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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Medical Cannabis for the Treatment of Dementia: A Review of Clinical Effectiveness and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	July 17, 2019
Report Length:	24 Pages

CADTH

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Cite As: Medical Cannabis for the Treatment of Dementia: A Review of Clinical Effectiveness and Guidelines. Ottawa: CADTH; 2019 Jul. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

ADEs	adverse drug events
CGI-S	Clinical Global Impression (-S, severity)
CMAI	Cohen–Mansfield Agitation Inventory
GABA	gamma amino butyric acid
MMSE	Mini-Mental State Examination
NPI	Neuropsychiatric Inventory Index
NPS	neuropsychiatric symptoms
PAS	Pittsburg Agitation Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
THC	delta-9 tetrahydrocannabinol
UPDRS	Unified Parkinson Disease Rating Scale
VAS	visual analog scale

Context and Policy Issues

Dementia refers to a set of symptoms and signs associated with a progressive deterioration of cognitive functions that affects daily activities.[1] Symptoms may include memory loss and difficulties with thinking, problem-solving or language, as well as changes in mood, perception, personality, or behaviour.[2,3]

According to the World Alzheimer Report 2018, about 50 million people worldwide lived with dementia in 2018, with the number projected to increase to 152 million by 2050.[4] In Canada, the estimated number of people living with dementia in 2016 was 564,000, and this is expected to increase to 937,000 by 2031.[5] The total health care system costs and out of pocket costs of caring for people with dementia were $10.4 billion in 2016, and are projected to double by 2031.[5]

Alzheimer's disease is the most common type of dementia, accounting for about two thirds of all dementia.[4] Other types of dementia that occur less frequently include vascular dementia, mixed dementia, Lewy body dementia, frontotemporal dementia, and young-onset dementia.[1,3] Neuropsychiatric symptoms (NPS) are common to all dementia types and may manifest as agitation, aggression, wandering, apathy, sleep disorders, depression, anxiety, psychosis, and eating disorders.[3] These behavioral symptoms of dementia present significant risks of injury to the patients and caregivers, reduce quality of life, and may cause distress or depression.

The progressive course of dementia cannot be altered since there is no known cure or disease-modifying therapy.[6] However, there are interventions to manage NPS, although they are based on limited and disparate evidence.[3] The first-line treatment of NPS comprises a range of nonpharmacological interventions based on identifying unmet physical and emotional needs, such as inadequately treated pain and unpleasant environmental factors, which may trigger the symptoms. Pharmacological therapies are the second-line treatment in patients for whom nonpharmacological interventions were unsuccessful and who present a potential risk of injury to either themselves or others. Pharmacological interventions commonly involve off-label use of atypical antipsychotics or

second-generation antidepressants, usually in combination the nonpharmacological strategies.[3]

Given the limited currently available therapeutic options, their side-effect profiles, and inconsistent evidence base, there is a need for alternate therapies in the growing population of dementia patients.[7-9] Medical cannabis has been investigated as one the potential alternative treatments for dementia.[10,11] Cannabis (also known as marijuana) is a plant that contains over 70 different chemical compounds called cannabinoids.[2] Although their mechanism of action in dementia is not well elucidated, they have been shown to interact with neurotransmitter systems that have been implicated in the manifestations of NPS.[11] Currently, patients living in Canada who have a prescription from an authorized health care professional can legally use cannabis for medical purposes, if they are registered with a licensed producer or Health Canada.[12,13]

The objective of this report is to summarize the evidence regarding the clinical effectiveness of medical cannabis for the treatment of dementia and the evidence-based guidelines for its use in this condition.

Research Questions

1. What is the clinical effectiveness of medical cannabis for the treatment of dementia?
2. What are the evidence-based guidelines associated with the use of medical cannabis for the treatment of dementia?

Key Findings

Limited evidence from one systematic review[3] and one uncontrolled before-and-after study[10] suggested that medical cannabis may be effective for treating agitation, disinhibition, irritability, aberrant motor behaviour, and nocturnal behaviour disorders as well as aberrant vocalization and resting care, which are neuropsychiatric symptoms associated with dementia. There was also limited evidence of improvement in rigidity and cognitive scores as assessed by Mini-Mental State Examination. The evidence from the systematic review came from four of its primary studies, whereas its remaining eight included studies did not find favourable or unfavourable evidence regarding the effectiveness of cannabinoids in the treatment of dementia. Sources of uncertainty included the low quality of evidence in the primary studies of the systematic review[3] and the fact that the uncontrolled before-and-after study[10] was a nonrandomized pilot study in 10 dementia patients that reported descriptive outcomes without statistical analysis. No relevant evidence-based clinical guidelines regarding the use of medical cannabis for treating dementia were identified.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were cannabis and

dementia. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2009, and June 18, 2019.

Selection Criteria and Methods

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

Table 1: Selection Criteria

Population	Adults with dementia (all types)
Intervention	Medical cannabis, any form/route/dose
Comparator	Q1: ○ Any treatment (e.g., opioids); ○ No treatment; ○ Placebo Q2: ○ Guidelines
Outcomes	Q1: ○ Clinical effectiveness and safety (e.g., agitation reduction, mental health symptoms, benefits and harms, drug interactions) Q2: ○ Guidelines
Study Designs	Health technology assessment, systematic reviews and meta-analyses, randomized controlled trials, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1; they were duplicate publications or were published before 2009. Systematic reviews[11,14-18] with relevant included studies fully captured in an already selected systematic review (i.e., complete overlap), and primary studies[19-24] that were included in an already selected systematic review, were also excluded.

