

Cannabis-based medicinal products

[B] Evidence review for chronic pain

NICE guideline NG144

*Evidence review underpinning recommendations 1.2.1 to 1.2.3
in the NICE guideline*

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Final

*These evidence reviews were developed
by NICE Guideline Updates Team*

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Effectiveness of cannabis-based medicinal products for the treatment of chronic pain

Introduction

Chronic pain has recently been [defined by the ICD-11](#) as pain that persists or recurs for longer than 3 months. Chronic primary pain is defined as pain in one or more anatomical regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or functional disability. Chronic secondary pain syndromes are linked to other diseases as the underlying cause, where pain becomes a problem in its own right. In practice, the division between acute and chronic pain can be difficult to establish. This is particularly true in children and young people, and the committee felt that the looser (non-temporal) term 'persistent pain' is more commonly used in this group.

According to the British Medical Association briefing paper [chronic pain: supporting safer prescribing of analgesics](#), chronic pain affects about 13% of adults in the UK, and about 8% of children experience severe pain. NICE has published a [summary on the evidence base on medicines optimisation in chronic pain](#). A NICE guideline on [chronic pain: assessment and management](#) is in development. This guideline is intended to be used alongside existing NICE guidance for specific conditions that cause pain, including [headaches](#), [low back pain and sciatica](#), [rheumatoid arthritis](#), [osteoarthritis](#), [spondyloarthritis](#), [endometriosis](#) and [irritable bowel syndrome](#).

The aim of this review was to find out how effective cannabis-based medicinal products are in managing chronic pain, particularly when conventional treatment options have failed or not been tolerated. The review looked into the safety profile (including complications and contraindications) and examined what individual patient requirements, treatment durations, reviewing and stopping criteria need to be considered when prescribing cannabis-based medicinal products.

Review question

What is the clinical and cost effectiveness of cannabis-based medicinal products for people with chronic pain?

This review question also answered the following as part of the evidence review:

- What is the clinical and cost effectiveness of cannabis-based medicinal products for people with chronic pain?
- What are the adverse effects or complications of cannabis-based medicinal products for people with chronic pain?
- What are the contraindications, potential interactions and risks and cautions for use of cannabis-based medicinal products for people with chronic pain?
- What are the individual patient monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn or stopped, for use of cannabis-based medicinal products for people with chronic pain?

The review protocol for this review question is in [Appendix A](#). The PICO table below formed part of the search strategy to identify studies associated with chronic pain.

PICO table

Population	Adults, young people, children and babies with chronic pain. Specific considerations were given to: <ul style="list-style-type: none"> • Young people, children and babies • Pregnant women and women who are breastfeeding • People with existing substance abuse • People with hepatic and renal failure
Interventions	Cannabis-based medicinal product
Comparator	<ul style="list-style-type: none"> • Placebo
Outcomes	<ul style="list-style-type: none"> • Participant reported pain relief of 30% or greater • Participant reported pain relief of 50% or greater (to assist the economic analysis) • Reduction in analgesics required • Change in pain intensity using Numerical Rating Scale', or Visual Analogue Scale' • Functional impairment specific to the type of pain. For neuropathic pain: McGill Pain Questionnaire. For nociceptive pain: Brief Pain Inventory. • Participant/Patient/Subject Global Impression of Change (PGIC or SGIG) scale • Quality of life score using SF-36 or EQ-5D • Serious adverse events • Adverse events including but not limited to: sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Misuse/diversion • Hepatic and renal failure <p>Outcomes requiring a narrative synthesis:</p> <ul style="list-style-type: none"> • Contraindications as listed in exclusion criteria <p>Monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn stopped as discussed in the methods of individual RCTs</p>

Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual \(2018\)](#). Methods specific to this review question are described in the review protocol in Appendix B.

Declarations of interest were recorded according to [NICE's 2018 conflicts of interest policy](#).

A broad search strategy was used to identify all studies that examined the effectiveness of cannabis-based medicinal products in the treatment of intractable nausea and vomiting, chronic pain, spasticity and severe treatment-resistant epilepsy. The review protocol

highlighted in Table 1 and [Appendix A](#) was used to identify studies associated with chronic pain.

For the adult population, randomised controlled trials (RCTs) and systematic review of RCTs were considered. The review protocol also specified that in the event of fewer than 5 RCTs being identified, prospective cohort studies would also be considered for inclusion.

For children, RCTs and systematic review of RCTs were considered. The review protocol also specified that in the event of fewer than 5 RCTs being identified, prospective and retrospective cohort studies would also be considered for inclusion. This is because the committee highlighted that there may be fewer studies performed in children.

Additional information on safety concerns and contraindications were obtained from the Summary of Product Characteristics and other relevant sources, such as the U.S Food and Drugs Administration.

Studies were also excluded if they:

- Examined the use of synthetic cannabinoids in schedule 1 of the 2001 regulations,
- Examined the use of smoked cannabis-based products
- Did not clearly report the amount of cannabis-based constituents in the intervention

The review protocol specified that where possible for adults, data would be stratified according to the ICD-11 definition of pain as primary or secondary pain. For primary pain, data was analysed according to whether it was chronic widespread pain, complex regional pain syndrome, chronic primary visceral pain or chronic primary musculoskeletal pain.

For secondary pain, the data was analysed according to whether it is chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic secondary visceral pain and chronic secondary musculoskeletal pain.

The review protocol also specifies that where possible, subgroup analyses would be conducted to explore the effectiveness of cannabis-based medicinal products in young people, children and babies, pregnant women and women who are breastfeeding, people with existing substance abuse and people with hepatic and renal failure.

The committee agreed that the clinical outcome that matters most is mean change in pain intensity. This is widely used and easily understood. The next most important outcomes were the proportion of patients who experienced pain relief of 30% or 50% or more from baseline. These are also direct measurements of pain. However, the committee felt that they are less descriptive outcomes; information is lost when converting continuous data into dichotomous data.

The next most important outcome is functional impairment caused by pain. This is arguably a more useful measurement compared to pain intensity because it captures the effect that pain has on people's lives. However, functional impairment caused by pain is not measured often and when measured, it is usually measured in an inconsistent way across studies. Therefore, average pain intensity is more useful for meta-analysing outcomes across studies compared to functional impairment caused by pain.

After these direct measurements of pain, the committee were most interested in opioid sparing with a view to reducing adverse events caused by opioids.

The next most important clinical outcomes are those which are influenced by pain but are also influenced by other factors that may be unrelated to pain, such as mood. These outcomes include Patient Global Impression of Change and measurements of quality of life.

Clinical evidence

A total of 19,491 RCTs and systematic reviews were identified from the search. After removing duplicates, 9,341 references were screened on their titles and abstracts. 292 studies were obtained and reviewed against the inclusion criteria as described in the review protocol for chronic pain ([Appendix A](#)). Overall, 20 RCTs (14 parallel and 6 crossover) were included (see [Appendix E](#) for evidence tables). 272 references were excluded because they did not meet the eligibility criteria.

Because fewer than 5 RCTs were found for children, an additional search was conducted for observational studies. A total of 5,975 observational studies were identified from the search. After removing duplicates, 4,028 references were screened on their titles and abstracts. No studies were identified as being potentially relevant to chronic pain.

See [Appendix E](#) for evidence tables and [Appendix J](#) for excluded studies.

There were 20 RCTs, see table 2, summary of included studies.

No studies were identified which included the following subgroups:

- Pregnant women and women who are breastfeeding
People with hepatic or renal failure

Quality assessment of clinical studies included in the evidence review

In this review, parallel RCTs and crossover RCTs were identified. The quality of the evidence was initially graded as high.

With regard to crossover studies, the committee identified 1 week as an adequate washout period. It should be noted that this could lead to symptoms of THC withdrawal, including heightened anxiety, which might obscure any potential analgesic effect of the study product.

See [Appendix G](#) for full GRADE tables and [Appendix F](#) for forest plots in situations where data have been meta-analysed.

Interventions

Of the 20 studies included, 5 looked at treatment of cancer pain. The included studies looked at the following interventions:

- Oromucosal spray containing 2.7 mg THC and 2.5 mg CBD per 100 microlitre actuation. This is abbreviated in this document to THC:CBD spray.
- Oromucosal spray containing 2.7 mg THC only per 100 microlitre actuation

Of the 20 studies included, 7 looked at treatment of neuropathic pain (including multiple sclerosis, peripheral neuropathic pain and neuropathic pain characterised by allodynia). The included studies looked at the following interventions:

- Oromucosal spray containing THC:CBD
- Oral delta-9-THC (dronabinol)

Of the 20 studies included, 3 looked at treatment of musculoskeletal pain (including rheumatoid arthritis, cramps and spasticity). The included studies looked at the following interventions:

- Oromucosal spray containing THC:CBD
- Oral delta-9-THC (dronabinol)
- Oral nabilone

Of the 20 studies included, 3 looked at treatment of visceral pain (including abdominal pain and oesophageal functional chest pain). The included studies looked at the following intervention:

- Oral delta-9-THC (dronabinol)

Of the 20 studies included, 2 looked at treatment of widespread pain (fibromyalgia). The included studies looked at the following interventions:

- Oral nabilone
- Vaporised 22.4 mg THC and <1 mg CBD
- Vaporised 13.4 mg THC and 17.8 mg CBD
- Vaporised <1 mg THC and 18.4 mg CBD

Summary of clinical studies included in the evidence review

Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
Blake 2006 Parallel RCT	Secondary pain: musculoskeletal (rheumatoid arthritis) Mean age (SD) Intervention: 60.9 (10.6) Placebo: 64.9 (8.5)	Oromucosal spray THC:CBD spray (n=30) Titration period: 12 days Maintenance dose: up to 6 actuations Mean dose with variance: 5.4 actuations (SD 0.84) Follow-up: 3 weeks Placebo (n=27)	Mean average pain intensity Functional impairment caused by pain: McGill Pain Questionnaire - Short Form, total intensity of pain Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related Withdrawals due to adverse events, all- causality Withdrawals due to adverse events, treatment-related	No information on the blinding method Follow-up <6 months ¹
de Vries 2017 Parallel RCT	Secondary pain: visceral (abdominal pain) Mean age (SD) Intervention: 53 (9) Placebo: 53 (9)	Oral delta-9-THC (dronabinol) (n=21) Titration period: 6-10 days Maintenance dose: 8 mg, three times a day Mean dose with variance: 5/21 had 5 mg, three times a day Follow-up: 41 days Placebo (n=29)	Mean average pain intensity Withdrawals due to adverse events, all- causality	Incomplete reporting of outcomes Follow-up <6 months ¹
Fallon 2017 Parallel RCT	Secondary pain: cancer Mean age (SD) Intervention: 60.0 (11.0) Placebo: 59.6 (11.0)	Oromucosal spray THC:CBD spray (n=136) Titration period: 2 weeks Maintenance dose: Up to 10 actuations Mean dose with variance: 6.3 actuations variance not given Follow-up: 3 weeks	Mean average pain intensity Change in analgesics: daily change in total dose, morphine equivalents Change in analgesics: daily change in breakthrough dose, morphine equivalents Change in analgesics: daily change in maintenance dose, morphine equivalents	No details regarding how randomisation and blinding took place (and all outcomes have a subjective aspect) Follow-up <6 months ¹

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Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
		Placebo (n=158)	<p>Patient Global Impression of Change (continuous)</p> <p>Patients experiencing adverse events, all-causality</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Patients experiencing serious adverse events, treatment-related</p> <p>Withdrawals due to adverse events, all-causality</p>	
Johnson 2010 Parallel RCT	<p>Secondary pain: cancer</p> <p>Mean age (SD) THC + CBD: 59.4 (12.1) THC: 61.3 (12.5) Placebo: 60.1 (12.3)</p>	<p>Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=48)</p> <p>Titration period: 1 week</p> <p>Maintenance dose: Up to 48 actuations</p> <p>Mean dose with variance: 8.79 actuations (SD 5.14)</p> <p>Follow-up: 2 weeks</p> <p>Oromucosal spray 2.7 mg THC only per 100 microlitre actuation (n=45)</p> <p>Titration period: 1 week</p> <p>Maintenance dose: Up to 48 actuations</p> <p>Mean dose with variance: 8.34 actuations (SD 5.17)</p> <p>Follow-up: 2 weeks</p> <p>Placebo (n=51)</p>	<p>Proportion of patients who experienced pain relief of 30% or more from baseline</p> <p>Mean average pain intensity</p> <p>Functional impairment caused by pain: Brief Pain Inventory - Short Form</p> <p>Change in analgesics: daily change in breakthrough dose, morphine equivalents</p> <p>Change in analgesics: daily change in maintenance dose, morphine equivalents</p> <p>Quality of life: mean QLQ-C30 global health status</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Patients experiencing serious adverse events, treatment-related</p> <p>Withdrawals due to adverse events, all-causality</p>	<p>No information provided on randomisation nor blinding. The THC + CBD arm has a much lower baseline morphine dose</p> <p>Follow-up <6 months¹</p>
Langford 2013 Parallel RCT	<p>Secondary pain: neuropathic (Multiple sclerosis)</p>	<p>Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=141)</p>	<p>Proportion of patients who experienced pain relief of 30% or more from baseline</p>	<p>Follow-up <6 months¹</p>

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Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
	<p>Mean age (SD) THC + CBD: 48.42 (10.43) Placebo: 49.51 (10.50)</p>	<p>Titration period: 1 week Maintenance dose: Up to 12 actuations Mean dose with variance: 8.8 actuations (SD 3.87) Follow-up: 2 weeks Placebo (n=156)</p>	<p>Proportion of patients who experienced pain relief of 50% or more from baseline Mean average pain intensity Functional impairment caused by pain: Brief Pain Inventory - Short Form Change in analgesics: breakthrough daily change in paracetamol, units not provided Patient Global Impression of Change (dichotomous) Quality of life: EQ-5D index Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality Withdrawals due to adverse events, all-causality</p>	
<p>Lichtman 2018 Parallel RCT</p>	<p>Secondary pain: cancer Mean age (SD) Intervention: 59.2 (12.0) Placebo: 60.7 (11.1)</p>	<p>Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=141) Titration period: 2 weeks Maintenance dose: Up to 10 actuations Mean dose with variance: 6.4 actuations variance not given Follow-up: 3 weeks Placebo (n=150)</p>	<p>Mean average pain intensity Change in analgesics: daily change in total dose, morphine equivalents Change in analgesics: daily change in breakthrough dose, morphine equivalents Change in analgesics: daily change in maintenance dose, morphine equivalents Patient Global Impression of Change (continuous) Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality</p>	<p>No information on randomisation and blinding. High dropout rates: 30% in the THC + CBD arm and 20% in the placebo arm. Follow-up <6 months¹</p>

Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
			<p>Patients experiencing serious adverse events, treatment-related</p> <p>Withdrawals due to adverse events, all-causality</p> <p>Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness, all-causality</p>	
Malik 2017 Parallel RCT	<p>Secondary pain: visceral (Functional chest pain: oesophageal)</p> <p>Mean age (SD) Intervention: 46 Placebo: 35.5</p>	<p>Oral delta-9-THC (dronabinol) (n=7)</p> <p>Titration period: none</p> <p>Maintenance dose: 5 mg twice a day</p> <p>Mean dose with variance: Not given</p> <p>Follow-up: 4 weeks</p> <p>Placebo (n=6)</p>	Adverse events	Follow-up <6 months ¹
Nurnikko 2007 Parallel RCT	<p>Secondary pain: neuropathic (Neuropathic pain characterised by allodynia)</p> <p>Mean age (SD) Intervention: 52.4 (15.8) Placebo: 54.3 (15.2)</p>	<p>Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=50)</p> <p>Titration period: 7-10 days</p> <p>Maintenance dose: Up to 48 actuations</p> <p>Mean dose with variance: 10.9 actuations (SD 6.8)</p> <p>Follow-up: 5 weeks</p> <p>Placebo (n=55)</p>	<p>Mean average pain intensity</p> <p>Functional impairment caused by pain: Pain Disability Index</p> <p>Patients experiencing adverse events, all-causality</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Patients experiencing serious adverse events, treatment-related</p> <p>Withdrawals due to adverse events, all-causality</p> <p>Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness, all-causality</p>	Follow-up <6 months ¹

Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
Portenoy 2012 Parallel RCT	Secondary pain: cancer Mean age (SD) 1-4 sprays: 59 (12.3) 5-10 sprays: 59 (13.1) 11-16 sprays: 58 (11.2) Placebo: 56 (12.2)	Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=197) Titration period: 1 week Maintenance dose: Up to 16 actuations Mean dose with variance: ~1/3 had 1-5, ~1/3 had 6-10, ~1/3 had 11-16 Follow-up: 4 weeks Placebo (n=66)	Proportion of patients who experienced pain relief of 30% or more from baseline Mean average pain intensity Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related Withdrawals due to adverse events, all-causality	Follow-up <6 months ¹
Rog 2005 Parallel RCT	Secondary pain: neuropathic (Multiple sclerosis) Mean age (SD) Intervention: 50.3 (6.7) Placebo: 48.1 (9.7)	Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=32) Titration period: 4-5 days? Maintenance dose: Up to 48 actuations Mean dose with variance: 9.6 actuations (range 2 to 25) Follow-up: 5 weeks Placebo (n=32)	Mean average pain intensity Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality Withdrawals due to adverse events, all-causality Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness, all-causality	Follow-up <6 months ¹
Schimrigk 2017 Parallel RCT	Secondary pain: neuropathic (Multiple sclerosis) Mean age (SD) Intervention: 48.4 (9.6) Placebo: 47.0 (9.7)	Oral delta-9-THC (dronabinol) (n=105) Titration period: 4 weeks Maintenance dose: 7.5 to 15 mg per day Mean dose with variance: 12.7 mg ± 2.9 mg (range 0 to 15.9 mg) Follow-up: 12 weeks Placebo (n=104)	Mean average pain intensity Patients experiencing adverse events, all-causality Patients experiencing adverse events, treatment-related Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related	Follow-up <6 months ¹

Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
			Withdrawals due to adverse events, all-causality	
Serpell 2014 Parallel RCT	Secondary pain: neuropathic (Peripheral neuropathic pain) Mean age (SD) Intervention: 57.6 (14.4) Placebo: 57.0 (14.1)	Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=79) Titration period: 3-4 days? Maintenance dose: Up to 24 actuations Mean dose with variance: 8.9 actuations variance not given Follow-up: 15 weeks Placebo (n=94)	Proportion of patients who experienced pain relief of 30% or more from baseline Proportion of patients who experienced pain relief of 50% or more from baseline Mean average pain intensity Functional impairment caused by pain: Brief Pain Inventory - Short Form Change in analgesics: daily change in paracetamol, number of rescue (breakthrough) medication paracetamol tablets Patient Global Impression of Change (dichotomous) Quality of life: EQ-5D index Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related Withdrawals due to adverse events, all- causality	Cannabis arm dropout rate being 40%; staff were assigning patients to arms. Therefore, there was no allocation concealment. Sealed envelopes were used Follow-up <6 months ¹
Skrabek 2008 Parallel RCT	Primary pain: widespread (Fibromyalgia) Mean age (SD) Intervention: 47.5 (9.13) Placebo: 50.11 (5.96)	Oral nabilone (synthetic mimic of THC) (n=15) Titration period: 3 weeks Maintenance dose: 1 mg twice a day Mean dose with variance: All who completed had 1 mg twice a day Follow-up: 1 week Placebo (n=18)	Mean average pain intensity Functional impairment caused by pain: Fibromyalgia Impact Questionnaire Patients experiencing adverse events, all-causality Withdrawals due to adverse events, all- causality	Very little information on the randomisation method and blinding Follow-up <6 months ¹

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Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
Wade 2004 Parallel RCT	Secondary pain: neuropathic (Multiple sclerosis) Mean age (SD) THC/CBD: 51.0 (9.4) Placebo: 50.4 (9.3)	Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=77) Titration period: Not given Maintenance dose: Up to 48 actuations Mean dose with variance: Mean ~26 actuations (SE±2) Follow-up: 6 weeks Placebo (n=77)	Mean average pain intensity Withdrawals due to adverse events, all-causality	Allocation sequence was probably not concealed Follow-up <6 months ¹
de Vries 2015 Crossover RCT	Secondary pain: visceral (Abdominal pain) Mean age (SD) 51.8 (9.3)	Oral delta-9-THC (dronabinol) (n=12) Titration period: None Maintenance dose: 8 mg single dose Mean dose with variance: Not given Follow-up: None Placebo (n=10)	Mean average pain intensity Patients experiencing adverse events, all-causality Withdrawals due to adverse events, all-causality	Only a single dose was given. This is not a realistic way to assess chronic pain treatment.
Lynch 2014 Crossover RCT	Secondary pain: cancer Mean age (SD) Not provided	Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=18) Titration period: 6-12 days Maintenance dose: Up to 12 actuations Mean dose with variance: 8 actuations (range 3 to 12) Follow-up: 4 weeks Placebo (n=18)	Mean average pain intensity Quality of life: SF-36 physical Quality of life: SF-36 mental	Follow-up <6 months ¹
Svendsen 2004 Crossover RCT	Secondary pain: neuropathic (Multiple sclerosis) Mean age (SD) 50 (range 23-55)	Oral delta-9-THC (dronabinol) (n=12) Titration period: 6 days Maintenance dose: 5 mg twice a day Mean dose with variance: 3/12 had 7.5 mg 1/12 had 5 mg Follow-up: 18-21 days	Median average pain intensity Quality of life: SF-36 median average Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality	Follow-up <6 months ¹

Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
		Placebo (n=12)	Withdrawals due to adverse events, all-causality	
van de Donk 2019 Crossover RCT	Primary pain: widespread (Fibromyalgia) Mean age (SD) 39 ± 13 years	Vaporised 22.4 mg THC and <1 mg CBD (n=20) Titration period: None Maintenance dose: Single dose Mean dose with variance: All had 22.4mg THC and <1mg CBD Follow-up: 3 hours Vaporised 13.4 mg THC and 17.8 mg CBD (n=20) Titration period: None Maintenance dose: Single dose Mean dose with variance: All had 22.4mg THC and <1mg CBD Follow-up: 3 hours Vaporised <1 mg THC and 18.4 mg CBD (n=20) Titration period: None Maintenance dose: Single dose Mean dose with variance: All had 22.4mg THC and <1mg CBD Follow-up: 3 hours Placebo (n=20)	Mean average pain intensity Proportion of patients who experienced pain relief of 30% or more from baseline Proportion of patients who experienced pain relief of 50% or more from baseline	The incidence of patients experiencing adverse events was not reported. Data for the proportion of patients who experienced pain relief of 30% or 50% or more from baseline was not provided in an extractable format for 2 of the 3 interventions Only one dose given and outcomes were recorded 3 hours afterwards. This is not a realistic way of assessing chronic pain treatment.
Weber 2010 Crossover RCT	Secondary pain: musculoskeletal (Cramps) Mean age (SD)	Oral delta-9-THC (dronabinol) (n=11) Titration period: No dose titration. Maintenance dose: 5mg twice daily	Mean average pain intensity Patients experiencing adverse events, all-causality	Follow-up <6 months ¹

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Reference	Population	Intervention(s) and placebo	Outcomes	Limitations
	57 (12)	Mean dose with variance: 6 drops equivalent to 5 mg taken twice daily (10mg total). Follow-up: 2 weeks Placebo (n=11)		
Wissel 2006 Crossover RCT	Secondary pain: musculoskeletal (Spasticity) Mean age (SD) 44.8 (14.3)	Oral nabilone (synthetic mimic of THC) (n=13) Titration period: 1 week Maintenance dose: Up to 48 actuations Mean dose with variance: 8.34 actuations (SD 5.17) Follow-up: 2 weeks Placebo (n=13)	Median average pain intensity Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality Withdrawals due to adverse events, all-causality	No information provided on randomisation, blinding nor baseline characteristics Follow-up <6 months ¹
<p>1. The committee agreed that a follow-up period of 6 months is a realistic duration for assessing chronic pain treatments. This was agreed when making research recommendations after the evidence had been presented. Therefore, this did not influence our risk of bias assessments. Nevertheless, a follow-up period of <6 months is a study limitation.</p>				

See [Appendix E](#) for evidence tables and [Appendix H](#) for further information on adverse events.

As part of this evidence review, in addition to reviewing efficacy and safety data, studies were reviewed for information about patient monitoring and reviewing and stopping criteria when cannabis-based medicinal products were prescribed.

The interventions, doses, monitoring and stopping criteria are summarised in the table below:

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=5)	Cancer	Up to between 10 to 48 actuations For 2-4 weeks	Three studies did not describe patient monitoring. For one study, patients were contacted by phone for follow-up safety evaluations 2 weeks after the final dose. For another study there were “Study visits throughout the trial”.	No study had stopping criteria.
Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=5)	Neuropathic pain (including multiple sclerosis, peripheral neuropathic pain and neuropathic pain characterised by allodynia)	Up to between 12 to 48 actuations For 2-15 weeks	One study described a phone call, performed by nursing staff, 14 to 20 days after the 5-week follow-up trial was initiated. Another study explained that during the initial dose titration phase, patients recorded the time and number of actuations per day, in a dosing diary. Regular telephone contact was maintained according to individual patient requirements and a brief safety visit was conducted after two weeks. Another study described that periodic telephone monitoring was undertaken at pre-arranged times during home dosing to check the patient’s condition and to answer any queries.	No study had stopping criteria.
Oromucosal spray 2.7 mg THC with 2.5 mg CBD per 100 microlitre actuation (n=1)	Musculoskeletal pain (rheumatoid arthritis)	Up to 6 actuations For 3 weeks	Not described	None
Oral delta-9-THC (dronabinol) (n=2)	Neuropathic pain (multiple sclerosis)	Maximum doses were 15 mg per day and 5 mg twice a day	In one study, for safety analysis, vital signs, laboratory parameters, (serious) AEs (SAEs) including (serious) adverse reactions (SARs) were regularly assessed.	No study had stopping criteria.

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
		For 18 days to 12 weeks		
Oral delta-9-THC (dronabinol) (n=2)	Visceral pain (abdominal pain and oesophageal functional pain)	Maximum doses were 8 mg single dose, 5 mg twice a day, 8 mg three times a day For no duration (single dose) to 4 weeks	For the study that had a 4-week duration, efficacy and safety assessments were conducted preceding medication intake on day 1, after 15 treatment days, and 50–52 treatment days. Several phone calls were performed by the investigators during and after the treatment period (days 4–5, 9–10, 21–23, 28–30, 38–40, and 59–61) to evaluate the tolerability, safety, and compliance.	No study had stopping criteria.
Oral delta-9-THC (dronabinol) (n=1)	Musculoskeletal pain (cramps)	Maximum dose was 5 mg twice a day For 2 weeks	Not described	None
Oral nabilone (n=1)	Widespread pain (fibromyalgia)	Maximum dose was 1 mg twice a day For 1 week	Not described	None
Oral nabilone (n=1)	Musculoskeletal pain (spasticity)	Maximum dose was 1 mg once a day For 3 weeks	There were clinic visits where monitoring occurred. However, the timing of these is not provided.	None

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Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
Oromucosal spray 2.7 mg THC only per 100 microlitre actuation (n=1)	Cancer	Up to 48 actuations For 2 weeks	“Study visits throughout the trial”	None
Vaporised 22.4 mg THC and <1 mg CBD (n=1)	Widespread pain (fibromyalgia)	Complete content was inhaled by all Single dose	N/A (single dose)	N/A
Vaporised 13.4 mg THC and 17.8 mg CBD (n=1)	Widespread pain (fibromyalgia)	Complete content was inhaled by all Single dose	N/A	N/A
Vaporised <1 mg THC and 18.4 mg CBD (n=1)	Widespread pain (fibromyalgia)	Complete content was inhaled by all Single dose	N/A	N/A

Economic evidence

Included studies

No economic studies were included in this review.

Excluded studies

A global search conducted for this guideline returned 1,863 hits. 1 full paper was ordered for this review question and subsequently excluded. More detail is available in Appendix J.

Summary of studies included in the economic evidence review

No studies included.

Economic model

A *de novo* economic model was developed to address this review question. The model considered the CBMPs + the Standard of Care (SoC) versus the SoC alone. Subgroup analyses were conducted for specific treatments and for specific types of chronic pain where data were available to do so.

The economic model was comprised of five health states in each arm; on treatment response (OTR), on treatment no response (OTNR), discontinued with response (DR), discontinued with no response (DNR) and dead. In the SoC arm the “on treatment” states were nominal only, simply reflecting different levels of change from baseline observed in the underpinning trials. The model was run in monthly cycles over a lifetime time horizon and costs and QALYs were discounted at 3.5% per year.

Patients were categorised into one of the health states after one model cycle by combining the distribution of pain at baseline with the continuous outcomes from the clinical review for this question. Patients with a >30% response were assumed to remain as responders until they discontinued or died. The model calculated costs and QALYs from the distribution of pain scores within each health state, with lower pain scores having higher QoL and lower background management costs. Costs and QALYs associated with adverse events were also included, along with the costs of downstream radiofrequency denervation for the low back pain subgroup.

For all treatment and condition specific subgroups the model produced ICERs far in excess of the usually accepted £20,000-£30,000/QALY range. This was principally due to the modest treatment effects and the high and ongoing cost of treatment with CBMPs. The model had a number of limitations including the lack of long term data on almost all parameters but no plausible variations in any of the model’s input parameters produced ICERs close to £20,000-£30,000/QALY.

Details of the *de novo* economic model developed for this review question are available in [Appendix I](#).

Summary of evidence

The summary of evidence reflects the evidence on effectiveness of cannabis-based medicinal products. Evidence summaries are stratified by population and reflect evidence that was significant. Further information on adverse events is also provided. The format of the summary of evidence is explained in the methods in Appendix B. Further information on adverse events is provided in Appendix I.

THC:CBD spray vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Proportion of people who experienced pain relief of 30% or more from baseline for neuropathic and cancer pain (values greater than 1 favour THC + CBD)					
4 (Langford 2013, Serpell 2014, Johnson 2010, Portenoy 2012)	Parallel RCT	826	OR 1.49 (1.10, 2.01)	Low	Favours THC + CBD
Functional impairment caused by pain: Pain Disability Index for neuropathic pain (0 to 70). Dose: up to 48 actuations (values greater than 0 favour placebo)					
1 (Nurmikko 2007)	Parallel RCT	105	MD -5.85 (-9.61, -2.09)	High	Favours THC + CBD
Patient Global Impression of Change (dichotomous¹) for neuropathic pain (multiple sclerosis / peripheral neuropathic pain). Dose: up to 24 actuations (values greater than 1 favour THC + CBD)					
2 (Langford 2013, Serpell 2014)	Parallel RCT	470	OR 1.58 (1.16, 2.15)	Low	Favours THC + CBD
Patient Global Impression of Change (continuous) for cancer pain. Dose: up to 10 actuations (values greater than 0 favour placebo)					
2 (Fallon 2017, Lichtman 2018)	Parallel RCT	585	MD -0.26 (-0.43, -0.09)	Low	Favours THC + CBD
Quality of life: SF-36 physical for cancer pain. Dose: up to 12 actuations (values greater than 0 favour THC + CBD)					
1 (Lynch 2014)	Crossover RCT	16	MD -11.00 (-17.13, -4.87)	Moderate	Favours placebo

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Quality of life: SF-36 mental for cancer pain. Dose: up to 12 actuations (values greater than 0 favour THC + CBD)					
1 (Lynch 2014)	Crossover RCT	16	MD 10.95 (4.02, 17.88)	Moderate	Favours THC + CBD
People experiencing adverse events, all-causality for multiple sclerosis, neuropathic pain characterised by allodynia and cancer pain (values greater than 1 favour placebo)					
6 (Rog 2005, Langford 2013 Nurmikko 2007, Portenoy 2012, Lichtman 2018, Fallon 2017)	Parallel RCT	1,665	OR 1.5 (1.20, 1.87)	Moderate	Favours placebo
Withdrawals due to adverse events, all-causality for neuropathic, cancer and musculoskeletal pain (values greater than 1 favour placebo)					
10 (Wade 2004, Serpell 2014, Rog 2005, Nurmikko 2007, Langford 2013, Portenoy 2012, Lichtman 2018, Johnson 2010, Fallon 2017, Blake 2006)	Parallel RCT	2,267	OR 1.74 (1.18, 2.56)	Very low	Favours placebo
1. For the PGIC outcome, the two treatment groups were compared using ordinal logistic regression and the proportional odds model, incorporating centre group.					

Commonly reported adverse events for THC:CBD spray included: dizziness, somnolence, nausea, vertigo and fatigue.

Further details of the quality assessments can be found [here in the GRADE tables](#).

Subgroups were analysed and can be seen [here in the forest plots](#).

Oral delta-9-THC (dronabinol), 7.5 to 16 mg per 24 hours vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
People experiencing adverse events, treatment-related for neuropathic pain (multiple sclerosis) (values greater than 1 favour placebo)					

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No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
1 (Schimrigk 2017)	Parallel RCT	240	OR 2.87 (1.66, 4.94)	High	Favours placebo
People experiencing serious adverse events, all-causality for neuropathic pain (multiple sclerosis) (values greater than 1 favour placebo)					
Withdrawals due to adverse events, all-causality for neuropathic and visceral pain (values greater than 1 favour placebo)					
4 (Schimrigk 2017, Svendsen 2004, de Vries 2015, de Vries 2017)	Parallel RCTs and 1 crossover RCT	398	OR 6.08 (1.83, 20.23)	Low	Favours placebo

Commonly reported adverse events for oral delta-9-THC (dronabinol) included: dizziness, vertigo, fatigue, nausea and headache.

Further details of the quality assessments can be found [here in the GRADE tables](#).

Subgroups were analysed and can be seen [here in the forest plots](#).

Oral nabilone, 1 to 2 mg per 24 hours vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Functional impairment caused by pain: Fibromyalgia Impact Questionnaire for widespread pain (fibromyalgia) (0 to 100) (values greater than 0 favour placebo)					
1 (Skrabek 2008)	Parallel RCT	33	MD -10.76 (-18.45, -3.07)	Low	Favours nabilone
People experiencing adverse events, all-causality for musculoskeletal and widespread pain (values greater than 1 favour placebo)					
2 (Skrabek 2008, Wissel 2006)	Parallel RCT and crossover RCT	46	OR 1.60 (1.06, 2.42)	Low	Favours placebo

Commonly reported adverse events for oral nabilone included: drowsiness, dry mouth, ataxia, confusion and headache.

Further details of the quality assessments can be found [here in the GRADE tables](#).

Subgroups were analysed and can be seen [here in the forest plots](#).

Oromucosal spray 2.7 mg THC only per 100 microlitre actuation, maximum 48 actuations per 24 hours vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Functional impairment caused by pain: Brief Pain Inventory - Short Form (0 to 10) for cancer pain (values greater than 0 favour placebo)					
1 (Johnson 2010)	Parallel RCT	96	MD -4.07 (-8.05, -0.09)	Low	Favours placebo
Change in analgesics: daily total dose change, morphine equivalents for cancer pain (values greater than 0 favour placebo)					
1 (Johnson 2010)	Parallel RCT	96	MD 68.30 (3.74, 132.86)	Low	Favours placebo
People experiencing serious adverse events (all-causality) for cancer pain (values greater than 1 favour placebo)					
1 (Johnson 2010)	Parallel RCT	117	OR 3.34 (1.27, 8.78)	Low	Favours placebo

Commonly reported adverse events for THC spray included: somnolence, dizziness, nausea, vomiting and confusion.

Further details of the quality assessments can be found [here in the GRADE tables](#).

Vaporised 13.4 mg THC and 17.8 mg CBD vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Proportion of people who experienced pain relief of 30% or more from baseline (fibromyalgia) (values greater than 1 favour placebo)					
1 (van de Donk 2019)	Crossover RCT	20	OR 7.36 (1.35, 40.55)	Very low	Favours THC + CBD

Commonly reported adverse events for vaporised THC:CBD included: drug high, coughing, sore throat, bad taste and nausea.

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Further details of the quality assessments can be found [here in the GRADE tables](#).

See [Appendix K](#) for further information on the research questions' PICO's.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Outcomes were discussed *a priori*. After reviewing the evidence, the opinion of the committee did not change. Outcomes that matter most are discussed in the [Methods and process](#) section.

The quality of the evidence

There was limited evidence of high quality. The main reason for this is that the maintenance dose duration is relatively short in most studies. The committee agreed that a maintenance dose duration of up to 6 weeks is unrealistic for assessing chronic pain treatments. Additionally, many studies did not provide details of methods for randomisation or blinding.

The majority of the RCTs are for CBD in combination with THC. There was only one RCT for THC alone and two for nabilone. There was no evidence for CBD alone and the preparation that had CBD with a small amount of THC (<1 mg) was poor quality.

Benefits and harms

There is evidence to suggest that CBD reduces chronic pain: Nabilone reduced functional impairment caused by pain compared with placebo in a population of 33 participants who had fibromyalgia. THC reduced mean functional impairment caused by pain in a population of 96 participants who had cancer. However, where cannabis-based medicinal products reduced chronic pain, the benefit is small and economic analysis shows that this compares poorly with the high costs of the intervention (see below).

There was high quality evidence which could not differentiate reduction in pain intensity between dronabinol and placebo in a population of 389 participants who had multiple sclerosis, abdominal pain or cramps.

The data could not differentiate THC:CBD for functional pain, change in opioid dose or quality of life. However, the committee considered these are outcomes to be less important compared with mean pain intensity which could not be differentiated between THC:CBD and placebo.

With regard to research recommendation 1, people who have fibromyalgia or persistent treatment-resistant neuropathic pain are often prescribed high doses of analgesia over long periods of time. This can be associated with adverse events including nausea, drowsiness, mood disturbance and fatigue. It is hoped that CBD might have an opioid-sparing effect and therefore reduce the incidence of adverse events such as these. The committee noted that of this significant population with chronic pain, around 15% are referred for specialist pain management. They also noted that this population is usually on many medications, including opioids and treatments for neuropathic pain. In this population, it is unclear whether cannabis-based medicinal products could improve safety by reducing doses of other

medicines. Therefore, a research recommendation was made. The committee defined standard treatment as WHO pain ladder step 3: opioids plus adjuvants. RCTs should have at least 6 months follow-up to reflect the chronic nature of these conditions.

With regard to research recommendation 2, there is currently no evidence that explores whether the addition of cannabis-based medicinal products as an adjunct to standard care improves the pain experience in children with rare conditions experiencing persistent pain symptoms, for example children with intractable cancer-related pain or chronic pain associated with specific diseases such as epidermolysis bullosa. The reason for the lack of research so far is probably because there are relatively few children with these conditions. In addition, opioids may not control pain effectively in these conditions and may cause adverse effects. Therefore, a research recommendation was made. The committee defined 'intractable cancer-related pain' as cancer-related pain that does not respond to multiple interventions including non-pharmacological and drug therapies sufficiently to enable a reasonable quality of life. The committee defined standard care in this context as tertiary specialist pain/palliative care management. An additional benefit from such research could be a reduction in resource use.

The committee felt that CBD has the potential to be cost effective for all these research populations if they could be robustly demonstrated to improve quality of life and reduce resource use associated with complex conditions requiring standard tertiary specialist pain/palliative care management. For example, if children and young people with chronic pain achieved benefits sufficient for them to be able to receive their care in an outpatient rather than an inpatient setting.

See [Appendix K](#) for further information on the research questions' PICO's.

Cost effectiveness and resource use

No published health economic analyses met the inclusion criteria for this review, but this area was prioritised for de novo economic modelling because the potential eligible population, and therefore potential resource impact, were deemed to be large. The committee considered that outcomes measuring change in pain were the most important in the clinical review and thought it important that the economic model structure should be directly tied to these outcomes. The clinical review provided both continuous (11 studies) and dichotomous (4 studies) data. A continuous model structure was chosen because continuous outcome data were more plentiful, because the continuous data approximated the dichotomous data very well under the assumption that treatment response was normally distributed and because it allowed the model to tie pain to costs and quality of life in a more detailed way.

The intermediate results from the model showed that ~54% of people in the cannabis arm and ~46% of people in the placebo arm achieved a 30% reduction in pain from baseline, while ~31% and ~25% achieved a treatment response of 50% respectively, which was similar to data observed in the clinical trials. Following an initial period of some treatment discontinuation, mean pain scores across the cohorts in both model arms settled into a steady state somewhat lower than the baseline level. The committee noted that adverse events contributed relatively little in terms of costs or quality of life decrements and that there were some savings in pain management costs associated with the treatment effect. These savings were small in comparison to the costs of cannabis based medicinal products (CBMPs), however. Net avoidance of invasive long-term treatments in the cannabis arm also contributed a negligible amount to cost savings.

Using THC:CBD spray, which is the cheapest CBMP with a publicly available price, the model produced an incremental cost-effectiveness ratio (ICER) of over £150,000/QALY

gained over the standard of care, a value far higher than the commonly accepted decision threshold of £20,000-£30,000/QALY gained. The committee concluded that this finding was not surprising as CBMPs are not expected to extend life or be fundamentally disease modifying, treatment effects relating to symptom alleviation are modest (about a 0.4 improvement in pain on a 0 to 10 scale on average) and the cost of the treatments is high.

The committee noted the limitations of the model, including that only short term data were available from RCTs, that there were no robust estimates of resource use associated with different pain scores, that data on some parameters were extrapolated from indirect sources, that there were no good data linking either cannabis or pain scores to the downstream treatments that had been included in the model and that good quality data were lacking in some subgroups. These limitations were explored in sensitivity analyses showing that even under extreme assumptions, the model never produced ICERs close to those normally considered cost-effective. Furthermore, the probabilistic sensitivity analysis showed a 0% probability that CBMPs are cost-effective – using NICE’s ‘threshold’ of £20,000 to £30,000 per QALY over which treatments are not likely to be recommended for use in the NHS.

