Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
eAppendix. Supplementary Methods

This report is part of a larger systematic review project (also see Velayudhan et al 2020),1 the protocol for which was pre-registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019148869). The review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Figure 1) reporting guidelines.2 Studies were independently assessed by 2 researchers and disagreements resolved through consensus or discussions with a third researcher.

Search strategy

Two categories of search terms were used. For subject groups we used: ‘Aged’ OR ‘frail’ OR ‘elderly’ OR ‘older’ OR ‘aging’ OR ‘ageing’ OR ‘geriatric’ OR ‘dementia’ OR ‘Parkinson’s’ OR ‘Alzheimer’s’ OR ‘Huntington’s’ OR ‘demented’. For the intervention, we used: ‘Cannabinoids’ OR ‘cannabinoids’ OR ‘cannabinol’ OR ‘cannabidiol’ OR ‘tetrahydrocannabinol’ OR ‘THC’ OR ‘CBD’ OR ‘Sativex’ OR ‘nabilone’ OR ‘dronabinol’ OR ‘delta-9-tetrahydrocannabinol’ OR ‘delta-THC’ OR ‘medical cannabis’ OR ‘epidiolex’. The existing clinical query ‘Therapy/Broad’ was used in PubMed to select therapeutic studies. We identified additional studies from the reference lists of included studies and review articles. The search was complemented with information from ClinicalTrials.gov. We also contacted authors of the identified studies to clarify further appropriateness of inclusion if needed.

Study selection

Studies were included if (1) published from 1990 onwards; (2) included older adults (defined as mean age ≥50 years) or reported a distinct subgroup of older adults and provided separate results for this subgroup; and (3) provided data on the safety and tolerability of medical cannabinoids administered by any route, at any dose, for any duration and for any indication. Studies were excluded if they (1) included exclusively younger subjects (mean age <50 years); (2) studied effects of cannabinoids for recreational purposes or failed to provide the dosage of cannabinoids; and (3) were not reported in English language. Here we focus on results from randomised controlled trials (RCTs).

The search strategy identified 4132 citations (PubMed n = 1305; OVID (Medline, EMBASE and Psychinfo) n = 2041; CINAHL n =786). Adjustment for duplicates left 3688 citations. Of these, 3427 were excluded based on screening of title and abstract. 261 full text articles were retrieved and assessed based on the eligibility criteria. We therefore identified a total of 74 articles regarding safety issues of cannabinoid medications between January 1990 to 31st Oct 2020. Not all published cannabinoid trials provided safety information; we excluded randomized controlled trials3, because they did not report or quantify adverse events, and one study that used THCV.4 Limiting our focus to the analysis of randomised trials only left 44 articles to be included in our analysis(Supplement eTable 1a-b). Of these, four studies recruited participants over age ≥ 65 years (n=34; mean age, 72.4 (SD± 4.5)).5-8 Five articles studied both THC alone and THC:CBD combinations to compare with placebo.4,9-12 There was one article that had 2 phases, crossover challenge phase and RCT for same indication.13 Another article studied the same intervention for two treatment groups compared with separate placebo groups.7 Two articles used different doses of the same intervention compared with placebo group for each dose.14,15 This resulted in a final set of 30 RCTs investigating THC (reported as 15 crossover and 15 parallel-arm comparisons)5,6,8,10,12,13,15-34 and 24 studies investigating CBD:THC as treatment (reported as 5 crossover and 19 parallel-arm comparisons)7,9,12,14,35-48.