Critical Appraisal of Individual Studies

The included systematic review[3] was critically appraised using A Measurement Tool to Assess Systematic Reviews (AMSTAR 2),[25] while the prospective before-and-after study[10] was critically appraised using the Risk of Bias for Nonrandomized Studies (RoBANS)[26] tool. Summary scores were not calculated for the included studies; instead, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 570 citations were identified in the literature search. Following screening of titles and abstracts, 544 citations were excluded, and 26 potentially relevant reports from the electronic search were retrieved for full-text review. The grey literature search identified one additional relevant publication. Of the 27 potentially relevant articles, 25 papers were excluded for various reasons, and two reports that met the inclusion criteria were included in this review. These comprised one systematic review[3] and one uncontrolled before-and-after study.[10] Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[27] flowchart of the study selection process. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One systematic review[3] and one uncontrolled before-and-after prospective pilot study,[10] both published in 2019, were included in this report. The primary studies in the systematic review[3] were identified through a comprehensive literature search involving 27 online resources, including Medline, PsycINFO, and Embase. The databases were searched from inception (where possible) to January 1st, 2018. A total of 12 studies published from 1997 to 2017 were included in the systematic review.[3] They comprised six randomized controlled trials (RCTs), two cohort studies, and four case series or case studies.

Country of Origin

Reviewers from Australia authored the systematic review.[3] Four primary studies of the systematic review[3] were from the Netherlands, two each from the United Kingdom and United States of America, and one each from Germany, Israel, Switzerland, and Canada. The uncontrolled before-and-after prospective pilot study[10] was conducted in Switzerland.

Patient Population

The systematic review[3] involved a total of 178 patients, aged 65 years or older, across 12 included studies. The mean age ranged from 72.7 to 81.5 years. Five primary studies of the systematic review[3] included patients with any type of dementia, whereas four studies included participants with Alzheimer's disease only and three studies included one or two dementia types (Alzheimer's disease, vascular, mixed and frontotemporal). Seven primary studies in the systematic review[3] were undertaken in psychogeriatric units of hospitals. Two studies were conducted in the community. Another two studies took place in both the community and hospital, while one study was undertaken in the community and nursing home settings.

The uncontrolled before-and-after prospective pilot study[10] enrolled 10 female patients with dementia from different causes with persisting behavior problems, notwithstanding optimal conventional treatment. Patients had to have a neuropsychiatric inventory index (NPI) score higher than 10 to be eligible for inclusion. The average age of the patients was 79.5 years. The study was conducted at a nursing home specialized in the care of elderly with severe dementia.

Interventions and Comparators

Studies included in the systematic review[3] evaluated three different orally administered cannabinoids – dronabinol, delta-9 tetrahydrocannabinol (THC), and nabilone. The medications were given at daily dose ranges of 2.5 to 7.03 mg, 1.5 to 15 mg, and 0.5 to 2.0 mg, respectively. In all comparative studies, placebo was given to patients in the control arm. Overall, reporting of prior treatment for NPS was limited and varied across the included studies. Reported concomitant medications included antipsychotics, antidepressants, and neuromodulators. However, it was unclear if these drugs were indicated for treating NPS of dementia or co-morbid conditions.

Cannabis oil containing THC and cannabidiol (CBD) combination (THC/CBD) was the intervention in the uncontrolled before-and-after prospective pilot study.[10] The medication was given with a small piece of chocolate cake to facilitate intake. The average doses were titrated over the study period as follows: up to 7.6 mg THC/13.2 mg CBD daily over two weeks, 8.8 mg THC/17.6 mg CBD by one month, and 9.0 mg THC/18.0 mg CBD by two months. No information was provided about previous treatments or concomitant therapy during the study.

Outcomes

Six of the primary studies included in the systematic review[3] evaluated the effectiveness of cannabinoid therapy for treating NPS of dementia using more than one set of criteria. The most common assessment tool was the NPI, which was used in five primary studies. The NPI is a validated tool developed to assess dementia-related behavioral symptoms, and it is routinely used to evaluate the effects of treatment on these symptoms.[28] The instrument is administrated to caregivers of dementia patients, who assess 12 behavioral areas commonly affected in such patients. The 12 behavioral domains are: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, night-time behaviors, and appetite and eating disorders.[28] For each domain, there are four scores: frequency, severity, total (frequency × severity), and caregiver distress. The total possible score is 144, with higher scores denoting greater severity.[28] The Cohen–Mansfield Agitation Inventory (CMAI) was used in three included RCTs. The CMAI is a validated 29-item tool intended to assess the frequency of manifestations of agitated behaviors in elderly persons in the long-term care setting.[29] Each item is rated on a 7-point scale of frequency (i.e., from 1 = never to 7 = several times an hour).[29] A primary caregiver rates the elderly patients regarding the frequency with which they manifest physically aggressive, physically non-aggressive, and verbally agitated behaviors. Changes in cognition following cannabinoid treatment were reported by one study out of nine studies included in the systematic review[3] that assessed baseline cognition using the Mini-Mental State Examination (MMSE).

The NPI and CMAI were also used in the uncontrolled before-and-after prospective pilot study.[10] In addition, item 22 of the Unified Parkinson Disease Rating Scale (UPDRS), a widely-used clinical rating scale consisting of a 31-item questionnaire for Parkinson's disease,[30] was used to assess the degree of rigidity with passive movements, on a scale of 0 (absent) to 4 (severe, range of motion achieved with difficulty).[31] Lastly, a 0 to 10 visual analog scale (VAS) was used to evaluate the most "invalidating daily activity" or "disturbing behavior" (as determined by staff; however these were not defined).