Overall, the committee considered the economic model to be directly applicable with minor limitations for decision-making. They considered that the CBMPs that they had seen evidence for would have to be around 8 times more effective (accrue 1.22 QALYs compared with 0.162 QALY in the base case) or 6 times less expensive (or some equivalent combination) or associated with very significant pain management savings for the average patient to bring the ICER down to an acceptable level. The committee was aware that given the findings from the clinical evidence, the additional effectiveness is unrealistic. Given how unlikely it would be to observe changes of this scale they concluded that, at current prices, these CBMPs do not represent an effective use of resources in the management of chronic pain. They therefore decided to make a recommendation against their use in the specific populations that were considered in the evidence base for this review. They discussed gaps in the evidence and made a series of recommendations for research into the use of CBMPs in specialised settings. Poor quality evidence on CBD alone was included in this review and the committee were aware of anecdotal evidence that many people with chronic pain are accessing this outside the NHS and reporting benefit. They therefore thought it important to include this intervention in their recommendations for research. They also noted that, although the clinical review had found some evidence showing no difference in opiate use between cannabis and standard of care, the trials were too short in duration to be reliable. As a matter of theory, this outcome might importantly influence decisions to prescribe CBMPs and could also influence their cost-effectiveness in certain populations. They therefore highlighted this is an outcome of interest.

This evidence review supports recommendations 1.2.1 to 1.2.3 and the research recommendations on fibromyalgia or persistent treatment-resistant neuropathic pain in adults and chronic pain in children and young people.

Glossary

Cannabis-based medicinal products

In this guideline cannabis-based medicinal products include:

- cannabis-based products for medicinal use as set out by the UK Government in the [2018 Regulations](#)
- the licensed products delta-9-tetrahydrocannabinol and cannabidiol (Sativex) and nabilone
- plant-derived cannabinoids such as pure cannabidiol (CBD)
- synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-tetrahydrocannabinol (THC), for example, dronabinol.

Appendices

Appendix A – Review protocols

Review protocol for effectiveness of cannabis based medicinal products for people with chronic pain

Field (based on PRISMA-P)	Content
Review question	<p>What is the clinical and cost effectiveness of cannabis-based medicinal products for people with chronic pain?</p> <p>What are the adverse effects or complications of cannabis-based medicinal products for people with chronic pain?</p> <p>What are the contraindications, potential interactions and risks and cautions for use of cannabis-based medicinal products for people with chronic pain?</p> <p>What are the individual patient monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn or stopped, for use of cannabis-based medicinal products for people with chronic pain?</p>
Type of review question	Intervention
Objective of the review	To determine the effectiveness, harms and cost-effectiveness of cannabis based medicinal products in reducing chronic pain in adults and persisting pain in children.
Eligibility criteria – population/disease/condition/issue/do main	<p>Adults, young people, children and babies.</p> <p>Specific considerations were given to:</p> <ul style="list-style-type: none"> • Young people, children and babies • Pregnant women and women who are breastfeeding

	<ul style="list-style-type: none">• People with existing substance abuse• People with hepatic and renal failure <p>Chronic pain for adults is defined as pain lasting for 3 months or longer.</p> <p>The committee agreed that any pain in children which is not acute is considered as chronic pain. The term 'persisting pain' may be more used in a paediatric population than 'chronic pain'.</p>
Eligibility criteria – intervention	<ol style="list-style-type: none">1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which:<ul style="list-style-type: none">• is or contains cannabis, cannabis resin, cannabidiol or a cannabidiol derivative (not being dronabinol or its stereoisomers)• is produced for medicinal use in humans; and• is a medicinal product, or• a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations)2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol3. Licensed products Sativex and nabilone4. Plant-derived cannabinoids such as pure cannabidiol <p>For the purpose of this guideline, all the interventions above were classed as cannabis-based medicinal products.</p>

Eligibility criteria – comparator	Placebo
Outcomes	<ul style="list-style-type: none"> • Participant reported pain relief of 30% or greater • Participant reported pain relief of 50% or greater (to assist the economic analysis) • Reduction in analgesics required • Change in pain intensity using Numerical Rating Scale', or Visual Analogue Scale' • Functional impairment specific to the type of pain. For neuropathic pain: McGill Pain Questionnaire. For nociceptive pain: Brief Pain Inventory. • Participant/Patient/Subject Global Impression of Change (PGIC or SGIG) scale • Quality of life score using SF-36 or EQ-5D. • Serious adverse events • Adverse events including but not limited to: sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product.

	<ul style="list-style-type: none"> • Misuse/diversion • Hepatic and renal failure <p>Outcomes requiring a narrative synthesis:</p> <ul style="list-style-type: none"> • Contraindications as listed in exclusion criteria <p>Monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn stopped as discussed in the methods of individual RCTs</p>
<p>Eligibility criteria – study design</p>	<p>For adults:</p> <ul style="list-style-type: none"> • RCTs • Systematic reviews of RCTs <p>If less than five RCTs identified, prospective cohort studies were to be used.</p> <p>For children:</p> <ul style="list-style-type: none"> • RCTs • Systematic reviews of RCTs <p>If less than five RCTs identified, prospective and retrospective cohort studies were to be used.</p> <p>Additional information on safety concerns and contraindications were obtained from the Summary of Product Characteristics and other relevant sources, such as the U.S Food and Drugs Administration.</p>
<p>Other inclusion/exclusion criteria</p>	<p>Inclusion</p> <p>Cannabis-based products for the medicinal use when other treatments haven't helped or have been discounted.</p> <p>Exclusion</p> <ul style="list-style-type: none"> • Synthetic cannabinoids in schedule 1 of the 2001 regulations,

	<ul style="list-style-type: none"> • Smoked cannabis-based products • Studies which do not report the doses or the concentration of cannabinoid constituents. • Headaches and orofacial pain. However, headaches caused by cancer were included. • For randomised crossover studies, washout periods of less than 1 week.
Sub-group analysis	<p>Where possible for adults, data were stratified according to the ICD-11 definition of pain as primary or secondary pain. For primary pain, data was analysed according to whether it was chronic widespread pain, complex regional pain syndrome, chronic primary visceral pain or chronic primary musculoskeletal pain.</p> <p>For secondary pain, data was analysed according to whether it was chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic secondary visceral pain or chronic secondary musculoskeletal pain.</p> <p>Subgroups, where possible, included:</p> <ul style="list-style-type: none"> • Young people, children and babies • Pregnant women and women who are breastfeeding • People with existing substance abuse
Selection process – duplicate screening/selection /analysis	<p>10% of the abstracts was reviewed by two reviewers, with any disagreements being resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts was reviewed by two reviewers, with this process continuing until agreement was achieved between the two reviewers. From this point, the remaining abstracts were screened by a single reviewer.</p>
Data management (software)	<p>See Appendix B.</p>
Information sources – databases and dates	<p>Sources to be searched</p> <ul style="list-style-type: none"> • Clinical searches - Medline, Medline in Process, Medline Epub Ahead of Print, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records), HTA, MHRA.

	<ul style="list-style-type: none"> ○ Economic searches - Medline, Medline in Process, Medline Epub Ahead of Print, Embase, Econlit, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. <p>Supplementary search techniques</p> <ul style="list-style-type: none"> • None identified <p>Limits</p> <ul style="list-style-type: none"> • Studies reported in English • Study design RCT, SR and Observational filter was applied (as agreed) • Animal studies were excluded from the search results • Conference abstracts were excluded from the search results • No date limit was set.
Identify if an update	N/A
Author contacts	Guideline updates team
Highlight if amendment to previous protocol	This is a new protocol.
Search strategy – for one database	For details please see appendix C of relevant chapter.
Data collection process – forms/duplicate	A standardised evidence table format was used, and published as appendix D (clinical evidence tables) or AppendixH (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	<p>Study checklists were used to critically appraise individual studies. For details please see appendix H of Developing NICE guidelines: the manual</p> <p>The following checklists were used:</p>

	<p>Risk of bias of intervention studies - systematic reviews and meta-analyses were assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist</p> <p>Risk of bias of intervention studies – randomised controlled trials (individual or cluster) were assessed using the Cochrane risk of bias (RoB) 2.0 tool</p> <p>Risk of bias of cohort studies were assessed using Cochrane ROBINS-I</p> <p>The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group http://www.gradeworkinggroup.org/</p>
Criteria for quantitative synthesis	For details please see section 6 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual .
Confidence in cumulative evidence	For details please see sections 6 and 9 of Developing NICE guidelines: the manual

Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	<p>A multidisciplinary committee [add link to history page of the guideline] developed the evidence review. The committee was convened by [add name of developer] and chaired by [add name of Chair] in line with section 3 of Developing NICE guidelines: the manual.</p> <p>Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.</p>
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being ‘includes’ or ‘excludes’ during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies’ lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis.

Because most of the studies reported odds ratios which could not be converted to risk ratios, all dichotomous outcomes were reported as odds ratios for consistency. Due to the nature of the data reported in the studies, absolute risks could not be calculated for the outcomes.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.

- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. In analysis which included subgroups from more than 1 ICD classification of pain, random-effects were fitted to account for differences in populations.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

Where data for multiple subgroups (i.e. different doses of medicinal cannabis) were combined, this was done in accordance to the advice given in the Cochrane Handbook for Systematic Reviews of Interventions.

Meta-analyses were performed in Cochrane Review Manager V5.3.

Numerical Rating Scale (NRS) is used to score pain intensity on a scale of 0 to 10. Visual Analog Scale (VAS) is used to score pain intensity on a scale of 0 to 100. The committee agreed that if a study only uses VAS, we should transform it to NRS by dividing the score by 10.

Combining groups within studies

When combining the arms of studies, we used Cochrane's advice and formula for combining groups. In doing so, we assumed equal SD for the placebo and intervention arm.

Minimal clinically important differences (MIDs)

The guideline committee were asked to prospectively specify outcomes where they felt a consensus MID could be defined from their experience. The committee specified a key outcome is participant reported pain relief of 30% or greater. This is in line with the recommended measure of minimal important difference in pain intensity (IMMPACT 2005). For this measure, other dichotomous measures and measures of functional pain, the committee agreed that any statistically significant difference in outcomes would be of interest to them. Therefore, it was decided that the line of no effect was to be used as the MID (OR = 1 and mean or median difference = 0). For mean difference measures between arms reported on the visual analogue scale (VAS) or numerical rating scale (NRS), a clinically important difference of -0.8 was used. This is the same MID used by the Cochrane Pain, Palliative and Supportive Care Group (Mücke 2018) and similar to the median average MID for pain intensity reported in a systematic review of chronic pain intensity MIDs (Olsen 2018).

Therefore, a mean difference and confidence interval below -0.8 would show a clinical benefit to reduction in pain intensity in the treatment arm compared to the comparator.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in '[Developing NICE guidelines: the manual \(2018\)](#)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in **Table 1**.

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	<p>Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.</p> <p>Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level.</p> <p>Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.</p>
Indirectness	<p>Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.</p> <p>Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.</p> <p>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.</p>
Inconsistency	<p>Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic.</p> <p>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.</p> <p>Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded.</p> <p>Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level.</p> <p>Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.</p>
Imprecision	<p>For outcomes where the line of no effect was defined as the MID, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any</p>

GRADE criteria	Reasons for downgrading quality
	<p>realistic effect size could have been detected (<40 participants). For outcomes with specified MIDs (-0.9 for pain intensity reported on the NRS or VAS scales), these were downgraded once if the 95% confidence interval for the effect size crossed one MID. The sample size was also considered as a factor for downgrading for imprecision.</p> <p>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.</p>

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Summary of evidence

The evidence is presented in the form of a table because the committee agreed in advance that effect sizes would be an important consideration. Summary of evidence is stratified by comparison and reflects evidence that was statistically significant.

Where the data are only consistent, at a 95% confidence level, with an effect in one direction, and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. In all other cases, we state that the evidence could not differentiate between the comparators.

Appendix C – Literature search strategies

A single systematic search was conducted for all of the questions within this evidence review between 19th December 2018 and 21st January 2019. The following databases were searched MEDLINE, MEDLINE in Process, MEDLINE e pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews CENTRAL (all via the Wiley platform), and the HTA and DARE databases (both via the CRD platform). NICE inhouse RCT, systematic review, and observational filters were attached where appropriate.

The MEDLINE strategy is presented below. This was translated for other databases

- 1 Medical Marijuana/
- 2 cannabinoids/ or cannabidiol/ or cannabinol/ or cannabis/
- 3 ((cannabi* or hemp or marijuana or marihuana) adj4 (medicine* or medicinal or medical or oil or oils or product* or extract* or therap* or CBD or vap* or spray* or inhal* or compound* or resin* or derivative*)).tw.
- 4 (epidiolex* or cannabidiol* or cannabinoid*).tw.
- 5 (sativex or THC:CBD spray or tetrabinex or nabidiolex).tw.
- 6 (nabilone or cesamet).tw.
- 7 (tilray* or bedrocan* or bedrobinol* or bedica* or bediol* or bedrolite*).tw.
- 8 Dronabinol/
- 9 (dronabinol* or marinol* or syndros*).tw.
- 10 (9-ene-tetrahydrocannabinol* or 9enetetrahydrocannabinol*).tw.
- 11 (THC or tetrahydrocannabinol*).tw.
- 12 ("delta(1)-thc*" or "delta(1)-tetrahydrocannabinol*" or "delta(9)-thc*" or "delta(9)-tetrahydrocannabinol*").tw.
- 13 (9-delta-tetra-hydrocannabinol* or "9-delta-THC*" or "9 delta tetra hydrocannabinol*" or "9 delta THC*").tw.
- 14 (1-delta-tetra-hydrocannabinol* or "1-delta-THC*" or "1 delta tetra hydrocannabinol" or "1 delta thc*").tw.
- 15 THCa.tw.
- 16 CBDa.tw.
- 17 cannabinol*.tw.
- 18 cannabigerol*.tw.
- 19 cannabichromene*.tw.
- 20 (tetrahydrocannabivarin* or THCV).tw.

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- 21 (cannabidivarin* or CBDV).tw.
- 22 or/1-21
- 23 animals/ not humans/
- 24 22 not 23
- 25 limit 24 to english language
- 26 Randomized Controlled Trial.pt.
- 27 Controlled Clinical Trial.pt.
- 28 Clinical Trial.pt.
- 29 exp Clinical Trials as Topic/
- 30 Placebos/
- 31 Random Allocation/
- 32 Double-Blind Method/
- 33 Single-Blind Method/
- 34 Cross-Over Studies/
- 35 ((random\$ or control\$ or clinical\$) adj3 (trial\$ or stud\$)).tw.
- 36 (random\$ adj3 allocat\$).tw.
- 37 placebo\$.tw.
- 38 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw.
- 39 (crossover\$ or (cross adj over\$)).tw.
- 40 or/20-33
- 41 Meta-Analysis.pt.
- 42 Network Meta-Analysis/
- 43 Meta-Analysis as Topic/
- 44 Review.pt.
- 45 exp Review Literature as Topic/
- 46 (metaanaly\$ or metanaly\$ or (meta adj3 analy\$)).tw.
- 47 (review\$ or overview\$).ti.
- 48 (systematic\$ adj5 (review\$ or overview\$)).tw.
- 49 ((quantitative\$ or qualitative\$) adj5 (review\$ or overview\$)).tw.

- 50 ((studies or trial\$) adj2 (review\$ or overview\$)).tw.
- 51 (integrat\$ adj3 (research or review\$ or literature)).tw.
- 52 (pool\$ adj2 (analy\$ or data)).tw.
- 53 (handsearch\$ or (hand adj3 search\$)).tw.
- 54 (manual\$ adj3 search\$).tw.
- 55 or/35-48
- 56 34 or 49
- 57 19 and 50
- 58 Observational Studies as Topic/
- 59 Observational Study/
- 60 Epidemiologic Studies/
- 61 exp Case-Control Studies/
- 62 exp Cohort Studies/
- 63 Cross-Sectional Studies/
- 64 Controlled Before-After Studies/
- 65 Historically Controlled Study/
- 66 Interrupted Time Series Analysis/
- 67 Comparative Study.pt.
- 68 case control\$.tw.
- 69 case series.tw.
- 70 (cohort adj (study or studies)).tw.
- 71 cohort analy\$.tw.
- 72 (follow up adj (study or studies)).tw.
- 73 (observational adj (study or studies)).tw.
- 74 longitudinal.tw.
- 75 prospective.tw.
- 76 retrospective.tw.
- 77 cross sectional.tw.
- 78 or/26-45

79 25 and 46

80 57 or 79

Searches to identify economic evidence were run on 20th December 2018 in MEDLINE, MEDLINE in Process, MEDLINE e pub Ahead of print, Econlit and Embase (all va the Ovid platform), NHS EED and the Health Technology Assessment Database (via the CRD platform). NICE inhouse economic evaluation and Quality of Life filters were attached to lines 1 to 25 of the core strategy (lines 1 to 25 of the Medline version shown above) in the Medline and Embase databases. The Medline version of the filters is displayed below.

Economic evaluations

- 1 Economics/
- 2 exp "Costs and Cost Analysis"/
- 3 Economics, Dental/
- 4 exp Economics, Hospital/
- 5 exp Economics, Medical/
- 6 Economics, Nursing/
- 7 Economics, Pharmaceutical/
- 8 Budgets/
- 9 exp Models, Economic/
- 10 Markov Chains/
- 11 Monte Carlo Method/
- 12 Decision Trees/
- 13 econom\$.tw.
- 14 cba.tw.
- 15 cea.tw.
- 16 cua.tw.
- 17 markov\$.tw.
- 18 (monte adj carlo).tw.
- 19 (decision adj3 (tree\$ or analys\$)).tw.
- 20 (cost or costs or costing\$ or costly or costed).tw.
- 21 (price\$ or pricing\$).tw.
- 22 budget\$.tw.
- 23 expenditure\$.tw.
- 24 (value adj3 (money or monetary)).tw.
- 25 (pharmacoeconomic\$ or (pharmaco adj economic\$)).tw.
- 26 or/1-25

Quality of Life

1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
7. disability adjusted life.tw.

8. daly\$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health\$ year\$ equivalent\$.tw.
19. utilit\$.tw.
20. (hui or hui1 or hui2 or hui3).tw.
21. disutilit\$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble\$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

A search of the MHRA was undertaken on the 24th January 2019 to look for safety updates, alerts and recalls. The search terms are displayed below.

Sativex

Dronabinol

Epidiolex

THC:CBD spray

Abalone

Tetrabinex

Nabidiolex

Cesamet

Tilray

Bedrocan

Bedrobinol

Bedica

Bediol

Bedrolite

Marinol

Syndros

THC

Tetrahydrocannabinol

Cannabinol

Cannibigerol

Cannabichromene

Tetrahydrocannabivarin

Cannabidivarin

Quality of Life

- 1 "Quality of Life"/
- 2 quality of life.tw.
- 3 "Value of Life"/
- 4 Quality-Adjusted Life Years/
- 5 quality adjusted life.tw.
- 6 (qaly\$ or qald\$ or qale\$ or qtime\$).tw.
- 7 disability adjusted life.tw.
- 8 daly\$.tw.
- 9 Health Status Indicators/ (22343)
- 10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
- 11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
- 12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
- 13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
- 14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
- 15 (euroqol or euro qol or eq5d or eq 5d).tw.
- 16 (qol or hql or hqol or hrqol).tw.
- 17 (hye or hyes).tw.
- 18 health\$ year\$ equivalent\$.tw.
- 19 utilit\$.tw.
- 20 (hui or hui1 or hui2 or hui3).tw.
- 21 disutili\$.tw.
- 22 rosser.tw.
- 23 quality of wellbeing.tw.
- 24 quality of well-being.tw.
- 25 qwb.tw.
- 26 willingness to pay.tw.
- 27 standard gamble\$.tw.
- 28 time trade off.tw.
- 29 time tradeoff.tw.
- 30 tto.tw.
- 31 or/1-30

MHRA search:**Database: MHRA**

- [Alerts and recalls for drugs and medical devices](#)
- [Drug safety update](#)

Strategy used:

Sativex

Dronabinol

Epidiolex

THC:CBD spray

Nabilone

Tetrabinex

Nabidiolex

Cesamet

Tilray

Bedrocan

Bedrobinol

Bedica

Bediol

Bedrolite

Marinol

Syndros

THC

Tetrahydrocannabinol

Cannabinol

Cannibigerol

Cannabichromene

Tetrahydrocannabivarin

Cannabidivarin

Search history – observational studies

Databases	Date searched	Version/files	No. retrieved	RefMan data
Embase (Ovid)	20/12/2018	1974 to 2018 December 18	2011	2427-4437
MEDLINE (Ovid)	20/12/2018	1946 to December 19, 2018	2264	1-2264
MEDLINE In-Process (Ovid)	20/12/2018	December 19, 2018	132	2265-2396
MEDLINE epubs (Ovid)	20/12/2018	December 19, 2018	30	2397-2426
MHRA – Drug Safety Alerts ²				

Search history – observational studies: Medline search

Database: MEDLINE
<p>Strategy used:</p> <p>Database: Ovid MEDLINE(R) <1946 to December 18, 2018></p> <p>Search Strategy:</p> <p>-----</p> <ol style="list-style-type: none"> 1 Medical Marijuana/ (732) 2 cannabinoids/ or cannabidiol/ or cannabinol/ or cannabis/ (14684) 3 ((cannabi* or hemp or marijuana or marihuana) adj4 (medicine* or medicinal or medical or oil or oils or product* or extract* or therap* or CBD or vap* or spray* or inhal* or THC or tetrahydrocannabinol* or 9-delta-tetra-hydrocannabinol* or "9 delta tetra hydrocannabinol" or compound*)).tw. (5770) 4 (epidiolex* or cannabidiol* or cannabinoid*).tw. (15896) 5 (sativex or THC:CBD spray or tetrabinex or nabidiolex).tw. (173) 6 (nabilone or cesamet).tw. (237) 7 (tilray* or bedrocan* or bedrobinol* or bedica* or bediol* or bedrolite*).tw. (7) 8 or/1-7 (25311)

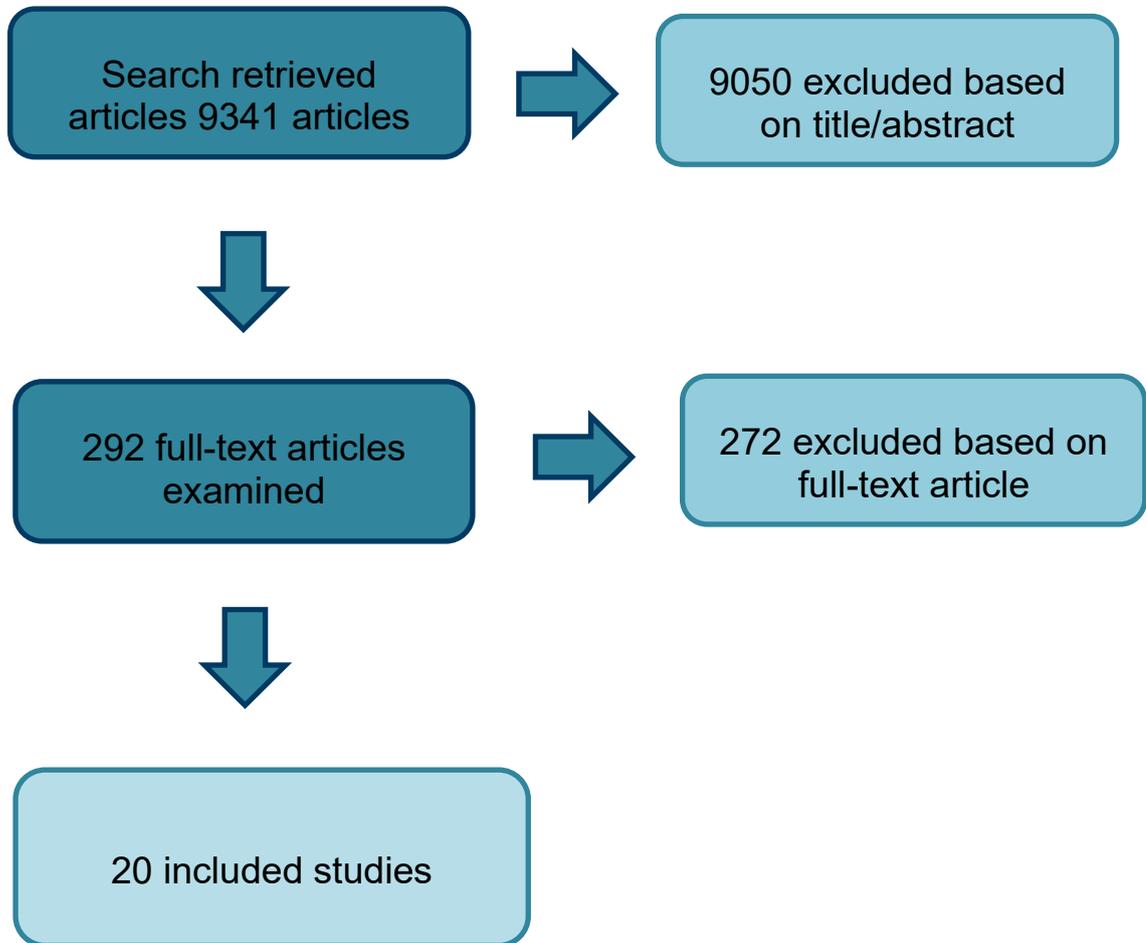
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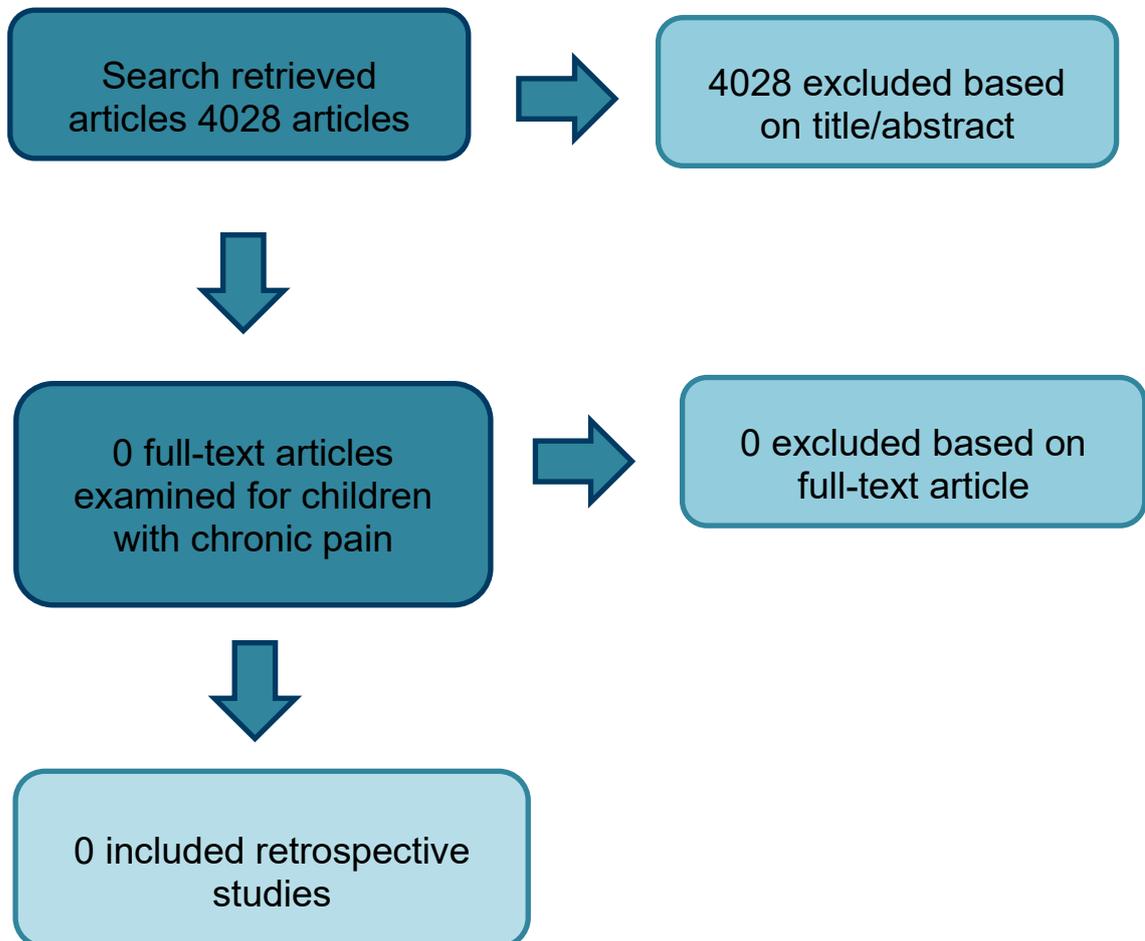
- 9 Observational Studies as Topic/ (3464)
- 10 Observational Study/ (55720)
- 11 Epidemiologic Studies/ (7826)
- 12 exp Case-Control Studies/ (960041)
- 13 exp Cohort Studies/ (1807116)
- 14 Cross-Sectional Studies/ (281284)
- 15 Controlled Before-After Studies/ (366)
- 16 Historically Controlled Study/ (146)
- 17 Interrupted Time Series Analysis/ (512)
- 18 Comparative Study.pt. (1816843)
- 19 case control\$.tw. (101282)
- 20 case series.tw. (51003)
- 21 (cohort adj (study or studies)).tw. (138635)
- 22 cohort analy\$.tw. (5562)
- 23 (follow up adj (study or studies)).tw. (42522)
- 24 (observational adj (study or studies)).tw. (71051)
- 25 longitudinal.tw. (179685)
- 26 prospective.tw. (445972)
- 27 retrospective.tw. (382273)
- 28 cross sectional.tw. (241222)
- 29 or/9-28 (4036363)
- 30 8 and 29 (3359)
- 31 animals/ not humans/ (4493878)
- 32 30 not 31 (2413)
- 33 limit 32 to english language (2270)

Appendix D – Clinical evidence study selection

RCTs and systematic reviews of RCTs search



Observational studies search for children



Appendix E – Clinical evidence table

E.1 Parallel RCTs

Blake 2006

Blake, 2006

Bibliographic Reference	Blake, D. R.; Robson, P.; Ho, M.; Jubb, R. W.; McCabe, C. S.; Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis; Rheumatology (Oxford, England); 2006; vol. 45 (no. 1); 50-2
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Study details

Study type	Randomised controlled trial (RCT)
Study location	8 centres in the UK
Study setting	Centres
Study dates	Not provided. Study was accepted for publication in 2005.
Duration of follow-up	5 weeks
Sources of funding	GW Pharmaceuticals
Inclusion criteria	Diagnosis of rheumatoid arthritis Using American College of Rheumatology guidelines, with active arthritis not adequately controlled by standard medication. NSAID and prednisolone regimes had to have been stabilized for 1 month and DMARDs for 3 months prior to enrolment, and were maintained constant throughout the study.
Exclusion criteria	Psychiatric disorders History of psychiatric disorders History of seizures Known history of alcohol or substance abuse

Study type	Randomised controlled trial (RCT)
	Patients with history of renal, hepatic, cardiovascular, convulsive disorder, or with sensitivity to cannabis
Sample size	At start: 58 Completed: 57
Split between study groups	At start: intervention: 31; placebo: 27 Completed: intervention: 30; placebo: 27
Loss to follow-up	Intervention: 1 Placebo: 0
% Female	Intervention: 74% Placebo: 85%
Mean age (SD)	Intervention: 60.9 (10.6) Placebo: 64.9 (8.5)
Outcome measures	<p>Mean average pain intensity</p> <p>Functional impairment caused by pain: McGill Pain Questionnaire - Short Form, total intensity of pain</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Patients experiencing serious adverse events, treatment-related</p> <p>Withdrawals due to adverse events, all-causality</p> <p>Withdrawals due to adverse events, treatment-related</p>

Study arms

Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 30)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	Dosing was restricted to the evening to minimize possible intoxication-type reactions. Starting dose was one actuation within 0.5 h of retiring, and this was increased by one actuation every 2 days to a maximum of six actuations according to individual response.
What the maintenance dose was	Maximum of six actuations
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	Not described
Stopping criteria	None
Arm 2	Placebo (N = 27)
Formulation	No details provided
How long the maintenance dose was sustained for	3 weeks

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(No information on blinding.)

Overall Directness

Directly applicable

de Vries 2017

De Vries, 2017

Bibliographic Reference de Vries, Marjan; van Rijckevorsel, Dagmar C. M.; Vissers, Kris C. P.; Wilder-Smith, Oliver H. G.; van Goor, Harry; Pain; Nociception Neuroscience Research, Group; Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study; Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association; 2017; vol. 15 (no. 7); 1079-1086.e4

Study details

Study type	Randomised controlled trial (RCT)
Study location	Not described
Study setting	Not described
Study dates	Not provided
Duration of follow-up	41 days
Sources of funding	Supported by a grant of the European Union, the European Fund for Regional Development (EFRO), and the Province of Gelderland
Inclusion criteria	Age 18 or over, male or female Chronic pain resulting from surgery Abdominal pain lasting for at least 3 months Chronic pain resulting from chronic pancreatitis Lasting for at least 3 months
Exclusion criteria	Previous cannabis use Daily cannabis use in past 3 years Known hypersensitivity to cannabinoids Pain from other concomitant conditions

Study type	Randomised controlled trial (RCT)
	<p>Serious illness/medical condition likely to interfere with study assessment Including a significant exacerbation of illness during the past 2 weeks</p> <p>Patients who had received therapies expected to confound the study outcome</p> <p>Psychiatric disorders Major psychiatric illness</p> <p>Severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment</p> <p>History of seizures</p> <p>Affected sensory input Such as diabetic neuropathy</p> <p>High body mass index >36.0 kg/m²</p> <p>Known history of alcohol or substance abuse</p> <p>Pregnant or lactating Or intending to conceive a child</p> <p>Clinically relevant abnormalities in investigations Including blood results and ECG</p> <p>Participating in another investigational study Of another drug within 90 days</p>
Sample size	<p>At start: 62</p> <p>Completed: 50</p>
Split between study groups	<p>At start: intervention: 30; placebo: 32</p> <p>Completed: intervention: 21; placebo: 29</p>

Study type	Randomised controlled trial (RCT)
Loss to follow-up	Intervention: 9 Placebo: 3
% Female	Intervention: 57% Placebo: 45%
Mean age (SD)	Intervention: 53 (9) Placebo: 53 (9)
Outcome measures	Mean average pain intensity Withdrawals due to adverse events, all-causality

Study arms

Arm 1	Oral delta-9-THC (dronabinol) (N = 21)
Formulation	Oral delta-9-THC
How dose was titrated up	Step-up phase: days 1–5: 3mg 3 times a day; days 6–10: 5 mg 3 times a day.
What the maintenance dose was	Days 11-52: 8mg 3 times a day. It was permitted to taper the dosage to 5 mg TID when 8 mg was not tolerated.
How long the maintenance dose was sustained for	41 days
Monitoring/reviewing procedure	Efficacy and safety assessments were conducted preceding medication intake on day 1 (visit 2), after 15 treatment days (visit 3), and 50–52 treatment days (visit 4). Several phone calls were performed by the investigators during an

	after the treatment period (days 4–5, 9–10, 21–23, 28–30, 38–40, and 59–61) to evaluate the tolerability, safety, and compliance.
Stopping criteria	Not described
Arm 2	
Formulation	"Identical matching placebo"
How dose was titrated up	"Identical matching placebo"
How long the maintenance dose was sustained for	41 days
Monitoring/reviewing procedure	Same as intervention

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Cochrane Risk of Bias Tool 2.0

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

High

(Five serious adverse events occurred but no details of which arm.)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

High

(Five serious adverse events occurred but no details of which arm.)

Overall Directness

Directly applicable

Fallon 2017

Fallon, 2017

Bibliographic
Reference

Fallon, Marie T.; Albert Lux, Eberhard; McQuade, Robert; Rossetti, Sandro; Sanchez, Raymond; Sun, Wei; Wright, Stephen; Lichtman, Aron H.; Kornyeveva, Elena; Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies; British journal of pain; 2017; vol. 11 (no. 3); 119-133

Study details

Study type	Randomised controlled trial (RCT)
Study location	101 centres in Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the United Kingdom and the United States.
Study setting	Centres
Study dates	Not provided. Study was published in 2017.
Duration of follow-up	3 weeks
Sources of funding	Otsuka Pharmaceutical Development & Commercialization, Inc.
Inclusion criteria	<p>Age 18 or over, male or female</p> <p>Pain due to cancer Unalleviated by an optimized maintenance dose of Step 3 opioid therapy. Opioid therapy was considered optimized if (1) a dose increase was clinically inappropriate due to opioid-related side effects or (2) further efficacy benefit was not expected at higher doses (for the second definition, patients had to be receiving ≥ 90 mg morphine equivalents/day, inclusive of maintenance and breakthrough opioids). The maintenance opioid was preferably a sustained-release formulation, but an around-the-clock immediate-release formulation was acceptable. To be eligible, patients also had to fulfil the following criteria on each of three consecutive days during the screening period: ≤ 4 opioid breakthrough analgesic episodes per day (averaged over the 3 days), a stable maintenance opioid therapy dose, average pain ≥ 4 and ≤ 8 on a 0–10 NRS and average pain scores on the NRS that did not change by more than 2 points from the beginning to end of screening (i.e. no more than a 2-point difference between the highest and lowest scores, with all scores remaining between 4 and 8).</p> <p>Advanced incurable stage of cancer</p>
Exclusion criteria	<p>High baseline dose of morphine Baseline use of morphine at >500 mg morphine equivalents/day (inclusive of maintenance and breakthrough opioids)</p> <p>More than 1 type of breakthrough opioid analgesic</p> <p>Planned clinical interventions that would affect pain</p> <p>Known history of alcohol or substance abuse</p> <p>Any history of schizophrenia</p>
Sample size	At start: 399

Study type	Randomised controlled trial (RCT)
	Completed: 294
Split between study groups	At start: intervention: 200; placebo: 199 Completed: intervention: 136; placebo: 158
Loss to follow-up	Intervention: 64 Placebo: 41
% Female	Intervention: 47% Placebo: 40.4%
Mean age (SD)	Intervention: 60.0 (11.0) Placebo: 59.6 (11.0)
Outcome measures	Mean average pain intensity Change in analgesics: daily change in total dose, morphine equivalents Change in analgesics: daily change in breakthrough dose, morphine equivalents Change in analgesics: daily change in maintenance dose, morphine equivalents Patient Global Impression of Change (continuous) Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related Withdrawals due to adverse events, all-causality

Study arms

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Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 136)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	Eligible patients entered an initial titration period lasting up to 14 days. Treatment was initiated as a single spray in the evening of the first day of treatment and was gradually increased by one additional spray per day (15 minutes apart) according to a pre-specified dose escalation protocol until patients experienced unacceptable side effects, received acceptable pain relief, or reached the maximum allowed daily dosage of 10 sprays per day (patients were advised to reach at least 3 sprays per day). Patients were advised to take the medication at home and to remain home until at least 3 hours after their first dose due to potential sleepiness and dizziness following the medication. Patients were advised to initiate treatment with a single evening spray, as the most common side effects of the THC + CBD, especially during the early titration stage, are somnolence and dizziness. To avoid undesirable side effect during the day, patients were recommended to administer higher number of sprays in the evening hours.
What the maintenance dose was	Maximum allowed daily dosage of 10 sprays per day. The average number of sprays administered per day during the first week of therapy was 3.7 in both treatment groups. Average daily dosing plateaued and remained stable for the remaining 4 weeks of the treatment period, with placebo-treated patients self-administering, on average, 1 spray more per day than THC + CBD treated patients (7.4 vs. 6.3 sprays per day). Consistent with this, a greater number of patients in the placebo group took more than 6 sprays of study medication per day, on average, over the entire treatment period (119 (60.1%) vs. 84 (42.2%)).
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	Following the 2-week THC + CBD or placebo titration period, patients continued study drug administration at the same dose (in other words, the same number of sprays per day) for an additional 3 weeks. Whenever possible, stable doses of all other prescribed pain medications were to be continued during the study period. Two weeks after the end of treatment, patients were contacted by phone for follow-up safety evaluations.
Stopping criteria	None

Arm 2	Placebo (N = 158)
Formulation	"Matching placebo"
How dose was titrated up	"Matching placebo"
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	"Matching placebo"

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(No details on the randomisation process.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Cochrane Risk of Bias Tool 2.0

Risk-of-bias judgement for this domain

High

(No details regarding how blinding took place. All outcomes have a subjective aspect.)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

High

(No details regarding how randomisation and blinding took place. All outcomes have a subjective aspect.)