Rationale for age cut-off:

For this meta-regression analysis, we chose mean age ≥ 50 years as the cut-off as the clinical conditions (diabetes, cancer, neurodegenerative disorders, cancer etc) for which CBMs are often considered afflict people more commonly from around this age. This period of life onwards is also characterised by multi-morbidities, polypharmacy and age-related bodily changes that may affect pharmacokinetics and tolerability of medications. In addition, the age range as well as median and interquartile range of the mean ages of study participants included in the studies that constitute our meta-analysis clearly indicate that people over 65 and 75 years are currently being recruited into studies of CBMs for various indications. However, while there is a larger evidence base of studies with mean age of participants ≥ 50 years this is very modest for studies where all participants are ≥ 65 years (n=3 studies for THC studies and n=1 for THC:CBD study), the typical cut-off age for defining ‘elderly’. In light limited power of individual RCTs to unravel patterns of side-effects, the growing use of CBMs in the elderly and the general perception that they are safe to use, it may be particularly important to examine this by synthesizing currently available evidence to help inform about the safety and tolerability profile of CBMs in those aged 50 years and over rather than wait for the evidence base to mature. Therefore, we
have taken the approach to focus on studies with a mean participant age $\geq 50$ years which also capture a substantial number of people who are $\geq 65$ years. Future attempts at evidence synthesis may be able to focus only on studies of people $\geq 65$ years when a sufficient number of studies have accumulated.

**Data extraction**

All relevant available data for examination of the safety and tolerability of different CBMs (THC:CBD combination or THC or CBD alone) was collected from eligible studies. This was complemented with information from ClinicalTrials.gov and author responses. Data was extracted for study design, participant characteristics, indication, dosage and duration of intervention, all cause and treatment-related AEs and SAEs, AE-related withdrawals and deaths. AEs and SAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) ‘system organ classes’ (SOC). Data was also extracted for the top 5 (as reported by each study) AEs for each SOC, where available. Data extraction and coding was verified by a medically qualified researcher and discrepancies resolved following discussions with senior researcher. In the present report, we focus on the AEs categorized under the nervous system or psychiatric disorder of MedDRA SOC to investigate their association with dose/s of CBM/s used.

**Quality assessment**

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria to assess the overall quality of evidence and rate risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect. We have summarised the GRADE ratings of very low-, low-, moderate-, or high-quality evidence to reflect the extent to which we have confidence in the effect estimates are correct. This was done by one reviewer (KM) and checked by a second reviewer (LV), and disagreements were resolved via discussion with a third reviewer (SB).

Out of all the RCTs included, we judged 30 (56%) trials (THC studies = 21; CBD:THC studies = 9) to be at low risk of bias, 20 (37%) trials (THC studies = 6; CBD:THC studies =14) at unclear risk of bias and four (7%) trials (THC studies =3; CBD:THC studies =1) to have high risk of bias for safety outcome reporting. Overall, 35 trials were judged to be of moderate to high quality (THC studies = 18; CBD:THC studies =17), of which 15 (43%) trials (THC studies = 10; CBD:THC studies =5) reported all AEs.

The formulations used in THC studies were nabilone (6), dronabinol (marinol) (14), THC (3), THC extract spray (2) and Namisol (5). The combination THC-CBD trials used THC:CBD spray (18), and cannabis extract (6).

A broad range of disease conditions/clinical indications were investigated in these RCTs and included: Alzheimer’s disease, Parkinson’s disease, Huntington’s disease. Amyotrophic lateral sclerosis, Multiple sclerosis, motor neuron disease, neuropathic pain, cancer (cancer or chemotherapy related anorexia, pain or nausea/vomiting), type 2 diabetes mellitus, chronic obstructive pulmonary disease, fibromyalgia, raised intraocular pressure, cervical dystonia, healthy, pancreatitis, obstructive sleep apnoea and Levodopa induced dyskinesia in Parkinson’s disease.

**Data synthesis and analysis:**

We estimated total exposure to active intervention in person-years by first calculating this for each individual study by multiplying the number of subjects in the active intervention arm with the duration of treatment for that arm for each study and then adding up these study-specific values for all studies under each broad category (THC, THC:CBD) of intervention investigated here.

We estimated pooled effect-sizes if there were 2 or more RCTs for each individual neuropsychiatric AE within each broad category of intervention (THC, THC:CBD) under the random-effects model using the restricted maximum-likelihood estimator because of anticipated heterogeneity. For each broad category of intervention, analyses combined both parallel-arm and crossover RCTs, with the latter treated as parallel-arm design for pooled analyses. We estimated incident rate ratio (IRR) for individual AEs. Studies with more than one active treatment arm were treated as independent studies. We combined the data for all conditions for the analysis of AEs.