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Review

The systematic review[3] followed the PRISMA guidelines, and it was registered with International Prospective Register of Systematic Reviews (PROSPERO). The research objective was stated clearly, and inclusion and exclusion criteria were specified. The population, intervention, and control (comparator) of interest, as well as the outcome measures, were defined. The review authors searched multiple databases, with search dates ranging from inception to January 1st, 2018. Also, the reference lists of relevant studies were hand-searched to identify additional studies. However, the search was limited to studies published in English and older patients (≥65 years old). Studies undertaken in younger populations (<65 years) were excluded. Study selection and data extraction were performed in duplicate by two review authors, with disagreements between them resolved by a third reviewer. The review authors did not explain their selection of the study designs for inclusion in the review. However, given the limited number of high-quality RCTs on the subject, it seems reasonable to include peer-reviewed studies regardless of the study design, as they did. The included primary studies were listed in tabular form, with the relevant characteristics of each study. A list of excluded studies was not provided; however, the number of studies excluded and the reasons for exclusion were specified in the PRISMA flow chart illustrating the study selection process. The risk of bias and methodological quality of the studies were evaluated using the Johanna Briggs Institute and Cochrane Collaboration critical appraisal tools (i.e., for observation studies and RCTs, respectively). Disagreements were resolved with a third reviewer. Overall, the included studies were of low quality with a high risk of bias, except for one RCT and one cohort study that were rated as having moderate risk of bias by the authors. The systematic review[3] considered the risk of bias in individual studies in the discussions of the results and conclusions, and stated that they had no conflicts of interest to disclose. However, they also acknowledged funding support from a cannabis manufacturing firm, although they noted that the firm and its employees were not involved in undertaking the systematic review[3] or interpreting its results.

Primary Study

On account of its non-randomized design, the included uncontrolled before-and-after study[10] was inherently likely to have more systemic biases as it lacked the risk-diminishing property of randomization. It was unknown if all consecutive eligible patients were considered for inclusion or if the study participants were intentionally targeted. Thus, the risk of bias due to inappropriate selection was unclear. Data for the study[10] were collected prospectively, which minimized risk of bias. Selection bias due to an inappropriate comparison group was low because data were available for all the same study participants both before and after the intervention. Although there was no reference to a pre-specified protocol for the study, the expected main outcomes were included, and results were measured with validated scales, suggesting a reduced risk of bias due to selective outcome reporting. However, it was unknown if the outcome assessors were blinded to the study hypothesis or exposure to the medication. Thus, the risk of confirmation bias due to inappropriate blinding of assessors was unclear. Also, it was not reported how the cannabis oil was standardized or how the stated doses were determined. Therefore, there was uncertainty about the level of risk of performance bias that could arise from variability in the

intended doses the patients received. The severity of dementia among the patients precluded patient-reported feedback. Therefore, the assessments were based on the perception of third parties (i.e., family members and caregivers).

There was no indication that the uncontrolled before-and-after study[10] or any of the primary studies of the systematic review,[3] had any mechanism to identify and adjust for potential confounding factors that could affect the observed outcomes beyond the cannabinoids medication. Overall, the quality of evidence from the systematic review[3] and the uncontrolled before-and-after study[10] included in this report was limited.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Medical Cannabis for the Treatment of Dementia

The included systematic review[3] reported study-level findings without meta-analysis. Four of the 12 primary studies in the systematic review[3] found that treatment of patients with dementia with medical cannabis resulted in significant improvements in a range of neuropsychiatric symptoms associated with dementia. The remaining eight primary studies did not find evidence to support the efficacy of cannabinoids in the treatment of dementia. They comprised five placebo-controlled RCTs, and one case series and two case studies without controls. Three of the RCTs evaluated THC (two studies) or dronabinol (one study) for agitation and behavior changes. Another RCT evaluated THC for static and dynamic balance as well as gait, and one RCT assessed safety. Doses of THC used varied between 0.75 mg twice daily to 1.5 mg three times daily, with follow-up varying from 14 to 84 days across the studies. Dronabinol was dosed at 2.5 mg twice daily for 84 days. The case series evaluated nabilone for NPS titrating doses from 0.5 mg twice to thrice daily for 78 days. The period of dose titration was not mentioned. The two case studies also assessed nabilone, with change in behaviours as outcome for one and observed response to nabilone outcome for the other. None of these two case studies provided quantifiable results, and it was not possible to determine significant effect.

The following paragraphs summarize the findings from the four primary studies of the included systematic review[3] and the uncontrolled before-and-after study.[10]

Effectiveness

Changes in overall symptoms score

One RCT with a crossover design included in the systematic review[3] compared dronabinol 2.5 mg at night to placebo in two patients and found that after 28 days of treatment with dronabinol the overall NPI score was reduced by 10 points in patient and 11 points in the other. The significance of this reduction was not clear. One open-label prospective cohort study with 11 patients included in the systematic review[3] found that the overall NPI was reduced by 31.6 points ($P < 0.001$) after 28 days of treatment with up to 7.5 mg/day of THC. Also, one uncontrolled before-and-after study[10] found that the overall NPI was reduced by 32.9 points (*P*-value not reported) after two months of treatment with up 9.0/18 mg/day of THC/CBD. One case series included in the systematic review[3] reported that, in comparison to before treatment, a significantly lower total NPI ($P < 0.05$) was observed after 14 days of treatment with 2.5 mg oral dronabinol at night (the score values were not reported).