Overall Directness

Directly applicable

Johnson 2010

Johnson, 2010

Bibliographic
Reference

Johnson, Jeremy R.; Burnell-Nugent, Mary; Lossignol, Dominique; Ganae-Motan, Elena Doina; Potts, Richard; Fallon, Marie T.; Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain; Journal of pain and symptom management; 2010; vol. 39 (no. 2); 167-79

Study details

Study type	Randomised controlled trial (RCT)
Study location	28 European centres
Study setting	Centres
Study dates	Not provided. Study was accepted for publication in 2009.
Duration of follow-up	2 weeks

Study type	Randomised controlled trial (RCT)
Sources of funding	GW Pharma
Inclusion criteria	<p>Age 18 or over, male or female</p> <p>Pain due to cancer Patients who had been using strong opioids for at least one week to relieve pain</p> <p>Advanced incurable stage of cancer</p>
Exclusion criteria	<p>Cancer affecting the oral cavity Including radiotherapy to the floor of the mouth</p> <p>Psychiatric disorders Major psychiatric disorders</p> <p>Severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment</p> <p>Patients who had received therapies expected to confound the study outcome Epidural analgesia within 48 hours of screening; palliative radio-, chemo-, or hormonal therapy within two weeks of screening; or CBs within seven days of randomisation</p> <p>Patients taking certain medications Patients taking levodopa, sildenafil, or fentanyl were excluded on safety grounds</p> <p>Known hypersensitivity to cannabinoids</p>
Sample size	<p>At start: 177</p> <p>Completed: 144</p>
Split between study groups	<p>At start: THC + CBD: 60; THC: 58; placebo: 59</p> <p>Completed: THC + CBD: 48; THC: 45; placebo: 51</p>
Loss to follow-up	<p>THC + CBD: 12</p> <p>THC: 13</p>

Study type	Randomised controlled trial (RCT)
	Placebo: 8
% Female	THC + CBD: 45% THC: 48% Placebo: 46%
Mean age (SD)	THC + CBD: 59.4 (12.1) THC: 61.3 (12.5) Placebo: 60.1 (12.3)
Outcome measures	Proportion of patients who experienced pain relief of 30% or more from baseline Mean average pain intensity Functional impairment caused by pain: Brief Pain Inventory - Short Form Change in analgesics: daily change in breakthrough dose, morphine equivalents Change in analgesics: daily change in maintenance dose, morphine equivalents Quality of life: mean QLQ-C30 global health status Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related Withdrawals due to adverse events, all-causality

Study arms

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Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 48)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation.
How dose was titrated up	The maximum permitted dose was eight actuations in any three-hour period and 48 actuations in any 24-hour period. This exceeds the recommended dose in the SPC, which has 12 as the maximum number of actuations per 24 hours. Patients self-titrated to their optimal dose over the seven days of Week 1, based on efficacy, tolerability, and the maximum permitted dose. Patients could increase the total number of sprays each day by a maximum of 50% until they either had satisfactory relief of their symptoms or developed unwanted effects, such as intoxication (“high”). The total number of sprays was spread over the day with a minimum of 15 minutes between any two sprays. If unwanted effects developed on a new number of sprays, the patient would not take any further sprays for three to four hours. The patient would then go back to taking their further sprays at a similar level to the previous day.
What the maintenance dose was	Once the patient had found the maximum number of sprays per day that they tolerated well or the number that provided good symptom relief, they continued with approximately the same number of sprays per day for the remainder of the study.
How long the maintenance dose was sustained for	2 weeks
Monitoring/reviewing procedure	“Study visits throughout the trial”
Stopping criteria	Not mentioned
Arm 2	Placebo (N = 51)
Formulation	Each actuation of placebo delivered only excipients plus colorants.
How dose was titrated up	Same as intervention

How long the maintenance dose was sustained for	2 weeks
Monitoring/reviewing procedure	“Study visits throughout the trial”
Arm 3	Oromucosal spray THC 2.7 mg per 100 microlitre actuation (N = 45)
Formulation	Oromucosal spray THC 2.7 mg per 100 microlitre actuation
How dose was titrated up	The maximum permitted dose was eight actuations in any three-hour period and 48 actuations in any 24-hour period. Patients self-titrated to their optimal dose over the seven days of Week 1, based on efficacy, tolerability, and the maximum permitted dose. Patients could increase the total number of sprays each day by a maximum of 50% until they either had satisfactory relief of their symptoms or developed unwanted effects, such as intoxication (“high”). The total number of sprays was spread over the day with a minimum of 15 minutes between any two sprays. If unwanted effects developed on a new number of sprays, the patient would not take any further sprays for three to four hours. The patient would then go back to taking their further sprays at a similar level to the previous day.
What the maintenance dose was	Once the patient had found the maximum number of sprays per day that they tolerated well or the number that provided good symptom relief, they continued with approximately the same number of sprays per day for the remainder of the study.
How long the maintenance dose was sustained for	2 weeks
Monitoring/reviewing procedure	“Study visits throughout the trial”
Stopping criteria	Not mentioned

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

High

(No information provided on randomisation nor blinding. The baseline morphine dose was much lower in the THC + CBD arm compared to the other arms.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

High

(No information provided on randomisation nor blinding.)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

High

(No information provided on randomisation nor blinding. The THC + CBD arm has a much lower baseline morphine dose compared to the other arms.)

Overall Directness

Directly applicable

Langford 2013

Langford, 2013

Bibliographic Reference	Langford, R. M.; Mares, J.; Novotna, A.; Vachova, M.; Novakova, I.; Notcutt, W.; Ratcliffe, S.; A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis; Journal of neurology; 2013; vol. 260 (no. 4); 984-97
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Study details

Study type	Randomised controlled trial (RCT)
Study location	33 study sites - UK (12), Czech republic (7), Canada (5), Spain (5), France (4)
Study setting	Not disclosed
Study dates	Not disclosed. Study was submitted for publication in 2012.
Duration of follow-up	Phase A (standard RCT): 14 weeks Phase B (withdrawal RCT): 14 weeks
Sources of funding	GW Pharma LTD
Inclusion criteria	Central neuropathic pain due to multiple sclerosis for at least 3 months Sum score of at least 24 on a pain 0 to 10 point NRS on the last 6 days Stable analgesia regimen for at least 2 weeks prior to study entry
Exclusion criteria	Pain from other concomitant conditions Other pain that was not central neuropathic pain Patients with a history of significant psychiatric conditions (other than depression) Patients with history of renal, hepatic, cardiovascular, convulsive disorder, or with sensitivity to cannabis

Study type	Randomised controlled trial (RCT)
Sample size	<p>Phase A (standard RCT): At start: 339; Completed: 297</p> <p>Phase B (withdrawal RCT): At start: 42; Completed: 41</p>
Split between study groups	<p>Phase A (standard RCT): THC + CBD: 141; placebo: 156</p> <p>Phase B (withdrawal RCT): THC + CBD: 21; placebo: 20</p>
Loss to follow-up	<p>Phase A (standard RCT): THC + CBD: 26; placebo: 16</p> <p>Phase B (withdrawal RCT): THC + CBD: 0; placebo: 1</p>
% Female	<p>Phase A (standard RCT): THC + CBD: 68%; placebo: 68%</p> <p>Phase B (withdrawal RCT): THC + CBD: 52%; placebo: 67%</p>
Mean age (SD)	<p>Phase A (standard RCT): THC + CBD: 48.42 (10.43); placebo: 49.51 (10.50)</p> <p>Phase B (withdrawal RCT): THC + CBD: 46.20 (10.39); placebo: 49.82 (9.75)</p>
Outcome measures	<p>Proportion of patients who experienced pain relief of 30% or more from baseline</p> <p>Proportion of patients who experienced pain relief of 50% or more from baseline</p> <p>Mean average pain intensity</p> <p>Functional impairment caused by pain: Brief Pain Inventory - Short Form</p> <p>Change in analgesics: breakthrough daily change in paracetamol, units not provided</p> <p>Patient Global Impression of Change (dichotomous)</p> <p>Quality of life: EQ-5D index</p> <p>Patients experiencing adverse events, all-causality</p>

Study type	Randomised controlled trial (RCT)
	Patients experiencing serious adverse events, all-causality Withdrawals due to adverse events, all-causality

Study arms

Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 141)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation.
How dose was titrated up	1-week baseline period allowing for dosing optimization preceded the 14-week treatment phase. During the baseline period, patients self-titrated, titrating upwards via a pre-defined escalation scheme to reach their optimal dose depending on efficacy, tolerability, and maximum permitted dose.
What the maintenance dose was	Patients were restricted to a maximum of 12 sprays per 24-h period.
How long the maintenance dose was sustained for	14 days
Monitoring/reviewing procedure	Review at 14 days
Stopping criteria	None described
Arm 2	Placebo (N = 156)
Formulation	Placebo delivered the excipient plus colorants.
How dose was titrated up	The same protocol was used for the placebo as for the medicinal cannabis.

How long the maintenance dose was sustained for	14 days
Monitoring/reviewing procedure	Reviewed at 14 days.
Arm 3	Withdrawal arm: Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 21)
Inclusion criteria	French and Czech patients who had completed phase A of the study were invited to take part in phase B. Patients were required to have received an average of three or more sprays of THC/CBD per day in the 7 days prior to completion of phase A, shown tolerability to the study medication, and maintained a stable treatment regimen throughout the study for all neuropathic pain medications.
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	To escalate the dose to a maximum of 12 daily sprays during the phase B
What the maintenance dose was	Maximum dose of 12 daily sprays.
How long the maintenance dose was sustained for	28 days
Monitoring/reviewing procedure	No details provided
Stopping criteria	No details provided

Arm 4	Withdrawal arm: Placebo (N = 20)
Inclusion criteria	French and Czech patients who had completed phase A of the study were invited to take part in phase B. Patients were required to have received an average of three or more sprays of THC/CBD per day in the 7 days prior to completion of phase A, shown tolerability to the study medication, and maintained a stable treatment regimen throughout the study for all neuropathic pain medications.
Formulation	Placebo delivered the excipient plus colorants.
How dose was titrated up	Same as intervention arm
How long the maintenance dose was sustained for	28 days
Monitoring/reviewing procedure	No details provided

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Cochrane Risk of Bias Tool 2.0

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Lichtman 2018

Lichtman, 2018

Bibliographic
Reference

Lichtman, Aron H.; Lux, Eberhard Albert; McQuade, Robert; Rossetti, Sandro; Sanchez, Raymond; Sun, Wei; Wright, Stephen; Korniyeyeva, Elena; Fallon, Marie T.; Results of a Double-Blind, Randomized, Placebo-Controlled Study of THC:CBD spray Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain; Journal of pain and symptom management; 2018; vol. 55 (no. 2); 179-188.e1

Study details

Study type	Randomised controlled trial (RCT)
Study location	114 centres participated in Belgium, Bulgaria, the Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the U.K., and the U.S.
Study setting	Centres
Study dates	Not provided. This study was accepted for publication in 2017.

Study type	Randomised controlled trial (RCT)
Duration of follow-up	3 weeks
Sources of funding	Otsuka Pharmaceutical Development & Commercialization, Inc.
Inclusion criteria	<p>Age 18 or over, male or female</p> <p>Advanced incurable stage of cancer</p> <p>Pain due to cancer</p> <p>Cancer-related pain that was unalleviated by an optimized maintenance dose of Step 3 opioid therapy. Opioid therapy was considered optimized if: 1) a dose increase was clinically inappropriate due to opioid-related side effects or 2) further efficacy benefit was not expected at higher doses (for the second definition, patients had to be receiving ≥ 90 mg morphine equivalents/day, inclusive of maintenance, and breakthrough opioids). The maintenance opioid was preferably a sustained-release formulation, but an around-the-clock immediate-release formulation was acceptable.</p>
Exclusion criteria	<p>High baseline dose of morphine Baseline use of morphine at > 500 mg morphine equivalents/day (inclusive of maintenance and breakthrough opioids).</p> <p>More than 1 type of breakthrough opioid analgesic To be eligible, patients also had to fulfill the following criteria on each of three consecutive days during the screening period: \leq four opioid breakthrough analgesic episodes per day (averaged over the three days); a stable maintenance opioid therapy dose; average pain \geq four and \leq eight on a 0 to 10 Numerical Rating Scale (NRS); and average pain scores on the NRS that did not change by more than two points (i.e., no more than a two-point difference between the highest and lowest scores, with all scores remaining between four and eight).</p> <p>Planned clinical interventions that would affect pain</p> <p>Any history of schizophrenia</p> <p>Known history of alcohol or substance abuse</p>
Sample size	<p>At start: 397</p> <p>Completed: 291</p>
Split between study groups	<p>At start: intervention: 199; placebo: 198</p> <p>Completed: intervention: 141; placebo: 150</p>

Study type	Randomised controlled trial (RCT)
Loss to follow-up	Intervention: 58 Placebo: 48
% Female	Intervention: 44.2% Placebo: 48%
Mean age (SD)	Intervention: 59.2 (12.0) Placebo: 60.7 (11.1)
Outcome measures	Mean average pain intensity Change in analgesics: daily change in total dose, morphine equivalents Change in analgesics: daily change in breakthrough dose, morphine equivalents Change in analgesics: daily change in maintenance dose, morphine equivalents Patient Global Impression of Change (continuous) Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related Withdrawals due to adverse events, all-causality Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness, all-causality

Study arms

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Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 141)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	Treatment was initiated as a single spray in the evening of the first day of treatment and was gradually titrated by one additional spray per day according to a prespecified dose escalation protocol (shown on a supplementary table) until patients experienced unacceptable side effects, experienced acceptable pain relief, or reached the maximum allowed daily dosage of 10 sprays per day. Titration was completed within 14 days, after which patients continued study drug administration at the same dose for another three weeks, for a total treatment period of five weeks.
What the maintenance dose was	Maximum allowed daily dosage of 10 sprays per Day.
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	Not described.
Stopping criteria	Not given.
Arm 2	Placebo (N = 150)
Formulation	"Matching placebo"
How dose was titrated up	"Matching placebo"
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	"Matching placebo"

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Some concerns

(High dropout rate of 30% in the THC + CBD arm and 25% in the placebo arm.)

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

(No information as to whether the assessors were blinded.)

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(No information on randomisation and blinding. High dropout rates: 30% in the THC + CBD arm and 20% in the placebo arm.)

Overall Directness

Cochrane Risk of Bias Tool 2.0

Directly applicable

Malik 2017

Malik, 2017

Bibliographic Reference	Malik, Z.; Bayman, L.; Valestin, J.; Rizvi-Toner, A.; Hashmi, S.; Schey, R.; Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial; Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus; 2017; vol. 30 (no. 2); 1-8
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Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Hospital
Study dates	Not provided. Study was published in 2017.
Duration of follow-up	4 weeks
Sources of funding	ACG clinical research grant
Inclusion criteria	Functional chest pain Of presumed esophageal origin according to Rome III - after various empirical therapies including PPI's, TCA, and SSRI had proved to be ineffective for at least 3 months. At least two weekly episodes of chest pain for the last 3 months. All patients had to have evidence of esophageal hypersensitivity with an abnormal esophageal balloon distention test (EBDT). Age 18 or over, male or female
Exclusion criteria	Pain from other concomitant conditions Over 75 years of age Clinically relevant abnormalities in investigations

Study type	Randomised controlled trial (RCT)
	<p>Patients taking certain medications History of requiring narcotics, other pain medications.</p> <p>Known history of alcohol or substance abuse</p> <p>Other disease of clinical importance Barrett's esophagus or peptic stricture and significant physical or psychiatric comorbidity.</p>
Sample size	<p>At start: 19 Completed: 13</p>
Split between study groups	<p>At start: intervention: 10; placebo: 9 Completed: intervention: 7; placebo: 6</p>
Loss to follow-up	<p>Intervention: 3 Placebo: 3</p>
% Female	<p>Intervention: not provided</p> <p>Placebo: not provided</p>
Mean age (SD)	<p>Intervention: 46</p> <p>Placebo: 35.5</p>
Outcome measures	<p>Adverse events</p>

Study arms

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Arm 1	Oral dronabinol (N = 7)
Formulation	Oral dronabinol
How dose was titrated up	No dose titration phase
What the maintenance dose was	Oral capsules of 5 mg dronabinol twice daily
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	Patients were contacted every 3 days by the research coordinators
Stopping criteria	Not described

Arm 2	Placebo (N = 6)
Formulation	Placebo capsules were matched accordingly to resemble dronabinol capsules
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	Patients were contacted every 3 days by the research coordinators

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Cochrane Risk of Bias Tool 2.0

High

(No information about the randomisation process. The ages of the participants in the dronabinol group was a median of 10 years older compared to the placebo group.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

High

(No data comparing the treatment effects in both arms. Quality of life measurements have p-values of 1, which is meaningless (100% uncertainty))

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Some concerns

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

High

(No data comparing the treatment effects in both arms.)

Overall bias and Directness

Risk of bias judgement

High

(No data comparing the treatment effects in both arms. Quality of life measurements have p-values of 1, which is meaningless (100% uncertainty). No information about the randomisation process. The ages of the participants in the dronabinol group was a median of 10 years older compared to the placebo group.)

Overall Directness

Directly applicable

Nurmikko 2007

Nurmikko, 2007

Bibliographic Reference	Nurmikko, Turo J.; Serpell, Mick G.; Hoggart, Barbara; Toomey, Peter J.; Morlion, Bart J.; Haines, Derek; Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial; Pain; 2007; vol. 133 (no. 13); 210-20
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Study details

Study type	Randomised controlled trial (RCT)
Study location	United Kingdom and Belgium
Study setting	Clinics
Study dates	Not disclosed. This study was submitted for publication in 2007.
Duration of follow-up	5 weeks
Sources of funding	GW Pharma
Inclusion criteria	<p>Unilateral peripheral neuropathic pain and allodynia</p> <p>Age 18 or over, male or female</p> <p>A history of at least 6 months duration of pain due to a clinically identifiable nerve lesion</p> <p>Demonstrate mechanical allodynia and impaired sensation within the territory of affected nerve(s) on clinical examination</p> <p>Patients with complex regional pain syndrome (CRPS) were eligible if they showed evidence of peripheral nerve lesion (diagnosed as CRPS type II)</p> <p>A baseline severity score of at least 4 on the numerical rating scale for spontaneous pain for at least 4 of 7 days in the baseline week</p> <p>A stable medication regimen of analgesics for at least 2 weeks prior to study entry</p>

Study type	Randomised controlled trial (RCT)
	<p>Female patients of childbearing potential and male patients whose partner was of childbearing potential had to agree to use effective contraception</p> <p>Willing for his or her name to be notified to the UK Home Office</p>
Exclusion criteria	<p>Cannabinoid use (cannabis, Marinol— (synthetic THC) or nabilone (synthetic cannabinoid analogue)) at least 7 days before randomisation. Subjects were required to abstain from use of cannabis during the study</p> <p>Schizophrenia, psychosis, or other major psychiatric condition beyond depression with underlying condition</p> <p>Concomitant severe non-neuropathic pain or the presence of cancer related neuropathic pain or from diabetes mellitus</p> <p>Known history of alcohol or substance abuse</p> <p>Severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment</p> <p>Scheduled surgery or anaesthesia</p> <p>Terminal illness or subjects inappropriate for placebo therapies</p> <p>Known hypersensitivity to cannabinoids</p> <p>Participation within a trial in the last 12 weeks</p>
Sample size	<p>At start: 125</p> <p>Completed: 105</p>
Split between study groups	<p>At start: intervention: 63; placebo: 62</p> <p>Completed: intervention: 50; placebo: 55</p>
Loss to follow-up	<p>Intervention: 13</p> <p>Placebo: 7</p>

Study type	Randomised controlled trial (RCT)
% Female	Intervention: 35% Placebo: 39%
Mean age (SD)	Intervention: 52.4 (15.8) Placebo: 54.3 (15.2)
Outcome measures	<p>Mean average pain intensity</p> <p>Functional impairment caused by pain: Pain Disability Index</p> <p>Patients experiencing adverse events, all-causality</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Patients experiencing serious adverse events, treatment-related</p> <p>Withdrawals due to adverse events, all-causality</p> <p>Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness, all-causality</p>

Study arms

Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 50)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	Initial dosing was under clinical supervision at the study site. A pre-dose 100 mm “Intoxication” (0 = no intoxication and 100 = extreme intoxication) Visual Analogue Scale (VAS) was obtained and vital signs were checked. A maximum of 8 sprays were administered over 2 h with Intoxication VAS and vital signs checked at regular intervals. If, following any dose, patients scored higher than 25 mm, or there were clinical concerns, e.g. the patients showing

	dysphoria or cardiovascular changes, subsequent doses were omitted. After satisfactory completion of initial dosing, patients began home dose titration and were allowed a maximum dose of 8 sprays per 3-hour interval and a maximum of 48 sprays per 24 h. At the next visit (after 7–10 days) titration, compliance and adverse events were reviewed, and patients advised on how to optimise dosing for the rest of the study period.
What the maintenance dose was	A maximum dose of 8 sprays per 3-hour interval and a maximum of 48 sprays per 24 h
How long the maintenance dose was sustained for	5 weeks
Monitoring/reviewing procedure	Periodic telephone monitoring was undertaken at pre-arranged times during home dosing to check the patient's condition and to answer any queries. Throughout the study, allowable concomitant medications or treatments were continued to provide adequate background analgesia at a constant dose.
Stopping criteria	None
Arm 2	Placebo (N = 55)
Formulation	The placebo medication was identical in composition, appearance, odour and taste with the study medication but without cannabis extract. That the smell and taste of the cannabinoid preparation might lead to unblinding was averted by disguising them with addition of peppermint oil to both preparations. All medication was provided in identical amber vials packaged and labelled by the sponsor.
How dose was titrated up	Same as for intervention
What the maintenance dose was	N/A
How long the maintenance dose was sustained for	5 weeks

Monitoring/reviewing
procedure

Same as for intervention

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

(There is always a chance that a system involving sealed envelopes can be abused.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Low

Cochrane Risk of Bias Tool 2.0

Overall Directness

Directly applicable

Portenoy 2012

Portenoy, 2012

Bibliographic
Reference

Portenoy, Russell K.; Ganae-Motan, Elena Doina; Allende, Silvia; Yanagihara, Ronald; Shaiova, Lauren; Weinstein, Sharon; McQuade, Robert; Wright, Stephen; Fallon, Marie T.; THC:CBD spray for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial; *The journal of pain : official journal of the American Pain Society*; 2012; vol. 13 (no. 5); 438-49

Study details

Study type	Randomised controlled trial (RCT)
Study location	84 study centres across North America, Europe, Latin America, and South Africa.
Study setting	Centres
Study dates	Not provided. Study was received for publication in 2011.
Duration of follow-up	1-week blinded dose titration period followed by 4 weeks of stable dosing.
Sources of funding	GW Pharmaceuticals and Otsuka. Supported in part by the Huntsman Cancer Foundation
Inclusion criteria	Age 18 or over, male or female Pain due to cancer Chronic. Moderate or severe despite a stable opioid regimen that could not be made more effective by further opioid dose titration.
Exclusion criteria	Psychiatric disorders Major psychiatric disorders.

Study type	Randomised controlled trial (RCT)
	<p>Severe cardiovascular disorder</p> <p>History of renal or hepatic disorder</p> <p>Pregnancy Or lactating or not using adequate contraception</p> <p>Patients who had received therapies expected to confound the study outcome Or who were to receive them.</p> <p>Prior cannabinoid use Within 30 days</p>
Sample size	<p>At start: 360 Completed: 263</p>
Split between study groups	<p>At start: 4 sprays: 91; 10 sprays: 88; 16 sprays: 90; placebo: 91 Completed: 4 sprays: 71; 10 sprays: 67; 16 sprays: 59; placebo: 66</p>
Loss to follow-up	<p>4 sprays: 20; 10 sprays: 21; 16 sprays: 31; placebo: 25</p>
% Female	<p>4 sprays: 50.5%; 10 sprays: 44.3%; 16 sprays: 46.7%; placebo: 51.6%</p>
Mean age (SD)	<p>4 sprays: 59 (12.3); 10 sprays: 59 (13.1); 16 sprays: 58 (11.2); placebo: 56 (12.2)</p>
Outcome measures	<p>Proportion of patients who experienced pain relief of 30% or more from baseline</p> <p>Mean average pain intensity</p> <p>Patients experiencing adverse events, all-causality</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Patients experiencing serious adverse events, treatment-related</p>

Study arms

Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 71), 1-4 actuations per day
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	1-week blinded dose titration period followed by 4 weeks of stable dosing. Patients randomly assigned to Group 1 (low dose) were instructed to titrate the study medication to between 1 and 4 sprays per day. Those assigned to Group 2 (medium dose) titrated the number of sprays to between 6 and 10 sprays per day, and those assigned to Group 3 (high dose) titrated to between 11 and 16 sprays per day. During the 1-week titration period, a schedule specific for each group was followed. In all groups, patients followed the titration schedule until they achieved the maximum target dose for the specific dose range, unless intolerable side effects prevented further dose escalation. Patients who were unable to reach the minimum target dose in the dose range to which they had been randomized were discontinued from the study.
What the maintenance dose was	1-4 actuations per day
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	After the 1-week titration period, the daily dose of the study medication was kept stable, unless exigent clinical problems prevented this. They were allowed to use their breakthrough opioid analgesic as required.
Stopping criteria	None mentioned
Arm 2	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 67), 6-10 actuations per day
Formulation	Same as above
How dose was titrated up	Same as above

What the maintenance dose was	6-10 actuations per day
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	Same as above
Stopping criteria	Not mentioned
Arm 3	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 59), 11-16 actuations per day
Formulation	Same as above
How dose was titrated up	Same as above
What the maintenance dose was	11-16 actuations per day
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	Same as above
Stopping criteria	Not mentioned

Arm 4	Placebo (N = 66)
Formulation	Each placebo dose contained only excipients plus colourants.
How dose was titrated up	Same as above
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	Same as above
Stopping criteria	Not mentioned

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Cochrane Risk of Bias Tool 2.0

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(No details on the randomisation process nor blinding.)

Overall Directness

Directly applicable

Rog 2005

Rog, 2005

Bibliographic
Reference

Rog, David J.; Nurmikko, Turo J.; Friede, Tim; Young, Carolyn A.; Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis; Neurology; 2005; vol. 65 (no. 6); 812-9

Study details

Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	Tertiary neurology centre
Study dates	Between March and July 2002
Duration of follow-up	5 weeks
Sources of funding	GW Pharmaceuticals
Inclusion criteria	Central neuropathic pain due to multiple sclerosis

Study type	Randomised controlled trial (RCT)
	The pain was of at least 3 months duration
Exclusion criteria	Pain from other concomitant conditions Other pain that was not central neuropathic pain Patients with a history of significant psychiatric conditions (other than depression) Cannabinoid use (cannabis, Marinol (synthetic THC) or nabilone (synthetic cannabinoid analogue)) at least 7 days before randomisation. Subjects were required to abstain from use of cannabis during the study Scheduled surgery or anaesthesia Known hypersensitivity to cannabinoids Pregnant or lactating
Sample size	At start: 66 Completed: 64
Split between study groups	At start: intervention: 34; placebo: 32 Completed: intervention: 32; placebo: 32
Loss to follow-up	Intervention: 2; placebo: 0
% Female	79%
Mean age (SD)	Intervention: 50.3 (6.7) Placebo: 48.1 (9.7)
Outcome measures	Mean average pain intensity Patients experiencing adverse events, all-causality

Study type	Randomised controlled trial (RCT)
	<p>Patients experiencing serious adverse events, all-causality</p> <p>Withdrawals due to adverse events, all-causality</p> <p>Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness, all-causality</p>

Study arms

Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 32)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation.
How dose was titrated up	<p>On the first day of treatment, up to four sprays were delivered in 2 hours and any signs of intoxication observed over 4 hours by the investigator and recorded by the patient on a 100-mm visual analogue scale (VAS) (0 = no intoxication and 100 = extreme intoxication). If the patient scored >25 mm on a predose VAS or the investigator had concerns, a dose could be omitted. Patient who satisfactorily completed initial dosing were given written instructions to begin home dose titration the following day.</p> <p>No specific target dose was set, and the patients were advised to increase the number of sprays stepwise on consecutive days up to 48 sprays (THC 129.6 mg: CBD 120 mg) in 24 hours. For safety reasons, the patients were advised to take no more than eight sprays (THC 21.6 mg: CBD 20 mg) within any 3-hour interval and refrain from up-titrating the daily dose by more than 50% from the previous day.</p> <p>If intoxication was experienced, patients were advised to reduce or omit a dose. If a maximum tolerated dose was thus established, it was only exceeded with caution. During telephone follow-up, patients were advised to optimize dosing when suboptimal benefit had been achieved.</p>
What the maintenance dose was	48 sprays (THC 129.6 mg: CBD 120 mg) in 24 hours.
How long the maintenance dose was sustained for	5 weeks

Monitoring/reviewing procedure	A phone call, performed by nursing staff, 14 to 20 days after the 5-week follow-up trial was initiated, included specific queries regarding the patient's titration of study medication, acceptability of dosing, AEs, changes in concomitant medication, and diary completion.
Stopping criteria	None
Arm 2	Placebo (N = 32)
Formulation	Placebo was designed to match the appearance, smell, and taste of the active formulation but contained no active components, in ethanol:propylene glycol (50:50) excipient.
How dose was titrated up	Same as medicinal cannabis
How long the maintenance dose was sustained for	5 weeks
Monitoring/reviewing procedure	Same as for medicinal cannabis

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Cochrane Risk of Bias Tool 2.0

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Schimrigk 2017

Schimrigk, 2017

Bibliographic
Reference

Schimrigk, Sebastian; Marziniak, Martin; Neubauer, Christine; Kugler, Eva Maria; Werner, Gudrun; Abramov-Sommariva, Dimitri; Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients; European neurology; 2017; vol. 78 (no. 56); 320-329

Study details

Study type

Randomised controlled trial (RCT)

Study location

Germany

Study type	Randomised controlled trial (RCT)
Study setting	Not described
Study dates	June 2007 to March 2010
Duration of follow-up	12 weeks
Sources of funding	Bionorica research GmbH
Inclusion criteria	<p>Age 18 or over, male or female</p> <p>Central neuropathic pain due to multiple sclerosis</p> <p>Using the McDonald criteria. Moderate to severe pain for at least 3 months.</p>
Exclusion criteria	<p>Over 70 years of age</p> <p>Other pain that was not central neuropathic pain</p> <p>History of psychotic illness</p> <p>Severe cardiovascular disorder</p> <p>Known history of alcohol or substance abuse</p> <p>Patients who had received therapies expected to confound the study outcome</p> <p>Amitriptyline and gabapentin</p>
Sample size	<p>At start: 240</p> <p>Completed: 209</p>
Split between study groups	<p>At start: intervention: 124; placebo: 116</p> <p>Completed: intervention: 105; placebo: 104</p>

Study type	Randomised controlled trial (RCT)
Loss to follow-up	Intervention: 19 Placebo: 12
% Female	Intervention: 71% Placebo: 75%
Mean age (SD)	Intervention: 48.4 (9.6) Placebo: 47.0 (9.7)
Outcome measures	Mean average pain intensity Patients experiencing adverse events, all-causality Patients experiencing adverse events, treatment-related Patients experiencing serious adverse events, all-causality Patients experiencing serious adverse events, treatment-related Withdrawals due to adverse events, all-causality

Study arms

Arm 1	Oral dronabinol (N = 105)
Formulation	Oral dronabinol
How dose was titrated up	4 weeks titration period to establish the patient-specific tolerable dose. Dosing was increased every 5 days by 2.5 mg to reach a daily dose between 7.5 and 15.0 mg.

What the maintenance dose was	A daily dose between 7.5 and 15.0 mg.
How long the maintenance dose was sustained for	12 weeks
Monitoring/reviewing procedure	For safety analysis, vital signs, laboratory parameters, (serious) AEs (SAEs) including (serious) adverse reactions (SARs) were regularly assessed.
Stopping criteria	Not described
Arm 2	
Formulation	Not described
How dose was titrated up	Not described
How long the maintenance dose was sustained for	12 weeks
Monitoring/reviewing procedure	For safety analysis, vital signs, laboratory parameters, (serious) AEs (SAEs) including (serious) adverse reactions (SARs) were regularly assessed.

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Cochrane Risk of Bias Tool 2.0

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Serpell 2014

Serpell, 2014

Bibliographic
Reference

Serpell, M.; Ratcliffe, S.; Hovorka, J.; Schofield, M.; Taylor, L.; Lauder, H.; Ehler, E.; A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment; European journal of pain (London, England); 2014; vol. 18 (no. 7); 999-1012

Study details

Study type	Randomised controlled trial (RCT)
Study location	The study took place at 21 centres in the United Kingdom (UK), seven centres in Czech Republic, six centres in Romania, four centres in Belgium and one centre in Canada.
Study setting	Clinical centres
Study dates	September 2005 to October 2006
Duration of follow-up	15 weeks
Sources of funding	GW Pharma
Inclusion criteria	<p>Age 18 or over, male or female</p> <p>Allodynia mechanical allodynia within the territory of the affected nerve(s) (confirmed by either a positive response to stroking the allodynic area with a brush 05 or to force applied by a 5.07 g monofilament)</p> <p>Neuropathic pain At least 6 months and peripheral. Eligible patients had at least one of the following underlying conditions, which caused their PNP: post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy or Complex Regional Pain Syndrome (CRPS) type 2. Patients also had a sum score of at least 24 on a pain 0–10 NRS for more than 6 days (baseline days 2–7) during the baseline period (average 0–10 NRS score of 4/10), and pain that was not wholly relieved by their current therapy.</p> <p>A stable medication regimen of analgesics for at least 2 weeks prior to study entry</p>
Exclusion criteria	<p>Pain from other concomitant conditions</p> <p>Patients with history of renal, hepatic, cardiovascular, convulsive disorder, or with sensitivity to cannabis</p> <p>Pain resulting from diabetes</p> <p>Any analgesics taken on a when required basis</p> <p>Changes to current analgesia</p> <p>Known history of alcohol or substance abuse</p>

Study type	Randomised controlled trial (RCT)
	<p>Women of child-bearing potential or their partners were excluded unless willing to ensure effective contraception was used throughout the study</p> <p>Patients who had received an investigational medical product Within 12 weeks of screening</p> <p>Pregnant or lactating</p> <p>Patients with any physical abnormality Any abnormalities that, in the opinion of the investigator, would prevent the patient from safely participating in the study</p> <p>Prior cannabinoid use Within the past year</p> <p>Patients receiving prohibited medication</p> <p>Patients intending to travel</p> <p>Patients intending to donate blood</p>
Sample size	<p>At start: 246</p> <p>Completed: 173</p>
Split between study groups	<p>At start: intervention: 128; placebo: 118</p> <p>Completed: intervention: 79; placebo: 94</p>
Loss to follow-up	<p>Intervention: 49</p> <p>Placebo: 24</p>
% Female	<p>Intervention: 66%</p> <p>Placebo: 55%</p>

Study type	Randomised controlled trial (RCT)
Mean age (SD)	Intervention: 57.6 (14.4) Placebo: 57.0 (14.1)
Outcome measures	<p>Mean average pain intensity</p> <p>Proportion of patients who experienced pain relief of 30% or more from baseline</p> <p>Proportion of patients who experienced pain relief of 50% or more from baseline</p> <p>Functional impairment caused by pain: Brief Pain Inventory - Short Form</p> <p>Change in analgesics: daily change in paracetamol, number of rescue (breakthrough) medication paracetamol tablets</p> <p>Patient Global Impression of Change (dichotomous)</p> <p>Quality of life: EQ-5D index</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Patients experiencing serious adverse events, treatment-related</p> <p>Withdrawals due to adverse events, all-causality</p>

Study arms

Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 79)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation.
How dose was titrated up	Patients self-administered the medication to their optimal dose, but were restricted to a maximum of eight sprays in a 3-h period up to a maximum of 24 sprays per 24-h period. Initially, patients began at a maximum of one spray per 4-

	period. Thereafter patients were advised to self-titrate their medication to symptom relief or maximum dose, but increases were limited to a maximum of 50% of the previous day's dose.
What the maintenance dose was	Maximum of 24 sprays per 24-h period
How long the maintenance dose was sustained for	15 weeks
Monitoring/reviewing procedure	Not described
Stopping criteria	Not described
Arm 2	Placebo (N = 94)
Formulation	Each spray of placebo delivered the excipients plus colorants. Both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste.
How dose was titrated up	Same as intervention
How long the maintenance dose was sustained for	15 weeks
Monitoring/reviewing procedure	Not described

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

High

(Staff were assigning. The randomised process should have been assigning patients to arms.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

High

(Staff were assigning. The randomised process should have been assigning patients to arms. In addition, the investigators had sealed envelopes that had details of assignment. Sealed envelope systems can be abused.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

High

(Very high dropout rate in the cannabis arm (40%). Staff were assigning. The randomised process should have been assigning patients to arms. In addition, the investigators had sealed envelopes that had details of assignment. Sealed envelope systems can be abused.)

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Some concerns

(40% dropout rate in the cannabis arm.)

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

High

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

High

(Staff were assigning. The randomised process should have been assigning patients to arms. In addition, the investigators had sealed envelopes that had details of assignment. Sealed envelope systems can be abused. Cannabis arm had a 40% dropout rate.)

Cochrane Risk of Bias Tool 2.0

Overall Directness

Directly applicable

Skrabek 2008

Skrabek, 2008

Bibliographic
Reference

Skrabek, Ryan Quinlan; Galimova, Lena; Ethans, Karen; Perry, Daryl; Nabilone for the treatment of pain in fibromyalgia; The journal of pain : official journal of the American Pain Society; 2008; vol. 9 (no. 2); 164-73

Study details

Study type	Randomised controlled trial (RCT)
Study location	Canada
Study setting	Outpatient clinic
Study dates	April to November 2006
Duration of follow-up	1 week
Sources of funding	Valeant Canada Limited and an HSC Medical Staff Council Fellowship Fund
Inclusion criteria	Fibromyalgia According to the American College of Rheumatology criteria. Continued pain despite the use of other oral medications Age 18 or over, male or female
Exclusion criteria	Over 70 years of age Prior cannabinoid use For pain management Clinically relevant abnormalities in investigations Routine blood tests

Study type	Randomised controlled trial (RCT)
	History of psychotic illness Severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment Known hypersensitivity to cannabinoids
Sample size	At start: 40 Completed: 33
Split between study groups	At start: intervention: 20; placebo: 20 Completed: intervention: 15; placebo: 18
Loss to follow-up	Intervention: 5 Placebo: 2
% Female	Intervention: 100% Placebo: 85%
Mean age (SD)	Intervention: 47.5 (9.13) Placebo: 50.11 (5.96)
Outcome measures	Mean average pain intensity Functional impairment caused by pain: Fibromyalgia Impact Questionnaire Patients experiencing adverse events, all-causality Withdrawals due to adverse events, all-causality

Study arms

Arm 1	
	Oral nabilone (N = 15)
Formulation	Oral nabilone
How dose was titrated up	Subjects in the treatment group received 0.5 mg nabilone once at bedtime for a 1-week period, with instructions to increase to 0.5 mg twice a day after 7 days. At the 2-week visit, subjects were evaluated for the presence of side effects and drug tolerance, and if they consented to continue, had the prescription increased to nabilone 0.5 mg once in the morning and 1 mg once at bedtime, with instructions to increase to 1 mg twice a day after 7 days.
What the maintenance dose was	2 mg (1 mg twice a day)
How long the maintenance dose was sustained for	1 week
Monitoring/reviewing procedure	Not described
Stopping criteria	Not described
Arm 2	
Formulation	Identical to intervention
How dose was titrated up	Identical to intervention
How long the maintenance dose was sustained for	1 week

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Some Concerns

("Examiners" were blinded. However, no mention of other staff.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for this domain

Some concerns

(In the nabilone arm, the dropout rate was 25% compared to 10% in the placebo arm.)

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

Some concerns

(Lack of information about randomisation and blinding.)

Overall Directness

Cochrane Risk of Bias Tool 2.0

Directly applicable

Wade 2004

Wade, 2004

Bibliographic Reference	Wade, Derick T.; Makela, Petra; Robson, Philip; House, Heather; Bateman, Cynthia; Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients; Multiple sclerosis (Houndmills, Basingstoke, England); 2004; vol. 10 (no. 4); 434-41
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Study details

Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	3 clinical centres
Study dates	Not reported. This study was submitted for publication in 2004.
Duration of follow-up	6 weeks
Sources of funding	GW Pharmaceuticals
Inclusion criteria	<p>Diagnosis of MS of any type</p> <p>Stable symptoms Over previous 4 weeks with no relapse</p> <p>Stable treatment Unchanged in 4 weeks before study entry</p> <p>Willing to abstain from other cannabis use during trial 7 days before screening and throughout study</p>

Study type	Randomised controlled trial (RCT)
	<p>1 of 5 target symptoms at a sufficient level of severity Spasticity, spasms, bladder problems, tremor, pain (not musculoskeletal). If more than 1, patients nominated most troublesome</p>
Exclusion criteria	<p>Primary symptom rated less than 50% maximal severity using VAS</p> <p>Known history of alcohol or substance abuse</p> <p>Patients with a history of significant psychiatric conditions (other than depression) Other than depression associated with MS</p> <p>Severe cardiovascular disorder</p> <p>History of renal or hepatic disorder</p> <p>History of seizures</p> <p>Planned travel abroad during study</p>
Sample size	<p>At start: 160</p> <p>Completed: 154</p>
Split between study groups	<p>At start:</p> <p>THC/CBD: 80 (20 with spasticity primary symptom; 18 with pain)</p> <p>Placebo: 80 (19 with spasticity primary symptom; 19 with pain)</p> <p>Completed: intervention: 77; placebo 77</p>
Loss to follow-up	<p>THC/CBD: 3</p> <p>Placebo: 3</p>

Study type	Randomised controlled trial (RCT)
% Female	THC/CBD: 58.7% Placebo: 65%
Mean age (SD)	THC/CBD: 51.0 (9.4) Placebo: 50.4 (9.3)
Outcome measures	Mean average pain intensity Visual Analogue Scale (0 to 100) Incidences of adverse events

Study arms

Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 77)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	Supervision of the first dose, given in the clinic, was followed by instructions to titrate slowly during home dosing, aiming for optimal balance of symptom relief and unwanted effects. Guidelines were given for increments up to a maximum of 120 mg THC and 120 mg CBD per day with no more than 20 mg of each in any 3-hour period.
What the maintenance dose was	This study exceeded the SPC's advice of a maximum of 12 actuations per day. The mean average number of actuations was 17.5 per day.
How long the maintenance dose was sustained for	6 weeks
Monitoring/reviewing procedure	During the initial dose titration phase, patients recorded the time and number of actuations per day, in a dosing diary. Regular telephone contact was maintained according to individual patient requirements and a brief safety visit was conducted after two weeks, to review dosing and adverse events.
Stopping criteria	None

Arm 2	Placebo (N = 77)
Formulation	The placebo spray contained excipients only. All preparations incorporated a peppermint flavour and colouring to disguise the taste and appearance of medicinal cannabis.
How dose was titrated up	Same as the medicinal cannabis
What the maintenance dose was	Same as the medicinal cannabis
How long the maintenance dose was sustained for	6 weeks
Monitoring/reviewing procedure	Same as the medicinal cannabis
Stopping criteria	None

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomization process

Risk of bias judgement for this domain

High

(Staff treating the patients were probably not blinded.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Risk of bias for this domain

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Cochrane Risk of Bias Tool 2.0

Risk of bias judgement for this domain

Low

Domain 3. Bias due to missing outcome data

Risk-of-bias judgement for this domain

Low

Domain 4. Bias in measurement of the outcome

Risk-of-bias judgement for this domain

Low

Domain 5. Bias in selection of the reported result

Risk-of-bias judgement domain

Low

Overall bias and Directness

Risk of bias judgement

High

(The pharmacist assigned treatments using a sequential patient number order from an appropriate randomisation list. The methods section does not state that the pharmacist was blinded. The methods section explains that the patients and assessors were blinded, but not the staff managing the patients.)

