015.
3. Sawa GM, Zacchi J, Mathews FE, *et al.* Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry* 2009; 194: 202–219.
4. Panza F, Solfrizzi V, Seripa D, *et al.* Progresses in treating agitation: a major clinical challenge in Alzheimers disease. *Expert Opin Pharmacother* 2015; 16: 2581–2588.
5. Ismail Z, Smith EE, Geda Y, *et al.* Neuropsychiatric symptoms as early manifestations of early dementia: provisional diagnostic criteria for mild behavioural impairment. *Alzheimers Dement* 2016; 12: 195–202.
6. Australian and New Zealand Society for Geriatric Medicine. Management of behavioural and psychological symptoms of dementia (BPSD). Position statement 26, 2016. www.anzsgm.org/documents/26BPSD12Aug2016.pdf (2016, accessed 26 February 2018).
7. Gitlin LN, Kales HC and Lyketsos CG. Nonpharmacological management of behavioural symptoms in dementia. *JAMA* 2012; 308: 2020–2009.
8. Sjhin I, Carter M, Masterman D, *et al.* Neuropsychiatric symptoms and quality of life in Alzheimer disease. *Am J Geriatr Psychiatry* 2005; 13: 469–474.
9. Kales HC, Gitlin LN, Lyketsos CG; Detroit Expert Panel on Assessment and Management of Neuropsychiatric Symptoms of Dementia. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *J Am Geriatr Soc* 2014; 62: 762–769.

10. Baycrest. Behavioural and psychological symptoms of dementia. Assessment and treatment, www.baycrest.org/Baycrest/Education-Training/Educational-Resources/Behavioural-Psychological-Symptoms-of-Dementia/Assessment-and-Treatment (accessed 26 February 2018).

11. Agency for Healthcare Research and Quality. Off-label use of atypical antipyschotics: an update. 11(12-EHC087–3), www.ncbi.nlm.nih.gov/pubmedhealth/PMH0048473/pdf/PubMedHealth_PMH0048473.pdf (2012, accessed 26 February 2018).

12. Pharmaceutical Benefits Scheme, www.pbs.gov.au/medicine/item/1842Y-1846E (accessed 26 February 2018).

13. GOV.UK. Guidance: antipsychotic medicines, https://www.gov.uk/government/publications/antipsychotic-medicines-licensed-products-uses-and-side-effects/antipsychotic-medicines (2005, accessed 26 February 2018).

14. Kamble P, Shere J, Chen H, *et al*. Off-label use of second-generation antipsychotic agents among elderly nursing home residents. *Psychiatr Serv* 2010; 61: 130–136.

15. Schneider LS, Tariot PN, Dagerman KS, *et al*. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med* 2006; 355: 1525–1538.

16. Byrne GL. Pharmacological treatment of behavioural problems in dementia. *Aust Prescr* 2005; 28: 67–70.

17. Seitz DP, Afuniru N, Gruneir A, *et al*. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst* 2011; CD008191.

18. Gallagher D and Herrmann N. Antiepileptic drugs for the treatment of agitation and aggression in dementia: do they have a place in therapy? *Drugs* 2014; 74: 1747–1755.

19. Soto M, Andrieu S, Nourhashemi F, *et al*. Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design. *Int Psychogeriatr* 2015; 27: 181–197.

20. Liu CS, Chau SA, Ruthirakuhan M, *et al*. Cannabinoids for the treatment of agitation and aggression in Alzheimer's disease. *CNS Drugs* 2015; 29: 615–623.

21. Amanullah S, MacDougall K, Sweeney N, *et al*. Synthetic cannabinoids in dementia with agitation: case studies and literature review. *Clin Neuropsychiatry* 2013; 10: 142–147.

22. Moher D, Liberati A, Tetzlaff J, *et al*.; The PRISMA Group. Preferred reporting items for systematic review and meta-analyses: the PRISMA statement. *PLoS Med* 2009; 6.

23. The Joanna Briggs Institute. The Joanna Briggs Institute critical appraisal tools, http://joannabriggs.org/research/critical-appraisal-tools.html (2017, accessed 1 March 2018).

24. The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions, http://methods/cochrane.org/bias/assessing-risk-bias-included-studies (2011, accessed 1 March 2018).

25. Walther SMD, Schupbach BMD, Seifritz EMD, *et al*. Randomized, controlled crossover trial of dronabinol, 2.5 mg, for agitation in 2 patients with dementia. *J Clin Psychopharmacol* 2011; 31: 256–258.

26. 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.

27. 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.

28. Volicer L, Stelly M, Morris J, *et al*. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; 12: 913–919.

29. Van Den Elsen GAH, Tobben L, Ahmed AIA, *et al*. Effects of tetrahydrocannabinol on balance and gait in patients with dementia: a randomised controlled crossover trial. *J Psychopharmacol* 2017; 31: 184–191.

30. Ahmed AI, Van den Elsen GA, Colbers A, *et al*. Safety, pharmacodynamics, and pharmacokinetics of multiple oral doses of delta-9-tetrahydrocannabinol in older persons with dementia. *Psychopharmacology* 2015; 232: 2587–2595.

31. 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.

32. Woodward MR, Harper DG, Stolyar A, *et al*. Dronabinol for the treatment of agitation and aggressive behavior in acutely hospitalized

severely demented patients with noncognitive behavioral symptoms. *Am J Geriatr Psychiatr* 2014; 22: 415–419.

33. Walther S, Mahlberg R, Eichmann U, *et al.* Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology* 2006; 185: 524–528.
34. Zajac DM, Sikkema SR and Chandrasena R. Nabilone for the treatment of dementia-associated sexual disinhibition. *Prim Care Companion CNS Disord* 2015; 17: 10.4088/PCC.14l01695.
35. Passmore MJ. The cannabinoid receptor agonist nabilone for the treatment of dementia-related agitation. *Int J Geriatr Psychiatr* 2008; 23: 116–117.
36. The Independent Hospital Pricing Authority. Standardised mini-mental state examination (SMMSE) - Guidelines for administration and scoring instructions, 2014, https://www.ihpa.gov.au/sites/g/files/net636/publications/smmse-guidelines-v2.pdf (accessed 1 March 2018).
37. Perrault A, Oremus M, Demers L, *et al.* Review of outcome measurement instruments in Alzheimer's disease: psychometric properties of behaviour and mood scales. *J Geriatr Psychiatr Neurol* 2000; 13: 181–196.
38. Weiner MF, Tractenberg RE, Jin S, *et al.* Assessing Alzheimer's disease with the Cohen-Mansfield Agitation Inventory: scoring and clinical implications. *J Psychiatr Res* 2002; 34: 19–25.
39. Smith LA, Azariah F, Lavender V, *et al.* Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database Syst Rev* 2015: CD009464.
40. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; 42: 327–360.
41. Echo Pharmaceuticals. Drug Delivery Technology Alitra(r). www.echo-pharma.com/clinical-development/ (accessed 29 April 2019).
42. Krishnan S, Cairns R and Howard R. Cannabinoids for the treatment of dementia. *Cochrane Database Syst Rev* 2009; CD007204.
43. Weier M and Hall W. The use of cannabinoids in treating dementia. *Curr Neurol Neurosci Rep* 2017; 17.
44. Lim K, Yuen MS and Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. *Clin Psychopharmacol Neurosci* 2017; 15: 301–312.