One cohort study included in the systematic review,[3] which assessed patient outcomes using the Pittsburg Agitation Scale (PAS), found significant improvements ($P < 0.05$) in the

overall mean PAS among 40 patients after treatment with dronabinol at a mean dose of 7.3 mg/ day for a mean duration of 16.88 days.

Changes in specific symptoms

One open-label prospective cohort study included in the systematic review[3] found statistically significant improvements ($P < 0.05$) in the NPI subscales agitation, disinhibition, irritability, aberrant motor behaviour, and nocturnal behaviour disorders among 11 patients, following 28 days treatment with medical cannabis oil containing THC given orally at doses up to 7.5 mg twice daily. Caregiver burden was also reduced significantly ($P < 0.05$). One case series included in the systematic review[3] also reported significantly lower ($P < 0.05$) NPI sub-scores in six patients for aberrant motor behavior, agitation and night-time behaviors, after 14 days of treatment with 2.5 mg oral dronabinol at night. However, the study did not report the actual score values.

One cohort study included in the systematic review[3] found significant improvements ($P < 0.05$) in aberrant vocalization, motor agitation, aggressiveness and resting care as assessed on PAS among 40 patients, after treatment with dronabinol at a mean dose of dose of 7.3 mg/ day for a mean duration of use of 16.88 days.

One RCT with a crossover design (involving two patients) included in the systematic review3 found a 67% reduction in nightly movement counts by the third week of treatment with dronabinol. It was unclear if this symptom referred to nocturnal behavior disorders. However, in the fourth week, nocturnal activity returned to baseline in one patient and increased in the other patient. One case series included in the systematic review3 involving six patients found that nocturnal activity significantly decreased ($P < 0.05$) after 14 days of treatment with 2.5 mg oral dronabinol at night. It was unclear whether this symptom referred to nocturnal behavior disorders or aberrant motor behavior.

One uncontrolled before-and-after study10 found that baseline agitation as measured by CMAI, and rigidity scores on UPDRS, decreased from 74.5 to 47.5, and 3.4 to 1.7, respectively, in 10 patients with severe dementia after two months follow-up. Statistical significance was not assessed.

One uncontrolled before-and-after study10 involving 10 patients with severe dementia who were treated with THC/CBD (at doses up to 9.0/18.0 mg daily), found that persistent screaming stopped almost entirely in two women (20%) and frequent vomiting stopped in one patient (10%) after two months. Also, two patients (20%) stopped all morphine within three months, one patient (10%) decreased morphine by two-thirds in two months, and one patient (10%) stopped two antipsychotic medications after one month.

Cognitive changes

One open-label prospective cohort study included in the systematic review[3] found that among 11 patients, there were statistically significant improvements in the MMSE scores from baseline (10.0) to following 28 days of treatment (11.0) with oral medical cannabis oil containing THC given at an initial dose of 2.5 mg twice daily and titrated up to 7.5 mg twice daily ($P < 0.05$).

Safety

Adverse events (AEs) were reported in 10 included studies in the systematic review,[3] whereas one case series and one case study did not report AEs. Overall, the most common AE reported was sedation, observed in 10 (24.4%) out of a total of 41 patients from two

studies. The AEs were described as mostly mild. The exact numbers of patients involved were not clearly reported. Serious AEs (SAEs) were observed in three primary studies in the systematic review.[3] One RCT reported one seizure (7%) and two serious infections (13.4%). Another included RCT found SAEs in the form of gastroenteritis, worsening of NPS, and exacerbation of vestibular disorder and malignancy. One included cohort study reported three SAEs (dysphagia, fall, and confusion). No values were specified in either study.

One uncontrolled before-and-after study[10] reported that no patient stopped the cannabinoids for reasons of side effects; however, one patient died after one month for reasons unrelated to the cannabinoid medication.

Evidence-Based Guidelines Associated with the Use of Medical Cannabis for the Treatment of Dementia

The literature search for this review did not identify any clinical guidelines associated with the use of medical cannabis for the treatment of dementia; therefore, no summary can be provided.

Limitations

The systematic review[3] included primary studies of generally low quality and high risk of bias, except two studies with moderate risk of bias. The primary studies evaluated three isolated orally administered cannabinoids, with no study examining botanical cannabis or its crude extract. Also, no other route of administering cannabis was explored apart from the oral route. Thus, it is unknown if the finding will be generalizable to patients who used different medical cannabis preparations (i.e., not ingested orally). The authors of the systematic review[3] did not calculate effect estimates from the multiple studies due to the scarcity and heterogeneity of identified studies. Therefore, it was difficult to draw a generally representative conclusion on the effectiveness of the interventions.

Further, the systematic review[3] was limited to dementia patients 65 years or older, and studies undertaken in patients less than 65 years were excluded. Thus, it is unclear if the reported findings will be generalizable in younger populations. Patients in the uncontrolled before-and-after study were all female. Therefore, the generalizability of the results to male patients is unknown. Apart from one case study conducted in Canada, which was included in the systematic review,[3] all other studies, including the uncontrolled before-and-after study,[10] were undertaken outside Canada. Therefore, the generalizability of the findings to the Canadian context is unclear, given the potential for differences in practice patterns that might impact the interpretation of the results or the resources used to achieve them.

Although the uncontrolled before-and-after study[10] was conducted in patients with dementia with persisting severe behavior problems, notwithstanding optimal conventional treatment, medical cannabis was not compared with any active intervention in any of the studies[3,10] included in this report. Thus, the comparative effectiveness of medical cannabis to standard care for dementia could not be determined conclusively. Also, none of the included studies[3,10] had long-term effectiveness and safety data. However, in both the systematic review[3] and the uncontrolled before-and-after study[10] patients with dementia of all origins were eligibility for inclusion, which implies a good generalizability across patients with various kinds of dementia.