Overall Directness

Directly applicable

E.2 Crossover RCTs

de Vries 2016

de Vries, 2016

Bibliographic
Reference

de Vries, Marjan; Van Rijckevorsel, Dagmar C. M.; Vissers, Kris C. P.; Wilder-Smith, Oliver H. G.; Van Goor, Harry; Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability; British journal of clinical pharmacology; 2016; vol. 81 (no. 3); 525-37

Study details

Study type	Cross-over randomised controlled trial
Study location	The Netherlands
Study setting	Medical centre
Study dates	October 2011 to May 2013
Duration of follow-up	4 weeks
Sources of funding	European Union, the European Fund for Regional Development
Inclusion criteria	<p>Age 18 or over, male or female</p> <p>Chronic pain resulting from chronic pancreatitis</p> <p>All patients had chronic abdominal pain, persistent or intermittent on a daily basis during the past 3 months, and considered their pain as severe enough for medical treatment (numeric rating scale (NRS) ≥ 3). Patients in the opioid subgroup took stable doses of prescribed opioids, whereas patients in the non-opioid subgroup had not taken opioids or only occasionally for pain flares in the past 2 months.</p>
Exclusion criteria	<p>Prior cannabinoid use During the previous year</p> <p>Known hypersensitivity to cannabinoids</p> <p>High body mass index BMI <18.0 or >31.2 kg/m²</p> <p>Pain from other concomitant conditions</p> <p>Patients who had received therapies expected to confound the study outcome</p> <p>Serious illness/medical condition likely to interfere with study assessment</p> <p>Psychiatric disorders</p> <p>Patients taking certain medications More than 1 daily defined dose (DDD) benzodiazepines 6 h prior to or following intake of study medication in the opioid subgroup or more than 1 DDD benzodiazepines according to prescription in the non-opioid subgroup (1 DDD was defined as 20 mg oxazepam).</p>

Study type	Cross-over randomised controlled trial
	<p>History of seizures</p> <p>Known history of alcohol or substance abuse</p> <p>Pregnant or lactating</p> <p>Clinically relevant abnormalities in investigations</p> <p>Participating in another investigational study</p> <p>Within 90 days of study entry</p>
Sample size	<p>At start: 24</p> <p>Completed: 22</p>
Loss to follow-up	2
% Female	37.5%
Mean age (SD)	51.8 (9.3)
Outcome measures	<p>Mean average pain intensity</p> <p>Patients experiencing adverse events, all-causality</p> <p>Withdrawals due to adverse events, all-causality</p>

Study arms

Arm 1	Oral delta-9-THC (dronabinol) (N = 24)
Formulation	Oral delta-9-THC

How dose was titrated up	One 8 mg dose was given only.
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What the maintenance dose was	N/A
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How long the maintenance dose was sustained for	N/A
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Arm 2

Formulation	Placebo was not described
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How dose was titrated up	1 dose only was given
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Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Cochrane Risk of Bias Tool 2.0

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Indirectly applicable

Only 1 dose given. This is not a realistic assessment for the treatment of chronic pain.

Lynch 2014

Lynch, 2014

Bibliographic
Reference

Lynch, Mary E.; Cesar-Rittenberg, Paula; Hohmann, Andrea G.; A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain; Journal of pain and symptom management; 2014; vol. 47 (no. 1); 166-73

Study details

Study type	Cross-over randomised controlled trial
Study location	Canada and/or USA
Study setting	Not provided
Study dates	Not provided
Duration of follow-up	4 weeks

Study type	Cross-over randomised controlled trial
Sources of funding	GW Pharmaceuticals
Inclusion criteria	Neuropathic pain caused by chemotherapy For over 3 months. Pain intensity had to score 4/10 or more. Concurrent analgesics had to be stable for 14 days before entry into the trial.
Exclusion criteria	Severe cardiovascular disorder History of seizures History of psychotic illness Known history of alcohol or substance abuse Within the previous 2 years Pregnancy
Sample size	At start: 18 Completed: 16
Loss to follow-up	2
% Female	83%
Mean age (SD)	Not provided
Outcome measures	Mean average pain intensity Quality of life: SF-36 physical Quality of life: SF-36 mental

Study arms

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Arm 1	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation (N = 18)
Formulation	Oromucosal spray THC 2.7 mg and CBD 2.5 mg per 100 microlitre actuation
How dose was titrated up	The patients were instructed to start with one spray of the study medication under the tongue or inside of the cheek before bed the first night. Participants then increased the study medication by one to two sprays per day until they reached a dose that helped their pain; they were asked not to exceed 12 sprays per day and stop increases if limiting side effects, such as sedation, were encountered.
What the maintenance dose was	Maximum of 12 sprays per day
How long the maintenance dose was sustained for	4 weeks
Monitoring/reviewing procedure	Not described
Stopping criteria	At the end of the first study period, they were instructed to decrease the medication by one to two sprays per day until discontinued and underwent a two week washout phase before returning for the second study medication. The terminal elimination half-lives of the cannabinoids in THC:CBD spray are 24-36 hours or longer. Thus, the two week washout was chosen to assure no carry over effect between study arms.
Arm 2	Placebo (N = 18)
Formulation	The placebo was packaged in exactly the same way as the intervention, with a similar yellowish colour and peppermint flavour.
How dose was titrated up	Same as intervention

How long the maintenance dose was sustained for	4 weeks
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Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Cochrane Risk of Bias Tool 2.0

Overall Directness

Directly applicable

Svendsen 2004

Svendsen, 2004

Bibliographic
Reference

Svendsen, Kristina B.; Jensen, Troels S.; Bach, Flemming W.; Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial; BMJ (Clinical research ed.); 2004; vol. 329 (no. 7460); 253

Study details

Study type	Cross-over randomised controlled trial
Study location	Denmark
Study setting	Outpatient clinics
Study dates	February to May 2002
Duration of follow-up	Median of 18 to 20 days
Sources of funding	Danish Multiple Sclerosis Society
Inclusion criteria	<p>Central neuropathic pain due to multiple sclerosis</p> <p>Multiple sclerosis (clinical definite multiple sclerosis and laboratory supported definite multiple sclerosis), age between 18 and 55 years, and central pain at the maximal pain site with a pain intensity score ≥ 3 on a 0 to 10 numerical rating scale. A doctor assessed central pain after a clinical examination. The criterion for central pain was pain in a body territory with abnormal sensation to pinprick, touch, warmth, or cold, evaluated by the bedside, or quantitative sensory testing corresponding to at least one lesion in the central nervous system.</p>
Exclusion criteria	<p>Pain from other concomitant conditions</p> <p>Known hypersensitivity to cannabinoids</p> <p>Psychiatric disorders</p>

Study type	Cross-over randomised controlled trial
	<p>Known history of alcohol or substance abuse</p> <p>Pregnant or lactating Or at risk of becoming pregnant</p> <p>Patients taking certain medications Treatment with tricyclic antidepressants, anticholinergic agents, antihistamine, or central nervous system depressant drugs (with the exception of spasmolytic drugs); use of analgesic drugs except paracetamol.</p> <p>Severe heart disease</p> <p>Participating in another investigational study Within the previous month</p> <p>Previous cannabis use Within 3 months before the study</p>
Sample size	24
Loss to follow-up	None
% Female	58%
Mean age (SD)	50 (range 23-55)
Outcome measures	<p>Median average pain intensity</p> <p>Quality of life: SF-36 median average</p> <p>Patients experiencing adverse events, all-causality</p> <p>Patients experiencing serious adverse events, all-causality</p> <p>Withdrawals due to adverse events, all-causality</p>

Study arms

Arm 1	Oral delta-9-THC (dronabinol) (N = 24)
Formulation	Oral delta-9-THC
How dose was titrated up	2.5 mg capsules and used dosage escalation. The initial dose was 2.5 mg daily, and the dose was increased by 2.5 mg every other day to a maximum dose of 5 mg (two capsules) twice daily.
What the maintenance dose was	5 mg (two capsules) twice daily
How long the maintenance dose was sustained for	18-21 days
Monitoring/reviewing procedure	Not described
Stopping criteria	None
Arm 2	Placebo (N = 24)
Formulation	Placebo capsules were administered as identical looking capsules. The active capsules contained delta-9-THC solution in sesame oil, and the placebo capsules contained pure sesame oil.
How dose was titrated up	Same as for intervention
How long the maintenance dose was sustained for	18-21 days

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

van de Donk 2019

van de Donk, 2019

Bibliographic Reference van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain*. 2019 Apr;160(4):860-869

Study details

Study type	Cross-over randomised controlled trial
Study location	The Netherlands
Study setting	Medical centre
Study dates	Not provided
Duration of follow-up	3 hours after the single dose
Sources of funding	Bedrocan International BV
Inclusion criteria	Fibromyalgia A pain score 5 or more for most of the day (on a verbal pain scale from 0 = no pain to 10 = most pain imaginable) and positive diagnostic criteria of the 2010 American College of Rheumatology. Female
Exclusion criteria	Pain from other concomitant conditions Known hypersensitivity to cannabinoids Recent cannabinoid use An addiction to illicit substances (including marijuana) or alcohol Pregnant or lactating Age under 18 years Any medical, neurological or psychiatric illness Use of strong opioids or other painkillers except paracetamol and/or ibuprofen Benzodiazepine use

Study type	Cross-over randomised controlled trial
Sample size	At start: 25 Completed: 20
Loss to follow-up	5
% Female	100%
Mean age (SD)	39 ± 13 years
Outcome measures	Mean average pain intensity Proportion of patients who experienced pain relief of 30% or more from baseline Proportion of patients who experienced pain relief of 50% or more from baseline

Study arms

Arm 1	Vaporised 22.4 mg THC and <1 mg CBD
Formulation	A single dose of vaporised <1 mg THC and 18.4 mg CBD
Arm 2	Vaporised 13.4 mg THC and 17.8 mg CBD
Formulation	A single dose of vaporised 13.4 mg THC and 17.8 mg CBD
Arm 3	Vaporised <1 mg THC and 18.4 mg CBD
Formulation	A single dose of vaporised <1 mg THC and 18.4 mg CBD

Arm 4	Placebo
Formulation	A single dose of vaporised placebo

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

High

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

Cochrane Risk of Bias Tool 2.0

The incidence of patients experiencing adverse events was not reported. Data for the proportion of patients who experienced pain relief of 30% or 50% or more from baseline was not provided in an extractable format for 2 of the 3 interventions.

Overall Directness

Indirectly applicable

(Only one dose given, and the outcome was measured 3 hours afterwards. This is not a realistic way of assessing chronic pain treatment.)

Weber 2010

Weber, 2010

Bibliographic Reference	Weber, M.; Goldman, B.; Truniger, S.; Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: a randomised, double-blind crossover trial; Journal of neurology, neurosurgery, and psychiatry; 2010; vol. 81 (no. 10); 1135-40
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Study details

Study type	Cross-over randomised controlled trial
Study location	Switzerland
Study setting	Not disclosed
Study dates	May 2005 to February 2008
Duration of follow-up	2 weeks
Sources of funding	Amyotrophic Lateral Sclerosis Association (ALSA)
Inclusion criteria	Cramps caused by amyotrophic lateral sclerosis Adult patients diagnosed as having possible, probable laboratory supported, probable or definite ALS according to the revised El Escorial criteria and with an average daily cramp severity score of 4 and more (on a visual analogue scale (VAS)) were eligible.
Exclusion criteria	Prior cannabinoid use At least 1 month prior to entry

Study type	Cross-over randomised controlled trial
	Other disease of clinical importance Patients were excluded if they were demented, had significant concomitant illness(-es), had a past history of a psychiatric disorder, explicitly of schizophrenia, were current drug or alcohol abusers. Known hypersensitivity to cannabinoids
Sample size	24
Loss to follow-up	2
% Female	26%
Mean age (SD)	57 (12)
Outcome measures	Mean average pain intensity Patients experiencing adverse events, all-causality

Study arms

Arm 1	Oral delta-9-THC (dronabinol) (N = 24)
Formulation	Oral delta-9-THC
How dose was titrated up	No dose titration
What the maintenance dose was	The study medication (six drops equivalent to 5 mg delta-9-THC) was taken twice daily (10 mg total).
How long the maintenance dose was sustained for	2 weeks
Monitoring/reviewing procedure	Not mentioned

Stopping criteria	None
Arm 2	Placebo (N = 24)
Formulation	Placebo was not described
How long the maintenance dose was sustained for	2 weeks

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Low

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

Low

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Cochrane Risk of Bias Tool 2.0

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

Low

Overall Directness

Directly applicable

Wissel 2006

Wissel, 2006

Bibliographic
Reference

Wissel, Jorg; Haydn, Tanja; Muller, Jorg; Brenneis, Christian; Berger, Thomas; Poewe, Werner; Schelosky, Ludwig D.; Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial; Journal of neurology; 2006; vol. 253 (no. 10); 1337-41

Study details

Study type	Cross-over randomised controlled trial
Study location	Austria, Germany, Switzerland
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	4 weeks per treatment (1 week washout period)
Sources of funding	Not reported
Inclusion criteria	Chronic upper motor neuron syndrome Spasticity Disabling spasticity-related pain

Study type	Cross-over randomised controlled trial
	Current therapy failed to provide adequate relief Passive stretch of the spastic muscles had to result in increased pain perception in the stimulated muscles
Exclusion criteria	None
Sample size	13
Split between study groups	Cross-over trial (all 13 patients completed both trials)
Loss to follow-up	None reported
% Female	69.2%
Mean age (SD)	44.8 (14.3)
Outcome measures	Median average pain intensity Patients experiencing adverse events, all-causality Patients experiencing serious adverse events, all-causality Withdrawals due to adverse events, all-causality

Study arms

Arm 1	Oral nabilone (N = 13)
Formulation	Nabilone capsules
How dose was titrated up	1 week titration phase

	Week 1: 0.5 mg per day Week 3: 1 mg per day
What the maintenance dose was	1 mg per day
How long the maintenance dose was sustained for	3 weeks
Monitoring/reviewing procedure	No information on timing of clinic visits Monitoring included review of spasticity, motor performance, Barthel Index, other medication usage, adverse events
Stopping criteria	No information provided
Arm 2	Placebo (N = 13)
Formulation	Identical placebo capsules
How long the maintenance dose was sustained for	3 weeks

Cochrane Risk of Bias Tool 2.0

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

High

(No information provided on randomisation, blinding nor baseline characteristics.)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Cochrane Risk of Bias Tool 2.0

Some concerns

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

Some concerns

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Some concerns

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Low

Overall bias and Directness

Risk of bias judgement

High

(No information provided on randomisation, blinding nor baseline characteristics.)

Overall Directness

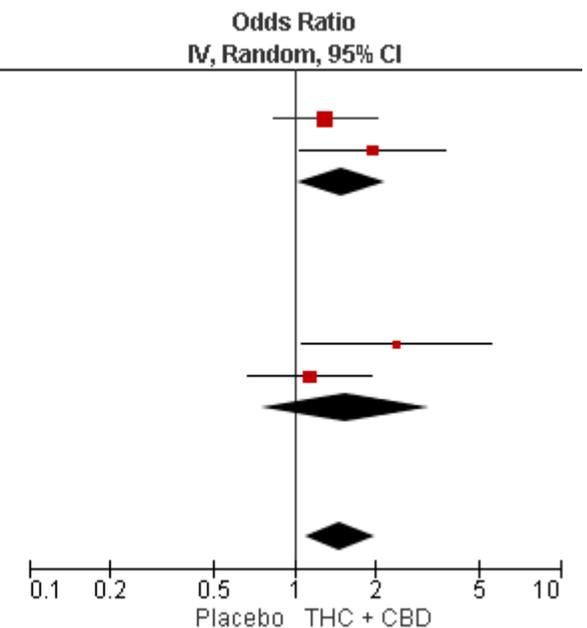
Directly applicable

Appendix F – Forest plots

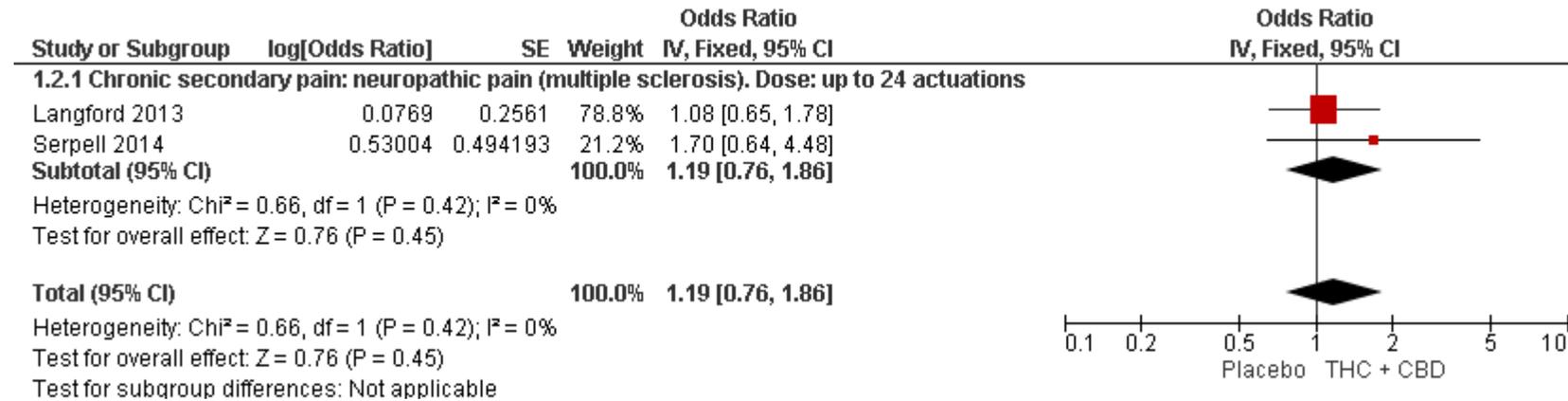
THC:CBD spray vs placebo

Proportion of people who experienced pain relief of 30% or more from baseline

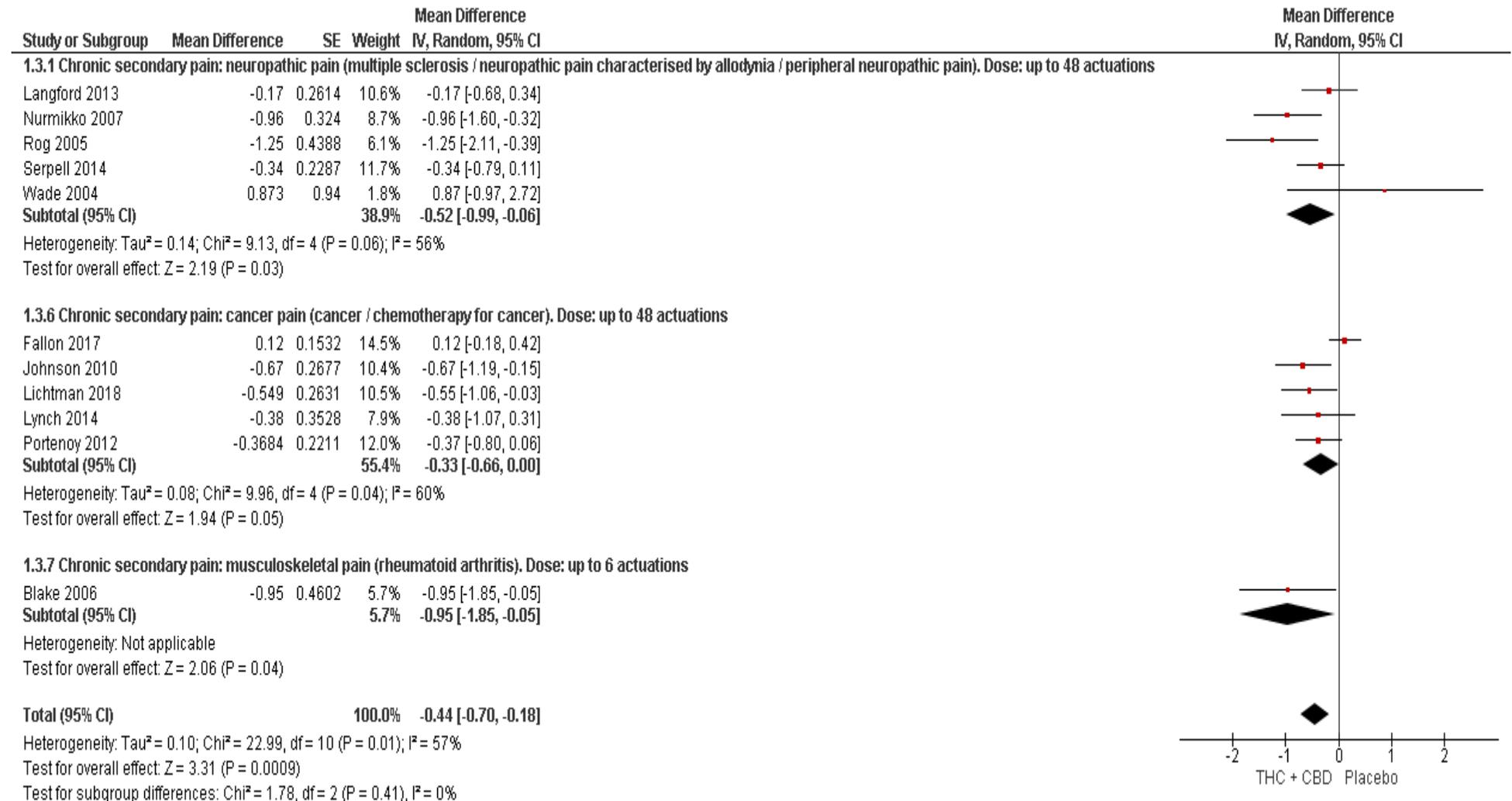
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Chronic secondary pain: neuropathic pain (multiple sclerosis / peripheral neuropathic pain). Dose: up to 24 actuations				
Langford 2013	0.270027	0.226353	38.5%	1.31 [0.84, 2.04]
Serpell 2014	0.678034	0.321693	20.8%	1.97 [1.05, 3.70]
Subtotal (95% CI)			59.3%	1.51 [1.03, 2.20]
Heterogeneity: Tau ² = 0.01; Chi ² = 1.08, df = 1 (P = 0.30); I ² = 7%				
Test for overall effect: Z = 2.12 (P = 0.03)				
1.1.3 Chronic secondary pain: cancer pain. Dose: up to 48 actuations				
Johnson 2010	0.887891	0.419013	12.8%	2.43 [1.07, 5.52]
Portenoy 2012	0.1363	0.2733	27.9%	1.15 [0.67, 1.96]
Subtotal (95% CI)			40.7%	1.56 [0.76, 3.22]
Heterogeneity: Tau ² = 0.16; Chi ² = 2.26, df = 1 (P = 0.13); I ² = 56%				
Test for overall effect: Z = 1.20 (P = 0.23)				
Total (95% CI)			100.0%	1.49 [1.10, 2.01]
Heterogeneity: Tau ² = 0.01; Chi ² = 3.36, df = 3 (P = 0.34); I ² = 11%				
Test for overall effect: Z = 2.57 (P = 0.01)				
Test for subgroup differences: Chi ² = 0.01, df = 1 (P = 0.93), I ² = 0%				



Proportion of people who experienced pain relief of 50% or more from baseline

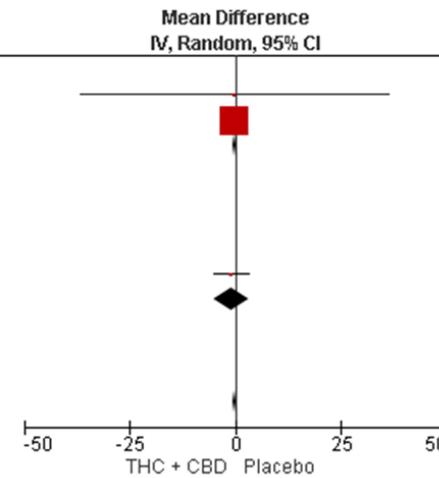


Mean average pain intensity: Numerical Rating Scale (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS

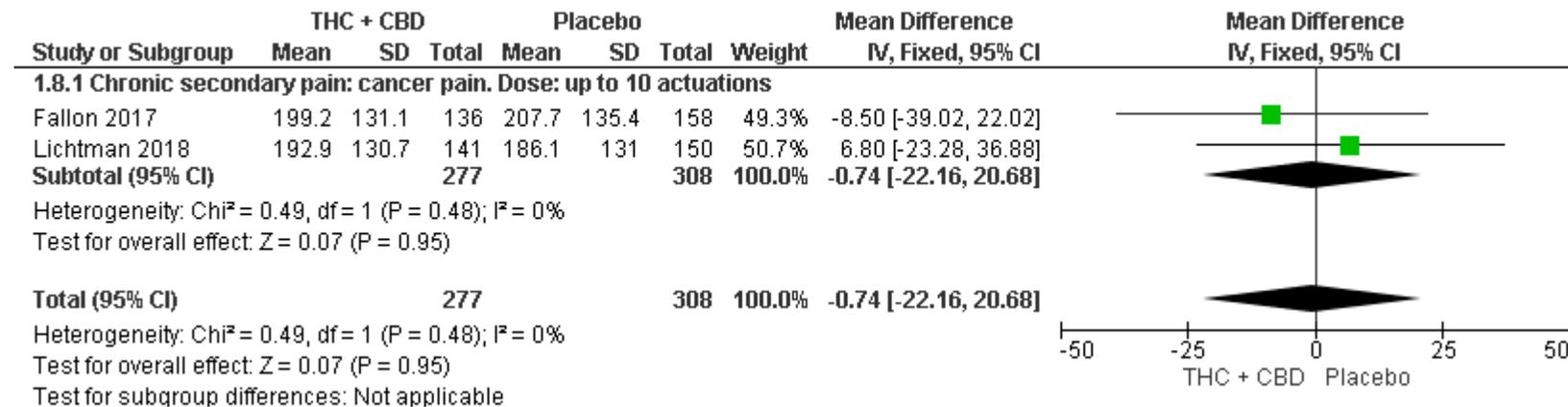


Functional impairment caused by pain: Brief Pain Inventory - Short Form

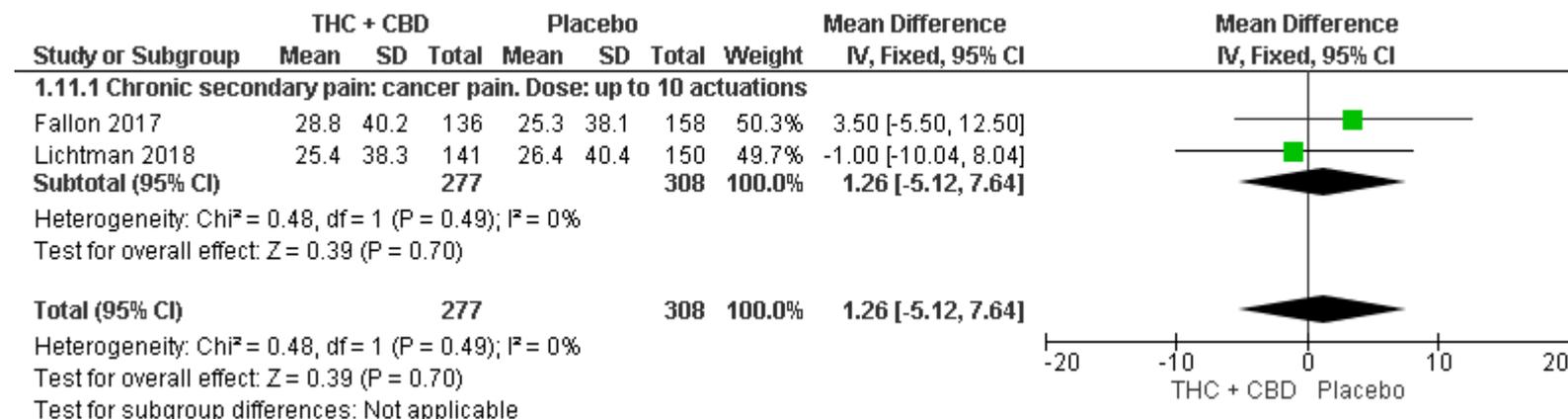
Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Chronic secondary pain: neuropathic pain (multiple sclerosis / peripheral neuropathic pain). Dose: up to 24 actuations				
Langford 2013	-0.12	18.6292	0.0%	-0.12 [-36.63, 36.39]
Serpell 2014	-0.25	0.2345	98.7%	-0.25 [-0.71, 0.21]
Subtotal (95% CI)			98.8%	-0.25 [-0.71, 0.21]
Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); I ² = 0%				
Test for overall effect: Z = 1.07 (P = 0.29)				
1.6.2 Chronic secondary pain: cancer pain. Dose: up to 48 actuations				
Johnson 2010	-1.04	2.0847	1.2%	-1.04 [-5.13, 3.05]
Subtotal (95% CI)			1.2%	-1.04 [-5.13, 3.05]
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.50 (P = 0.62)				
Total (95% CI)			100.0%	-0.26 [-0.72, 0.20]
Heterogeneity: Tau ² = 0.00; Chi ² = 0.14, df = 2 (P = 0.93); I ² = 0%				
Test for overall effect: Z = 1.12 (P = 0.26)				
Test for subgroup differences: Chi ² = 0.14, df = 1 (P = 0.71), I ² = 0%				



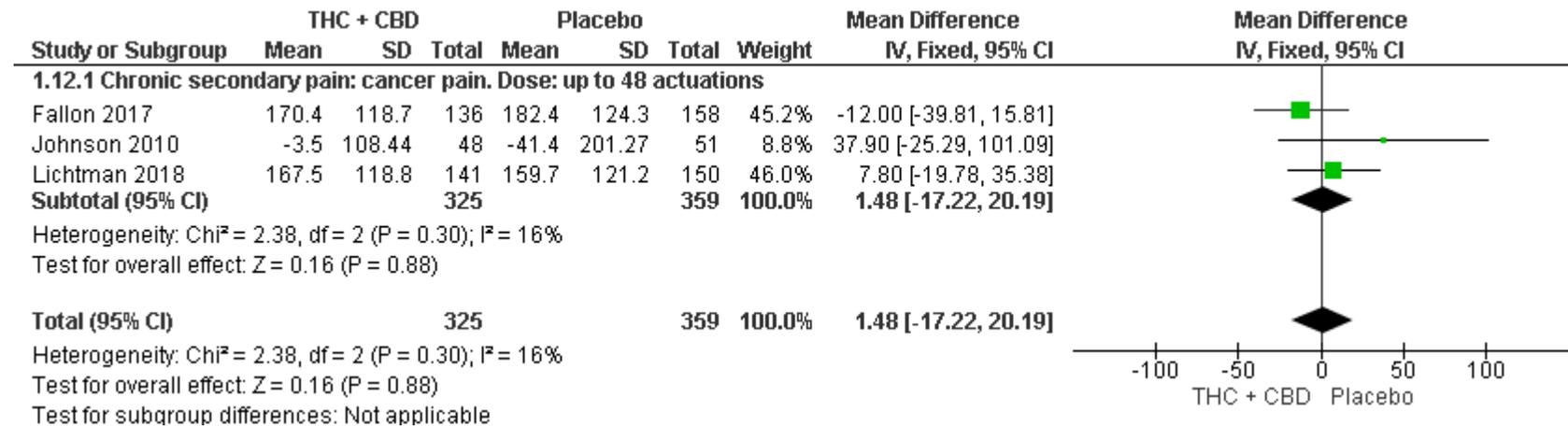
Change in analgesics: daily change in total dose, morphine equivalents



Change in analgesics: daily change in breakthrough dose, morphine equivalents

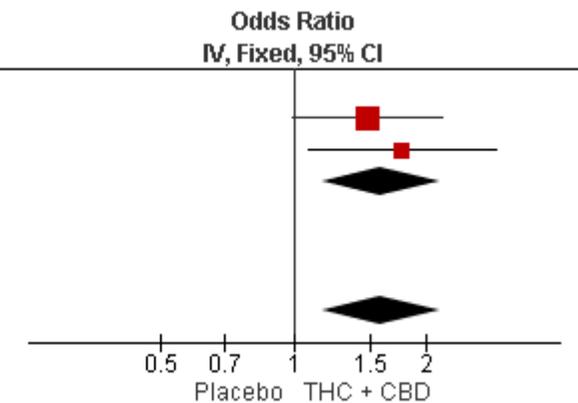


Change in analgesics: daily change in breakthrough dose, morphine equivalents



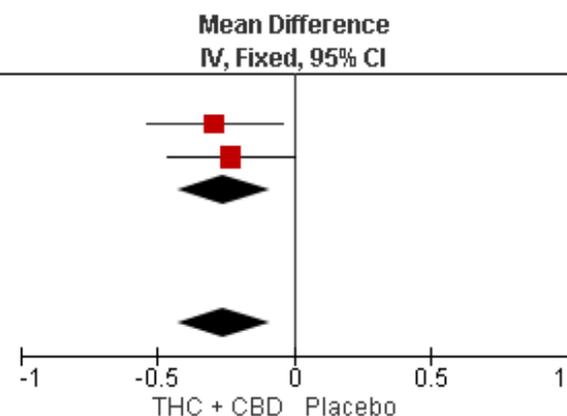
Patient Global Impression of Change (dichotomous)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
1.13.1 Chronic secondary pain: neuropathic pain (multiple sclerosis / peripheral neuropathic pain). Dose: up to 24 actuations				
Langford 2013	0.385262	0.201371	60.6%	1.47 [0.99, 2.18]
Serpell 2014	0.56645	0.249857	39.4%	1.76 [1.08, 2.88]
Subtotal (95% CI)			100.0%	1.58 [1.16, 2.15]
Heterogeneity: Chi ² = 0.32, df = 1 (P = 0.57); I ² = 0%				
Test for overall effect: Z = 2.91 (P = 0.004)				
Total (95% CI)			100.0%	1.58 [1.16, 2.15]
Heterogeneity: Chi ² = 0.32, df = 1 (P = 0.57); I ² = 0%				
Test for overall effect: Z = 2.91 (P = 0.004)				
Test for subgroup differences: Not applicable				



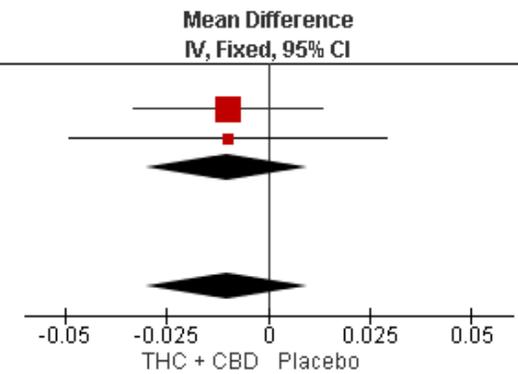
Patient Global Impression of Change (continuous)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
1.14.1 Chronic secondary pain: cancer pain. Dose: up to 10 actuations				
Fallon 2017	-0.29	0.1259	46.7%	-0.29 [-0.54, -0.04]
Lichtman 2018	-0.23	0.1179	53.3%	-0.23 [-0.46, 0.00]
Subtotal (95% CI)			100.0%	-0.26 [-0.43, -0.09]
Heterogeneity: Chi ² = 0.12, df = 1 (P = 0.73); I ² = 0%				
Test for overall effect: Z = 3.00 (P = 0.003)				
Total (95% CI)			100.0%	-0.26 [-0.43, -0.09]
Heterogeneity: Chi ² = 0.12, df = 1 (P = 0.73); I ² = 0%				
Test for overall effect: Z = 3.00 (P = 0.003)				
Test for subgroup differences: Not applicable				

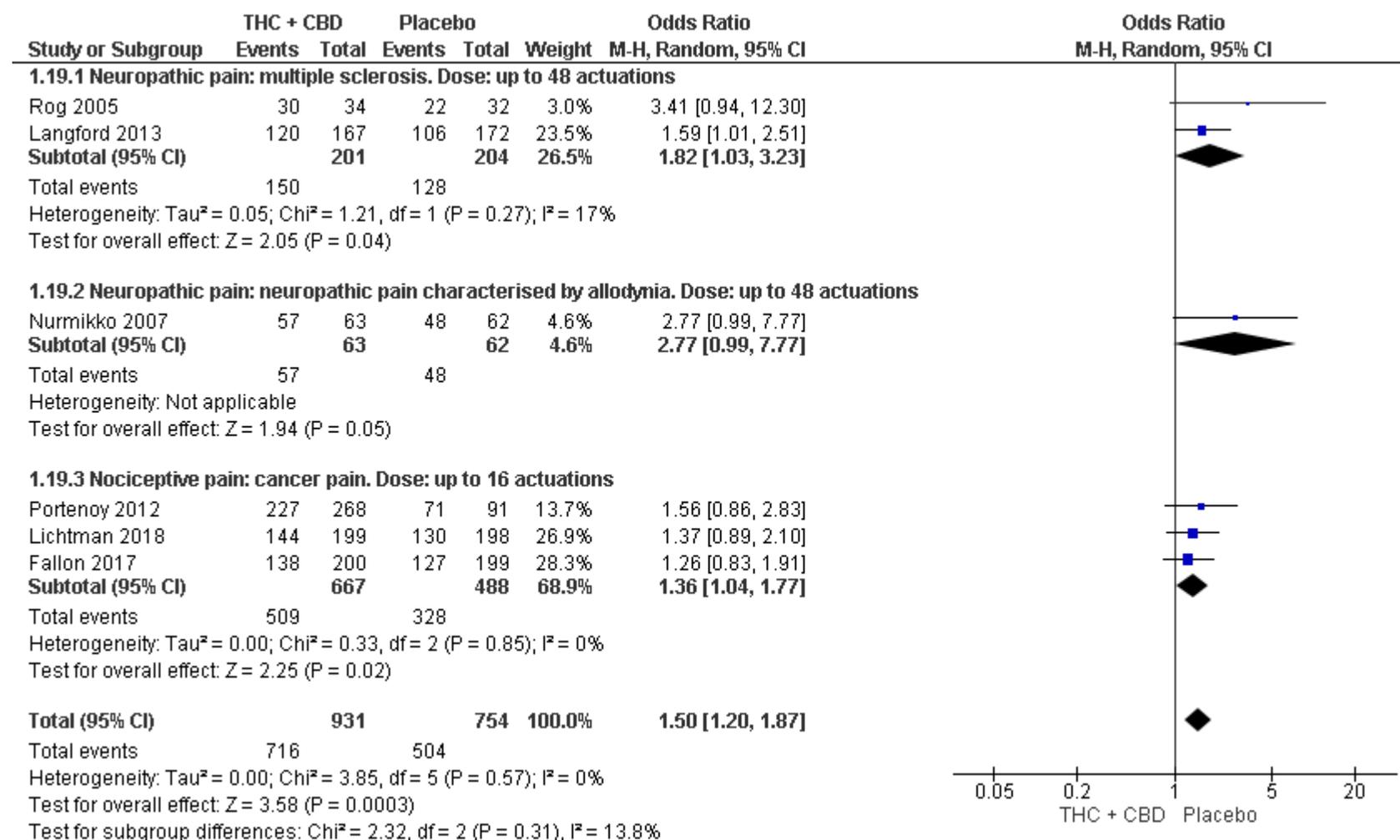


Quality of life: EQ-5D index

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference	
				IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.16.1 Chronic secondary pain: neuropathic pain (multiple sclerosis / peripheral neuropathic pain). Dose: up to 24 actuations					
Langford 2013	-0.01	0.0118	74.0%	-0.01	[-0.03, 0.01]
Serpell 2014	-0.01	0.0199	26.0%	-0.01	[-0.05, 0.03]
Subtotal (95% CI)			100.0%	-0.01	[-0.03, 0.01]
Heterogeneity: Chi ² = 0.00, df = 1 (P = 1.00); I ² = 0%					
Test for overall effect: Z = 0.99 (P = 0.32)					
Total (95% CI)			100.0%	-0.01	[-0.03, 0.01]
Heterogeneity: Chi ² = 0.00, df = 1 (P = 1.00); I ² = 0%					
Test for overall effect: Z = 0.99 (P = 0.32)					
Test for subgroup differences: Not applicable					



People experiencing adverse events, all-causality



People experiencing serious adverse events, all-causality

Study or Subgroup	THC + CBD		Placebo		Weight	Odds Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
1.20.1 Chronic secondary pain: neuropathic pain (multiple sclerosis / neuropathic pain characterised by allodynia / peripheral neuropathic pain). Dose: up to 48 actuations							
Langford 2013	2	167	1	172	1.9%	2.07 [0.19, 23.08]	
Nurmikko 2007	9	63	6	62	8.0%	1.56 [0.52, 4.67]	
Rog 2005	0	34	0	32		Not estimable	
Serpell 2014	10	128	6	118	8.7%	1.58 [0.56, 4.50]	
Subtotal (95% CI)		392		384	18.5%	1.61 [0.78, 3.31]	

Total events 21 13
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)

1.20.4 Chronic secondary pain: cancer pain. Dose: up to 48 actuations

Fallon 2017	35	199	44	198	24.3%	0.75 [0.46, 1.23]	
Johnson 2010	14	60	7	59	9.5%	2.26 [0.84, 6.09]	
Lichtman 2018	36	199	27	198	22.0%	1.40 [0.81, 2.41]	
Portenoy 2012	81	268	23	91	22.1%	1.28 [0.75, 2.20]	
Subtotal (95% CI)		726		546	77.8%	1.20 [0.80, 1.79]	

Total events 166 101
Heterogeneity: Tau² = 0.07; Chi² = 5.36, df = 3 (P = 0.15); I² = 44%
Test for overall effect: Z = 0.87 (P = 0.38)

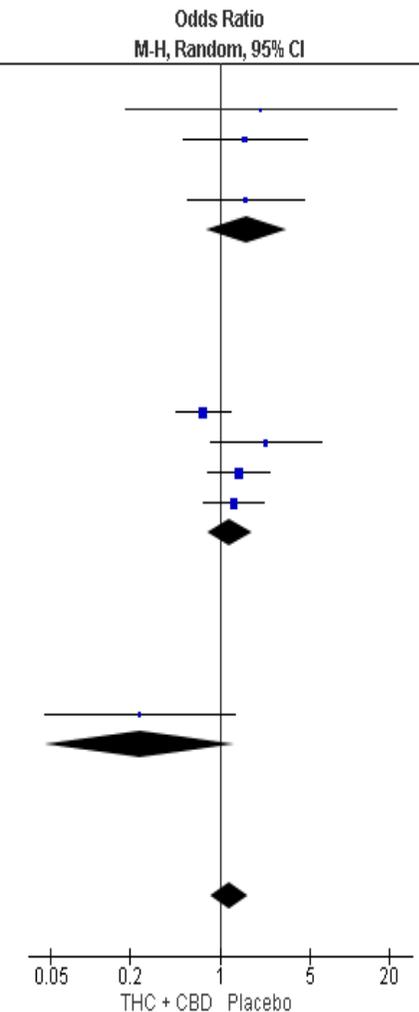
1.20.5 Chronic secondary pain: musculoskeletal pain (rheumatoid arthritis). Dose: up to 6 actuations

