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

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 caregivers. 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 \( \geq 65 \) 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

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7} Other reported impacts on carers include reduced quality of life, depression, distress and reduced employment income.\textsuperscript{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.\textsuperscript{9} First-line treatment for NPS in dementia involves a range of nonpharmacological interventions, despite a limited and disparate evidence base.\textsuperscript{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.\textsuperscript{7,10} Complementary nonpharmacological interventions include carer education and carer support.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{12} A similar arrangement is available in the UK.\textsuperscript{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.\textsuperscript{14} The evidence for effectiveness of atypical antipsychotics to treat NPS of dementia is limited.\textsuperscript{15,16} Systematic reviews have found modest improvements in agitation and psychosis in dementia.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 |
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 effectivenes
tness, 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 PRISMA 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®;
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 $\geq 10$ 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

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

| Citation | Year and country of origin | Study design description | Study setting | Intervention | Types of dementia included | Participants | Male % and age(s) | MMSE baseline score (SD) | NPS history of participants | Prior treatment for NPS |
|-----------|-----------------------------|--------------------------|---------------|--------------|-----------------------------|--------------|-------------------|--------------------------|---------------------------|---------------------------|
| Walther et al. | 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. | 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 arm 14.0 (6.8) | Agitation, aggression or aberrant motor behaviour for at least one month prior and NPI ≥ 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. | 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 > 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. | 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. | 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 ≥ 10 and clinically stable | Not explicitly stated, however, 28% of participants were on psychotropic medications [antidepressants, benzodiazepines, antipsychotics and antiepileptics] |
| Ahmed et al. | 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 1–4) 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 > 10] | Not reported |

(Continued)
### Table 2. (Continued)

| Citation       | Year and country of origin | Study design description | Study setting | Intervention | Types of dementia included | Participants | Male % and age(s) | MMSE baseline score (SD) | NPS history of participants | Prior treatment for NPS |
|----------------|----------------------------|--------------------------|---------------|--------------|-----------------------------|--------------|--------------------|-------------------------|---------------------------|--------------------------|
| Cohort studies \(n = 2\) |                            |                          |               |              |                             |              |                    |                         |                           |                          |
| Shelef et al.\(^{21}\) | 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 [SD 8.99 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.\(^{22}\) | 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.\(^{23}\) | 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 (SD 6.1) | 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.\(^{24}\) | UK, 2015                   | Case study: refractory to treatment | Hospital   | Nabilone 0.5 mg b.d. to 0.5 mg t.d.s. | Mixed | 1 | 100%, 71 | Not reported | Sexual disinhibition refractory to treatment | Nonpharmacological treatment, sertraline, divalproex, trazodone, risperidone, antipsychotics 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\(^{25}\) | Canada, 2008               | Case study               | Hospital   | Nabilone 0.5 mg orally daily then increased to b.d. | Alzheimer’s disease | 1 | 100%, 72 | Not reported | Agitation, aggression and disinhibition | Gabapentin, trazodone, quetiapine, olanzapine, lorazepam and clonazepam |

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 | Cannabinoids administration route, dose-exposure period [days], comparator or control | Primary outcome(s) | Secondary outcomes | Risk of bias | Potential for bias |
| Walther | 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 | 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 = −2.4 to 1.4) [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)
| Study | Cannabinoid | Administration route, dose-exposure period | Comparator or control | Primary outcomes | Secondary outcomes | Risk of bias | Potential for bias |
|-------|-------------|---------------------------------------------|----------------------|------------------|---------------------|-------------|------------------|
| Van den Elsen | 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 | 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) | No significant differences on CMAI and ZBI between groups for either dose of THC (p values given, no p values) | 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) | No significant effect on Tinetti–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) | THC significantly affected on internal perception mean difference THC versus placebo = 0.0325 (95% CI = 0.01−0.04, p = 0.0014) |

This study used a robust design to determine the efficacy and safety of THC including an intention-to-treat analysis; there were two dropouts in the study. There are numerous missing values for participants. There are two groups in this study (ambulatory and hospitalized) which differ substantially at baseline. It is unknown how these two groups were randomized; results not stratified by setting.