The literature search for this report did not identify any clinical guidelines regarding the use of medical cannabis for the treatment of dementia. However, the search was limited to

English-language documents, and it is unknown if potentially relevant guidelines in other languages were missed. Given these limitations, there is a need for further studies to evaluate the use of medical cannabis in dementia, and establish clear guidelines for its use, if proven safe and effective.

Conclusions and Implications for Decision or Policy Making

One systematic review[3] of 12 primary studies and one uncontrolled before-and-after prospective pilot study[10] provided the information in this report. No relevant evidence-based clinical guidelines regarding the use of medical cannabis for treating dementia were identified. The primary studies of the systematic review[3] assessed the safety and efficacy of three isolated cannabinoids (dronabinol, THC, and nabilone) that were orally administered to patients with dementia at various doses. In the uncontrolled before-and-after prospective pilot study,[10] patients were given cannabis oil containing THC/CBD given with small pieces of chocolate cake to facilitate intake at doses from an initial dose of 7.6 mg THC/13.2 mg CBD titrated up to 9.0 mg THC/18.0 mg CBD daily over two months. None of the studies examined raw botanical cannabis or explored another route of administration apart from oral.

Overall, limited evidence from the studies[3,10] included this report suggested that medical cannabis may be effective for treating neuropsychiatric symptoms associated with dementia (i.e., agitation, disinhibition, irritability, aberrant motor behaviour, nocturnal behaviour disorders, and aberrant vocalization and resting care). There was also limited evidence of improvement in rigidity and cognitive scores as assessed by MMSE.

However, the data were inconclusive, given the limitations previously discussed. Key sources of uncertainty included the low quality of evidence in the primary studies of the systematic review[3] and the fact that the uncontrolled before-and-after study[10] was a nonrandomized pilot study in 10 dementia patients that reported descriptive outcomes without statistical analysis. Given these limitations, there is a need for a well-designed randomized controlled trial to confirm the effectiveness of medical cannabis for the treatment of dementia using different formulations that explore varieties of routes of administration.

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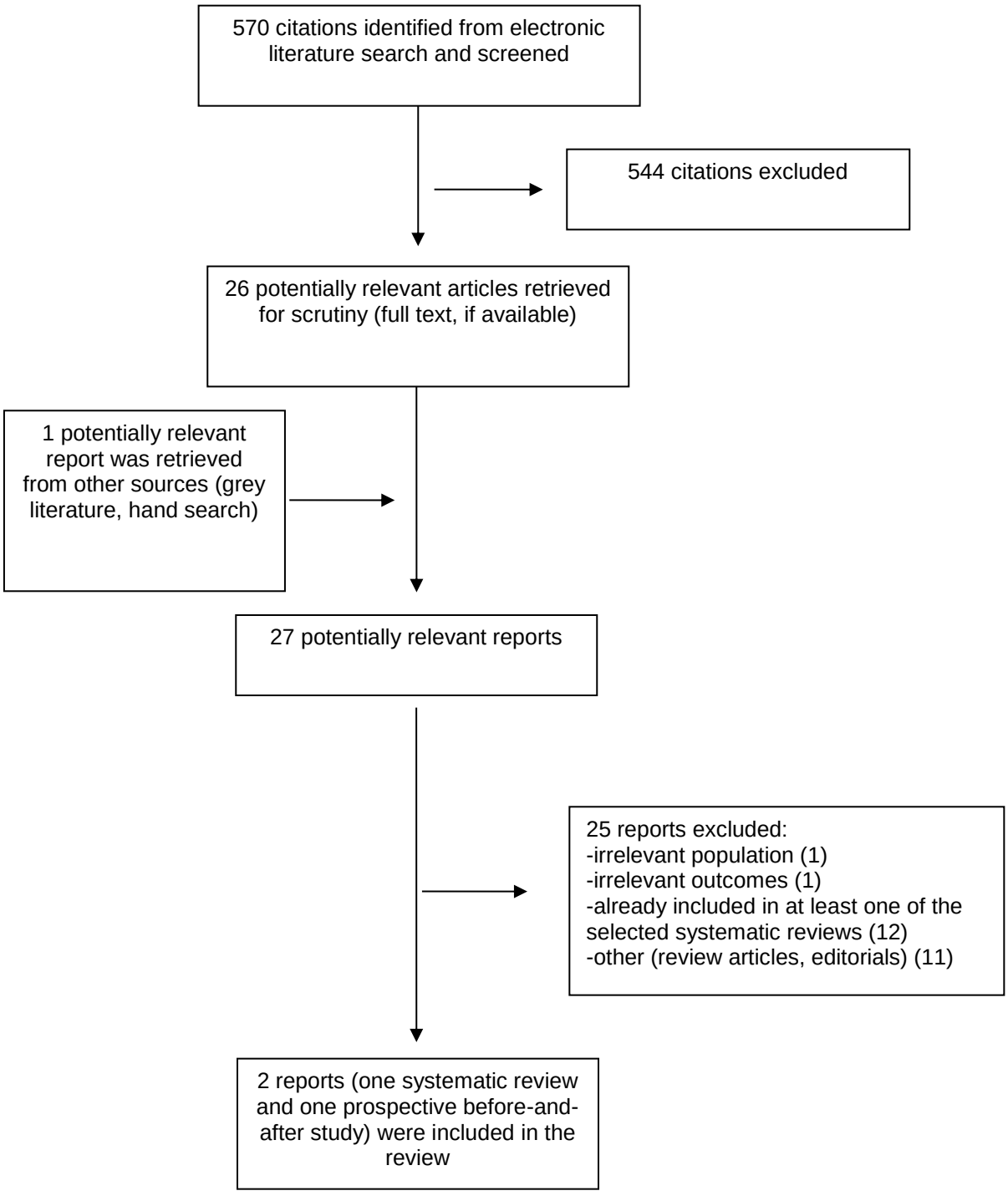
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Hillen et al., 2019[3] Australia	A total of 12 studies published from 1997 to 2017. Six studies were RCTs, two were cohort studies (prospective cohort = 1, retrospective cohort = 1), and four were case series or case studies Original peer-reviewed studies assessing the safety and or effectiveness of any cannabinoid in treating NPS in dementia patients were included, regardless of publication date.	A total of 178 patients ⩾ 65 years with a diagnosis of dementia of all origins, exhibiting NPS. The mean age ranged from 72.7 to 81.5 years, with the proportion of males included ranging from 30 to 100%. The number of participants in the studies ranged from 2 to 50. In nine studies that reported baseline cognition as (assessed using the MMSE), scores ranged from 4 (severe cognitive impairment) to 22 (mild cognitive impairment). Four RCTs included patients with NPI score ⩾ 10.	Three different orally administered cannabinoids (dronabinol at doses ranging from 2.5 to 7.03 mg/day; THC at doses ranging from 1.5 to 15 mg/day; and nabilone at doses ranging from 0.5 to 2.0 mg/day). Overall, reporting of prior treatment for NPS was limited and varied across the included studies. Reported concomitant medications included antipsychotics, antidepressants, and neuromodulators; however, it was often unclear which medications were indicated for treating NPS of dementia.	Effectiveness of cannabinoid therapy for treating NPS of dementia as assessed by tools such as the NPI, CMAI, Pittsburg Agitation Scale, CGI, and negative affect score Safety as assessed by • Reporting AEs. Methods for ascertaining AEs included participant and caregiver reports, predetermined lists of AEs to aid in identification, medical notes or clinical observation or a combination of these; • Physical parameters related to safety such blood pressure, heart rate, electrocardiogram, and weight.