Blake 2006	2	31	6	27	3.7%	0.24 [0.04, 1.32]	
Subtotal (95% CI)		31		27	3.7%	0.24 [0.04, 1.32]	

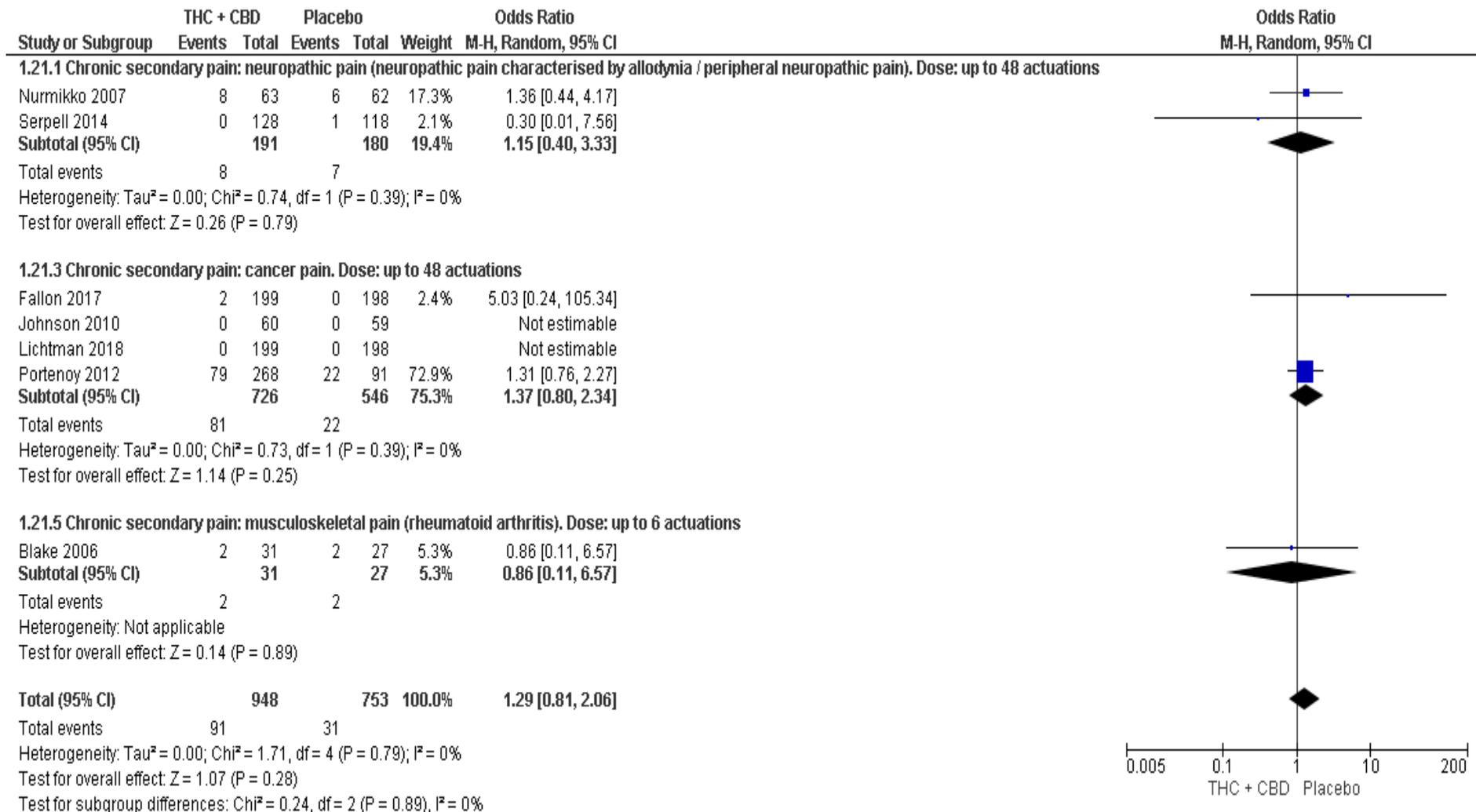
Total events 2 6
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)

Total (95% CI) 1149 957 100.0% **1.19 [0.85, 1.66]**

Total events 189 120
Heterogeneity: Tau² = 0.06; Chi² = 9.49, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Chi² = 4.07, df = 2 (P = 0.13), I² = 50.8%



People experiencing serious adverse events, treatment-related



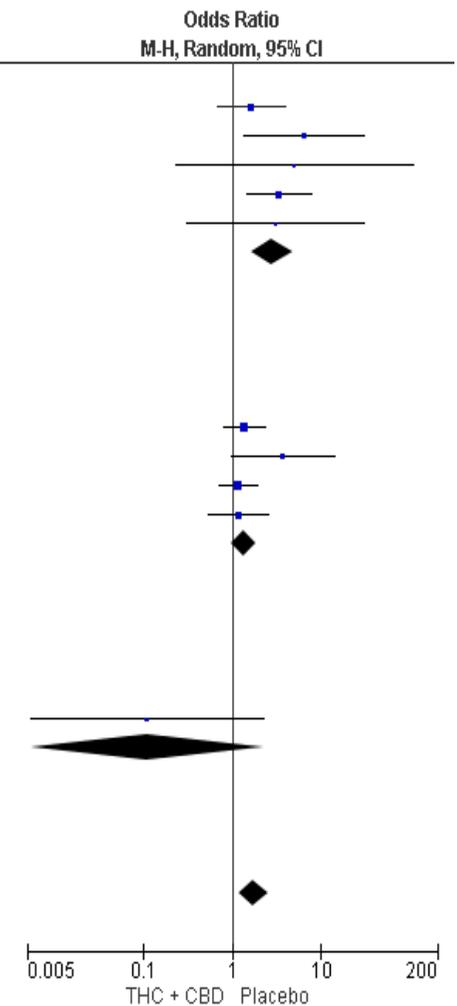
Withdrawals due to adverse events, all-causality

Study or Subgroup	THC + CBD		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
1.22.1 Chronic secondary pain: neuropathic pain (multiple sclerosis / neuropathic pain characterised by allodynia / peripheral neuropathic pain). Dose: up to 48 actuations						
Langford 2013	14	167	9	172	12.6%	1.66 [0.70, 3.94]
Nurmikko 2007	11	63	2	62	5.3%	6.35 [1.34, 29.95]
Rog 2005	2	34	0	32	1.5%	5.00 [0.23, 108.25]
Serpell 2014	25	128	8	118	13.1%	3.34 [1.44, 7.73]
Wade 2004	3	80	1	80	2.7%	3.08 [0.31, 30.24]
Subtotal (95% CI)		472		464	35.1%	2.77 [1.62, 4.75]
Total events	55		20			
Heterogeneity: Tau ² = 0.00; Chi ² = 2.81, df = 4 (P = 0.59); I ² = 0%						
Test for overall effect: Z = 3.72 (P = 0.0002)						

1.22.4 Chronic secondary pain: cancer pain. Dose: up to 48 actuations						
Fallon 2017	38	199	29	198	20.8%	1.38 [0.81, 2.34]
Johnson 2010	10	60	3	59	6.7%	3.73 [0.97, 14.33]
Lichtman 2018	40	199	35	198	21.6%	1.17 [0.71, 1.94]
Portenoy 2012	31	269	9	91	14.2%	1.19 [0.54, 2.60]
Subtotal (95% CI)		727		546	63.3%	1.33 [0.97, 1.83]
Total events	119		76			
Heterogeneity: Tau ² = 0.00; Chi ² = 2.61, df = 3 (P = 0.46); I ² = 0%						
Test for overall effect: Z = 1.74 (P = 0.08)						

1.22.5 Chronic secondary pain: musculoskeletal pain (rheumatoid arthritis). Dose: up to 6 actuations						
Blake 2006	0	31	3	27	1.6%	0.11 [0.01, 2.25]
Subtotal (95% CI)		31		27	1.6%	0.11 [0.01, 2.25]
Total events	0		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						

Total (95% CI)		1230		1037	100.0%	1.74 [1.18, 2.56]
Total events	174		99			
Heterogeneity: Tau ² = 0.12; Chi ² = 13.71, df = 9 (P = 0.13); I ² = 34%						
Test for overall effect: Z = 2.78 (P = 0.005)						
Test for subgroup differences: Chi ² = 8.31, df = 2 (P = 0.02), I ² = 75.9%						



Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness

Study or Subgroup	THC + CBD		Placebo		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
1.24.1 Chronic secondary pain: neuropathic pain (multiple sclerosis / neuropathic pain characterised by allodynia). Dose: up to 48 actuations						
Nurmikko 2007	1	63	0	62	33.4%	3.00 [0.12, 75.07]
Rog 2005	1	34	0	32	33.0%	2.91 [0.11, 74.08]
Subtotal (95% CI)		97		94	66.4%	2.96 [0.30, 28.97]

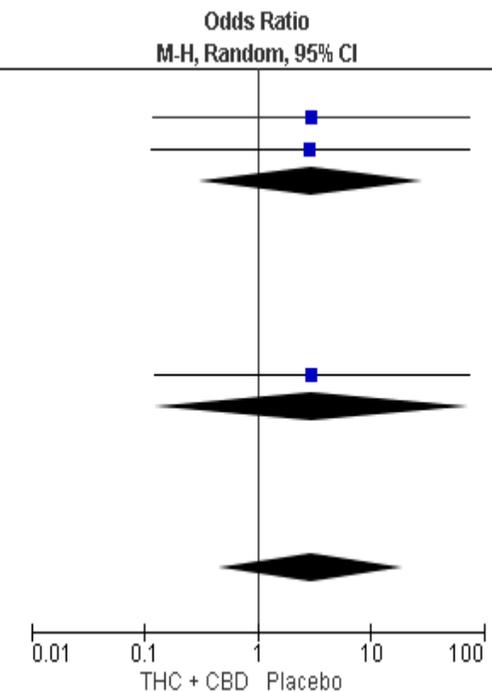
Total events: 2 (THC + CBD), 0 (Placebo)
Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 0.00$, $\text{df} = 1$ ($P = 0.99$); $I^2 = 0\%$
Test for overall effect: $Z = 0.93$ ($P = 0.35$)

1.24.3 Chronic secondary pain: cancer pain. Dose: up to 10 actuations						
Lichtman 2018	1	199	0	198	33.6%	3.00 [0.12, 74.09]
Subtotal (95% CI)		199		198	33.6%	3.00 [0.12, 74.09]

Total events: 1 (THC + CBD), 0 (Placebo)
Heterogeneity: Not applicable
Test for overall effect: $Z = 0.67$ ($P = 0.50$)

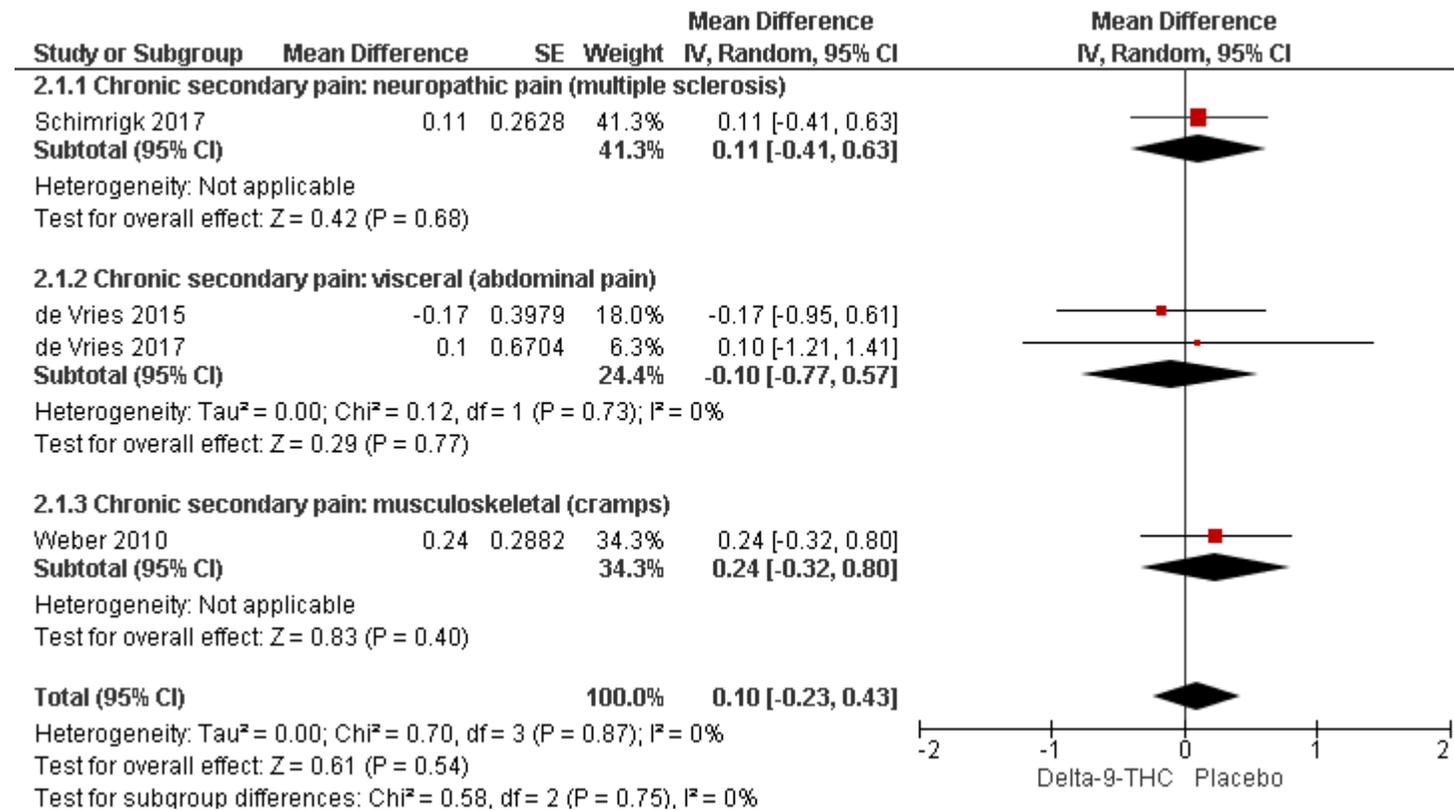
Total (95% CI)		296		292	100.0%	2.97 [0.46, 19.07]
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Total events: 3 (THC + CBD), 0 (Placebo)
Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 0.00$, $\text{df} = 2$ ($P = 1.00$); $I^2 = 0\%$
Test for overall effect: $Z = 1.15$ ($P = 0.25$)
Test for subgroup differences: $\text{Chi}^2 = 0.00$, $\text{df} = 1$ ($P = 0.99$), $I^2 = 0\%$

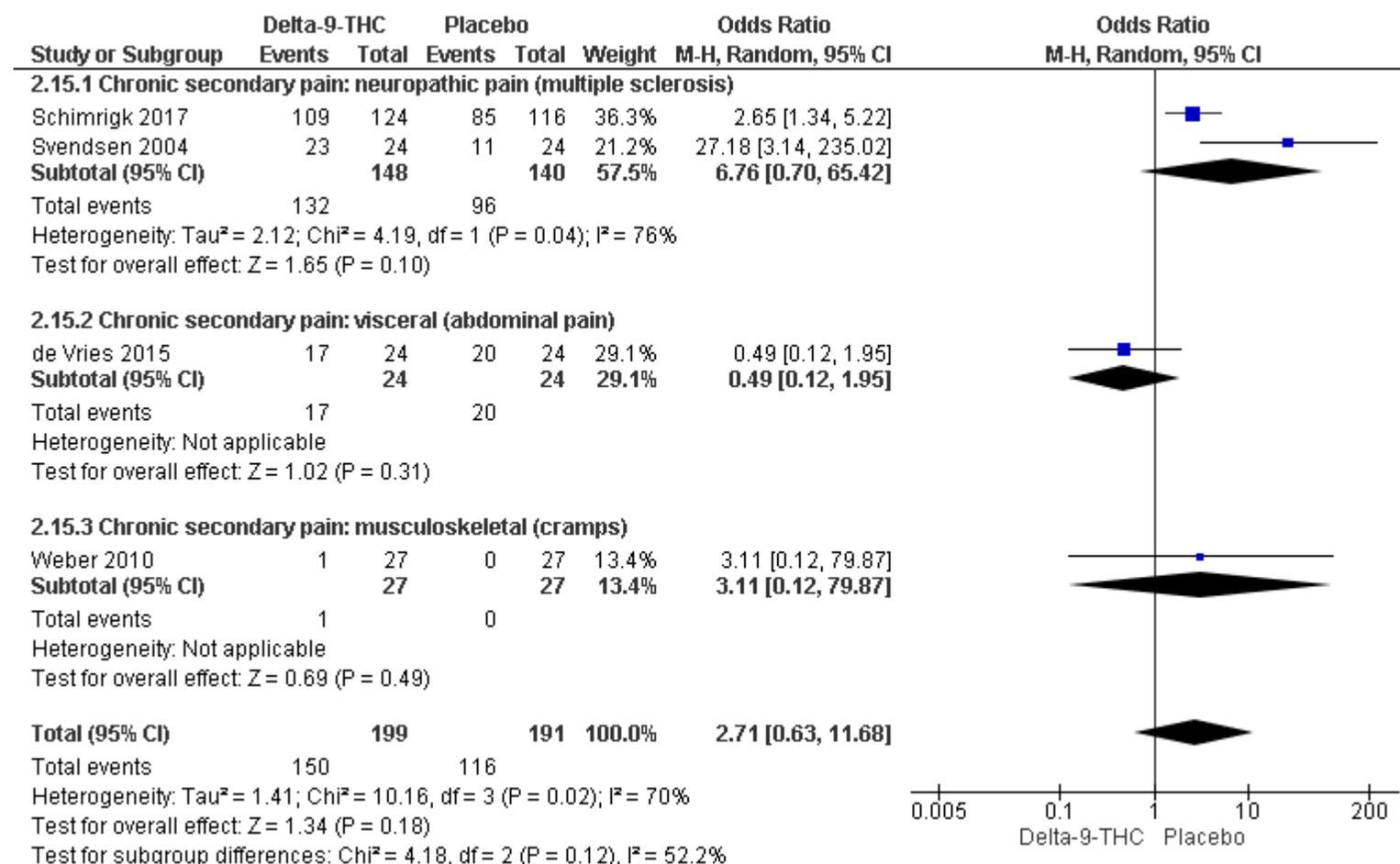


Oral delta-9-THC (dronabinol), 7.5 to 16 mg per 24 hours vs placebo

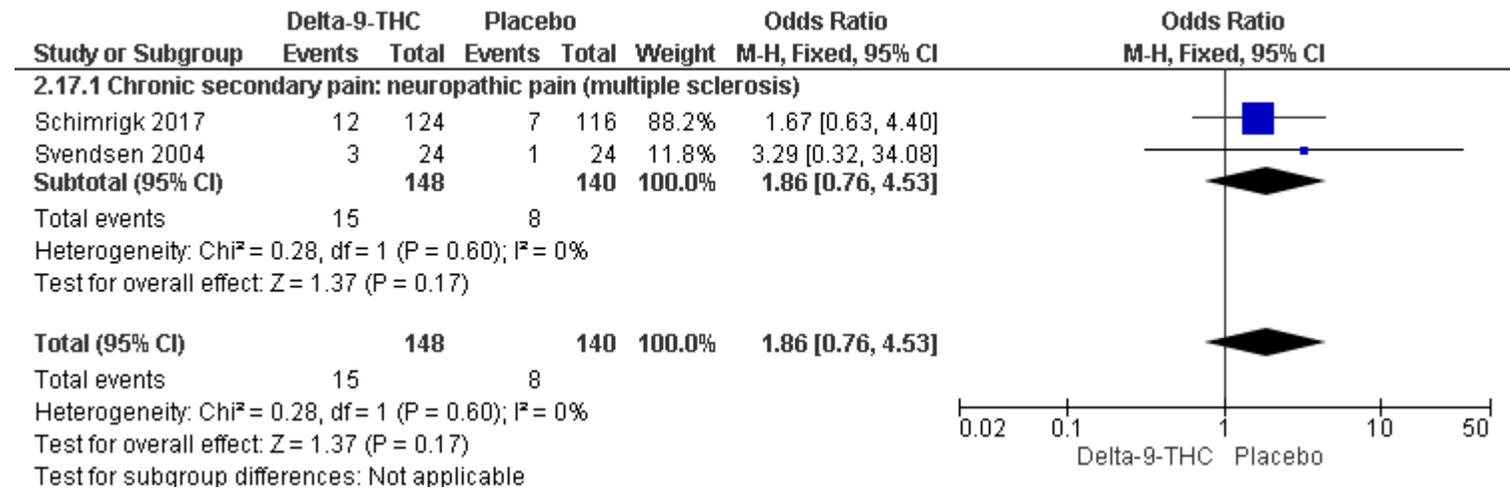
Mean average pain intensity: Numerical Rating Scale' (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS



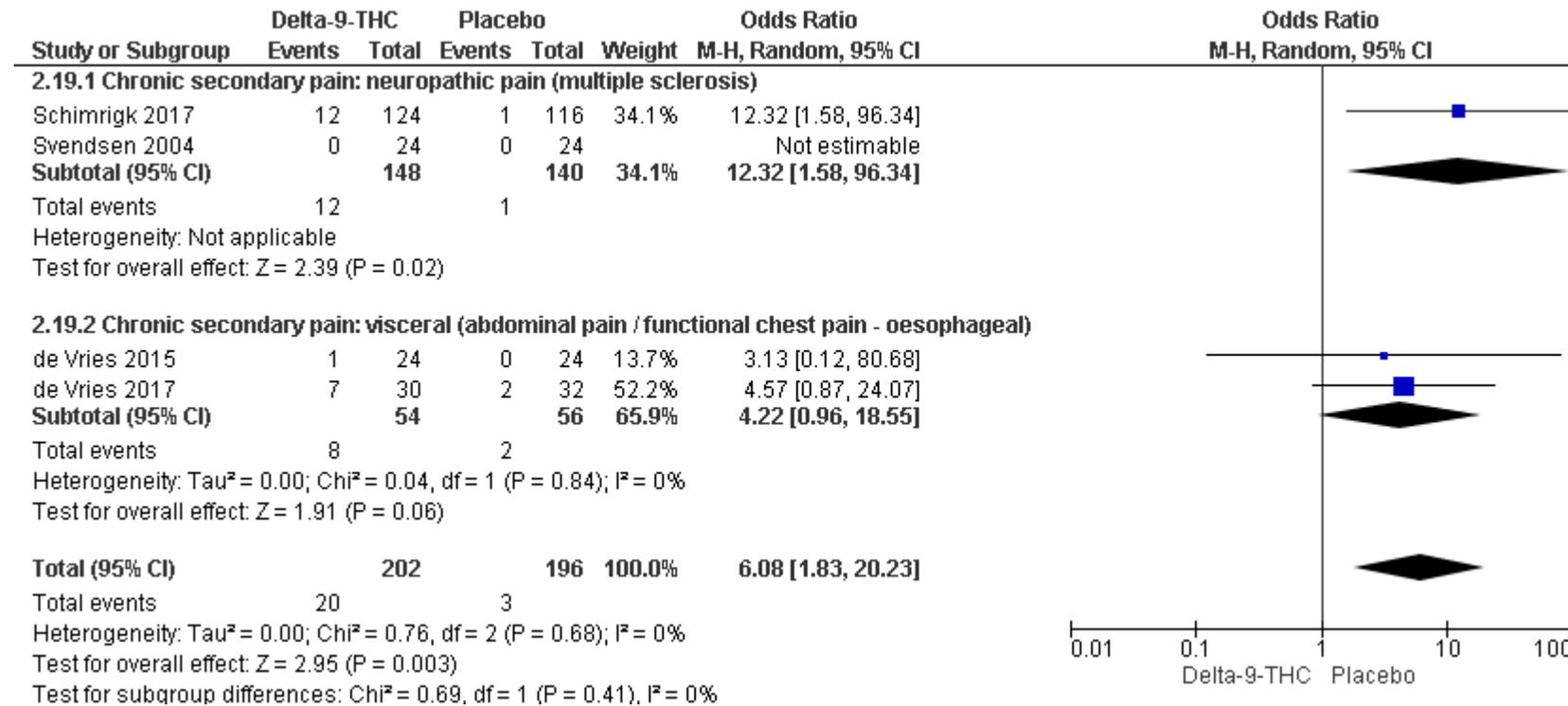
People experiencing adverse events, all-causality



People experiencing serious adverse events, all-causality

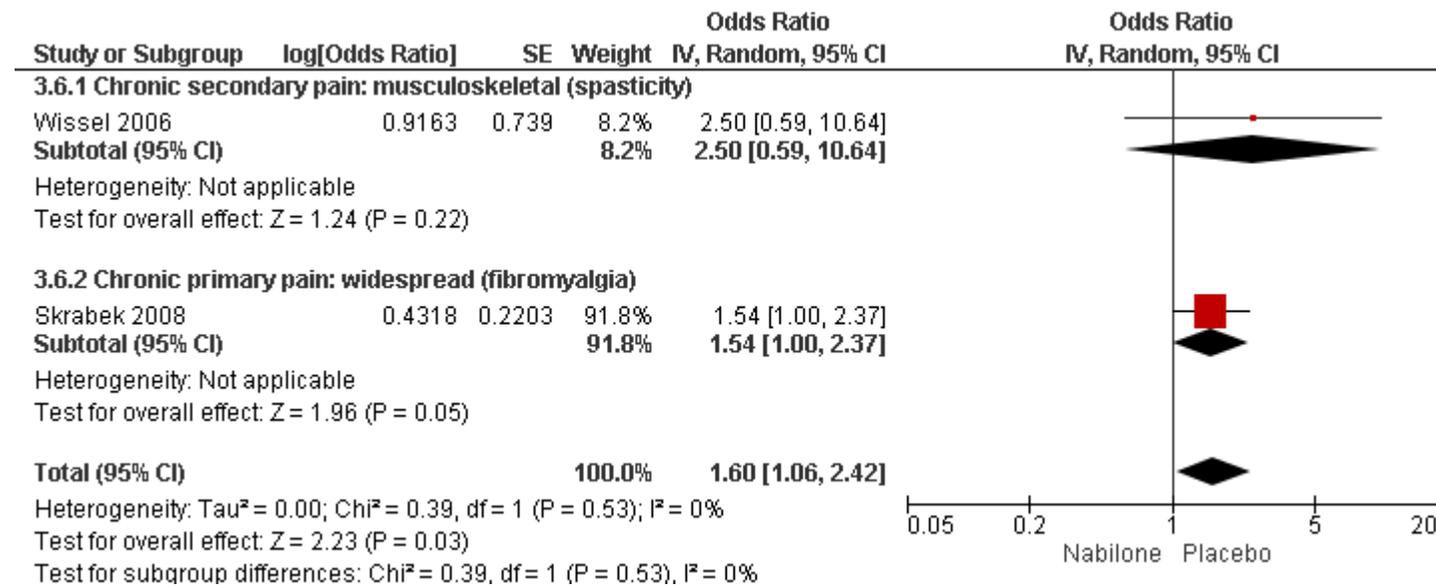


Withdrawals due to adverse events, all-causality

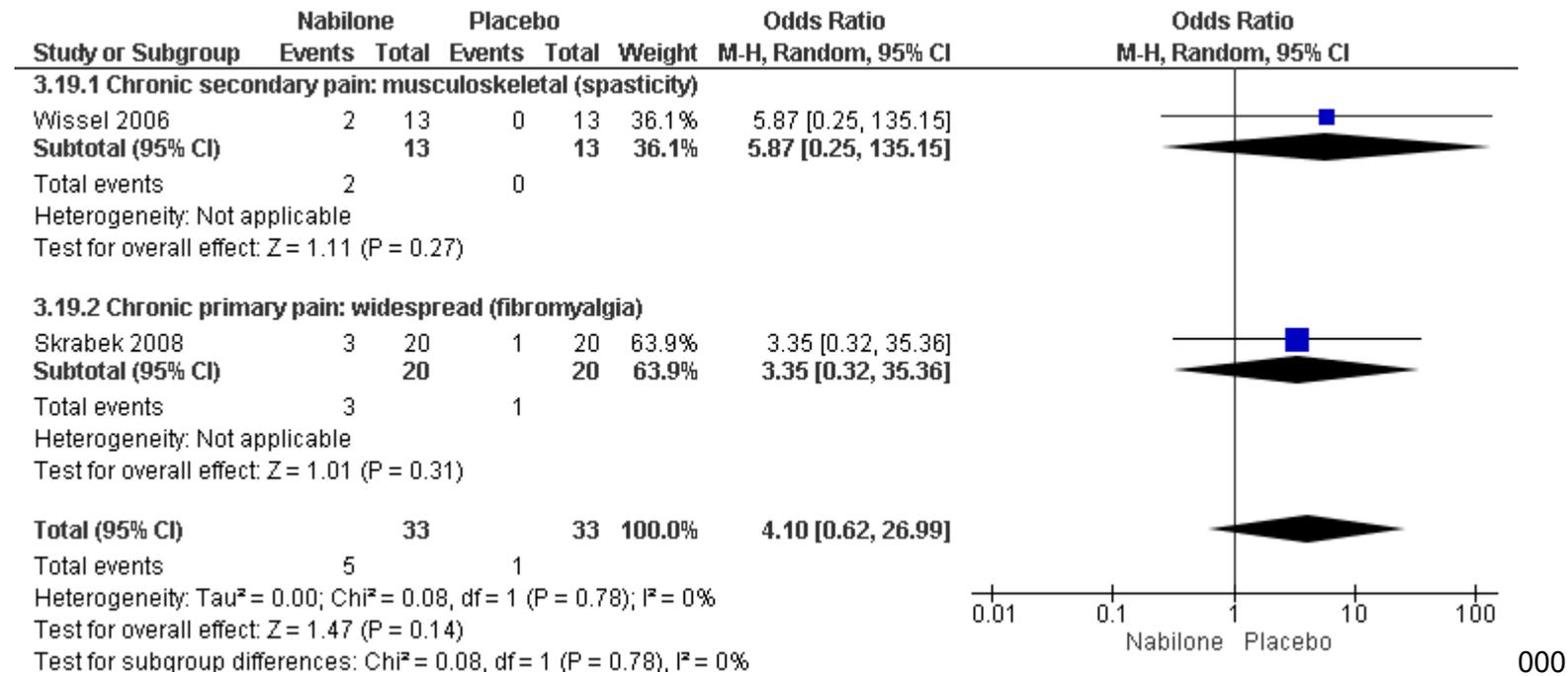


Oral nabilone, 1 to 2 mg per 24 hours vs placebo

People experiencing adverse events, all-causality



Withdrawals due to adverse events, all-causality



Appendix G – GRADE tables

THC:CBD spray vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Proportion of people who experienced pain relief of 30% or more from baseline for neuropathic and cancer pain (values greater than 1 favour THC + CBD)								
4 (Langford 2013, Serpell 2014, Johnson 2010, Portenoy 2012)	Parallel RCT	826	OR 1.49 (1.10, 2.01)	Very serious ^{1,2}	Not serious	Not serious	Not serious	Low
Proportion of people who experienced pain relief of 50% or more from baseline for neuropathic pain (multiple sclerosis). Dose: up to 24 actuations (values greater than 1 favour THC + CBD)								
2 (Langford 2013, Serpell 2014)	Parallel RCT	470	OR 1.19 (0.76, 1.86)	Very serious ¹	Not serious	Not serious	Serious ⁴	Very low
Mean average pain intensity: Numerical Rating Scale (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS for neuropathic, cancer and musculoskeletal pain (values greater than 1 favour placebo)								
11 (Langford 2013, Nurmikko 2007, Rog 2005, Serpell 2014, Wade 2004, Fallon 2017,	Parallel RCTs and 1 crossover RCT	1,833	MD -0.44 (-0.70, -0.18)	Very serious ^{1,2,5,6,7,8}	Serious ³	Not serious	Not serious	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Johnson 2010, Lichtman 2018, Lynch 2014, Portenoy 2012, Blake 2006)								
Functional impairment caused by pain: Pain Disability Index (0 to 70) for neuropathic pain. Dose: up to 48 actuations (values greater than 0 favour placebo)								
1 (Nurmikko 2007)	Parallel RCT	105	MD -5.85 (-9.61, -2.09)	Not serious	N/A	Not serious	Not serious	High
Impairment caused by pain: McGill Pain Questionnaire - Short Form (0 to 45), total intensity of pain for musculoskeletal pain (rheumatoid arthritis). Dose: up to 6 actuations (values greater than 0 favour placebo)								
1 (Blake 2006)	Parallel RCT	57	MD 3.00 (-2.64, 8.64)	Serious ⁸	N/A	Not serious	Serious ⁴	Low
Functional impairment caused by pain: Brief Pain Inventory - Short Form (0 to 10) for neuropathic and cancer pain (values greater than 0 favour placebo)								
3 (Langford 2013, Serpell 2014, Johnson 2010)	Parallel RCT	569	MD -0.26 (-0.72, 0.20)	Very serious ^{1,2}	Not serious	Not serious	Serious ⁴	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in analgesics: daily change in paracetamol, number of rescue (breakthrough) medication paracetamol tablets for neuropathic pain (peripheral neuropathic pain). Dose: up to 24 actuations (values greater than 0 favour placebo)								
1 (Serpell 2014)	Parallel RCT	173	MD -0.38 (-0.85, 0.09)	Very serious ¹	N/A	Not serious	Serious ⁴	Very low
Change in analgesics: daily change in total dose, morphine equivalents for cancer pain. Dose: up to 10 actuations (values greater than 0 favour placebo)								
2 (Fallon 2017, Lichtman 2018)	Parallel RCT	585	MD -0.74 (-22.16, 20.68)	Very serious ^{6,7}	Not serious	Not serious	Serious ⁴	Very low
Change in analgesics: breakthrough daily change in paracetamol, units not provided for neuropathic pain (multiple sclerosis). Dose: up to 12 actuations (values greater than 0 favour placebo)								
1 (Langford 2013)	Parallel RCT	297	MD -0.24 (-0.57, 0.09)	Not serious	N/A	Not serious	Serious ⁴	Moderate
Change in analgesics: daily change in breakthrough dose, morphine equivalents for cancer pain. Dose: up to 48 actuations (values greater than 0 favour placebo)								
1 (Johnson 2010)	Parallel RCT	99	MD -0.04 (-0.23, 0.15)	Very serious ²	N/A	Not serious	Serious ⁴	Very low
Change in analgesics: daily change in breakthrough dose, morphine equivalents for cancer pain. Dose: up to 10 actuations (values greater than 0 favour placebo)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2 (Fallon 2017, Lichtman 2018)	Parallel RCT	585	MD 1.26 (-5.12, 7.64)	Very serious ^{6,7}	Not serious	Not serious	Serious ⁴	Very low
Change in analgesics: daily change in maintenance dose, morphine equivalents for cancer pain. Dose: up to 48 actuations (values greater than 0 favour placebo)								
3 (Fallon 2017, Johnson 2010, Lichtman 2018)	Parallel RCT	359	MD 1.48 (-17.22, 20.19)	Very serious ^{2,6,7}	Not serious	Not serious	Serious ⁴	Very low
Patient Global Impression of Change (dichotomous⁹) for neuropathic pain (multiple sclerosis / peripheral neuropathic pain). Dose: up to 24 actuations (values greater than 1 favour THC + CBD)								
2 (Langford 2013, Serpell 2014)	Parallel RCT	470	OR 1.58 (1.16, 2.15)	Very serious ¹	Not serious	Not serious	Not serious	Low
Patient Global Impression of Change (continuous) for cancer pain. Dose: up to 10 actuations (values greater than 0 favour placebo)								
2 (Fallon 2017, Lichtman 2018)	Parallel RCT	585	MD -0.26 (-0.43, -0.09)	Very serious ^{6,7}	Not serious	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Quality of life: mean QLQ-C30 global health status for cancer pain. Dose: up to 48 actuations (values greater than 0 favour THC + CBD)								
1 (Johnson 2010)	Parallel RCT	99	MD 2.47 (-3.81, 8.75)	Very serious ²	N/A	Not serious	Serious ⁴	Very low
Quality of life: EQ-5D index for neuropathic pain (multiple sclerosis / peripheral neuropathic pain). Dose: up to 24 actuations (values greater than 0 favour placebo)								
2 (Langford 2013, Serpell 2014)	Parallel RCT	470	MD -0.01 (-0.03, 0.01)	Very serious ¹	Not serious	Not serious	Serious ⁴	Very low
Quality of life: SF-36 physical for cancer pain. Dose: up to 12 actuations (values greater than 0 favour THC + CBD)								
1 (Lynch 2014)	Crossover RCT	16	MD -11.00 (-17.13, -4.87)	Not serious	N/A	Not serious	Serious ¹⁰	Moderate
Quality of life: SF-36 mental for cancer pain. Dose: up to 12 actuations (values greater than 0 favour THC + CBD)								
1 (Lynch 2014)	Crossover RCT	16	MD 10.95 (4.02, 17.88)	Not serious	N/A	Not serious	Serious ¹⁰	Moderate
People experiencing adverse events, all-causality for multiple sclerosis, neuropathic pain characterised by allodynia and cancer pain (values greater than 1 favour placebo)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
6 (Rog 2005, Langford 2013, Nurmikko 2007, Portenoy 2012, Lichtman 2018, Fallon 2017)	Parallel RCT	1,665	OR 1.5 (1.20, 1.87)	Very serious ^{6,7}	Not serious	Not serious	Not serious	Moderate
People experiencing serious adverse events, all-causality for neuropathic, cancer and musculoskeletal pain (values greater than 1 favour placebo)								
9 (Langford 2013, Nurmikko 2007, Rog 2005, Serpell 2014, Fallon 2017, Johnson 2010, Lichtman 2018, Portenoy 2012, Blake 2006)	Parallel RCT	1,643	OR 1.19 (0.85, 1.66)	Very serious ^{2,6,7}	Serious ³	Not serious	Serious ⁴	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
People experiencing serious adverse events, treatment-related for neuropathic, cancer and musculoskeletal pain (values greater than 1 favour placebo)								
7 (Nurmikko 2007, Serpell 2014, Fallon 2017, Johnson 2010, Lichtman 2018, Portenoy 2012, Blake 2006)	Parallel RCT	1,282	OR 1.29 (0.81, 2.06)	Very serious ^{1,2,6,7}	Not serious	Not serious	Serious ⁴	Very low
Withdrawals due to adverse events, all-causality for neuropathic, cancer and musculoskeletal pain (values greater than 1 favour placebo)								
10 (Wade 2004, Serpell 2014, Rog 2005, Nurmikko 2007, Langford 2013, Portenoy 2012,	Parallel RCT	2,267	OR 1.74 (1.18, 2.56)	Very serious ^{1,2,5,6,7}	Serious ³	Not serious	Not serious	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Lichtman 2018, Johnson 2010, Fallon 2017, Blake 2006)								
Withdrawals due to adverse events, treatment-related for musculoskeletal pain (rheumatoid arthritis). Dose: up to 6 actuations (values greater than 1 favour placebo)								
1 (Blake 2006)	Parallel RCT	57	OR 0.86 (0.16, 4.65)	Not serious	N/A	Not serious	Serious ⁴	Moderate
Adverse events: psychosis, such as hallucinations, delusions, confused and disturbed thoughts, or lack of insight and self-awareness, all-causality for neuropathic and cancer pain (values greater than 1 favour placebo)								
3 (Nurnikko 2007, Rog 2005, Lichtman 2018)	Parallel RCT	588	OR 2.97 (0.46, 19.07)	Very serious ⁷	Not serious	Not serious	Serious ⁴	Very low
<ol style="list-style-type: none"> 1. Downgrade 2 levels for very serious risk of bias due to Serpell 2014 cannabis arm dropout rate being 40%; staff were assigning patients to arms. Therefore, there was no allocation concealment. Sealed envelopes were used. 2. Downgrade 2 levels for very serious risk of bias due to Johnson 2010: No information provided on randomisation nor blinding. The THC + CBD arm has a much lower baseline morphine dose. 3. Downgrade 1 level because I² is between 33.3% and 66.7% 4. Downgrade 1 level because the 95% confidence interval crosses the line of no effect. 5. Downgrade 1 level because allocation sequence was probably not concealed in Wade 2004. 								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
6.	Downgrade 2 levels: Fallon 2017 has no details regarding how randomisation and blinding took place (and all outcomes have a subjective aspect).							
7.	Downgrade 2 levels: Lichtman 2018 has no information on randomisation and blinding. High dropout rates: 30% in the THC + CBD arm and 20% in the placebo arm.							
8.	Downgrade 1 level: Blake 2006 has no information on the blinding method.							
9.	For the PGIC outcome, the two treatment groups were compared using ordinal logistic regression and the proportional odds model, incorporating centre group.							
10.	Downgrade 1 level: sample size is relatively small (<40 people).							