To test our primary hypothesis, we carried out meta-regression analyses under the random-effects model using the restricted maximum-likelihood estimator to examine the association of individual neuropsychiatric AEs with the dose of THC used in THC studies and separately with the dose of THC and CBD used in THC:CBD studies.
For our primary analysis we focused on all studies with available data where the mean age of study participants was ≥50 years. We also explored the possibility to carry out sensitivity analysis by restricting the analyses to studies where all participants were ≥ 65 years of age. Sensitivity analyses at a different age cut-off of ≥ 65 years was not possible as there was data from fewer studies (3 THC studies and 1 THC:CBD study) than recommended for meta-regression analyses. We investigated heterogeneity using forest plots and the $I^2$ statistic and report these in Table 1 and forest-plots. We also carried out formal outlier and influence detection diagnostics for the AE of self-reported ‘thinking/ perception disorder’, which identified two studies as being influential. The association between THC dose and ‘thinking/ perception disorder’ no longer remained significant, though the direction of effect did not change. While outlier/ influence diagnostics are popular in meta-analysis, others have also recommended against their routine use, particularly because of challenges in distinguishing true outliers (where the data is erroneous) from large errors in sampling. Instead, they may be seen as a method of sensitivity analysis and inform confidence in findings. In the present case, this is especially important because one of the influential studies had the largest sample size (329 participants in the active intervention arm and 164 in the control intervention arm) as well as the longest duration of treatment (~3 years; with only one other study involving 1 year of treatment) in the meta-analytic dataset. Further, we observed that heterogeneity (as indexed by the $I^2$ statistic) decreased from $I^2=35.73\%$ when the analysis was conducted without THC dose as a moderator (i.e. simple meta-analysis investigating the pooled effect of THC treatment compared to control treatment in the RCTs included on the AE of self-reported ‘thinking/ perception disorder’) to $I^2=1.46\%$ when THC dose was included as a moderator, pointing towards the appropriateness of the meta-regression results presented herein. Therefore, these studies have not been excluded but the results presented and discussed with a caveat.

Statistical analyses were performed using the metafor package in R (version 3.6.3).
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eTable. Characteristics of Included Randomized Clinical Trials

Table 1a. Characteristics of included randomised controlled trials of THC in older adults (N=30)

| Study ID (country) | Study Design (RCT) | THC: Sample included/analysed N | Mean age (SD), Male % | Comparator: Sample included/analysed N | Mean age (SD), Male % | Indication | THC classification | Comparator THC treatment duration, weeks | Calculated daily average THC dose | Overall GRADE rating for study |
|-------------------|-------------------|---------------------------------|----------------------|----------------------------------------|----------------------|------------|-------------------|--------------------------------------------|---------------------------------|-----------------------------|
| Ahmed et al. 2014, (Netherlands) | Crossover          | 12/11 72.00 (5), 50         | 12/11 72.00 (5), 50 | Healthy older subjects                      | Namisol            | Placebo   | .4                      | 6.5 mg                            | Moderate                      |
| Ahmed et al. 2015 (Netherlands) | Crossover          | 10/10 77.30 (5.6), 70        | 10/10 77.30 (5.6), 70 | Dementia                                | Namisol            | Placebo   | 2.6                     | 3 mg                             | Moderate                      |
| Brisbois et al. 2011 (Canada) | Parallel-arm       | 24/11 67.00 (10.9), 64      | 22/10 65.50 (8), 50 | Cancer patients with chemosensory alterations | Dronabinol        | Placebo   | 2.6                     | 7.5 mg                            | Low                           |
| Carley et al. 2018 (USA) †       | Parallel-arm       | 21/21 52.70 (7.7), 76       | 25/25 58.80 (6.1), 72 | Obstructive Sleep Apnoea                | Dronabinol        | Placebo   | 6.0                     | 2.5 mg                            | Low                           |
| Carley et al. 2018 (USA) †       | Parallel-arm       | 27/27 54.70 (7), 67         | 25/25 58.80 (6.1), 72 | Obstructive Sleep Apnoea                | Dronabinol        | Placebo   | 6.0                     | 10 mg                            | Low                           |
| Curtis et al. 2009 (UK)          | Crossover          | 44/37 52.00 (9.5), 50       | 44/37 52.00 (9.5), 50 | Huntington’s disease                   | Nabilone           | Placebo   | 5.0                     | 2 mg                             | Low                           |
| De Vries et al. 2016 (Netherlands) | Crossover          | 25/24 52.00 (NR), 62        | 25/24 52.00 (NR), 62 | Chronic pancreatitis                  | Nabilone           | Diazepam  | .1                      | 8 mg                             | Moderate                      |
| Herrmann et al. 2019, (Canada)   | Crossover          | 39/38 87.00 (10), 77        | 39/38 87.00 (10), 77 | Alzheimer’s disease                    | Nabilone           | Placebo   | 6.0                     | 1.6 mg                            | Moderate                      |
| Jatoi et al. 2002 (USA)          | Parallel-arm       | 152/152 67.00 (10), 66      | 159/159 65.00 (11), 65 | Cancer-related anorexia                | Dronabinol        | Megestrol acetate | 8.1 | 5 mg | Low |