AEs = adverse drug events; CGI = Clinical Global Impression; CMAI = Cohen–Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory Index; NPS = neuropsychiatric symptoms; THC = delta-9 tetrahydrocannabinol.

Table 3: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Broers et al., 2019[10] Switzerland	Prospective before-and-after pilot study	Ten female patients with dementia from different origins with persisting severe behavior problems, notwithstanding optimal conventional treatment. The patients had average age of 79.5 years and	THC/CBD-based oral cannabis oil. The medication was given three times daily, with the average doses titrated upwards over the study period as follows:	NPI for severity of NPS CMAI for severity of agitation UPDRS (notably item 22) for degree of rigidity with passive movements Barthel index for daily activity

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		NPI score >10. No measures of variability (e.g., SD or SE) was reported.	• 7.6 mg THC/13.2 mg CBD daily after two weeks, • 8.8 mg THC/17.6 mg CBD after one month, and • 9.0 mg THC/18.0 mg CBD after two months. The medication was given with a small piece of chocolate cake to facilitate intake.	A 0 to 10 VAS for the most invalidating daily activity or disturbing behavior Descriptive results were reported after a follow-up period of two months

CBD = cannabidiol; CMAI = Cohen–Mansfield Agitation Inventory; NPI = Neuropsychiatric Inventory Index; NPS = neuropsychiatric symptoms; SD = standard deviation; SE = standard error; THC = delta-9 tetrahydrocannabinol; UPDRS = Unified Parkinson Disease Rating Scale; VAS = visual analog scale.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Review using AMSTAR[25]

Strengths	Limitations
Hillen et al., 2019[3]	
• This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with International Prospective Register of Systematic Reviews (PROSPERO). • The objectives of the systematic review were described clearly, and the research questions and inclusion criteria for the study were provided • A systematic search of 27 online sources, including healthcare databases and clinical trial databases, were searched from inception to January 01, 2018 for original peer-reviewed studies assessing the safety and or effectiveness of any cannabinoid in treating NPS in patients with a diagnosis of dementia of all origins • Two reviewers independently selected studies for inclusion and extracted the relevant information. Disagreements were resolved with a third reviewer • The characteristics of the included studies were described in adequate detail • Assessment of the quality of the individual included studies was undertaken independently by two reviewers using the Johanna Briggs Institute and the Cochrane Collaboration critical appraisal tools (i.e., for observational studies and RCTs, respectively). Disagreements were resolved with a third reviewer • The interpretation and discussions of the results appropriately considered the risk of bias in individual studies included in the review. • The authors declared that there was no conflict of interest	• Study selection was limited to studies in the older population (≥65 years old). Therefore, there is the likelihood of reduced generalizability to variants of dementia such as executive and frontal dementia, which are more common in younger population • The review authors did not explain their selection of the study designs for inclusion in the review. However, given the limited number of high-quality RCTs of the subject, it seems reasonable to include peer-reviewed studies regardless of the study design • A list of excluded studies was not provided, although the number of full-text articles excluded along with reasons for exclusion were reported in the PRISMA flow diagram of systematic search results and study selection • The study population included patients who were frail and had multiple comorbidities associated with multiple chronic medications making it challenging to delineate the precise effect of the intervention under review in the face of inadequately reported comorbidities and concomitant medication use • According to the authors, the quality of the studies identified for the systematic review was low, with eight out of the 12 studies (66.7%) assessed to have a high risk of bias. Sources of bias included incomplete reporting of study design, patient clinical characteristics, tools to measure change in NPS of dementia, and outcomes • Three orally administered isolated cannabinoids were investigated. No study examined botanical cannabis or its crude extract, and no other route of administration of cannabis was evaluated. Thus, it is unknown if the finding will be generalizable in patients who used different forms of medical cannabis • Given that cannabinoids at higher doses have been found to be effective in some conditions (e.g.,15 mg/m^2 oral dronabinol up to six times daily for nausea and vomiting, and 2 mg oral nabilone twice daily for chemotherapy-induced nausea and vomiting),[32] it is unknown if the doses of cannabinoids used in the studies of the systematic review may have been suboptimal. The dose ranges in the primary study of the systematic were 2.5 to 7.03 mg/day), 1.5 to 15 mg/day, and 0.5 to 2.0 mg/day for dronabinol, THC, and nabilone, respectively