Oral delta-9-THC (dronabinol), 7.5 to 16 mg per 24 hours vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean average pain intensity: Numerical Rating Scale' (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS neuropathic, visceral and musculoskeletal pain (values greater than 0 favour placebo)								
4 (Schimrigk 2017, de Vries 2017, de Vries 2015 Weber 2010)	Parallel RCTs and 1 crossover RCT	389	MD 0.10 (-0.23, 0.43)	Not serious	Not serious	Not serious	Not serious	High
Median average pain intensity: Numerical Rating Scale (0 to 10) for neuropathic pain (multiple sclerosis) (values greater than 0 favour placebo)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Svendsen 2004)	Crossover RCT	24	Median difference (IQR) -0.6 (-1.8, 0)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): physical functioning (values greater than 0 favour dronabinol)								
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 5.0 (0, 7.5)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): role physical (values greater than 0 favour dronabinol)								
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 0 (-25.0, 12.5)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): bodily pain (values greater than 0 favour dronabinol)								
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 9.8 (0, 21.5)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): general health (values greater than 0 favour dronabinol)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 0 (6.0, 5.0)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): vitality (values greater than 0 favour dronabinol)								
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 2.5 (-5, 10.0)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): social functioning (values greater than 0 favour dronabinol)								
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 6.3 (0, 12.5)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): mental health (values greater than 0 favour dronabinol)								
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 8.0 (0, 12.0)	Not serious	N/A	Not serious	Very serious ¹	Low
Quality of life: SF-36 median average for neuropathic pain (multiple sclerosis): role emotional (values greater than 0 favour dronabinol)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Svendsen 2004)	Crossover RCT	23	Median difference (IQR) 0 (-33, 0)	Not serious	N/A	Not serious	Very serious ¹	Low
People experiencing adverse events, all-causality for neuropathic, visceral and musculoskeletal pain (values greater than 1 favour placebo)								
2 (Schimrigk 2017, Svendsen 2004, de Vries 2015, Weber 2010)	Parallel RCT	390	OR 2.7 (0.63, 11.68)	Not serious	Very serious ³	Not serious	Serious ²	Very low
People experiencing adverse events, treatment-related for neuropathic pain (multiple sclerosis) (values greater than 1 favour placebo)								
1 (Schimrigk 2017)	Parallel RCT	240	OR 2.87 (1.66, 4.94)	Not serious	N/A	Not serious	Not serious	High
People experiencing serious adverse events, all-causality for neuropathic pain (multiple sclerosis) (values greater than 1 favour placebo)								
2 (Schimrigk 2017, Svendsen 2004)	Parallel RCT and crossover RCT	288	OR 1.86 (0.76, 4.53)	Not serious	Not serious	Not serious	Serious ²	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
People experiencing serious adverse events, treatment-related for neuropathic pain (multiple sclerosis (values greater than 1 favour placebo))								
1 (Schimrigk 2017)	Parallel RCT	240	OR 2.83 (0.11, 70.17)	Not serious	N/A	Not serious	Serious ²	Moderate
Withdrawals due to adverse events, all-causality for neuropathic and visceral pain (values greater than 1 favour placebo)								
4 (Schimrigk 2017, Svendsen 2004, de Vries 2015, de Vries 2017)	Parallel RCTs and 1 crossover RCT	398	OR 6.08 (1.83, 20.23)	Very serious ⁴	Not serious	Not serious	Not serious	Low
<ol style="list-style-type: none"> 1. Downgrade 2 levels as imprecision could not be assessed (confidence interval not available). Furthermore, the sample size is relatively small (<40 people) 2. Downgrade 1 level because the 95% confidence interval crosses the line of no effect. 3. Downgrade 2 levels because the I² is greater than 66.7% 4. Downgrade 2 levels because in de Vries 2017 there was incomplete reporting of outcomes 								

Oral nabilone 1 to 2 mg per 24 hours vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean average pain intensity: Numerical Rating Scale' (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS for widespread pain (fibromyalgia) (values greater than 0 favour placebo)								
1 (Skrabek 2008)	Parallel RCT	33	MD -1.43 (-2.80, -0.06)	Serious ¹	N/A	Not serious	Very serious ²	Very low
Median average pain intensity: Numerical Rating Scale (0 to 10) for musculoskeletal pain (spasticity) (values greater than 0 favour placebo)								
1 (Wissel 2006)	Crossover RCT	11	Median difference -2 (p-value <0.05)	Very serious ³	N/A	Not serious	Very serious ⁴	Very low
Functional impairment caused by pain: Fibromyalgia Impact Questionnaire for widespread pain (fibromyalgia) (0 to 100) (values greater than 0 favour placebo)								
1 (Skrabek 2008)	Parallel RCT	33	MD -10.76 (-18.45, -3.07)	Serious ¹	N/A	Not serious	Serious ⁷	Low
People experiencing adverse events, all-causality for musculoskeletal and widespread pain (values greater than 1 favour placebo)								
2 (Skrabek 2008, Wissel 2006)	Parallel RCT and crossover RCT	46	OR 1.60 (1.06, 2.42)	Very serious ^{1,3}	Not serious	Not serious	Not serious	Low
People experiencing serious adverse events, all-causality for musculoskeletal pain (spasticity) (values greater than 1 favour placebo)								

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Wissel 2006)	Crossover RCT	13	OR 5.87 (0.25, 135.15)	Very serious ³	N/A	Not serious	Very serious ⁵	Very low
Withdrawals due to adverse events, all-causality for musculoskeletal and widespread pain (values greater than 1 favour placebo)								
2 (Skrabek 2008, Wissel 2006)	Parallel RCT and crossover RCT	53	OR 4.10 (0.62, 26.99)	Very serious ^{1,3}	Not serious	Not serious	Serious ⁶	Very low
<ol style="list-style-type: none"> 1. Downgrade 1 level for Skrabek 2008: very little information on the randomisation method and blinding. 2. Downgrade 2 levels: the 95% confidence interval for the effect size crosses the MID (-0.8) and the sample size is <40. 3. Downgrade 2 levels for Wissel 2006: no information provided on randomisation, blinding nor baseline characteristics. 4. Downgrade 2 levels for Wissel 2006: uncertainty of precision as only p-value is available with no 95% CI and the sample size is very small (<40 people). 5. Downgrade 2 levels: because the 95% confidence interval crosses the line of no effect and the sample size is small (<40 people). 6. Downgrade 1 level: the 95% confidence interval for the effect size crosses the line of no effect. 7. Downgrade 1 level: sample size is small (<40 people). 								

Oromucosal spray 2.7 mg THC only per 100 microlitre actuation, maximum 48 actuations per 24 hours vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Proportion of people who experienced pain relief of 30% or more from baseline for cancer pain (values greater than 1 favour placebo)								
1 (Johnson 2010)	Parallel RCT	117	OR 1.02 (0.42, 2.51)	Very serious ¹	N/A	Not serious	Serious ²	Very low
Mean average pain intensity: Numerical Rating Scale' (0 to 10) or Visual Analogue Scale (0 to 100)/10 for cancer pain (values greater than 0 favour placebo)								
1 (Johnson 2010)	Parallel RCT	96	MD -0.32 (-0.86, 0.22)	Very serious ¹	N/A	Not serious	Not serious	Low
Functional impairment caused by pain: Brief Pain Inventory - Short Form for cancer pain (values greater than 0 favour placebo)								
1 (Johnson 2010)	Parallel RCT	96	MD -4.07 (-8.05, -0.09)	Very serious ¹	N/A	Not serious	Not serious	Low
Change in analgesics: daily total dose change, morphine equivalents for cancer pain (values greater than 0 favour placebo)								
1 (Johnson 2010)	Parallel RCT	96	MD 68.30 (3.74, 132.86)	Very serious ¹	N/A	Not serious	Not serious	Low
Quality of life: mean QLQ-C30 global health status for cancer pain (values greater than 0 favour placebo)								
1 (Johnson 2010)	Parallel RCT	96	MD 0.84 (-5.42, 7.10)	Very serious ¹	N/A	Not serious	Serious ²	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in analgesics: daily change in maintenance (background) dose, morphine equivalents for cancer pain (values greater than 0 favour placebo)								
1 (Johnson 2010)	Parallel RCT	96	MD 68.30 (-2.58, 139.18)	Very serious ¹	N/A	Not serious	Serious ²	Very low
Change in analgesics: daily change in breakthrough dose, morphine equivalents for cancer pain (values greater than 0 favour placebo)								
1 (Johnson 2010)	Parallel RCT	96	MD 0.01 (-0.14, 0.16)	Very serious ¹	N/A	Not serious	Serious ²	Very low
People experiencing serious adverse events (all-causality) for cancer pain (values greater than 1 favour placebo)								
1 (Johnson 2010)	Parallel RCT	117	OR 3.34 (1.27, 8.78)	Very serious ¹	N/A	Not serious	Not serious	Low
People experiencing serious adverse events (treatment-related) for cancer pain (values greater than 1 favour placebo)								
1 (Johnson 2010)	Parallel RCT	117	OR 3.10 (0.12, 77.78)	Very serious ¹	N/A	Not serious	Serious ²	Very low
Withdrawals due to adverse events (all-causality) for cancer pain (values greater than 1 favour placebo)								
1 (Johnson 2010)	Parallel RCT	117	OR 2.56 (0.63, 10.44)	Very serious ¹	N/A	Not serious	Serious ²	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1. Downgrade 2 levels for very serious risk of bias due to Johnson 2010: No information provided on randomisation nor blinding. The THC + CBD arm has a much lower baseline morphine dose. 2. Downgrade 1 level: the 95% confidence interval for the effect size crosses the line of no effect								

Vaporised 22.4 mg THC and <1 mg CBD vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean average pain intensity: Numerical Rating Scale' (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS (fibromyalgia) (values greater than 1 favour placebo)								
1 (van de Donk 2019)	Crossover RCT	20	MD 0.03 (-0.96, 1.02)	Very serious ¹	N/A	Very serious ²	Serious ³	Very low
1. Downgrade 2 levels: van de Donk 2019 had missing outcome data. 2. Downgrade 2 levels: van de Donk 2019 involved giving only 1 dose and follow-up 3 hours later. This is not a realistic assessment for chronic pain management. 3. Downgrade 1 level: sample size <40								

Vaporised 13.4 mg THC and 17.8 mg CBD vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean average pain intensity: Numerical Rating Scale' (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS (fibromyalgia) (values greater than 1 favour placebo)								
1 (van de Donk 2019)	Crossover RCT	20	MD -0.06 (-0.99, 0.87)	Very serious ¹	N/A	Very serious ²	Very serious ³	Very low
Proportion of people who experienced pain relief of 30% or more from baseline (fibromyalgia) (values greater than 1 favour placebo)								
1 (van de Donk 2019)	Crossover RCT	20	OR 7.36 (1.35, 40.55)	Very serious ¹	N/A	Very serious ²	Serious ⁴	Very low
Proportion of people who experienced pain relief of 50% or more from baseline (fibromyalgia) (values greater than 1 favour placebo)								
1 (van de Donk 2019)	Crossover RCT	20	OR 1.91 (0.52, 7.01)	Very serious ¹	N/A	Very serious ²	Very serious ⁵	Very low
<ol style="list-style-type: none"> 1. Downgrade 2 levels: van de Donk 2019 had missing outcome data. 2. Downgrade 2 levels: van de Donk 2019 involved giving only 1 dose and follow-up 3 hours later. This is not a realistic assessment for chronic pain management. 3. Downgrade 2 levels: the 95% confidence interval for the effect size crosses the MID (-0.8) and the sample size is relatively small (<40 people). 4. Downgrade 1 level: sample size is relatively small (<40 people). 5. Downgrade 2 levels: the 95% confidence interval for the effect size crosses the MID (-0.9) and the sample size is relatively small (<40 people). 								

Vaporised <1 mg THC and 18.4 mg CBD vs placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Mean average pain intensity: Numerical Rating Scale' (0 to 10) or Visual Analogue Scale (0 to 100)/10 converted to NRS (fibromyalgia) (values greater than 1 favour placebo)								
1 (van de Donk 2019)	Crossover RCT	20	MD 0.00 (-0.99, 0.99)	Very serious ¹	N/A	Very serious ²	Serious ³	Very low
<ol style="list-style-type: none"> 1. Downgrade 2 levels: van de Donk 2019 had missing outcome data. 2. Downgrade 2 levels: van de Donk 2019 involved giving only 1 dose and follow-up 3 hours later. This is not a realistic assessment for chronic pain management. 3. Downgrade 1 level: the sample size is relatively small (<40 people). 								

Appendix H – Adverse events

THC:CBD spray vs placebo

Study	Subgroup	Adverse events reported
Langford 2013	Neuropathic pain: multiple sclerosis	<p>Phase A (standard parallel RCT)</p> <p>Treatment-related: all severities</p> <p>THC + CBD (167 patients in the arm): cardiac disorders (0), Ear and labyrinth disorders (20) including vertigo (15); Eye disorders (7) including vision blurred (4); Gastrointestinal disorders (54) including nausea (13), dry mouth (12), diarrhoea (7), vomiting (5); General disorders and administration site conditions (40) including: fatigue (16), feeling abnormal (5), pain (0); Infections and infestations (34); Musculoskeletal and connective tissue disorders (17) including pain in extremity (0), muscular weakness (1); Nervous system disorders (73) including dizziness (34), somnolence (16), headache (7), disturbance in attention (6), dysgeusia (6), memory impairment (6), balance disorder (5), psychomotor skills impaired (5), neuralgia (1); Psychiatric disorders (27) including: depression (2); Respiratory, thoracic and mediastinal disorders (8) including: pharyngolaryngeal pain (2).</p> <p>Placebo (172 patients in the arm): cardiac disorders (1), Ear and labyrinth disorders (9) including vertigo (6); Eye disorders (5) including vision blurred (1); Gastrointestinal disorders (40) including nausea (7), dry mouth (10), diarrhoea (5), vomiting (5); General disorders and administration site conditions (30) including: fatigue (9), feeling abnormal (2), pain (1); Infections and infestations (27); Musculoskeletal and connective tissue disorders (20) including pain in extremity (1), muscular weakness (1); Nervous system disorders (51) including dizziness (7), somnolence (3), headache (6), disturbance in attention (1), dysgeusia (1), memory impairment (1), balance disorder (2), psychomotor skills impaired (0), neuralgia (1); Psychiatric disorders (12) including: depression (0); Respiratory, thoracic and mediastinal disorders (11) including: pharyngolaryngeal pain (1).</p>

Study	Subgroup	Adverse events reported
		<p>Treatment-related: severe</p> <p>THC + CBD (167 patients in the arm): serious disorientation (1), suicidal ideation (1).</p> <p>Placebo (172 patients in the arm): suicidal ideation (1).</p> <p>Phase B (withdrawal RCT)</p> <p>Treatment-related: all severities</p> <p>THC + CBD (21 patients in the arm): General disorders and administration site conditions (1) including: mucosal erosion (0), fatigue (0), feeling abnormal (0), pain (0); Investigations (0) including hepatic enzyme increased (0); Musculoskeletal and connective tissue disorders (0); Nervous system disorders (0); Psychiatric disorders (1) including: depression (1), insomnia (0); Skin and subcutaneous tissue disorders (0) including dry skin (0).</p> <p>Placebo (21 patients in the arm): General disorders and administration site conditions (0) including: mucosal erosion (0), fatigue (0), feeling abnormal (0), pain (0); Investigations (1) including hepatic enzyme increased (1); Musculoskeletal and connective tissue disorders (1); Nervous system disorders (2); Psychiatric disorders (1) including: depression (0), insomnia (1); Skin and subcutaneous tissue disorders (1) including dry skin (1).</p> <p>Severe adverse events</p> <p>All-causality</p> <p>THC + CBD (21 patients in the arm): serious disorientation (1), suicidal ideation (1)</p> <p>Placebo (21 patients in the arm): serious disorientation (0), suicidal ideation (1), accidental injury (1)</p> <p>Treatment-related</p>

Study	Subgroup	Adverse events reported
		<p>THC + CBD (21 patients in the arm): serious disorientation (1), suicidal ideation (1)</p> <p>Placebo (21 patients in the arm): serious disorientation (0), suicidal ideation (1)</p>
Rog 2005	Neuropathic pain: multiple sclerosis	<p>All-causality</p> <p>THC + CBD (34 patients in the arm): Nervous system including: dizziness (18), somnolence (3), disturbance in attention (2), headache (1); Psychiatric including: dissociation (3), euphoria (2); Gastrointestinal including: dry mouth (4), nausea (3), glossodynia (1), mouth ulceration (1), vomiting (1), dyspepsia (0), oral pain (0); General and administration site conditions including: falls (3), weakness (3), fatigue (2), feeling abnormal (1), feeling drunk (1), thirst (1), application site burning (0), chest discomfort (0); Respiratory including: pharyngitis (2), hoarseness (1), throat irritation (1), dyspnoea (0).</p> <p>Placebo (32 patients in the arm): Nervous system including: dizziness (5), somnolence (0), disturbance in attention (0), headache (3); Psychiatric including: dissociation (0), euphoria (0); Gastrointestinal including: dry mouth (0), nausea (2), glossodynia (3), mouth ulceration (0), vomiting (0), dyspepsia (1), oral pain (3); General and administration site conditions including: falls (2), weakness (0), fatigue (2), feeling abnormal (0), feeling drunk (1), thirst (0), application site burning (1), chest discomfort (1); Respiratory including: pharyngitis (1), hoarseness (0), throat irritation (0), dyspnoea (1).</p> <p>There were no serious adverse events</p>
Wade 2004	Neuropathic pain: multiple sclerosis	<p>Treatment-related</p> <p>THC + CBD (80 patients in the arm): dizziness (26), disturbance in attention (7), headache (7), fatigue (12), somnolence (7), disorientation (6), feeling drunk (4), vertigo (5), application site discomfort (21), nausea (7), diarrhoea (6), mouth ulceration (4).</p>

Study	Subgroup	Adverse events reported
		<p>Placebo (80 patients in the arm): dizziness (10), disturbance in attention (0), headache (13), fatigue (3), somnolence (1), disorientation (0), feeling drunk (0), vertigo (0), application site discomfort (18), nausea (5), diarrhoea (2), mouth ulceration (1).</p> <p>There was no mention of serious adverse events</p>
Selvarajah 2010	Neuropathic pain: diabetic neuropathy	Adverse events were not reported.
Nurmikko 2007	Neuropathic pain: characterised by allodynia	<p>Treatment-related adverse events experienced by 3 or more patients (approximately 5%) receiving THC + CBD compared with placebo</p> <p>THC + CBD (63 patients in the arm): dizziness (18), nausea (14), fatigue (13), dry mouth (11), vomiting (8), feeling drunk (6), headache (6), diarrhoea (4), nasopharyngitis (4), anorexia (4), somnolence (4), abdominal pain upper (3), disturbance in attention (3), memory impairment (3).</p> <p>Placebo (62 patients in the arm): dizziness (9), nausea (7), fatigue (5), dry mouth (3), vomiting (3), feeling drunk (1), headache (9), diarrhoea (0), nasopharyngitis (2), anorexia (0), somnolence (1), abdominal pain upper (1), disturbance in attention (0), memory impairment (0).</p> <p>Serious adverse events (treatment-related)</p> <p>THC + CBD (63 patients in the arm): Severe symptoms suggesting involvement of the nervous system (7), emotional stress associated with paranoid thinking (1).</p> <p>Placebo (62 patients in the arm): Severe symptoms suggesting involvement of the nervous system (5), confusion (1).</p> <p>Serious adverse events (all-causality)</p>

Study	Subgroup	Adverse events reported
		<p>THC + CBD (63 patients in the arm): Severe symptoms suggesting involvement of the nervous system (7), emotional stress associated with paranoid thinking (1), transient ischemic attack (1)</p> <p>Placebo (62 patients in the arm): Severe symptoms suggesting involvement of the nervous system (5), confusion (1).</p>
Serpell 2014	Neuropathic pain: peripheral neuropathic pain	<p>All-causality with an incidence of 3% or greater</p> <p>THC + CBD (128 patients in the arm): Nervous system disorders (79) including: dizziness (52), dysgeusia (14), headache (13), disturbance in attention (8), neuropathy peripheral (6), tremor (6), somnolence (5), balance disorder (4), memory impairment (4), sedation (4); Gastrointestinal disorders (60) including: nausea (23), vomiting (13), diarrhoea (12), dry mouth (11), abdominal pain upper (6), dyspepsia (6), constipation (4), mouth ulceration (4), oral pain (4); General disorders and administration site conditions including (45): fatigue (20), feeling drunk (8), application site pain (7); Psychiatric disorders (36) including: dissociation (9), disorientation (8), depression (6), anxiety (4), panic attack (4); Infections and infestations including (35): nasopharyngitis (9), gastroenteritis (4), lower respiratory tract infection (4); Metabolism and nutrition disorders (15) including: increased appetite (6), anorexia (4); Respiratory, thoracic and mediastinal disorders (15) including: pharyngolaryngeal pain (7), dyspnoea (4); Musculoskeletal and connective tissue disorders (11); Injury, poisoning and procedural complications (9); Skin and subcutaneous tissue disorders (9) including: rash (5); Eye disorders (7); Ear and labyrinth disorders (6) including: vertigo (5); Vascular disorders (4); Investigations (3); Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (3); Renal and urinary disorders (3); Cardiac disorders (2); Reproductive system and breast disorders (2); Immune system disorders (1); Blood and lymphatic system disorders (0).</p> <p>Placebo (118 patients in the arm): Nervous system disorders (34) including: dizziness (12), dysgeusia (2), headache (9), disturbance in attention (2), neuropathy peripheral (4), tremor</p>

Study	Subgroup	Adverse events reported
		<p>(0), somnolence (2), balance disorder (2), memory impairment (2), sedation (0); Gastrointestinal disorders (43) including: nausea (14), vomiting (7), diarrhoea (6), dry mouth (4), abdominal pain upper (1), dyspepsia (4), constipation (2), mouth ulceration (6), oral pain (3); General disorders and administration site conditions including (30): fatigue (8), feeling drunk (3), application site pain (2); Psychiatric disorders (11) including: dissociation (0), disorientation (0), depression (0), anxiety (1), panic attack (1); Infections and infestations including (26): nasopharyngitis (8), gastroenteritis (1), lower respiratory tract infection (3); Metabolism and nutrition disorders (6) including: increased appetite (1), anorexia (1); Respiratory, thoracic and mediastinal disorders (16) including: pharyngolaryngeal pain (5), dyspnoea (3); Musculoskeletal and connective tissue disorders (8); Injury, poisoning and procedural complications (6); Skin and subcutaneous tissue disorders (9) including: rash (4); Eye disorders (6); Ear and labyrinth disorders (1) including: vertigo (0); Vascular disorders (5); Investigations (3); Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (1); Renal and urinary disorders (2); Cardiac disorders (2); Reproductive system and breast disorders (1); Immune system disorders (0); Blood and lymphatic system disorders (2).</p> <p>Treatment-related with an incidence of 3% or greater</p> <p>THC + CBD (128 patients in the arm): Nervous system disorders (73) including: dizziness (50), dysgeusia (14), headache (8), disturbance in attention (8), neuropathy peripheral (3), tremor (4), somnolence (5), balance disorder (4), memory impairment (4), sedation (4); Gastrointestinal disorders (48) including: nausea (22), vomiting (6), diarrhoea (8), dry mouth (11), abdominal pain upper (4), dyspepsia (1), constipation (2), mouth ulceration (4), oral pain (4); General disorders and administration site conditions including (38): fatigue (19), feeling drunk (8), application site pain (7); Psychiatric disorders (30) including: dissociation (9), disorientation (8), depression (3), anxiety (3), panic attack (3); Infections and infestations including (1): nasopharyngitis (1), gastroenteritis (0), lower respiratory tract infection (0); Metabolism and nutrition disorders (10) including: increased appetite (6), anorexia (1); Respiratory, thoracic and mediastinal disorders (7) including:</p>

Study	Subgroup	Adverse events reported
		<p>pharyngolaryngeal pain (2), dyspnoea (1); Musculoskeletal and connective tissue disorders (2); Injury, poisoning and procedural complications (2); Skin and subcutaneous tissue disorders (2) including: rash (1); Eye disorders (5); Ear and labyrinth disorders (5) including: vertigo (5); Vascular disorders (3); Investigations (2); Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (0); Renal and urinary disorders (0); Cardiac disorders (1); Reproductive system and breast disorders (0); Immune system disorders (0); Blood and lymphatic system disorders (0).</p> <p>Placebo (118 patients in the arm): Nervous system disorders (20) including: dizziness (11), dysgeusia (2), headache (7), disturbance in attention (1), neuropathy peripheral (0), tremor (0), somnolence (2), balance disorder (2), memory impairment (2), sedation (0); Gastrointestinal disorders (30) including: nausea (9), vomiting (3), diarrhoea (2), dry mouth (4), abdominal pain upper (0), dyspepsia (3), constipation (0), mouth ulceration (6), oral pain (3); General disorders and administration site conditions including (23): fatigue (5), feeling drunk (3), application site pain (2); Psychiatric disorders (4) including: dissociation (0), disorientation (0), depression (0), anxiety (1), panic attack (0); Infections and infestations including (3): nasopharyngitis (1), gastroenteritis (0), lower respiratory tract infection (0); Metabolism and nutrition disorders (5) including: increased appetite (1), anorexia (1); Respiratory, thoracic and mediastinal disorders (5) including: pharyngolaryngeal pain (5), dyspnoea (0); Musculoskeletal and connective tissue disorders (1); Injury, poisoning and procedural complications (0); Skin and subcutaneous tissue disorders (2) including: rash (0); Eye disorders (3); Ear and labyrinth disorders (1) including: vertigo (0); Vascular disorders (2); Investigations (2); Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (0); Renal and urinary disorders (1); Cardiac disorders (0); Reproductive system and breast disorders (0); Immune system disorders (0); Blood and lymphatic system disorders (0).</p> <p>Serious adverse events</p> <p>All-causality</p>

Study	Subgroup	Adverse events reported
		<p>THC + CBD (128 patients in the arm): 10 (no details provided)</p> <p>Placebo (118 patients in the arm): 6 (no details provided)</p> <p>Treatment-related</p> <p>THC + CBD (128 patients in the arm): 0</p> <p>Placebo (118 patients in the arm): 1 (no details provided)</p>
Lynch 2014	Chemotherapy: neuropathic pain + possible nociceptive	<p>Treatment-related</p> <p>THC + CBD (128 patients in the arm): fatigue (7), dry mouth (5), dizziness (6), nausea (6), increased appetite (2), diarrhoea (2), decreased appetite (1), feeling “stoned” (1), anxiety (1), panic attack (1), headache (2), confusion (1), “fuzzy thinking” or “foggy brain” (2).</p> <p>Placebo (118 patients in the arm): fatigue (0), dry mouth (1), dizziness (0), nausea (1), increased appetite (0), diarrhoea (0), decreased appetite (0), feeling “stoned” (0), anxiety (0), panic attack (0), headache (0), confusion (0), “fuzzy thinking” or “foggy brain” (0).</p> <p>There were no serious adverse events</p>
Fallon 2017	Nociceptive pain: cancer pain	<p>All-causality in $\geq 5\%$</p> <p>THC + CBD (199 patients in the arm): neoplasm progression (32), somnolence (24), nausea (19), vomiting (18), dizziness (16), constipation (10).</p> <p>Placebo (198 patients in the arm): neoplasm progression (36), somnolence (8), nausea (16), vomiting (13), dizziness (9), constipation (13).</p> <p>Treatment-related in $\geq 5\%$</p>

Study	Subgroup	Adverse events reported
		<p>THC + CBD (199 patients in the arm): somnolence (18), dizziness (15), nausea (10). Placebo (198 patients in the arm): somnolence (6), dizziness (6), nausea (8).</p> <p>Serious adverse events</p> <p>All-causality</p> <p>THC + CBD (199 patients in the arm): 35 in total including: neoplasm progression (23), constipation (1), moderate disorientation and moderate somnolence (1)</p> <p>Placebo (198 patients in the arm): 44 in total including: neoplasm progression (31)</p> <p>Treatment-related</p> <p>THC + CBD (199 patients in the arm): 2 including: constipation (1), moderate disorientation and moderate somnolence (1)</p> <p>Placebo (198 patients in the arm): 0</p>
Johnson 2010	Nociceptive pain: cancer pain	<p>Treatment-related reported by ≥3 patients</p> <p>THC + CBD (60 patients in the arm): somnolence (8), dizziness (7), confusion (4), nausea (6), vomiting (3), raised gamma GT (2), hypercalcaemia (0), hypotension (3).</p> <p>Placebo (59 patients in the arm): somnolence (6), dizziness (3), confusion (1), nausea (4), vomiting (2), raised gamma GT (1), hypercalcaemia (3), hypotension (0).</p> <p>Serious adverse event</p> <p>All-causality</p>

Study	Subgroup	Adverse events reported
		<p>THC + CBD (60 patients in the arm): progression of cancer (8), urinary retention (1), tumour-related pain (1), worsened nausea (1), weakness (1), tumour haemorrhage (1), somnolence (1)</p> <p>Placebo (59 patients in the arm): progression of cancer (7)</p> <p>Treatment-related</p> <p>THC + CBD (60 patients in the arm): 0</p> <p>Placebo (59 patients in the arm): 0</p>
Lichtman 2018	Nociceptive pain: cancer pain	<p>All-causality in $\geq 5\%$ of patients</p> <p>THC + CBD (199 patients in the arm): neoplasm progression (37), nausea (31), vomiting (16), dizziness (16), decreased appetite (14), fatigue (12), constipation (11).</p> <p>Placebo (198 patients in the arm): neoplasm progression (34), nausea (21), vomiting (13), dizziness (8), decreased appetite (12), fatigue (10), constipation (13).</p> <p>Treatment-related in $\geq 5\%$ of patients</p> <p>THC + CBD (199 patients in the arm): nausea (17), dizziness (15).</p> <p>Placebo (198 patients in the arm): nausea (10), dizziness (5).</p> <p>Severe adverse events</p> <p>All-causality in $\geq 5\%$ of patients</p> <p>THC + CBD (199 patients in the arm): neoplasm progression (32), disorientation (1), visual hallucination (1), pancytopenia (1), pulmonary embolus (1)</p>

Study	Subgroup	Adverse events reported
		<p>Placebo (198 patients in the arm): neoplasm progression (25), vomiting (1), suicide (1)</p> <p>Treatment-related in $\geq 5\%$ of patients</p> <p>THC + CBD (199 patients in the arm): 0</p> <p>Placebo (198 patients in the arm): 0</p>
Portenoy 2012	Nociceptive pain: cancer pain	<p>Treatment-related in $\geq 5\%$ of patients</p> <p>All-causality</p> <p>THC + CBD all doses combined (268 patients in the arm):</p> <p>neoplasm progression (47), nausea (59), dizziness (51), vomiting (42), somnolence (39), disorientation (18), anorexia (22), constipation (20), dry mouth (22), anaemia (19), diarrhoea (17), dysgeusia (11), headache (15), asthenia (18), hallucination (8), decreased appetite (11), fatigue (13), pain (11), insomnia (8), stomatitis (10), weight decreased (8).</p> <p>THC + CBD 1-4 sprays (91 patients in the arm): neoplasm progression (24), nausea (16), dizziness (10), vomiting (9), somnolence (8), disorientation (5), anorexia (6), constipation (4), dry mouth (7), anaemia (6), diarrhoea (5), dysgeusia (1), headache (5), asthenia (6), hallucination (1), decreased appetite (4), fatigue (4), pain (4), insomnia (2), stomatitis (5), weight decreased (5).</p>

Study	Subgroup	Adverse events reported
		<p>THC + CBD 6-10 sprays (87 patients in the arm): neoplasm progression (11), nausea (18), dizziness (21), vomiting (14), somnolence (16), disorientation (5), anorexia (5), constipation (10), dry mouth (8), anaemia (5), diarrhoea (4), dysgeusia (7), headache (6), asthenia (7), hallucination (1), decreased appetite (5), fatigue (4), pain (2), insomnia (2), stomatitis (2), weight decreased (1).</p> <p>THC + CBD 11-16 sprays (90 patients in the arm): neoplasm progression (12), nausea (25), dizziness (20), vomiting (19), somnolence (15), disorientation (8), anorexia (11), constipation (6), dry mouth (7), anaemia (8), diarrhoea (8), dysgeusia (3), headache (4), asthenia (5), hallucination (6), decreased appetite (2), fatigue (5), pain (5), insomnia (4), stomatitis (3), weight decreased (2).</p> <p>Placebo (91 patients in the arm): neoplasm progression (13), nausea (12), dizziness (12), vomiting (7), somnolence (4), disorientation (1), anorexia (10), constipation (7), dry mouth (7), anaemia (4), diarrhoea (4), dysgeusia (2), headache (1), asthenia (6), hallucination (5), decreased appetite (2), fatigue (4), pain (2), insomnia (5), stomatitis (0), weight decreased (2).</p> <p>Serious adverse events</p> <p>THC + CBD all doses combined (268 patients in the arm): deaths (56), blood disorders (4), cardiac disorders (0), gastrointestinal disorders (8), general disorders and administration site conditions (9), hepatobiliary disorders (2), infections and infestations (11), injury,</p>

Study	Subgroup	Adverse events reported
		<p>poisoning and procedural complications (2), investigations (1), metabolism and nutrition disorders (5), musculoskeletal & connective tissue disorders (0), neoplasms, benign, malignant and unspecified (51), nervous system disorders (5), psychiatric disorders (4), renal and urinary disorders (4), respiratory, thoracic and mediastinal disorders (4), vascular disorders (4).</p> <p>THC + CBD 1-4 sprays (91 patients in the arm): deaths (25), blood disorders (4), cardiac disorders (0), gastrointestinal disorders (1), general disorders and administration site conditions (4), hepatobiliary disorders (0), infections and infestations (4), injury, poisoning and procedural complications (1), investigations (0), metabolism and nutrition disorders (1), musculoskeletal & connective tissue disorders (0), neoplasms, benign, malignant and unspecified (26), nervous system disorders (1), psychiatric disorders (1), renal and urinary disorders (0), respiratory, thoracic and mediastinal disorders (1), vascular disorders (0).</p> <p>THC + CBD 6-10 sprays (87 patients in the arm): deaths (14), blood disorders (0), cardiac disorders (0), gastrointestinal disorders (0), general disorders and administration site conditions (1), hepatobiliary disorders (1), infections and infestations (5), injury, poisoning and procedural complications (1), investigations (0), metabolism and nutrition disorders (1), musculoskeletal & connective tissue disorders (0), neoplasms, benign, malignant and unspecified (12), nervous system disorders (1), psychiatric disorders (1), renal and urinary disorders (0), respiratory, thoracic and mediastinal disorders (2), vascular disorders (0).</p> <p>THC + CBD 11-16 sprays (90 patients in the arm): deaths (17), blood disorders (0), cardiac disorders (0), gastrointestinal disorders (4), general disorders and administration site conditions (4), hepatobiliary disorders (1), infections and infestations (2), injury, poisoning</p>

Study	Subgroup	Adverse events reported
		<p>and procedural complications (0), investigations (1), metabolism and nutrition disorders (3), musculoskeletal & connective tissue disorders (0), neoplasms, benign, malignant and unspecified (51), nervous system disorders (3), psychiatric disorders (2), renal and urinary disorders (4), respiratory, thoracic and mediastinal disorders (1), vascular disorders (3).</p> <p>Placebo (91 patients in the arm): deaths (16), blood disorders (2), cardiac disorders (1), gastrointestinal disorders (2), general disorders and administration site conditions (2), hepatobiliary disorders (2), infections and infestations (2), injury, poisoning and procedural complications (1), investigations (0), metabolism and nutrition disorders (1), musculoskeletal & connective tissue disorders (1), neoplasms, benign, malignant and unspecified (15), nervous system disorders (0), psychiatric disorders (0), renal and urinary disorders (1), respiratory, thoracic and mediastinal disorders (1), vascular disorders (1).</p>
Blake 2006	Nociceptive pain: rheumatoid arthritis	<p>Treatment-related in more than 1 patient</p> <p>THC + CBD (31 patients in the arm): dizziness (all mild) (8), light-headedness (3), dry mouth (4), nausea (2), arthritic pains (1), constipation (1), drowsiness (1), fall (2), headache (1), palpitations (0), vomiting (0).</p> <p>Placebo (27 patients in the arm): dizziness (all mild) (1), light-headedness (1), dry mouth (0), nausea (1), arthritic pains (1), constipation (1), drowsiness (1), fall (0), headache (1), palpitations (2), vomiting (2).</p> <p>Serious adverse events</p> <p>All-causality</p> <p>THC + CBD (31 patients in the arm): constipation (1), malaise (1).</p> <p>Placebo (27 patients in the arm): unspecified (6)</p>

Study	Subgroup	Adverse events reported
		<p>Treatment-related</p> <p>THC + CBD (31 patients in the arm): constipation (1), malaise (1).</p> <p>Placebo (27 patients in the arm): unspecified (2)</p>

Oral delta-9-THC (dronabinol), 7.5 to 16 mg per 24 hours vs placebo

Study	Subgroup	Adverse events reported
Schimrigk 2017	Neuropathic pain: multiple sclerosis	<p>All-causality in $\geq 5\%$ of patients</p> <p>Delta-9-THC (124 patients in the arm): dizziness (25), vertigo (14), fatigue (10), dry mouth (9), adverse drug reaction (8), nausea (6), headache (5), diarrhoea (3), withdrawal syndrome (0), neuralgia (0), insomnia (1).</p> <p>Placebo (116 patients in the arm): dizziness (5), vertigo (3), fatigue (5), dry mouth (1), adverse drug reaction (0), nausea (4), headache (6), diarrhoea (0), withdrawal syndrome (0), neuralgia (0), insomnia (0).</p> <p>Serious adverse events</p> <p>All-causality</p> <p>Delta-9-THC (124 patients in the arm): (17)</p> <p>Placebo (116 patients in the arm): (10)</p> <p>Treatment-related</p>

Study	Subgroup	Adverse events reported
		<p>Delta-9-THC (124 patients in the arm): (2)</p> <p>Placebo (116 patients in the arm): (0)</p>
Svendsen 2004	Neuropathic pain: multiple sclerosis	<p>All-causality</p> <p>Delta-9-THC (24 patients in the arm): Central nervous system (19) including: dizziness or lightheadedness (14), tiredness or drowsiness (10), fatigue (1), balance difficulty (2), headache (6), migraine (1), speech disorders (1), feeling of drunkenness (2), sleep difficulty (1), multiple sclerosis aggravated (1); Musculoskeletal system (9) including: myalgia (6), muscle weakness (3), limb heaviness (1), distortion of wrist (1); Gastrointestinal disorders (5) including: mouth dryness (3), nausea (3), abdominal pain (0); Cardiovascular disorders (4) including: palpitations (4); Psychiatric disorders (3) including: euphoria (3), hyperactivity (1), nervousness (0); endocrine disorders (1) including: hot flushes (1); Vision disorders (0) including: diplopia (0); Whole body (4) including: anorexia (1), weight decrease (1), fever (0), chills (1), upper airway infection (1), tenderness in nose (1).</p> <p>Placebo (24 patients in the arm): Central nervous system (8) including: dizziness or light-headedness (4), tiredness or drowsiness (6), fatigue (0), balance difficulty (0), headache (1), migraine (0), speech disorders (0), feeling of drunkenness (0), sleep difficulty (2), multiple sclerosis aggravated (2); Musculoskeletal system (2) including: myalgia (1), muscle weakness (1), limb heaviness (0), distortion of wrist (0); Gastrointestinal disorders (4) including: mouth dryness (0), nausea (4), abdominal pain (1); Cardiovascular disorders (2) including: palpitations (2); Psychiatric disorders (1) including: euphoria (0), hyperactivity (0), nervousness (1); endocrine disorders (0) including: hot flushes (0); Vision disorders (1) including: diplopia (1); Whole body (2) including: anorexia (0), weight decrease (0), fever (1), chills (0), upper airway infection (1), tenderness in nose (0).</p> <p>Serious adverse events</p> <p>All-causality</p>

Study	Subgroup	Adverse events reported
		<p>Delta-9-THC (24 patients in the arm): (3)</p> <p>Placebo (24 patients in the arm): (1)</p>
De Vries 2017	Nociceptive pain: abdominal pain	<p>Treatment-related in $\geq 10\%$ Patients</p> <p>Delta-9-THC (24 patients in the arm): General: decreased appetite (6), increased appetite (7); Nervous system disorders: amnesia (4), balance disorder (3), disturbance in attention (4), dizziness (24), dysgeusia (3), headache (14), somnolence (15); Psychiatric disorders: confusional state (3), depressed mood (3), euphoric mood (4), irritability (2), sluggishness (3); Gastrointestinal system disorders: abdominal pain (3), constipation (4), diarrhoea (3), dry mouth (9), nausea (13); Skin and subcutaneous tissue disorders: hyperhidrosis (8), rash (0); Musculoskeletal and connective tissue disorders: tremor (1); Vision disorders: visual impairment (4).</p> <p>Placebo (24 patients in the arm): General: decreased appetite (1), increased appetite (6); Nervous system disorders: amnesia (1), balance disorder (4), disturbance in attention (0), dizziness (11), dysgeusia (1), headache (18), somnolence (11); Psychiatric disorders: confusional state (3), depressed mood (2), euphoric mood (2), irritability (2), sluggishness (0); Gastrointestinal system disorders: abdominal pain (0), constipation (5), diarrhoea (2), dry mouth (2), nausea (5); Skin and subcutaneous tissue disorders: hyperhidrosis (5), rash (5); Musculoskeletal and connective tissue disorders: tremor (4); Vision disorders: visual impairment (1).</p> <p>Details of the 5 serious adverse events were not reported</p>
De Vries 2015	Nociceptive pain: abdominal pain	<p>Treatment-related</p> <p>Delta-9-THC (24 patients in the arm): General: fatigue (7); Nervous system symptoms: somnolence (8), dizziness (4), headache (2), balance disorder (2), amnesia (1), paraesthesia (2), depressed level of consciousness (0); Psychiatric symptoms: confusional state (2),</p>

Study	Subgroup	Adverse events reported
		<p>indifference (1), euphoric mood (4), derealization (1), disorientation (1), tension (1), Gastro-intestinal system symptoms: nausea (3), vomiting (1), steatorrhoea (1), constipation (0), abdominal discomfort (1), dry mouth (5), throat irritation (1); Vision symptoms: visual impairment (3); Cardiac symptoms: heart rate increased (1); Eye symptoms: dry eye (1), photophobia (1).</p> <p>Placebo (22 patients in the arm): General: fatigue (8); Nervous system symptoms: somnolence (11), dizziness (6), headache (3), balance disorder (0), amnesia (0), paraesthesia (1), depressed level of consciousness (1); Psychiatric symptoms: confusional state (0), indifference (0), euphoric mood (2), derealization (0), disorientation (0), tension (0), Gastro-intestinal system symptoms: nausea (1), vomiting (0), steatorrhoea (0), constipation (1), abdominal discomfort (0), dry mouth (0), throat irritation (0); Vision symptoms: visual impairment (1); Cardiac symptoms: heart rate increased (1); Eye symptoms: dry eye (0), photophobia (0).0</p> <p>There were no serious adverse events</p>
Malik 2017	Nociceptive pain: functional chest pain (oesophageal)	<p>All-causality</p> <p>Delta-9-THC (10 patients in the arm): transient headache, fatigue (2), transient loose stools (1)</p> <p>Placebo (9 patients in the arm): transient nausea and loose stools (2)</p> <p>There were no serious adverse events</p>
Weber 2010	Nociceptive pain: cramps	<p>“Two serious adverse events occurred. Both patients were admitted to hospital. One patient developed pneumonia during the wash-out period (after THC period) and later died; the other developed deep venous thrombosis before the THC period. These adverse events were felt not to be study-related. None of the remaining patients withdrew from the study. One patient experienced mild dizziness while on THC (sequence 0/1). The patient continued the study with half the dosage. Otherwise, none of the patients reported any side effects.”</p>