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| Study                        | Design          | n/Treatment         | Mean Age (Range) | Condition                              | Treatment 1         | Treatment 2         | Dose | Strength |
|-----------------------------|-----------------|---------------------|------------------|----------------------------------------|---------------------|---------------------|------|----------|
| Johnson et al. 2010 (UK)    | Parallel-arm    | 58/58               | 61.30 (12.5), 52 | Patients with cancer-related pain      | THC extract spray   | Placebo             | 2.0  | Moderate |
| Lane et al. 1991 (USA)      | Parallel-arm    | 21/21               | 47.0 (20-68), 48 | Chemotherapy-induced nausea and vomiting | Dronabinol          | Prochlorperazine    | .9   | Low      |
| Meiri et al. 2007 (USA)     | Parallel-arm    | 17/17               | 61.60 (14.2), 53 | Chemotherapy-induced nausea and vomiting | Dronabinol          | Placebo             | .7   | Low      |
| Peball et al. 2020 (Austria)| Parallel-arm    | 19/19               | 65.4 (7.94), 53  | Parkinson’s disease                     | Nabilone            | Placebo             | 4.0  | Moderate |
| Sieradzan et al. 2001 (UK)  | Crossover       | 9/9                 | 59.00 (NR), 44   | Parkinson’s disease                     | Nabilone            | Placebo             | .1   | Very low |
| Strasser et al. 2006 (Germany) | Parallel-arm  | 100/100             | 60.00 (12), 54   | Cancer-related anorexia                 | THC                 | Placebo             | 6.0  | Low      |
| Svendsen et al. 2004 (Denmark) | Crossover   | 24/24               | 50.0 (NR), 42    | Multiple sclerosis                      | Dronabinol          | Placebo             | 3.0  | Moderate |
| Tomida et al. 2006 (UK)     | Crossover       | 6/6                 | 55.30 (5), 100   | Intraocular pressure                    | THC extract spray   | Placebo             | .1   | Low      |
| Toth et al. 2012 (Canada)   | Parallel-arm    | 13/13               | 60.80 (15.3), 38 | Diabetic peripheral neuropathic pain    | Nabilone            | Placebo             | 5.0  | Low      |
| Van Amerongen et al. 2017, 2 (Netherlands) | Crossover | 24/24               | 54.30 (8.9), 33  | Multiple sclerosis                      | THC                 | Placebo             | .1   | Moderate |
| Van Amerongen et al. 2017, 1 (Netherlands) | Parallel-arm | 12/12               | 57.30 (9), 33    | Multiple sclerosis                      | THC                 | Placebo             | 4.0  | Moderate |
| Van den Elsen et al. 2015, 1 (Netherlands) | Parallel-arm | 24/24               | 79.00 (8), 46    | Dementia                                | Namisol             | Placebo             | 3.0  | Moderate |
| Study                        | Design       | Participants | Age (Median ± Range) | Condition                  | Intervention 1 | Intervention 2 | Dose1 | Dose2 | Outcome |
|------------------------------|--------------|--------------|----------------------|----------------------------|----------------|----------------|-------|-------|---------|