Strengths	Limitations
	• Long-term effectiveness and safety were not established in the studies due to short exposure times • Due to the heterogeneity of identified studies, a meta-analysis was not undertaken, and overall, it was difficult to generalize about the safety and effectiveness of cannabinoids in treating NPS of dementia • The authors acknowledged funding support from a cannabis manufacturing firm. However, they stated that the firm and its employees were not involved in undertaking of the systematic review, nor the interpretation of the results.

NPS = neuropsychiatric symptoms; RCT = randomized controlled trial; THC = delta-9 tetrahydrocannabinol.

Table 5: Strengths and Limitations of Clinical Studies using ROBANS Tool[26]

Strengths	Limitations
Broers et al., 2019[10]	
• This before-and-after study collected data prospectively, thereby reducing risk of bias. • Outcomes were measured with validated scales and structured VAS. • The study population was the same both before and after the interventions. Therefore, selection bias due to inappropriate comparison target group was low. • All study participants had data for before-value and after-value; therefore, there was no risk of bias due to incomplete data outcome. • Although there was no reference to a pre-specified protocol for the study, most of the expected main outcomes were included; thus, reducing the risk of bias due to selective outcome reporting	• It was unknown if all eligible patients were consecutively enrolled or if the study participants were intentionally targeted. Therefore, the risk of bias due to inappropriate selection is unclear. • It was not reported if the cannabis oil was standardized or how the stated doses were measured. Thus, there was uncertainty about the level of risk of performance bias. • It is unknown if the outcome assessors were blinded to the study hypothesis or exposure to the medication. Thus, the risk of confirmation bias due to inappropriate blinding of assessors was unclear. • Because the patients had severe dementia, they could not personally give feedback, and confounding factors that could affect their behavior and symptoms beyond the cannabinoid medications were not identified or analyzed.

VAS = visual analog scale.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Review

Main Study Findings	Authors' Conclusion
Hillen et al., 2019[3]	
Four of the 12 primary studies in the SR found that treatment of dementia patients with medical cannabis resulted in significant improvements in a range of neuropsychiatric symptoms associated with dementia. The remaining eight primary studies did not find evidence to support the efficacy of cannabinoids in the treatment of dementia. They comprised five placebo-controlled RCTs, and one case series and two case studies without controls. Three of the RCTs evaluated THC (two studies) or dronabinol (one study) for agitation and behavior changes. Another RCT evaluated THC for static and dynamic balance as well as gait, and one RCT assessed safety. Doses of THC used varied between 0.75 mg twice daily to 1.5 mg three times daily, with follow-up varying from 14 to 84 days across the studies. Dronabinol was dosed at 2.5 mg twice daily for 84 days. The case series evaluated nabilone for NPS titrating doses from 0.5 mg twice to thrice daily for 78 days. The period of dose titration was not mentioned. The two case studies also assessed nabilone; with change in behaviours as outcome for one and observed response to nabilone outcome for the other. None of these two case studies provided quantifiable results, and it was not possible to determine significant effect. The following are the findings from the four primary studies of the included systematic review[3] and the uncontrolled before-and-after study.[10] *Overall symptoms score* • In one RCT with crossover design included in the SR, the overall NPI score of two patients treated with dronabinol 2.5 mg at night for 28 days improved from 18 and 44 at baseline to 8 and 33, respectively. One case series included in the SR, found significantly lower total NPI score and sub-scores of aberrant motor behavior, agitation and night-time behaviors in six patients with Alzheimer's disease and vascular dementia, after 14 days of treatment with 2.5 mg oral dronabinol at night (no values given, $P < 0.05$). • One open-label prospective cohort study included in the SR found that among 11 patients with Alzheimer's disease, there was a statistically significant improvement in the overall NPI score from baseline following 28 days treatment with medical cannabis oil containing THC given orally at an initial dose of 2.5 mg twice daily and titrated up to 7.5 mg twice daily (44.4 versus 12.8, $P < 0.01$).	"While the efficacy of cannabinoids was not proven in a robust RCT, observational studies showed promising responses, especially for refractory patients. Also, 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."[3] P. 21