Oral nabilone (1 to 2 mg per 24 hours vs placebo)

Study	Subgroup	Adverse events reported
Wissel 2006	Nociceptive pain: spasticity	<p>All-causality</p> <p>Nabilone (13 patients in the arm): one moderate transient weakness of the lower limbs (1), mild drowsiness (2), acute relapse of multiple sclerosis (1)</p> <p>Placebo (13 patients in the arm): mild drowsiness (1), mild dysphagia (1)</p> <p>Severe adverse events</p> <p>All-causality</p> <p>Nabilone (13 patients in the arm): acute relapse (1), exacerbation of weakness (1)</p> <p>Placebo (13 patients in the arm): 0</p>
Skrabek 2008	Uncertain aetiology: fibromyalgia	<p>All-causality at week 2</p> <p>Nabilone (18 patients in the arm): drowsiness (7), dry mouth (5), vertigo (2), ataxia (3), confusion (3), decreased concentration (1), disassociation (2), orthostatic hypotension (1), anorexia (1), headache (3), blurred vision (1), dysphoria (2), depression (0), euphoria (0), lightheaded (1), psychological high (1), nightmares (1), sensory disturbance (1), tachycardia (0), hallucination (0).</p> <p>Placebo (20 patients in the arm): drowsiness (3), dry mouth (5), vertigo (0), ataxia (0), confusion (0), decreased concentration (0), disassociation (0), orthostatic hypotension (0), anorexia (0), headache (2), blurred vision (1), dysphoria (0), depression (0), euphoria (0),</p>

Study	Subgroup	Adverse events reported
		<p>lightheaded (0), psychological high (1), nightmares (0), sensory disturbance (0), tachycardia (0), hallucination (0).</p> <p>All-causality at week 4</p> <p>Nabilone (15 patients in the arm): drowsiness (7), dry mouth (5), vertigo (4), ataxia (3), confusion (2), decreased concentration (2), disassociation (2), orthostatic hypotension (2), anorexia (2), headache (1), blurred vision (0), dysphoria (1), depression (0), euphoria (1), lightheaded (0), psychological high (0), nightmares (0), sensory disturbance (1), tachycardia (0), hallucination (0).</p> <p>Placebo (18 patients in the arm): drowsiness (1), dry mouth (1), vertigo (0), ataxia (1), confusion (1), decreased concentration (1), disassociation (0), orthostatic hypotension (1), anorexia (1), headache (3), blurred vision (0), dysphoria (0), depression (1), euphoria (1), lightheaded (0), psychological high (0), nightmares (1), sensory disturbance (0), tachycardia (1), hallucination (0).</p>

Oromucosal spray THC only per 100 microlitre actuation, maximum 48 actuations per 24 hours vs placebo

Study	Subgroup	Adverse events reported
Johnson 2010	Nociceptive pain: cancer pain	<p>Treatment-related reported by ≥3 patients</p> <p>THC (58 patients in the arm): somnolence (8), dizziness (7), confusion (1), nausea (4), vomiting (4), raised gamma GT (5), hypercalcaemia (0), hypotension (0).</p> <p>Placebo (59 patients in the arm): somnolence (6), dizziness (3), confusion (1), nausea (4), vomiting (2), raised gamma GT (1), hypercalcaemia (3), hypotension (0).</p> <p>Serious adverse event</p> <p>All-causality</p> <p>THC (58 patients in the arm): progression of cancer (8), metastases to the brain (1), gastric ulcer haemorrhage (1), syncope (1), bronchopneumonia (1), hyperglycaemia (1), confusion (1), oral candidiasis (1), somnolence (1), tremor (1), disorientation (1).</p> <p>Placebo (59 patients in the arm): progression of cancer (7)</p> <p>Treatment-related</p> <p>THC (58 patients in the arm): syncope (1)</p> <p>Placebo (59 patients in the arm): 0</p>

Vaporised 22.4 mg THC and <1 mg CBD vs placebo

Study	Subgroup	Adverse events reported
van de Donk 2019	Uncertain aetiology: fibromyalgia	<p>All-causality</p> <p>THC and CBD (20 patients in the arm): Drug high (16), coughing (14), sore throat (2), bad taste (5), dyspnoea (0), dizzy (3), headache (1), nausea (3), vomiting (0), sleepy (1)</p> <p>Placebo (20 patients in the arm): Drug high (2), coughing (0), sore throat (0), bad taste (0), dyspnoea (0), dizzy (0), headache (1), nausea (0), vomiting (0), sleepy (0)</p> <p>No serious adverse events</p>

Vaporised 13.4 mg THC and 17.8 mg CBD vs placebo

Study	Subgroup	Adverse events reported
van de Donk 2019	Uncertain aetiology: fibromyalgia	<p>All-causality</p> <p>THC and CBD (20 patients in the arm): Drug high (16), coughing (14), sore throat (7), bad taste (6), dyspnoea (1), dizzy (4), headache (2), nausea (6), vomiting (0), sleepy (0)</p> <p>Placebo (20 patients in the arm): Drug high (2), coughing (0), sore throat (0), bad taste (0), dyspnoea (0), dizzy (0), headache (1), nausea (0), vomiting (0), sleepy (0)</p> <p>No serious adverse events</p>

Vaporised <1 mg THC and 18.4 mg CBD vs placebo

Study	Subgroup	Adverse events reported
van de Donk 2019	Uncertain aetiology: fibromyalgia	<p>All-causality</p> <p>THC and CBD (20 patients in the arm): Drug high (8), coughing (13), sore throat (1), bad taste (5), dyspnoea (0), dizzy (2), headache (3), nausea (1), vomiting (1), sleepy (1)</p> <p>Placebo (20 patients in the arm): Drug high (2), coughing (0), sore throat (0), bad taste (0), dyspnoea (0), dizzy (0), headache (1), nausea (0), vomiting (0), sleepy (0)</p> <p>No serious adverse events</p>

Appendix I – Health economic analysis

Introduction

Chronic pain is common in the UK general population but has a heterogeneous aetiology. A recent epidemiological study found that roughly 43.5%, 28 million people in the UK general population were expected to have “severe and chronic pain that is unresponsive to treatment”. Treatment options vary widely depending on the cause of the pain but their effectiveness and side effects vary widely and there is very significant unmet clinical need in the population group whose pain is not adequately controlled by these conventional options. Some chronic pain patients self treat with cannabis based products purchased as health food supplements or online and there is widespread interest in whether Cannabis Based Medicinal Products (CBMPs) should be prescribed on the NHS. However, it is currently very rare for patients with chronic pain to be treated with CBMPs on the NHS.

The CBMPs that are currently on the market could cost several thousand pounds per patient per year, based on publicly available sources for price. This, along with the considerations above meant that the potential resource impact of a positive recommendation in this area could be extremely high. The committee therefore prioritised this question for *de novo* economic modelling as any positive recommendation would need to be underpinned by robust health economic evaluation.

Methods

Decision problem

The population of interest were people with chronic pain whose pain was not adequately controlled by conventional management. Since no CBMPs have a licence for treating chronic pain, it would not be appropriate to compare them to conventional management. Instead the model has 2 strategies, CBMP + usual care and usual care.

In the base case, the model considers all people with chronic pain as an aggregated group, which is broken down by pain aetiological subgroups in sensitivity analysis. The different aetiologies, decided upon by the committee following review of the available clinical evidence, were neuropathic pain, cancer pain and musculoskeletal pain. Separate analyses were conducted for different CBMPs; THC:CBD spray, oral dronabinol, oral nabilone and oromucosal THC.

Model Structure

The committee indicated that if CBMPs were to be used in the chronic pain population, they would be trialled for a month and discontinued if patients did not achieve a 30% reduction in pain from baseline as this is a well accepted Minimally Clinically Important Difference (MCID) in this population and a threshold that had been reported by studies in the clinical review. They indicated that a small proportion of patients who did not achieve a treatment response of 30% would remain on treatment if they felt they were getting some benefit from it. The 30% improvement threshold is based on the expert opinion at the committee. This parameter is only used to determine the continuation of treatment. The treatment response is based on the absolute NRS changes in the model.

We built a decision analytic model with five Markov states in each model arm; on treatment response (OTR), on treatment no response (OTNR), discontinued with response (DR), discontinued with no response (DNR) and dead. After being initially assigned to a Markov state through treatment effects, patients could transition from OTR to DR and from OTNR to DNR and patients could die from any state but no other transitions were possible (Figure 1). We adopted the same structure as this for the placebo arm because it is logical to operationalise the treatment and placebo effects within the same model structure, but people do not incur treatment cost in the usual care arm of the model despite nominally occupying a nominal “on treatment” state. This structural choice is not expected to have affected any of the results as the total distribution of patients’ pain scores within the usual care arm of the model is unaffected by grouping patients with higher and lower distributions into arbitrary Markov states in this way.

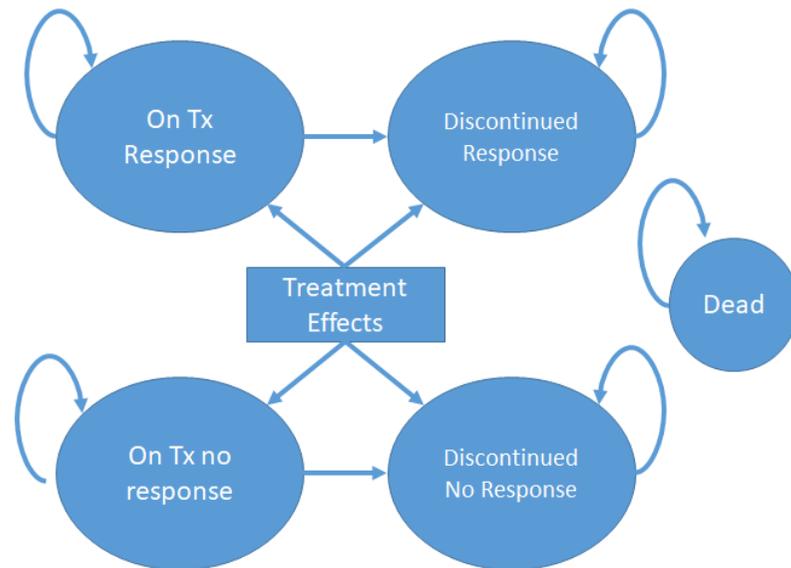


Figure 1: Model structure (for both model arms)

Effect Engine

Distribution of treatment effects

We chose to model treatment effects within our model using continuous (mean changes in pain score) rather than dichotomous (proportion of people achieving a 30% response) data on treatment effects from the clinical review. This decision was made firstly because more trials reported mean changes in pain score rather than proportions of people achieving at least a 30% improvement in pain and secondly because it provided a more detailed breakdown of treatment effects for us to examine the influence of CBMPs on costs and quality of life across the whole distribution of pain scores at different time points in the model.

We assumed that treatment effects would be normally distributed and tested this assumption by conducting simulations. There were two studies from the clinical review that allowed us to test how well normally distributed treatment effects would match empirically observed dichotomous outcomes, (Langford 2013 and Portenoy 2012). These were two of the larger studies included in the systematic review. Using the Langford data, we assumed baseline pain was normally distributed (we did not need to truncate this data to fit between 0 and 10 because of the relatively tight confidence intervals) and simulated 60,000 theoretical patients based on baseline mean and SD pain score. We then added a placebo or active treatment effect to each theoretical patient, randomly assigning values from a normal distribution with mean and SD taken from the change from baseline data in that study. Using the simulated data, we calculated the proportion of patients that received a 30% and 50% improvement in pain and compared them to the data from the trial. The results are in Table 2.

Table 2: Langford 2013 response data compared with normal distribution estimates

Outcome	Reported by study	Estimated
Patients achieving 30% pain reduction		
THC:CBD spray	50%	49%
Placebo	45%	46%
Patients achieving 50% pain reduction		
THC:CBD spray	30%	28%
Placebo	28%	25%

We then repeated this process for the Portenoy 2012 data, which provided dichotomous response data at many more levels of response. The data are in Figure 2.

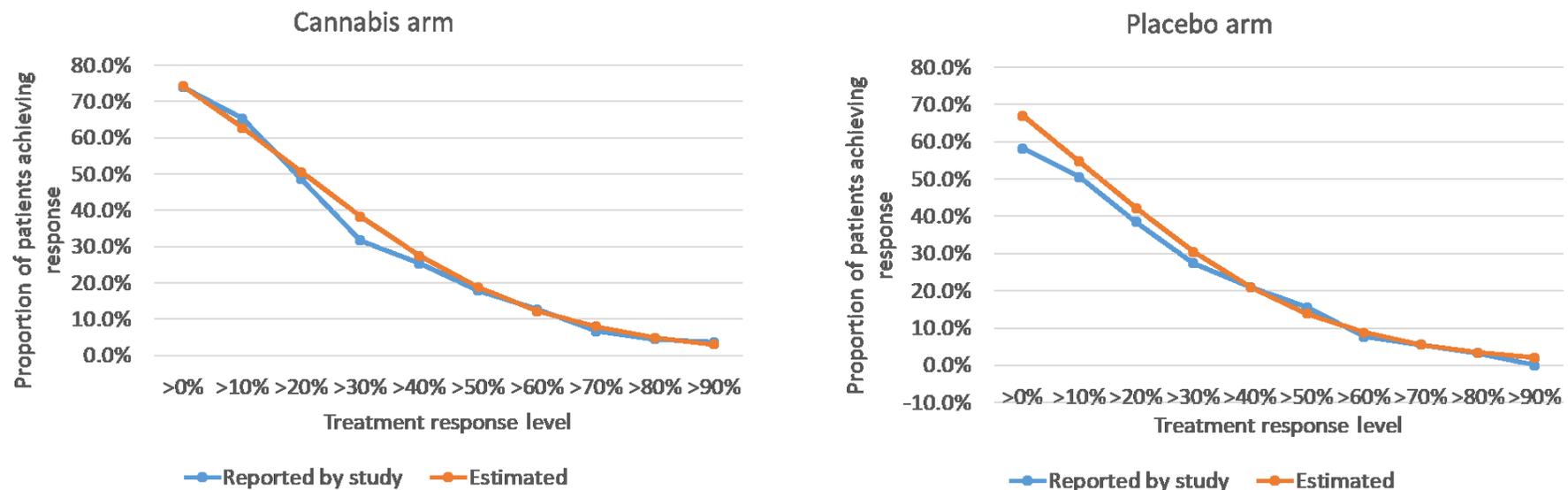


Figure 2: Portenoy response data compared with normal distribution estimates

Based on the fit of these data and their experience, the committee felt that it was clinically plausible that treatment effects are well approximated by a normal distribution.

Application of treatment effects

As detailed in the Natural History section below, the distribution of baseline pain in both model arms was calculated using a beta distribution to assign patients into 200 ‘bins’ representing each 0.05 pain increment from 0.025 to 9.975 on the NRS scale.

We calculated patients’ pain scores after treatment by combining the beta distribution of baseline score and the normal distribution for treatment effects. We were then able to use the normally distributed treatment effects to calculate the proportion of patients moving from each bin to every other bin.

Separate post-treatments distributions were then calculated for patients who achieved a $\geq 30\%$ treatment response and those who did not. This was implemented by calculating whether the difference between 2 bins was $\geq 30\%$ or not when combining distributions. This also allowed calculation of the proportion of the overall cohort achieving a treatment response. Calculating the pain distribution of those who had achieved a $\geq 30\%$ response and those who had not was important for assigning costs and utility values to those continuing treatment with CBMPs beyond the first cycle of the model.

We also calculated distributions for patients who discontinued due to lack of treatment response and patients who did achieve a response but discontinued for other reasons. We made the assumption that patients who did not continue treatment would drop back to baseline in both arms of the model. These two distributions combined are therefore equivalent to the distribution at baseline, but divided into patients who would have achieved a treatment response, and those who would not. The separation of these distributions was necessary because 10% of partial responders are assumed to continue with treatment and because we assumed that patients discontinuing from the OTR health state would transition to the DR health state and patients discontinuing from the OTNR health state would discontinue to the DNR health state.

Cycle Length, Discount Rate and Time Horizon

We adopted a 4-week cycle length as treatment effects were often reported over this time in clinical trials. We adopted a discount rate of 3.5% for both costs and benefits and a lifetime time horizon in line with the NICE reference case. The data available to populate the model were typically short term so we adopted a shorter time horizon in sensitivity analysis.

Input parameters

Natural History

The distribution of baseline pain in both model arms was calculated using a beta distribution to assign patients into 200 'bins' representing each 0.05 pain increment from 0.025 to 9.975 on the NRS scale. We used this distribution because it is not possible for a person to have a pain score below 0 or above 10. Using the 'method of moments' formulae, we converted the mean and SD of baseline pain from a large epidemiological study (Farrar 2001) to the alpha and beta parameters necessary for the distribution. We also used the average age and sex from this study to calculate utility values associated with each NRS score (see Utilities section).

In the base case, the assumption was made that pain score does not change over time (unless in response to treatment). This assumption was relaxed in sensitivity analysis by including capacity for increasing or decreasing pain score. Since a linearly changing score would mean that almost all of the cohort would end up with a pain score of either 0 or 10, we modelled the natural history such that pain asymptotically approaches 0 and 10. This was achieved by first specifying a "mean change in pain score per year". This was used to calculate a "hazard ratio", by dividing

baseline pain score and pain score after 1 year by 10, converting into instantaneous “rates”, and taking the ratio between the two. The resulting value was converted to a HR per cycle of the model. This was then applied to pain scores in each cycle, by converting scores into “rates”, applying the “HR” and then converting back to pain scores.

Table 3: Baseline Characteristics

Parameter	Mean	SD	Source
Age	60.32	10.93	Farrar 2001
% male	46%		Farrar 2001
Pain NRS at baseline	6.52	1.43	Farrar 2001

Treatment effects

We obtained treatment effect data from the systematic review for this review question for four separate cannabis based medicinal products (Table 4). These were either derived from single studies or from meta-analyses. Response in the SoC arm of the model was set equal to the control arm from Langford, the largest study in the review, in the base case. Treatment effect data were added to response in the SoC arm to calculate response in the cannabis arm. See [appendix E](#) and [AppendixF](#) for details.

Table 4: Baseline response and treatment effect data from the clinical review

	Mean	Lower CI	Upper CI
Treatment response in control arm			
Langford 2013	-1.76	-2.11465	-1.40535
Portenoy 2012	-0.8	-1.17394	-0.42606
THC:CBD spray			
Overall	-0.44	-0.7	-0.18
Neuropathic pain	-0.52	-0.99	-0.06
Cancer pain	-0.33	-0.66	0
Musculoskeletal pain	-0.95	-1.85	-0.05
Oral dronabinol			

	Mean	Lower CI	Upper CI
Overall	0.1	-0.23	0.43
Neuropathic pain	0.11	-0.41	0.63
Visceral pain	-0.1	-0.77	0.57
Musculoskeletal pain	0.24	-0.32	0.8
Oral nabilone			
Widespread pain	-1.43	-2.8	-0.06
THC - oromucosal spray			
Cancer pain	-0.32	-0.86	0.22

Discontinuation from Response

No direct, long term data on discontinuation were available for this population so we explored several options in the model. In the base case, discontinuation from response data were obtained from a large, publicly available individual patient dataset (Messina et al. 2017) on patients with advanced MS being treated with THC:CBD spray. These patients were treated for a period of 1 month with responders remaining on treatment and non-responders discontinuing. We selected only the responders, subtracted 28 days from the total time on treatment, converted the time on treatment from days to years and performed survival analysis on these patients where discontinuations were classed as events. Based on AIC/BIC statistics we selected a gompertz parametric curve to use within our economic model.

Table 5: Model fit statistics for discontinuation survival curve

Parametric Survival Regression	AIC	BIC
Weibull	2641	2652
Exponential	3145	3150
Gompertz	2412	2422

Parametric Survival Regression	AIC	BIC
Gamma	2497	2512
Lognormal	2588	2599
Loglogistic	2625	2635

While this dataset relates to the MS population rather than the population with chronic pain, the results indicate that THC:CBD spray is generally well tolerated and that treatment benefit appears to persist, with 80% of responders still being on treatment after 2 years. The most common reasons for discontinuation among those that responded were lack of effectiveness, adverse events or a combination of the two. We set up the model to use an alternative discount rate of 3.1% per cycle, calculated from Hoggart 2015, a study that was specific to cannabis use in chronic pain in scenario analysis.

In the base case we applied the discontinuation curve equally to responders in both the standard of care and active treatment arms of the model but explored no discontinuation and differential discontinuation in sensitivity analysis. For the differential discontinuation we modelled discontinuation by application of a hazard ratio. The hazard ratio was derived by creating an identical dataset to that in Messina 2017 but treating all patients who discontinued for adverse events alone as censors. This dataset was compared with the original using a cox proportional hazards model (HR = 0.482, se=0.06, proportional hazards assumption not rejected). The interpretation of this is that lower discontinuation would be expected in the standard of care arm because people cannot discontinue from pain response through adverse events alone. We included another option which fitted a competing risks model to the data, coding adverse events alone as a separate, competing risk to other discontinuations. We followed the methodology in section 6.3 of the CRAN-R documentation on the flexsurv package^a but used a gompertz model instead of the Weibull example given. The survival curve for the CBMP arm took account of both competing risks whereas the survival curve for the SoC arm included only non-adverse event related discontinuations. The competing risks model produced survival estimates that were very similar to those produced using the hazard ratio method outlined above. There were no deaths recorded in the dataset although there were a number of censoring events with no reason recorded and it is possible that some of these were in fact deaths. By handling deaths separately from discontinuation it is possible that there is a small amount of double counting in the economic model. Given the relatively low average age in the dataset and therefore low mortality rate, and the fact that this issue would apply to both model arms, we assessed this particular limitation as minor.

^a <https://cran.r-project.org/web/packages/flexsurv/vignettes/flexsurv.pdf>

Clearly there are limitations with all these approaches but in the absence of long term data on changes in response in either the active treatment or standard of care arm the committee acknowledged that they were the best available, noted them as limitations and explored them in sensitivity analysis.

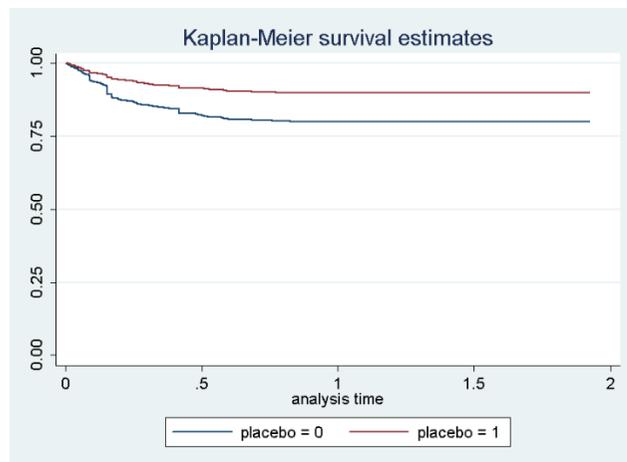


Figure 3: Discontinuation from THC:CBD spray in responders and simulated non-responders [the placebo=1 group] (Messina 2017)

Mortality

There is no data available on whether treatment with CBMPs affect mortality and they are not expected to be fundamentally disease modifying. We therefore did not vary mortality by model arm but modelled overall mortality by applying an SMR of 1.32 (0.08) for people with chronic pain from an epidemiological study (Torrance 2006) to standard population level life tables published by the Office for National Statistics.

Downstream treatments

While CBMPs are not expected to be fundamentally disease modifying, and the clinical review identified no randomised evidence that their use spares other medication, we were interested in whether their potential to reduce or delay invasive treatments would influence the results of the economic model. The committee advised us that the only invasive treatment that was common enough to potentially influence the model's results

was radiofrequency denervation (RFD) for people with chronic low back pain. This section is therefore only relevant when considering the patient population with low back pain. This part of the model was switched off for other subgroups.

Theoretically, any patient with chronic low back pain and an NRS greater than 5 is eligible for RFD and the committee estimated that around 10% of the eligible population might be trialled for RFD per year. The methodology for applying the costs and benefits of RFD was adapted from that employed in the [NICE guideline on Low back pain and sciatica in over 16s: assessment and management](#).

The trial for RFD consists of administration of a diagnostic block which is either positive or negative and to which some patients receive a HRQoL benefit (modelled as the same level of benefit as full RFD, as in the low back pain analysis) for prolonged response for the duration of that response. Negative patients will not receive RFD and 10% of positive patients will decline it. RFD and prolonged response to diagnostic block are implemented as a series of simultaneous tunnel states (i.e. they exist in parallel to the main on treatment/off treatment states). In each cycle, the % of patients with a pain score >5 is calculated using patient distributions, and this is used to determine the number of patients who undergo diagnostic block. Because of the tunnel state structure, the model ensures patients who are already in RFD or prolonged diagnostic block states cannot undergo diagnostic block again.

The QALY gain for RFD is determined by first applying the treatment effects from the NG59 model uniformly (having no specific evidence of non-uniformity) to each level of baseline pain within the initial distribution. The weighted average utility difference between the resulting distribution and the initial distribution is then taken and applied to the proportion of people who respond to diagnostic blocks or are in receipt of RFC benefit in any given cycle, with the treatment effect of RFD lasting two years. 10% of people who receive the full two years of RFD benefit were assumed to undergo repeat RFD after this time. The relevant parameters are in Table 6.

Table 6: Radiofrequency Denervation Parameters

Parameter	Mean	Lower CI	Upper CI	Source
Threshold for consideration of RFD (pain score)	5	4	6	NG59
Proportion of eligible patients in whom RFD is considered - per annum	10%	8%	12%	Committee assumption
Probability of a positive diagnostic block	69%			NG59
Probability of a prolonged response to diagnostic block	15%			NG59
Probability of declining RFD after successful diagnostic block	10%			NG59
Proportion of patients repeating successful RFD	10%			NG59
Initial appointment	£168	£135	£201	NG59

Parameter	Mean	Lower CI	Upper CI	Source
Diagnostic block procedure	£546	£439	£653	NG59
Follow-up visit	£121	£97	£145	NG59
Radiofrequency denervation procedure	£618	£497	£739	NG59
QoL gain from RFD < 4 months	0.091481			Calculated
QoL gain from RFD > 4 months	0.078471			Calculated

Adverse Events

We obtained adverse event and serious adverse event rates from a systematic review of patients being treated with CBMPs (Wang 2008) and used these data to calculate the events that occurred per cycle in the model. A wide range of non-serious adverse events were reported in this study but for simplicity we assumed them to be distributed among the five most important events selected by the committee; dizziness, dry mouth, fatigue, headache and nausea. We re-scaled the incidence of these five adverse events so that their sum matched the total event rate. Serious adverse events were assumed to be homogenous.

We assumed that all adverse events would be short term in nature, lasting only a few days and sourced temporary health related quality of life decrements from studies that reported the five most important adverse events selected by the committee. A quality of life decrement for grade 2 vomiting was used as a surrogate for serious adverse events because this was the most common non-condition specific adverse event reported in the Wang 2008 study. Grade 2 events are often not classified as serious in papers outside the CBMP field so it is possible that we may have slightly underestimated the QoL decrement associated with treatment related adverse events. 50% of non serious adverse events were assumed to incur a GP appointment and serious adverse events were assumed to incur an A&E visit, with 50% incurring a trip in an ambulance.

To obtain the adverse events for each Markov state in both arms of the model where patients were not on treatment, we multiplied the per cycle event rates for serious and non-serious AEs by the reciprocal of relative risks associated with different forms of CBMP in the clinical review. For patients in the on-treatment states these adverse event rates are unadjusted.

The above assumptions are subject to very serious limitations but, taken together, provide a rough estimate of the scale of the effect that adverse events have on the cost-effectiveness results. Sensitivity analyses including and excluding adverse events and varying input data to the extremes of their confidence intervals were undertaken. Since the only evidence we had indicated that adverse events are relatively rare and short term in nature, they are not expected to materially affect the cost-effectiveness of CBMPs.

Table 7: Adverse event parameters

Adverse events	Parameter	Lower CI	Upper CI	
Event rates per year				
Non-serious adverse events	10.37	10.0708	10.6692	Wang 2008
Serious adverse events	0.37	0.313484	0.426516	Wang 2008
Non-serious adverse events Placebo	6.87	6.626473	7.113527	Wang 2009
Serious adverse events Placebo	0.25	0.203544	0.296456	Wang 2010
Frequency of individual events				
% of events which are dizziness	56.8%			Wang 2008
% of events which are dry mouth	19.0%			Wang 2008
% of events which are fatigue	8.7%			Wang 2008
% of events which are headache	6.3%			Wang 2008
% of events which are nausea	9.3%			Wang 2008
Event rates per cycle				
Dizziness	0.451504			
Dry mouth	0.151134			
Fatigue	0.068927			
Headache	0.049956			
Nausea	0.073986			
Serious adverse events	0.028384			
Event rates per cycle				
Dizziness	0.299116			
Dry mouth	0.100124			
Fatigue	0.045663			
Headache	0.033095			
Nausea	0.049015			

Adverse events	Parameter	Lower CI	Upper CI	
Serious adverse events	0.019178			
Adverse event costs				
Unit costs				
GP visit	37			PSSRU - GP consultation including direct staff costs and qualification costs
A&E visit	225.8232			Reference costs - Weighted average of emergency medicine costs (excluding dental care, no investigation with no significant treatment, and dead on arrival)
Ambulance	251.9343			Reference costs - see and treat and convey
Resource use				
Dizziness - proportion of patients who visit GP	50%	40%	60%	Assumption
Dry mouth - proportion of patients who visit GP	50%	40%	60%	Assumption
Fatigue - proportion of patients who visit GP	50%	40%	60%	Assumption
Headache - proportion of patients who visit GP	50%	40%	60%	Assumption
Nausea - proportion of patients who visit GP	50%	40%	60%	Assumption
Serious adverse event - proportion of patients who require ambulance journey to A&E	50%	40%	60%	Assumption
Cost per event				
Dizziness	18.5			Calculated
Dry mouth	18.5			Calculated
Fatigue	18.5			Calculated
Headache	18.5			Calculated
Nausea	18.5			Calculated
Serious adverse event	351.7904			Calculated
Adverse event disutilities				
QoL decrements				

Adverse events	Parameter	Lower CI	Upper CI	
Dizziness	0.022	-0.009	0.054	Hagiwara 2018 - assumed to be equivalent to disutility of fatigue
Dry mouth	0.022	-0.009	0.054	Hagiwara 2018 - assumed to be equivalent to disutility of fatigue
Fatigue	0.022	-0.009	0.054	Hagiwara 2018
Headache	0.043	0.155573	0.264427	Stafford 2012 - equivalent to mild migraine
Nausea	0.062	0.025	0.103	Hagiwara 2018
Serious adverse event	0.095	-0.05	0.241	Hagiwara 2018 - grade 2 vomiting
Adverse event durations (days)				
Dizziness	3	1.824022	4.175978	Assumption
Dry mouth	7	4.25605	9.74395	Assumption
Fatigue	7	4.25605	9.74395	Assumption
Headache	3	1.824022	4.175978	Assumption
Nausea	3	1.824022	4.175978	Assumption
Serious adverse event	3	1.824022	4.175978	Assumption
QALY losses				
Dizziness	0.000181			Calculated
Dry mouth	0.000422			Calculated
Fatigue	0.000422			Calculated
Headache	0.000353			Calculated
Nausea	0.00051			Calculated
Serious adverse event	0.000781			Calculated

Costs

Treatment costs for THC:CBD spray and nabilone were taken from the Drug Tariff with daily doses being taken from representative studies from the clinical review (Langford 2013 and Skrabek 2008 respectively). There are currently no publicly available UK prices for dronabinol or for the various Bedrocan products but the overall cost per patient is expected to be higher than that for THC:CBD spray.

Table 8: CBMP Costs

Cannabis treatment costs	Mean	Lower CI	Upper CI	Source
THC:CBD spray				
Cost per pack	£300			Drug Tariff
Doses per day	8.8	8.16	9.43	Langford 2013
Cost per cycle	£342.2			Calculated
Nabilone				
Cost per pack	£196			Drug Tariff (March 2019)
Doses per day	2			Skrabek 2008
Cost per cycle	£548.8			Calculated

The committee informed us that patients treated with CBMPs might expect to receive four additional outpatient visits within the first year and two outpatient visits in subsequent years to monitor their medication. Outpatient visits were costed at £147 (NHS Reference Costs 2017/18 - non-admitted face-to-face consultant-led attendance, follow-up – pain management).

In line with methodology that had been employed in modelling the spasticity question for this guideline, we assigned resource use to different levels of pain NRS. The committee confirmed that this approach was reasonable and considered that improvement in pain levels might lead to a resource saving in pain management costs. From their clinical experience they estimated the number of community based visits, outpatient clinic visits, A&E visits, hospital admissions and home care visits associated with five broad pain levels, NRS 0-2, NRS 2-4, NRS 4-6, NRS 6-8, NRS 8-10. The overlapping naming is caused by dividing an 11-point scale by five. The overall management cost for a given Markov state in a given cycle

is the weighted average of their pain distribution rounded to the nearest fifth of the NRS scale multiplied by these costs. Given the uncertainty inherent in estimating background management costs in this way, these parameters were subject to extreme sensitivity analyses. We adjusted home care costs to account for the proportion that were self funded using data from [NICE's guideline on Parkinson's disease health economics report](#).

Adverse event costs are discussed in that section.

Table 9: Background pain management costs by NRS stage

Unit costs	Parameter	Source
GP visit	£37.00	PSSRU - GP consultation including direct staff costs and qualification costs
Outpatient visit	£147.00	NHS Reference costs - non-admitted face-to-face consultant-led attendance, follow-up - pain management
A&E visit	£225.82	Reference costs - Weighted average of emergency medicine costs (excluding dental care, no investigation with no significant treatment, and dead on arrival)
Hospital admission	£2,071.39	Reference costs - Weighted average of elective long stay, non-elective long stay and non-elective short stay for pain procedure HRGs: AB12Z, AB13Z, AB14Z, AB15Z, AB16Z, AB17Z, AB18Z, AB19Z, AB20Z, AB21Z, AB22Z, AB24Z
Home care visitor - cost per hour	£27.29	PSSRU 2018 - Cost per hour for home care worker (based on the price multipliers for independent sector home care provided for social services) - weighted average of weekday and weekend cost
Resource use per state		
State 1 (NRS 0-2)		
Community-based visits (annual)	0	Committee assumption
Outpatient clinic visits (annual)	0	Committee assumption
A&E visits (annual)	0	Committee assumption
Hospital admissions (annual)	0	Committee assumption
Home care visits (weekly)	0	Committee assumption
State 2 (NRS 2-4)		
Community-based visits (annual)	0	Committee assumption

Unit costs	Parameter	Source
Outpatient clinic visits (annual)	1	Committee assumption
A&E visits (annual)	0	Committee assumption
Hospital admissions (annual)	0	Committee assumption
Home care visits (weekly)	0	Committee assumption
State 3 (NRS 4-6)		
Community-based visits (annual)	0	Committee assumption
Outpatient clinic visits (annual)	2	Committee assumption
A&E visits (annual)	1	Committee assumption
Hospital admissions (annual)	0.5	Committee assumption
Home care visits (weekly)	0	Committee assumption
State 4 (NRS 6-8)		
Community-based visits (annual)	0	Committee assumption
Outpatient clinic visits (annual)	4	Committee assumption
A&E visits (annual)	2	Committee assumption
Hospital admissions (annual)	1	Committee assumption
Home care visits (weekly)	0	Committee assumption
State 5 (NRS 8-10)		
Community-based visits (annual)	12	Committee assumption
Outpatient clinic visits (annual)	8	Committee assumption
A&E visits (annual)	4	Committee assumption
Hospital admissions (annual)	2	Committee assumption
Home care visits (weekly)	1	Committee assumption
Home care funding sources		
Distribution of funding categories		
Self-funded	0.434	Parkinson's guideline

Unit costs	Parameter	Source
Part self- part NHS/PSS-funded	0.139	Parkinson's guideline
PSS funded	0.355	Parkinson's guideline
NHS continuing care funded	0.072	Parkinson's guideline
Part-self funded care		
Proportion of part self-funded care paid for by patients	0.5	Assumption
Cost per cycle		
State 1 (NRS 0-2)	£0.00	Calculated
State 2 (NRS 2-4)	£11.28	Calculated
State 3 (NRS 4-6)	£119.33	Calculated
State 4 (NRS 6-8)	£238.65	Calculated
State 5 (NRS 8-10)	£565.41	Calculated

Utilities

Utilities associated with each NRS pain level were sourced from a utility study that included 2,719 patients with chronic neuropathic pain (Gu 2012). This study provided dummy variable regression coefficients for each NRS level as well as age, gender and the constant. As well as having been collected from a large and broadly representative sample, the committee agreed that these data had face validity. The per cycle QALYs for each Markov state were the weighted average of the pain distribution and these utility values, with pain scores for the individual bins being rounded to the nearest integer.

Adverse event disutilities were obtained from a utility study which aimed to estimate the disutility associated with a series of common adverse events in patients with breast cancer. The patient group is clearly indirect and, as shown in the table below, several assumptions were necessary to operationalise adverse events in the model but as AEs were typically short term and non-severe, these limitations are not expected to materially influence the model's results. Please see the adverse events section for the relevant input data.

Regression equation - effect of NRS on EQ-5D	Mean	Lower CI	Upper CI	Source
Constant	0.684	0.617	0.751	Gu 2012
NRS 0	0.000			Gu 2012
NRS 1	-0.005	-0.062	0.052	Gu 2012
NRS 2	-0.088	-0.143	-0.033	Gu 2012
NRS 3	-0.098	-0.151	-0.045	Gu 2012
NRS 4	-0.138	-0.191	-0.085	Gu 2012
NRS 5	-0.152	-0.205	-0.099	Gu 2012
NRS 6	-0.188	-0.239	-0.137	Gu 2012
NRS 7	-0.260	-0.313	-0.207	Gu 2012
NRS 8	-0.328	-0.381	-0.275	Gu 2012
NRS 9	-0.398	-0.461	-0.335	Gu 2012
NRS 10	-0.464	-0.525	-0.403	Gu 2012
Age	0.003	0.001	0.005	Gu 2012
Gender	-0.034	-0.048	-0.020	Gu 2012

Table 10: Utility regression model coefficients for chronic pain

Sensitivity and scenario analyses

A large number of one-way and multi-way deterministic sensitivity analyses were conducted in order to test how sensitive the model's conclusions were to uncertainties in its input parameters. Probabilistic sensitivity analysis, where the model was run thousands of times with input parameters being sampled from appropriate probability distributions was also conducted to test the sensitivity of the model to combined statistical uncertainty. Pre-specified scenario analysis were:-

1. Using the costs and effects of nabilone instead of THC:CBD spray
2. Using treatment effect data for the neuropathic pain subgroup
3. Using treatment effect data for the cancer pain subgroup

4. Using treatment effect data for the musculoskeletal pain subgroup
5. Using discontinuation data from the Hoggart 2015 chronic pain study instead of the Messina 2017 MS individual patient data
6. Using control arm response from Portenoy 2012 instead of Langford 2013
7. Excluding the background management costs for chronic pain
8. Not allowing a proportion of sub<30% responders to continue with treatment
9. Including RFD as a downstream treatment for low back pain
10. Declining the treatment effect over time by reducing mean pain to match placebo
11. Declining the placebo effect (change from baseline) in both arms so that pain returns to baseline after 2 years
12. Allowing differential discontinuation from response in the standard of care arm equalling the hazard ratio
13. Assuming no discontinuation from response in either arm
14. All adverse events halved
15. All adverse events doubled
16. All pain management costs halved
17. All pain management costs doubled
18. All QoL coefficients set to high limits of confidence intervals
19. All QoL coefficients set to low limits of confidence intervals
20. Competing risks model from Messina for discontinuation
21. -0.55 treatment effect to force the model to produce a mean difference equal to the input treatment effect of -0.44

Results

The results section will focus on treatment with THC:CBD spray unless otherwise noted as this is the treatment with the most robust clinical evidence. The patient group will be all patients with chronic pain unless otherwise noted.

Intermediate Results

The model's intermediate results show that after the initial trial of treatment period, 54% of patients in the cannabis arm and 46% of patients in the standard of care arm achieved a 30% reduction from baseline while 31% and 25% achieved a 50% reduction respectively. These data were similar to data observed in the clinical trials. There is some discontinuation from response and then the model settles into a steady state where about 43% and 37% of patients remain as responders respectively (see Figure 4). Similarly, the graph of mean cohort pain over time shows an initial drop, followed by a slight increase and then a steady state of 4.9 for the cannabis arm and 5.2 for the standard of care with the slight increase being the result of the aforementioned discontinuation (see Figure 4). This is somewhat lower than the mean treatment effect and that is because only

patients with a 30% improvement are assumed to continue treatment and carry on receiving the benefits. All other patients drop back to baseline after ending treatment. We set up a sensitivity analysis to increase the mean difference between the arms to match the input effectiveness data.