| Van den Elsen et al. 2015   | Crossover    | 22/22        | 76.40 ± 5.3          | Dementia                   | Namisol        | Placebo        | 2.6   | 3 mg  | Moderate|
| (Netherlands)                |              | 22/22        | 76.40 ± 5.3          |                            |                |                |       |       |         |
| Volcier et al. 1997          | Crossover    | 15/12        | 72.70 ± 4.9          | Alzheimer's disease        | Dronabinol     | Placebo        | 6.0   | 5 mg  | Very low|
| (USA)                        |              | 15/12        | 72.70 ± 4.9          |                            |                |                |       |       |         |
| Walther et al. 2011          | Crossover    | 2/2          | 78.00 NR ± 4.9       | Alzheimer's disease        | Dronabinol     | Placebo        | 2.0   | 2.5 mg| Very low|
| (Switzerland)                |              | 2/2          | 78.00 NR ± 4.9       |                            |                |                |       |       |         |
| Ware et al. 2010             | Crossover    | 32/32        | 50.00 ± 11.2         | Fibromyalgia               | Nabilone       | Amitriptyline  | 2.0   | 1 mg  | Moderate|
| (Canada)                     |              |              | 50.00 ± 11.2         |                            |                |                |       |       |         |
| Weber et al. 2010            | Crossover    | 27/22        | 57.00 ± 12           | Amyotrophic lateral sclerosis | Dronabinol     | Placebo        | 2.0   | 10 mg | Moderate|
| (Switzerland)                |              | 27/22        | 57.00 ± 12           | patients with cramps       |                |                |       |       |         |
| Zadikoff et al. 2011         | Crossover    | 9/9          | 60.00 ± 7            | Cervical dystonia          | Dronabinol     | Placebo        | 3.0   | 15 mg | Low     |
| (Canada)                     |              |              | 60.00 ± 7            |                            |                |                |       |       |         |
| Zajicek et al. 2003          | Parallel-arm | 216/206      | 50.00 ± 8.2          | Multiple sclerosis         | Dronabinol     | Placebo        | 14.0  | 25mg  | Moderate|
| (UK)§                        |              |              | 50.00 ± 8.2          |                            |                |                |       |       |         |
| Zajicek et al. 2005          | Parallel-arm | 125/125      | 50.00 ± 8.2          | Multiple sclerosis         | Dronabinol     | Placebo        | 52.0  | 25 mg | Moderate|
| (UK)§                        |              |              | 50.00 ± 8.2          |                            |                |                |       |       |         |
| Zajicek et al. 2013          | Parallel-arm | 332/329      | 52.30 ± 7.6          | Multiple sclerosis         | Dronabinol     | Placebo        | 160.0 | 28 mg | Moderate|
| (UK)                         |              |              | 52.30 ± 7.6          |                            |                |                |       |       |         |