Table 3. [Continued]
| Study | Intervention | Outcome measures | Results | Quality of study | Potential for bias |
|-------|--------------|------------------|---------|-----------------|--------------------|
| Volicer et al. | RCT | Dronabinol (oil) oral 2.5 mg b.d. 84 days (4-week crossover) Placebo | [1] Weight gain [BMI% change, weight gain [lbs]] [2] Behaviour changes [CMAI and Lawton observed effect scale] | 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, \( p < 0.01 \)] | High |
| Van den Elsen | 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] 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 [\( p > 0.05 \)] | N/A | The authors questioned the clinical significance of these findings as the changes in balance and gait were very small |
| 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 (20) | 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 = 0.439); no serious ADEs reported | 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, nausea, fatigue) associated with THC | High | This study used a robust design to determine ADEs associated with THC; however, the sample size was small, there were missing data and the rating of ADEs associated with THC was objective |
| Study | Intervention | Outcome measures | Results | Quality of study |
|-------|--------------|------------------|---------|-----------------|
| Shelef et al.1 | 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) | (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 32.8, 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 | 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 |
| Study | Intervention | Outcome measures | Results | Quality of study |
|-------|--------------|------------------|---------|-----------------|
| Woodward | Cohort | Dronabinol oral<br>Mean dose of 7.3 mg/day<br>Mean duration of use was 16.88 days (range from 4 to 50 days)<br>No | NPS: (a) PAS; (b) CGI; and (c) GAF<br>[1] ADEs [frequency recorded in medical notes]<br>[2] Weight<br>[3] Comorbidity burden<br>[4] Sleep patterns (night-time waking and hours of sleep)<br>[5] Food consumption (% food consumed at meal-times)<br>[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 [2.50 (SD 1.01) 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]<br>[2] Significant improvements in CGI from baseline [5.15 (SD 0.92) versus 3.75 (SD 1.28), p < 0.05]<br>[3] No significant change in GAF from baseline [23.1 (SD 7.01) versus 25.22 (SD 8.66), p = 0.09] | High<br>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 | Potential for bias |
|-------|--------------|------------------|---------|------------------|--------------------|
| **Walther**<sup>33</sup> Case series | Dronabinol oral 2.5 mg nocte 14 days | Nocturnal motor activity, daytime rhythm disturbances and sundowning [Actometer wrist band] | 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 | 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**<sup>34</sup> Case study | Nabilone presumed oral 0.5 mg b.d., t.d.s. and 1 mg b.d. Months | Change in behaviours | Some improvement and return to NH | 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**<sup>31</sup> 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 | 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 | 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 |
| Study | Intervention | Outcome measures | Results | Quality of study |
|-------|--------------|------------------|---------|-----------------|
| Passmore<sup>35</sup> Case study | Nabilone oral 0.5 mg/d titrated up to b.d. 168 days | 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 |

Table 3. (Continued)
behaviour, agitation and night-time behaviours), 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). The fifth study, an RCT with two participants, reported improvement in overall NPI score. The Cohen–Mansfield Agitation Inventory (CMAI) was used in three RCTs with no significant changes reported.

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 and two studies (one RCT and one case series) reported no ADEs during the trial. 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). Serious ADEs were reported in three trials. One RCT reported three serious ADEs (one seizure and two serious infections). Another RCT reported four serious ADEs (gastroenteritis, worsening of NPS, exacerbation of vestibular disorder and malignancy). One cohort reported three serious ADEs (dysphagia, fall and confusion). 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. One RCT reported significant increases in body sway, stride and change in internal perception. Another RCT reported a significant increase in weight. One RCT reported significant decrease in balance and increase in stride. 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. Two RCTs formally assessed caregiver burden using the Zarit Burden Interview and Caregiver Clinical Global Impression of Change (CCGIC) 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.

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. 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. 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 waking; 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). 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. 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). 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. 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 nabolone 2 mg twice daily and oral dronabinol 10–15 mg/m² 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. 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. For example, a 10 mg oral dose of dronabinol has a bioavailability of approximately 6–7%. Namisol® is a THC formulation with reported enhanced bioavailability (up to 30%) due to Alitra®, a lipophilic delivery technology.
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 and a recently published review. Our systematic review identified two more RCTs than a review published in 2017 which assessed effectiveness of cannabinoids. 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.

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**Conflict of interest statement**

The authors declare that there is no conflict of interest.

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