Main Study Findings	Authors' Conclusion
• One cohort study included in the systematic review, which assessed patient outcomes using the PAS found significant improvements in overall mean (SD) among 40 patients after treatment with dronabinol at a mean dose of 7.3 mg/day for a mean duration of use of 16.88 days (9.68 [3.91] versus 5.25 [4.17], *P* < 0.05) *Changes in specific symptom scores* • One open-label prospective cohort study included in the SR found that among 11 patients with Alzheimer's disease, there were statistically significant improvements in the NPI subscales assessed from baseline following 28 days treatment with medical cannabis oil containing THC given orally at an initial dose of 2.5 mg twice daily and titrated up to 7.5 mg twice daily as follows: - 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) • One cohort study included in the SR, assessment with the PAS found significant improvements in the mean (SD) of each PAS domain from baseline as follows: - Aberrant vocalization (2.50 [1.06] versus 1.15 [1.09], *P* < 0.05); - Motor agitation (2.02 [1.0] versus 1.18 [0.98], *P* < 0.05); - Aggressiveness (2.25 [1.71] versus 1.08 [1.49], *P* < 0.05); and - Resting care (2.80 [1.86] versus 1.80 [1.62), *P* < 0.05). *Nocturnal activity disorder* • In one RCT with a crossover design involving two patients treated with dronabinol, decreased nocturnal activity (67% reduction in movement counts) was observed by the third week. It was unclear whether this symptom referred to nocturnal behavior disorders or some other measure. However, in the fourth week, nocturnal activity returned to baseline in one patient and increased in the other patient. • One case series included in the SR, involving six patients with Alzheimer's disease and vascular	

Main Study Findings	Authors' Conclusion
dementia, found that nocturnal activity, as assessed by the by actigraphy, significantly decreased after 14 days of treatment with 2.5 mg oral dronabinol at night (median activity counts 34.26 at baseline versus 10.79 after 14 days, $P < 0.05$). It was unclear whether this symptom referred to nocturnal behavior disorders or aberrant motor behavior. *Mini-Mental State Exam* • One open-label prospective cohort study included in the SR found that among 11 patients with Alzheimer's disease, there were statistically significant improvements in MMSE from baseline following 28 days treatment with medical cannabis oil containing THC given orally at an initial dose of 2.5 mg twice daily and titrated up to 7.5 mg twice daily (10.0 versus 11.0, $P < 0.05$) *Safety* • Adverse events were reported in 10 included studies of the SR, whereas one case series and one case study did not report AEs. Studies reported mostly mild adverse effects such as sedation, somnolence, and fatigue. The exact number of patients involved was not clear. • Overall, the most common AE reported was sedation, reported in 10 (24.4%) out of a total of 41 patients from two studies. • Serious AEs were reported in three trials. One RCT reported one seizure (7%) and two serious infections (13.4%). Serious AEs in the form of gastroenteritis, worsening of NPS, exacerbation of vestibular disorder and malignancy were reported by another RCT, whereas one cohort reported three serious AEs (dysphagia, fall, and confusion). No values were specified in either study.	

AEs = adverse drug events; CMAI = Cohen–Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory Index; NPS = neuropsychiatric symptoms; PAS = Pittsburg Agitation Scale; RCT = randomized controlled trial; SR = systematic review; THC = delta-9 tetrahydrocannabinol.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Broers et al., 2019[10]	
• The average NPI, CMAI, and UPDRS (rigidity) scores decreased from 71.1 to 38.3, 74.5 to 47.5, and 3.4 to 1.7, respectively, after two months follow-up. • The VAS score for the most invalidating behavior problem (screaming, aggressive behavior, tearing clothes) decreased from 9 to 5, after two months follow-up. - Persistent screaming in two women (20%) stopped almost entirely - Frequent vomiting stopped in one patient (10%) - Two patients (20%) stopped all morphine within three months, and one patient (10%) decreased by two-thirds in two months. Constipation also stopped in these three patients (30%). - One patient (10%) decreased benzodiazepine use by three-fourths after months, and - One patient (10%) stopped two antipsychotic medications after one month. • Systolic blood pressure decreased from an average of 135.4 to 120 mm Hg across patients, after two months follow-up, although other vital parameters (diastolic blood pressure, heart rate, weight) remained stable over time. Adverse events • One patient died after one month for reasons unrelated to the cannabinoid medication. • No patient stopped the cannabinoids for reasons of side effects.	"Our study suggests that a THC/CBD oral medication in severely demented patients with behavior problems is acceptable, well tolerated, and improves rigidity and behavior overall. It allowed the decrease or stop of other psychotropic medications in half of the patients."[10] P. 3

CMAI = Cohen–Mansfield Agitation Inventory; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory Index; THC/CBD = delta-9 tetrahydrocannabinol/cannabidiol; UPDRS =Unified Parkinson Disease Rating Scale; VAS = visual analog scale.

Appendix 5: Additional References of Potential Interest

Systematic reviews with relevant primary studies fully captured in the included systematic review

Hoch E, Niemann D, von Keller R, et al. How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. Eur Arch Psychiatry Clin Neurosci. 2019;269(1):87-105

Lim K, See YM, Lee J. A Systematic Review of the Effectiveness of Medical Cannabis for Psychiatric, Movement and Neurodegenerative Disorders. Clinical psychopharmacology and neuroscience: the official scientific journal of the Korean College of Neuropsychopharmacology. 2017;15(4):301-312

Noel C. Evidence for the use of "medical marijuana" in psychiatric and neurologic disorders. The mental health clinician. 2017;7(1):29-38.

Wilkinson ST, Radhakrishnan R, D'Souza DC. A Systematic Review of the Evidence for Medical Marijuana in Psychiatric Indications. J Clin Psychiatry. 2016;77(8):1050-1064.

Liu CS, Chau SA, Ruthirakuhan M, Lanctot KL, Herrmann N. Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease. CNS drugs. 2015;29(8):615-623

Van den Elsen GA, Ahmed AI, Lammers M, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing research reviews. 2014;14:56-64.