* Median age (range); † Included as median age for whole study population was ≥50; ‡ Article included more than one dose level; § Article included more than one cannabinoid intervention; ‖ Article included the results of multiple trials; ¶ Article included multiple study groups/indications; NR, Not recorded.
Table 1b: Characteristics of included randomised controlled trials of CBD:THC in older adults (N=24)

| Study ID (country) | Study Design | CBD/THC: Sample included/analysed N | Comparator: Sample included/analysed N | Indication | CBD/THC classification | Comparator | CBD/THC treatment duration, weeks | Calculated daily average CBD/THC dose | GRADE rating |
|-------------------|-------------|-----------------------------------|---------------------------------------|------------|------------------------|-----------|----------------------------------|----------------------------------------|------------|
| Blake et al. 2006 (UK) | Parallel-arm | 31/31 60.9 (10.6), 26 | 27/27 64.9 (8.5), 15 | Rheumatoid arthritis | THC:CBD spray | Placebo | 5.0 | 14.6mg THC: 13.5mg CBD | Low |
| Carroll et al. 2004 (UK) | Crossover | 19/17 67.0 (NR) 63 | 19/17 67.0 (NR) 63 | Levodopa induced dyskinesia in Parkinson’s disease | Cannabis extract | Placebo | 4.0 | 10.2mg THC: 5.1mg CBD | Moderate |
| Duran et al. 2010 (Spain) | Parallel-arm | 7/7 50 (41-70) * 0 | 9/9 50 (34-76) * 11 | Chemotherapy induced nausea and vomiting | THC:CBD spray | Placebo | .6 | 13mg THC: 12mg CBD | Moderate |
| Fallon et al. 2017, 1 (Multicentre) | Parallel-arm (withdrawal study) | 103/103 61.4 (10.9), 61 | 103103 61.6 (11.8), 53 | Advanced cancer patients with pain | THC:CBD spray | Placebo | 5.0 | 17.6mg THC: 16.3mg CBD | Moderate |
| Fallon et al. 2017, 2 (Multicentre) | Parallel-arm | 200/199 60.0 (11), 53 | 199/198 59.6 (11), 49 | Advanced cancer patients with pain | THC:CBD spray | Placebo | 5.0 | 17mg THC: 15.8mg CBD | Moderate |
| Johnson et al. 2010, (UK)§ | Parallel-arm | 60/60 59.4 (12.1), 55 | 59/59 60.1 (12.3), 54 | Patients with cancer-related pain | THC:CBD spray | Placebo | 2.0 | 25mg THC: 23mg CBD | Moderate |
| Litchman et al. 2018, | Parallel-arm | 199/199 59.2 (12), 56 | 198/198 60.7 (11.1), 52 | Advanced cancer patients with pain | THC:CBD spray | Placebo | 5.0 | 17.3mg THC: 16mg CBD | Moderate |

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| Study | Design | Patients | Intervention | Comparator | Dose | Effectiveness |
|-------|--------|----------|--------------|------------|------|---------------|
| Lynch et al. 2014 (USA) | Crossover | 18/16 | 56.0 (10.8), 17 | Chemotherapy-induced neuropathic pain | THC:CBD spray | Placebo 6.0 | 21.6mg THC:20mg CBD | Low |
| Markova et al. 2019, (Czech Republic) | Parallel-arm | 53/53 | 51.3 (10.2) 30 | Multiple sclerosis | THC:CBD spray | Placebo 12.0 | 19.7mg THC:18.3mg CBD | Low |
| Notcutt et al. 2012 (UK) | Parallel-arm (withdrawal study) | 18/18 | 59.7 (9) 50 | Multiple sclerosis | THC:CBD spray | Placebo 4.0 | 20.8mg THC:19.3mg CBD | Very low |
| Nurmikko et al. 2007, (UK) | Parallel-arm | 63/63 | 52.4 (15.8) 44 | Neuropathic pain | THC:CBD spray | Placebo 5.0 | THC 29.7mg: CBD 27.5mg | High |
| Pickerling et al. 2011, 1 (UK) ¶ | Crossover | 5/4 | 67.0 (NR) 50 | COPD | THC:CBD spray | Placebo .1 | 4.7mg THC: 4.4mg CBD | Low |
| Pickering et al. 2011, 2 (UK) ¶ | Crossover | 6/5 | 58.0 (NR) 80 | Healthy controls | THC:CBD spray | Placebo .1 | 10.3mg THC: 9.5mg CBD | Low |
| Portenoy et al. 2012, 1 (Multicentre) ‡ | Parallel-arm | 91/91 | 59.0 (12.3) 49 | Cancer patients with chronic pain | THC:CBD spray | Placebo 5.0 | 10.8mg THC: 10mg CBD | Moderate |
| Portenoy et al. 2012, 2 (Multicentre) ‡ | Parallel-arm | 88/87 | 59.0 (13.1) 56 | Cancer patients with chronic pain | THC:CBD spray | Placebo 5.0 | 27mg THC: 25mg CBD | Moderate |
| Authors               | Design          | Participants | THC:CBD spray | Placebo | THC dose | CBD dose | Pain type                        | Route | Efficacy |
|----------------------|-----------------|--------------|---------------|---------|----------|----------|----------------------------------|-------|----------|
| Portenoy et al. 2012 | Parallel-arm    | 90/90        | 58.0 (11.2)   | 91/91   | 56.0 (12.2) | Cancer patients with chronic pain | THC:CBD spray | Placebo | 5.0       | 43.2mg THC: 40mg CBD | Moderate |
| Riva et al. 2019     | Parallel-arm    | 30/29        | 58.4 (10.6)   | 30/30   | 57.2 (13.8) | Motor neuron disease              | THC:CBD spray | Placebo | 6.0       | 21.6mg THC: 20.0mg CBD | High |
| Serpell et al. 2014  | Parallel-arm    | 128/128      | 57.6 (14.4)   | 118/118 | 57.0 (14.1) | Neuropathic pain                  | THC:CBD spray | Placebo | 14.0      | 24mg THC: 22mg CBD    | Moderate |
| Strasser et al. 2016 | Parallel-arm    | 95/95        | 61.0 (12)     | 48/48   | 62.0 (10) | Cancer-related anorexia           | Cannabis extract | Placebo | 6.0       | 5mg THC: 2mg CBD      | Moderate |
| Vaney et al. 2004    | Crossover       | 57/50        | 55.0 (10)     | 57/50   | 55.0 (10) | Multiple sclerosis                | Cannabis extract | Placebo | 2.0       | 27.5mg THC: 9.9mg CBD | Low |
| Wade et al. 2004     | Parallel-arm    | 80/80        | 51.0 (9.4)    | 80/80   | 50.0 (9.3) | Multiple sclerosis                | THC:CBD spray | Placebo | 6.0       | 40.5mg THC: 37.5mg CBD | Moderate |
| Zajicek et al. 2003  | Parallel-arm    | 219/211      | 51.0 (7.6)    | 222/213 | 51.0 (7.6) | Multiple sclerosis                | Cannabis extract | Placebo | 14.0      | 25mg THC: 12.5mg CBD  | Moderate |
| Zajicek et al. 2005  | Parallel-arm    | 138/138      | 51.0 (7.6)    | 120/120 | 51.0 (7.6) | Multiple sclerosis                | Cannabis extract | Placebo | 52.0      | 25mg THC: 12.5mg CBD  | Moderate |
| Zajicek et al. 2012  | Parallel-arm    | 144/143      | 51.9 (7.7)    | 135/134 | 52.0 (7.9) | Multiple sclerosis                | Cannabis extract | Placebo | 12.0      | 25mg THC: 12.5mg CBD  | Moderate |

*, Median age (range); †, Included as median age for whole study population was ≥50; ‡, Article included more than one dose level; §, Article included more than one cannabinoid intervention; ‖, Article included the results of multiple trials; ¶, Article included multiple study groups/indications; NR, Not recorded.

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Records identified through database searching (n = 4132)

Additional records identified through other sources (n = 23)

Records after duplicates removed (n = 3688)

Records screened (n = 3688)

Records excluded (n = 3427) based on title/abstract

Full-text articles assessed for eligibility (n = 261)

Studies included (n = 44)

- Mean age of participants <50 years (n=58)
- Cannabinoid dosage not provided (n=19)
- Safety data not described (n=8)
- Reviews (n=61)
- Study older than 1990 (n=15)
- Re-analysis of previously reported study (n=7)
- Open label (n=22)
- Case report/series (n=9)
- Observational and chart review (n=12)
- Conference abstract, protocol or letter (n=4)
- Articles using THCV (n=1) and CBD alone (n=1)