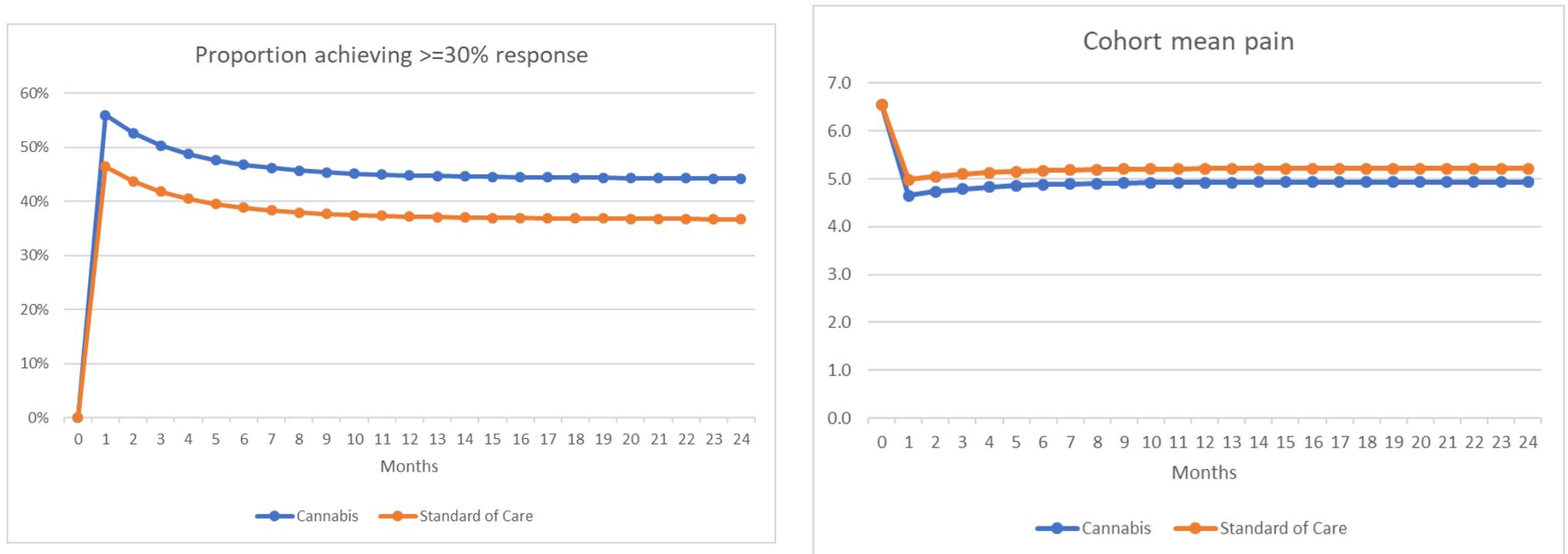


Figure 4: Intermediate model results

The relatively small difference between the intermediate outcomes in the model reflects the modest effectiveness of cannabis observed in the clinical review.

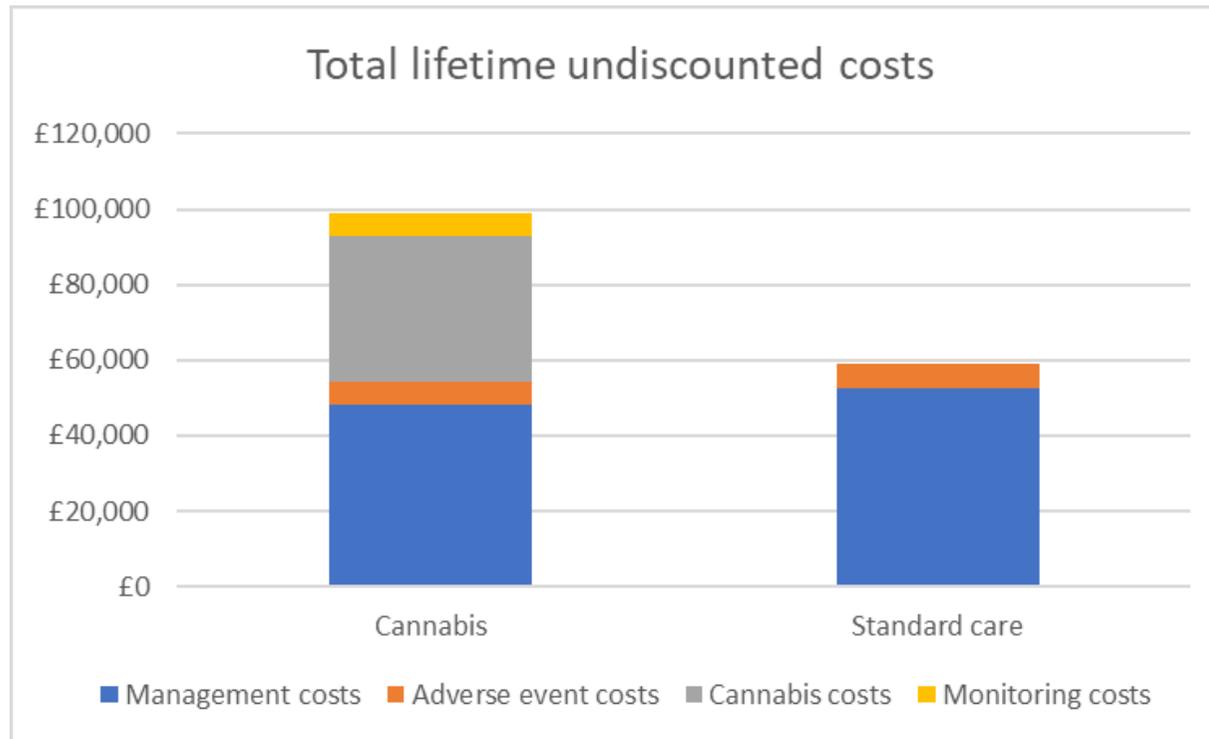


Figure 5: Total lifetime undiscounted costs by broad area and model arm

It can be seen from Figure 5 that cannabis only results in very small resource savings through reduction in pain scores and small increases in adverse event costs. These values are overwhelmed by the cost of cannabis treatment, however, along with a modest increase in monitoring costs.

Cost-utility Results

In the base case (THC:CBD spray costs and effects, overall chronic pain population, discontinuation data from Messina 2017, SoC response from Langford 2013, no treatment effect or SoC decline over time, no differential discontinuation from response, lifetime time horizon, discounting at 3.5% for both costs and benefits) the model produced incremental costs of £24,474 and incremental QALYs of 0.162 and therefore an ICER of £151,431/QALY gained.

The results for the mean of the probabilistic sensitivity analysis were very similar to this and that analysis found a 100% probability that cannabis is more effective, a 100% probability that it is more expensive and a 0.0% probability that cannabis is cost effective over standard care at the commonly accepted thresholds of £20,000 and £30,000/QALY gained.

Table 11: Cost-utility analysis results

Deterministic					
Strategy	Costs	QALYs	Inc costs	Inc QALYs	ICER
Standard of Care	£39,233	10.480			
Cannabis	£63,706	10.642	£24,474	0.162	£151,431
Mean of Probabilistic					
Strategy	Costs	QALYs	Inc costs	Inc QALYs	
Standard of Care	£39,414	10.442			
Cannabis	£63,924	10.606	£24,510	0.164	£149,454

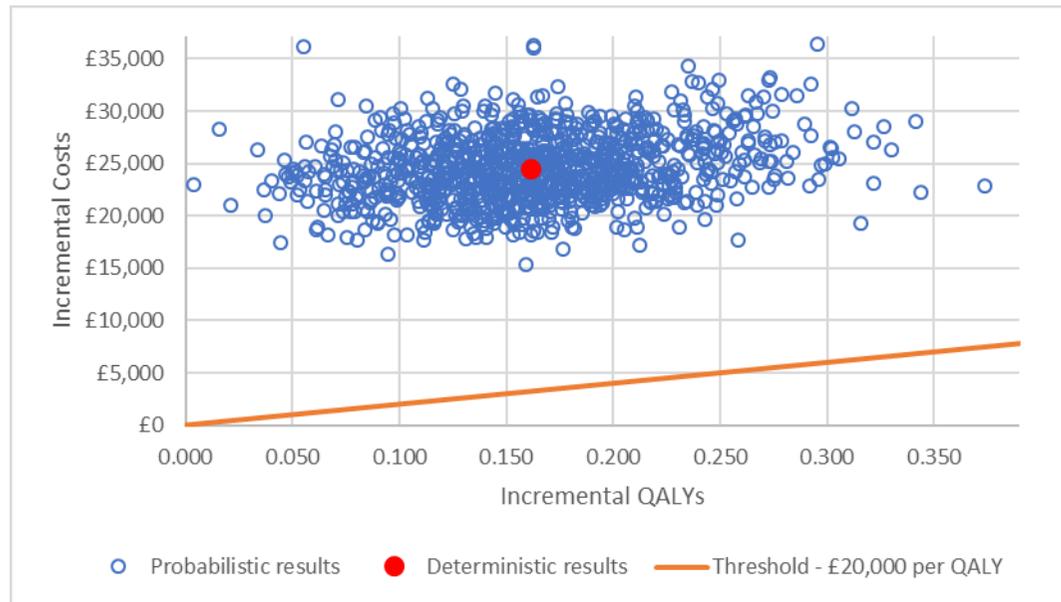


Figure 6: Probabilistic Sensitivity Analysis Scatterplot

Sensitivity and scenario analysis results

The tornado diagram in Figure 7 shows how the ICER changes in response to high and low values in important input parameters. The high and low values are typically limits of confidence intervals or other values selected to represent extreme scenarios. It can be seen from this diagram that no plausible variations in individual model parameters meaningfully affect the ICER.

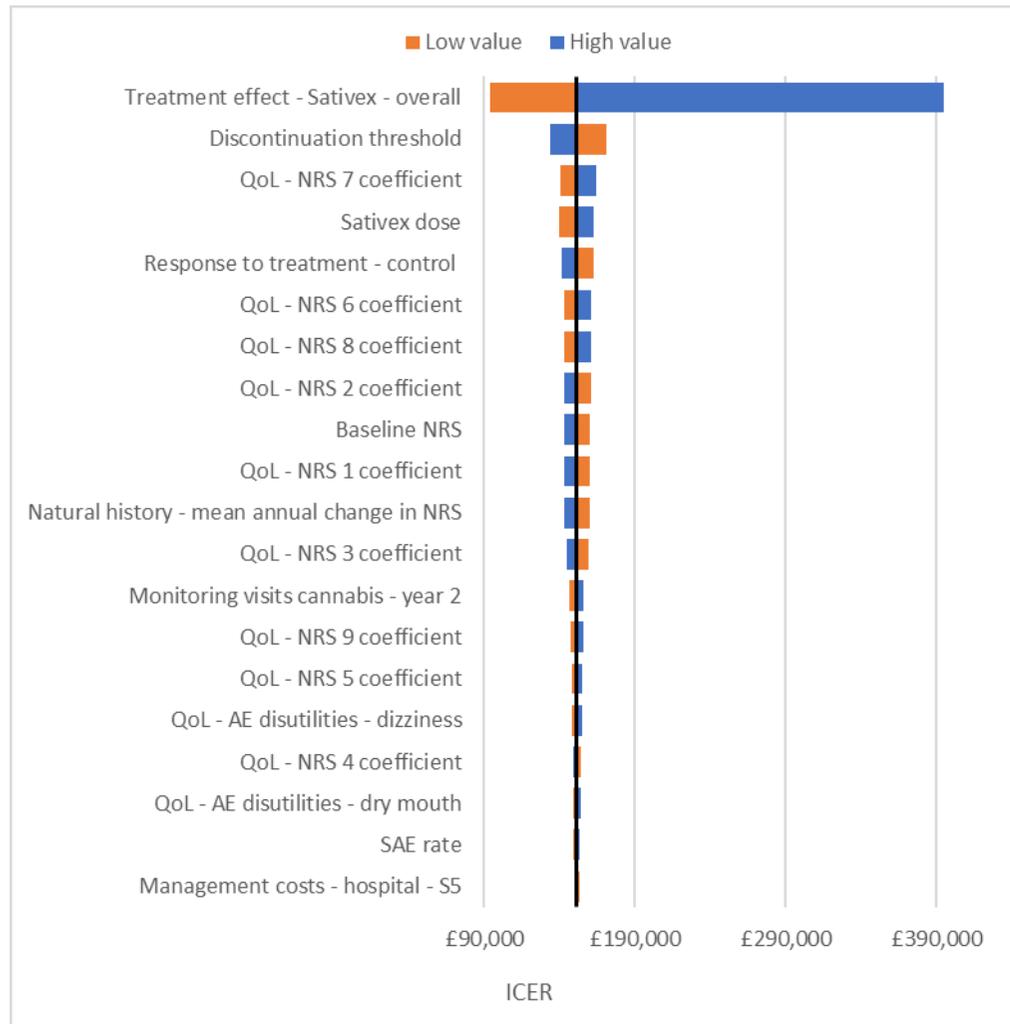


Figure 7: Tornado Diagram (most influential parameters)

Scenario analyses either involve changing the source data of input parameters, the structural assumptions of the model or groups of input parameters to represent, for example, ‘best’ and ‘worst’ case results. Full descriptions of the scenario analyses are available in that section above.

Table 12: Results of scenario analyses

Scenario	ICER (cannabis vs SoC)
1. Using the costs and effects of nabilone instead of nabiximols	£102,343
2. Using treatment effect data in the neuropathic pain subgroup	£127,321
3. Using treatment effect data for the cancer pain subgroup	£204,846
4. Using treatment effect data for the musculoskeletal pain subgroup	£68,759
5. Using discontinuation data from the Hoggart 2015 chronic pain study instead of the Messina 2017 MS individual patient data	£135,190
6. Using control arm response from Portenoy 2012 instead of Langford 2013	£107,943
7. Excluding the background management costs for chronic pain	£169,064
8. Not allowing a proportion of sub<30% responders to continue with treatment	£141,779
9. Including RFD as a downstream treatment for musceloskeletal pain	£153,671
10. Declining the treatment effect over time by reducing mean pain to match placebo	£1,072,864
11. Declining the placebo effect (change from baseline) in both arms so that pain returns to baseline after 2 years	£106,026
12. Allowing differential discontinuation from response in the standard of care arm equalling the hazard ratio	£386,084
13. Assuming no discontinuation from response in either arm	£217,680
14. All adverse events halved	£148,993
15. All adverse events doubled	£156,683
16. All pain management costs halved	£160,248
17. All pain management costs doubled	£133,797
18. All QoL coefficients set to high limits of confidence intervals	£164,453
19. All QoL coefficients set to low limits of confidence intervals	£140,320

Scenario	ICER (cannabis vs SoC)
20. Competing risks model from Messina for discontinuation	£414,759
21. -0.55 treatment effect to produce -0.44 intermediate outcome	£120,153

It can be seen from Table 12 that no scenario analyses bring the ICER close to £20,000-£30,000 per QALY gained. The ICER is lower for nabilone than for THC:CBD spray, but the clinical effectiveness data are much more uncertain and only available for a patient group with 'widespread pain'.

Discussion

The economic model was characterised by a number of limitations; the clinical input data were of low quality, input parameters were largely drawn from short term trials and extrapolated into the longer term, adverse events and background pain management incorporated several committee assumptions relating to their associated costs and HRQoL effects, costing the standard of care was ignored as cannabis was modelled as an add-on treatment and the only data we had on opioid sparing showed no effect and we had no data on pain progression or the behaviour of the placebo effect over time. Nevertheless, no plausible variations in any of the model parameters or structural assumptions produced ICERs remotely near the commonly accepted cost-effectiveness threshold of £20,000-£30,000 per QALY gained. This is principally because the CBMPs that are currently on the market and for which there is any clinical evidence are quite expensive, costing upwards of £4,000 per patient per year and only provide very modest clinical benefits. Indeed, these products would have to either be around 8 times more effective (accrue 1.22 QALYs compared with 0.162 QALY in the base case) or around 6 times less expensive or some equivalent combination of the 2 for the model to produce ICERs within the range normally accepted by NICE committees. The committee was aware that given the findings from the clinical evidence, the additional effectiveness is unrealistic.

There are a number of products not examined by this analysis because no data were available on their effectiveness or UK price; pure CBD oil, Bedrocen products and dronabinol have been omitted but could be included in an updated version of the model once such data become available.

Appendix J – Excluded studies

Clinical studies

Study	Reason for exclusion
Alharbi, G. S.; Chen, L. C.; Knaggs, R. (2016) Efficacy of anticonvulsant, antidepressant and opioid in treating neuropathic pain - A systematic review and meta-analysis. <i>Pharmacoepidemiology and drug safety</i> . Conference: 32nd international conference on pharmacoepidemiology and therapeutic risk management. Ireland. Conference start: 20160825. Conference end: 20160828 25: 582	Conference abstract
Allan, G. Michael, Finley, Caitlin R., Ton, Joey et al. (2018) Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. <i>Canadian family physician Medecin de famille canadien</i> 64(2): e78-e94	Review article. The bibliography was reviewed for possible includes
Allende-Salazar, Ruben F. and Rada, Gabriel (2017) Are cannabinoids an effective treatment for chronic non-cancer pain? Son los cannabinoides un tratamiento efectivo para el dolor cronico no asociado a cancer? <i>17(suppl2): e6972</i>	Non-English language article
Andreae, Michael H., Carter, George M., Shaparin, Naum et al. (2015) Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. <i>The journal of pain: official journal of the American Pain Society</i> 16(12): 1221-1232	Smoked cannabis
Aviram, J. and Samuely-Leichtag, G. (2017) Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. <i>Pain physician</i> 20(6): E755-E796	Review article. The bibliography was reviewed for possible includes
Beaulieu, Pierre (2006) Effects of nabilone, a synthetic cannabinoid, on postoperative pain. <i>Canadian journal of anaesthesia = Journal canadien d'anesthesie</i> 53(8): 769-75	Study is on acute postoperative pain

Study	Reason for exclusion
Beaulieu, Pierre, Boulanger, Aline, Desroches, Julie et al. (2016) Medical cannabis: considerations for the anesthesiologist and pain physician. Canadian journal of anaesthesia = Journal canadien d'anesthesie 63(5): 608-24	Narrative review
Berman, Jonathan S.; Symonds, Catherine; Birch, Rolfe (2004) Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 112(3): 299-306	Cross-over trial with inadequate washout period (<1 week)
Bestard, Jennifer A. and Toth, Cory C. (2011) An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain practice: the official journal of World Institute of Pain 11(4): 353-68	Non-randomised observational study
Blake, Alexia, Wan, Bo Angela, Malek, Leila et al. (2017) A selective review of medical cannabis in cancer pain management. Annals of palliative medicine 6(suppl2): S215-S222	Narrative review
Boychuk, Darrell G., Goddard, Greg, Mauro, Giovanni et al. (2015) The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. Journal of oral & facial pain and headache 29(1): 7-14	Review article. The bibliography was reviewed for possible includes
Campbell, F. A., Tramer, M. R., Carroll, D. et al. (2001) Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. British Medical Journal 323(7303): 13-16	Review article. The bibliography was reviewed for possible includes
Conte, Antonella, Bettolo, Chiara Marini, Onesti, Emanuela et al. (2009) Cannabinoid-induced effects on the nociceptive system: a neurophysiological study in patients with secondary progressive multiple sclerosis. European journal of pain (London, England) 13(5): 472-7	Experimental pain model and used electrophysiological outcomes
Corey, Susan (2005) Recent developments in the therapeutic potential of cannabinoids. Puerto Rico health sciences journal 24(1): 19-26	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Cote, Mathieu, Trudel, Mathieu, Wang, Changshu et al. (2016) Improving Quality of Life with Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. <i>The Annals of otology, rhinology, and laryngology</i> 125(4): 317-24	No outcomes of interest <i>[The results are in a format that it's not possible to data extract: All the data is either given as a narrative account or in form of graphs. This also includes adverse events.]</i>
Cunetti, L., Manzo, L., Peyraube, R. et al. (2018) Chronic Pain Treatment with Cannabidiol in Kidney Transplant Patients in Uruguay. <i>Transplantation proceedings</i> 50(2): 461-464	Observational study. No control group
Davies, B. H., Weatherstone, R. M., Graham, J. D. et al. (1974) A pilot study of orally administered DELTA(1)-trans-tetrahydrocannabinol in the management of patients undergoing radiotherapy for carcinoma of the bronchus. <i>British journal of clinical pharmacology</i> 1(4): 301-6	Non-randomised observational study
de Vries, M., van Rijckevorsel, D. C. M., Vissers, K. C. P. et al. (2016) Tetrahydrocannabinol Does Not Reduce Pain in Patients with Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. <i>Clinical gastroenterology and hepatology</i>	Conference abstract
Deng, Yunkun, Luo, Lei, Hu, Yuhuai et al. (2016) Clinical practice guidelines for the management of neuropathic pain: a systematic review. <i>BMC anesthesiology</i> 16: 12	Review article. The bibliography was reviewed for possible includes
Deshpande, Amol, Mailis-Gagnon, Angela, Zoheiry, Nivan et al. (2015) Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. <i>Canadian family physician Medecin de famille canadien</i> 61(8): e372-81	Review article. The bibliography was reviewed for possible includes
Felix, Elizabeth Roy (2014) Chronic neuropathic pain in SCI: evaluation and treatment. <i>Physical medicine and rehabilitation clinics of North America</i> 25(3): 545-viii	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Fitzcharles, M. A., Baerwald, C., Ablin, J. et al. (2016) Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): A systematic review of randomized controlled trials. <i>Schmerz</i> (Berlin, Germany) 30(1): 47-61	Review article. The bibliography was reviewed for possible includes
Fitzcharles, Mary-Ann, Ste-Marie, Peter A., Hauser, Winfried et al. (2016) Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials. <i>Arthritis care & research</i> 68(5): 681-8	Review article. The bibliography was reviewed for possible includes
Guy, G., Gover, J., Rogerson, M. et al. (2010) Positive data in sativex phase IIb trial: Support advancing into phase III development in cancer pain. <i>Revista de la Sociedad Espanola del Dolor</i> 17(4): 219-221	Letter (non-peer reviewed information)
Haroutiunian, Simon, Rosen, Gila, Shouval, Rivka et al. (2008) Open-label, add-on study of tetrahydrocannabinol for chronic nonmalignant pain. <i>Journal of pain & palliative care pharmacotherapy</i> 22(3): 213-7	Non-randomised observational study
Hauser, W., Fitzcharles, M. A., Radbruch, L. et al. (2018) Cannabinoids in pain management and palliative medicine - An overview of systematic reviews and prospective observational studies. <i>Deutsches Arzteblatt International</i> 115(9): 143	Review article. The bibliography was reviewed for possible includes
Hauser, W.; Petzke, F.; Fitzcharles, M. A. (2018) Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. <i>European journal of pain</i> (London, England) 22(3): 455-470	Review article. The bibliography was reviewed for possible includes
Hauser, Winfried, Fitzcharles, Mary-Ann, Radbruch, Lukas et al. (2017) Cannabinoids in Pain Management and Palliative Medicine. <i>Deutsches Arzteblatt international</i> 114(38): 627-634	Review article. The bibliography was reviewed for possible includes
Hill, Kevin P. (2015) Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. <i>JAMA</i> 313(24): 2474-83	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Hill, Kevin P., Palastro, Matthew D., Johnson, Brian et al. (2017) Cannabis and Pain: A Clinical Review. Cannabis and cannabinoid research 2(1): 96-104	Review article. The bibliography was reviewed for possible includes
Hoggart, B., Ratcliffe, S., Ehler, E. et al. (2015) A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. Journal of neurology 262(1): 27-40	Chronic pain study where placebo is not the comparator
Holdcroft, A., Smith, M., Jacklin, A. et al. (1997) Pain relief with oral cannabinoids in familial Mediterranean fever. Anaesthesia 52(5): 483-6	Case study with one patient
Holdcroft, A., Smith, M., Smith, B. et al. (1997) Clinical trial experience with cannabinoids. Pharmaceutical sciences 3(11): 546-550	Case study with one patient
Holdcroft, Anita, Maze, Mervyn, Dore, Caroline et al. (2006) A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology 104(5): 1040-6	Non-randomised observational study
Houze, Berengere; El-Khatib, Hejar; Arbour, Caroline (2017) Efficacy, tolerability, and safety of non-pharmacological therapies for chronic pain: An umbrella review on various CAM approaches. Progress in neuro-psychopharmacology & biological psychiatry 79(ptb): 192-205	Review article. The bibliography was reviewed for possible includes
Hunter, D., Oldfield, G., Tich, N. et al. (2018) Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis. Osteoarthritis and cartilage. Conference: 2018 osteoarthritis research society international, OARSI world congress. United Kingdom 26(supplement1): 26	Conference abstract
Iskedjian, Michael, Bereza, Basil, Gordon, Allan et al. (2007) Meta-analysis of cannabis-based treatments for neuropathic and multiple sclerosis-related pain. Current medical research and opinion 23(1): 17-24	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Issa, Mohammed A., Narang, Sanjeet, Jamison, Robert N. et al. (2014) The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. <i>The Clinical journal of pain</i> 30(6): 472-8	Cross-over trial with inadequate washout period (<1 week)
Iversen, L. (2001) Cannabinoids in pain management. Few well controlled trials of cannabis exist for systemic review. <i>BMJ (Clinical research ed.)</i> 323(7323): 1250-1	Letter (non-peer reviewed information)
Jensen, Troels S.; Madsen, Caspar S.; Finnerup, Nanna B. (2009) Pharmacology and treatment of neuropathic pains. <i>Current opinion in neurology</i> 22(5): 467-74	Review article. The bibliography was reviewed for possible includes
Jochimsen, P. R., Lawton, R. L., VerSteeg, K. et al. (1978) Effect of benzopyranoperidine, a DELTA-9-THC congener, on pain. <i>Clinical Pharmacology and Therapeutics</i> 24(2): 223-227	Study is on a synthetic cannabinoid not covered under the definition of cannabis-based products for medicinal use: It is not a cannabinol derivative and does not contain cannabis nor cannabis resin. Therefore, this is a Schedule 1 drug
Kantor, T. G. and Hopper, M. (1981) A study of levonantradol, a cannabinol derivative, for analgesia in post-operative pain. <i>Pain</i> 10(suppl1): 37	Conference abstract
Karst, Matthias, Salim, Kahlid, Burstein, Sumner et al. (2003) Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. <i>JAMA</i> 290(13): 1757-62	Study is on a synthetic cannabinoid not covered under the definition of cannabis-based products for medicinal use: It is not a cannabinol derivative and does not contain cannabis nor cannabis resin. Therefore, this is a Schedule 1 drug
Lee, Gemayel, Grovey, Brittany, Furnish, Tim et al. (2018) Medical Cannabis for Neuropathic Pain. <i>Current pain and headache reports</i> 22(1): 8	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Lynch, M. E. and Ware, Mark A. (2015) Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials. <i>Journal of neuroimmune pharmacology: the official journal of the Society on NeuroImmune Pharmacology</i> 10(2): 293-301	Review article. The bibliography was reviewed for possible includes
Lynch, Mary E. and Campbell, Fiona (2011) Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. <i>British journal of clinical pharmacology</i> 72(5): 735-44	Review article. The bibliography was reviewed for possible includes
Martin-Sanchez, Eva, Furukawa, Toshiaki A., Taylor, Julian et al. (2009) Systematic review and meta-analysis of cannabis treatment for chronic pain. <i>Pain medicine (Malden, Mass.)</i> 10(8): 1353-68	Review article. The bibliography was reviewed for possible includes
Mehta, Swati, McIntyre, Amanda, Janzen, Shannon et al. (2016) Systematic Review of Pharmacologic Treatments of Pain After Spinal Cord Injury: An Update. <i>Archives of physical medicine and rehabilitation</i> 97(8): 1381-1391.e1	Review article. The bibliography was reviewed for possible includes
Meng, Howard, Johnston, Bradley, Englesakis, Marina et al. (2017) Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis. <i>Anesthesia and analgesia</i> 125(5): 1638-1652	Review article. The bibliography was reviewed for possible includes
Mucke, Martin, Phillips, Tudor, Radbruch, Lukas et al. (2018) Cannabis-based medicines for chronic neuropathic pain in adults. <i>The Cochrane database of systematic reviews</i> 3: cd012182	Review article. The bibliography was reviewed for possible includes
Mucke, Martin, Weier, Megan, Carter, Christopher et al. (2018) Systematic review and meta-analysis of cannabinoids in palliative medicine. <i>Journal of cachexia, sarcopenia and muscle</i> 9(2): 220-234	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Narang, Sanjeet, Gibson, Daniel, Wasan, Ajay D. et al. (2008) Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. <i>The journal of pain: official journal of the American Pain Society</i> 9(3): 254-64	Cross-over trial with inadequate washout period (<1 week)
Narang, Sanjeet, Wasan, Ajay D., Ross, Edgar L. et al. (2008) Patients with chronic pain on opioid therapy taking dronabinol: incidence of false negatives using radioimmunoassay. <i>Journal of opioid management</i> 4(1): 21-6	Observational study. No control group
Nickel, J. Curtis (2018) Medical marijuana for urologic chronic pelvic pain. <i>Canadian Urological Association journal = Journal de l'Association des urologues du Canada</i> 12(6suppl3): S181-S183	Review article. The bibliography was reviewed for possible includes
Notcutt, William, Price, Mario, Miller, Roy et al. (2004) Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. <i>Anaesthesia</i> 59(5): 440-52	Results are presented in a narrative format. Essential information is missing, such as before and after comparisons and statistical variance
Novotna, A., Mares, J., Ratcliffe, S. et al. (2011) A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. <i>European journal of neurology</i> 18(9): 1122-31	Study at high risk of selection and reporting bias
Noyes, R., Jr., Brunk, S. F., Avery, D. A. et al. (1975) The analgesic properties of delta-9-tetrahydrocannabinol and codeine. <i>Clinical pharmacology and therapeutics</i> 18(1): 84-9	Cross-over trial with inadequate washout period (<1 week)
Noyes, R., Jr., Brunk, S. F., Baram, D. A. et al. (1975) Analgesic effect of delta-9-tetrahydrocannabinol. <i>Journal of clinical pharmacology</i> 15(23): 139-43	Cross-over trial with inadequate washout period (<1 week)
Nugent, Shannon M., Morasco, Benjamin J., O'Neil, Maya E. et al. (2017) The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. <i>Annals of internal medicine</i> 167(5): 319-331	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Nurmikko, T. J., Serpell, M. G., Hoggart, B. et al. (2005) A multi-centre, double-blind, randomized, controlled trial of oro-mucosal cannabis based medicine in the treatment of neuropathic pain characterized by allodynia. <i>Neurology</i> 64(suppl1): a374abstractnopo6119	Conference abstract
Nurmikko, T. J., Serpell, M. G., Hoggart, B. et al. (2005) A multi-centre, double-blind, randomized, placebo-controlled trial of oro-mucosal cannabis-based medicine in the treatment of neuropathic pain characterized by allodynia. <i>Neurology</i> 64(suppl1): a374	Conference abstract
Pini, Luigi Alberto, Guerzoni, Simona, Cainazzo, Maria Michela et al. (2012) Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. <i>The journal of headache and pain</i> 13(8): 677-84	Headaches and/or orofacial pain
Pinsger, M. (2012) Benefit of an Add-On-Treatment with a synthetic cannabinomimeticum on patients with chronic back pain-a randomized controlled trial. <i>European spine journal</i> . 21(11): 2366	Conference abstract
Pinsger, M., Schimetta, W., Volc, D. et al. (2006) Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial. <i>Wiener klinische wochenschrift</i> 118(1112): 327-335	Non-English language article
Rintala, Diana H., Fiess, Richard Neil, Tan, Gabriel et al. (2010) Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. <i>American journal of physical medicine & rehabilitation</i> 89(10): 840-8	Chronic pain study where placebo is not the comparator
Riva, N., Mora, G., Soraru, G. et al. (2016) The CANALS study: a randomized, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy on spasticity symptoms of a Cannabis Sativa extract in motor neuron disease patients. <i>European journal of neurology</i> 23(suppls2): 46abstractno01213	Conference abstract
Riva, N., Mora, G., Soraru, G. et al. (2016) The canals study: a randomized, double-blind, placebo-controlled, multicentre study to assess the safety and efficacy on spasticity symptoms of a cannabis sativa extract in motor neuron disease patients. <i>Amyotrophic lateral sclerosis & frontotemporal degeneration</i> 17(suppl1): 44abstractnoc62	Conference abstract

Study	Reason for exclusion
Rocco, Matias and Rada, Gabriel (2018) Are cannabinoids effective for fibromyalgia? Son los cannabinoides un tratamiento efectivo para la fibromialgia? 18(1): e7154	Review article. The bibliography was reviewed for possible includes
Rog, David J.; Nurmikko, Turo J.; Young, Carolyn A. (2007) Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clinical therapeutics 29(9): 2068-79	Chronic pain study where placebo is not the comparator <i>[This is an open-label extension of Rog 2005, which has been included.]</i>
Russo, E. (2003) Cannabis and Cannabis based medicine extracts: Additional results. Journal of Cannabis Therapeutics 3(4): 153-161	Review article. The bibliography was reviewed for possible includes
Russo, Ethan B. (2008) Cannabinoids in the management of difficult to treat pain. Therapeutics and clinical risk management 4(1): 245-59	Review article. The bibliography was reviewed for possible includes
Salim, Kahlid, Schneider, Udo, Burstein, Sumner et al. (2005) Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology 48(8): 1164-71	Study is on a synthetic cannabinoid not covered under the definition of cannabis-based products for medicinal use: It is not a cannabinol derivative and does not contain cannabis nor cannabis resin. Therefore, this is a Schedule 1 drug
Selvarajah, Dinesh, Gandhi, Rajiv, Emery, Celia J. et al. (2010) Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes care 33(1): 128-30	Study did not report the number of participants in each arm <i>[No details as to how many of the 30 patients were randomised to each arm. Six patients withdrew from the</i>

Study	Reason for exclusion
	<i>study. However, there is no information as to which arms they withdrew from.]</i>
Serpell, Michael G.; Notcutt, William; Collin, Christine (2013) Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. <i>Journal of neurology</i> 260(1): 285-95	Observational study. No control group
Snedecor, Sonya J., Sudharshan, Lavanya, Cappelleri, Joseph C. et al. (2013) Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. <i>Journal of pain research</i> 6: 539-47	Review article. The bibliography was reviewed for possible includes
Snedecor, Sonya J., Sudharshan, Lavanya, Cappelleri, Joseph C. et al. (2014) Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. <i>Pain practice: the official journal of World Institute of Pain</i> 14(2): 167-84	Review article. The bibliography was reviewed for possible includes
Sohler, Nancy L., Starrels, Joanna L., Khalid, Laila et al. (2018) Cannabis Use is Associated with Lower Odds of Prescription Opioid Analgesic Use Among HIV-Infected Individuals with Chronic Pain. <i>Substance use & misuse</i> 53(10): 1602-1607	Wrong intervention. This is about illegal use of cannabis
Staquet, M.; Gantt, C.; Machin, D. (1978) Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. <i>Clinical Pharmacology and Therapeutics</i> 23(4): 397-401	Study is on a synthetic cannabinoid not covered under the definition of cannabis-based products for medicinal use: It is not a cannabinol derivative and does not contain cannabis nor cannabis resin. Therefore, this is a Schedule 1 drug
Stockings, Emily, Campbell, Gabrielle, Hall, Wayne D. et al. (2018) Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. <i>Pain</i> 159(10): 1932-1954	Review article. The bibliography was reviewed for possible includes

Study	Reason for exclusion
Svendsen, K. B.; Jensen, T. S.; Bach, F. W. (2005) Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis--secondary publication. <i>Ugeskrift for laeger</i> 167(2531): 2772-2774	Non-English language article
Tateo, Sydney (2017) State of the evidence: Cannabinoids and cancer pain-A systematic review. <i>Journal of the American Association of Nurse Practitioners</i> 29(2): 94-103	Review article. The bibliography was reviewed for possible includes
Toth, Cory, Mawani, Shefina, Brady, Shauna et al. (2012) An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. <i>Pain</i> 153(10): 2073-82	Treatment phase is not randomised - only the withdrawal phase is
Tsang, Corey C. and Giudice, Mirella G. (2016) Nabilone for the Management of Pain. <i>Pharmacotherapy</i> 36(3): 273-86	Review article. The bibliography was reviewed for possible includes
Turcott, J., Guillen-Nunez, M. D. R., Flores, D. et al. (2018) The Effect of Nabilone on Appetite, Nutritional Status, and Quality of Life in Lung Cancer Patients: a Randomized, Double-Blind Clinical Trial. <i>Journal of thoracic oncology</i> . Conference: IASLC 19th world conference on lung cancer. Canada 13(10supplement): S360-S361	Conference abstract
Turcott, Jenny G., Del Rocio Guillen Nunez, Maria, Flores-Estrada, Diana et al. (2018) The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. <i>Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer</i> 26(9): 3029-3038	Conference abstract
Turcotte, D. A., Gomori, A. J., Esfahani, F. E. et al. (2011) Randomized, double-blinded, placebo-controlled study evaluating the efficacy and safety of nabilone adjunctive to gabapentin in managing multiple sclerosis-induced neuropathic pain. <i>European journal of pain supplements</i> . 5(1): 240-241	Conference abstract

Study	Reason for exclusion
Turcotte, D. A., Namaka, M. P., Gomori, A. J. et al. (2011) A randomized, double-blinded, placebo-controlled study evaluating the efficacy and safety of nabilone as an adjunctive to gabapentin in managing multiple sclerosis-induced neuropathic pain: an interim analysis. <i>Pain research & management</i> 15(2): 99	Conference abstract
Turcotte, D., Chateau, D., Doupe, M. et al. (2011) A randomised, double-blinded, placebo-controlled study evaluating the efficacy and safety of nabilone as an adjunctive to gabapentin in managing multiple sclerosis-induced neuropathic pain. <i>Multiple sclerosis</i> . 17(10suppl1): S475-S476	Conference abstract
Turcotte, Dana, Doupe, Malcolm, Torabi, Mahmoud et al. (2015) Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. <i>Pain medicine (Malden, Mass.)</i> 16(1): 149-59	Inadequate reporting of data: We cannot use data in graphs. Some data for the nabilone arm is given but not for the placebo arm.
Turcotte, D., Doupe, M., Torabi, M. et al. (2013) A randomized, double-blinded, placebo-controlled study evaluating efficacy and tolerability of nabilone as an adjunctive to gabapentin in the management of multiple sclerosis-induced neuropathic pain. <i>Multiple sclerosis</i> . 19(11suppl1): 112	Conference abstract
Van Amerongen, G., Beumer, T., Killestein, J. et al. (2014) Individualized dosing of a novel oral DELTA9-THC formulation improves subjective spasticity and pain in patients with progressive multiple sclerosis. <i>Multiple sclerosis (houndmills, basingstoke, england)</i> 20(1suppl1): 478-479	Conference abstract
van den Beuken-van Everdingen, Marieke H. J., de Graeff, Alexander, Jongen, Joost L. M. et al. (2017) Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review. <i>Pain practice: the official journal of World Institute of Pain</i> 17(3): 409-419	Review article. The bibliography was reviewed for possible includes
Wade, D. T., Makela, P. M., House, H. et al. (2006) Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. <i>Multiple sclerosis (Houndmills, Basingstoke, England)</i> 12(5): 639-45	One arm follow-up study <i>[Follow-up from Wade 2004]</i>

Study	Reason for exclusion
Wade, Derick T., Collin, Christine, Stott, Colin et al. (2010) Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. <i>Multiple sclerosis</i> (Houndmills, Basingstoke, England) 16(6): 707-14	Secondary publication of existing studies
Wade, Derick T., Robson, Philip, House, Heather et al. (2003) A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. <i>Clinical rehabilitation</i> 17(1): 21-9	Cross-over trial with inadequate washout period (<1 week)
Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. <i>Cochrane Database Syst Rev.</i> 2016 Jul 18;7:CD011694	Review article. The bibliography was reviewed for possible includes
Wallace, Mark S., Marcotte, Thomas D., Umlauf, Anya et al. (2015) Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. <i>The journal of pain: official journal of the American Pain Society</i> 16(7): 616-27	Smoked cannabis
Ware, Mark A., Fitzcharles, Mary-Ann, Joseph, Lawrence et al. (2010) The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. <i>Anesthesia and analgesia</i> 110(2): 604-10	Chronic pain study where placebo is not the comparator
Ware, Mark A., Wang, Tongtong, Shapiro, Stan et al. (2015) Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). <i>The journal of pain: official journal of the American Pain Society</i> 16(12): 1233-1242	Smoked cannabis
Whiting, Penny F., Wolff, Robert F., Deshpande, Sohan et al. (2015) Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. <i>JAMA</i> 313(24): 2456-73	Review article. The bibliography was reviewed for possible includes
Wilsey, Barth, Marcotte, Thomas D., Deutsch, Reena et al. (2016) An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease. <i>The journal of pain: official journal of the American Pain Society</i> 17(9): 982-1000	Cross-over trial with inadequate washout period (<1 week)

Study	Reason for exclusion
Wilsey, Barth, Marcotte, Thomas, Deutsch, Reena et al. (2013) Low-dose vaporized cannabis significantly improves neuropathic pain. <i>The journal of pain: official journal of the American Pain Society</i> 14(2): 136-48	Cross-over trial with inadequate washout period (<1 week)
Wirrell, E., Devinsky, O., Patel, A. et al. (2017) Cannabidiol (CBD) Significantly Reduces Drop and Total Seizure Frequency in Lennox Gastaut Syndrome (LGS): results of a Dose Ranging, Multicenter, Randomized, Double Blind, Placebo Controlled Trial (GWPCARE3). <i>Annals of neurology</i> 82(s21): S279-S280, Abstract no: 22	Conference abstract
Wissel, J., Entner, T., Muller, J. et al. (2004) Nabilone reduces spasticity related pain: a double-blind placebo-controlled cross-over trial. <i>Neurologie und rehabilitation</i> 10(4): 187-216	Non-English language article
Wu, G. Q. (1992) Pain-relief effect of tramadol HCL capsule for moderate and severe cancer pain. <i>Zhonghua zhong liu za zhi [chinese journal of oncology]</i> 14(3): 219-221	Non-English language article
Yassin, Mustafa; Oron, Amir; Robinson, Dror (2018) Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study. <i>Clinical and experimental rheumatology</i>	Non-randomised observational study
Zajicek, John, Ball, Susan, Wright, David et al. (2013) Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. <i>The Lancet. Neurology</i> 12(9): 857-865	The relevant symptoms are not included
Zalai, D., Chung, S. A., Hussain, N. et al. (2015) Does cannabinoid really improve sleep? Testing the sleep effects of nabilone in chronic pain patients: a placebo-controlled, randomized, pilot study. <i>Psychotherapy and psychosomatics</i> . 84: 81	Conference abstract

Economic studies

Appendix K – Research recommendations

1. For adults with fibromyalgia or persistent treatment-resistant neuropathic pain, what is the clinical and cost effectiveness of cannabidiol (CBD containing no or traces of THC) as an add-on to standard treatment?

There are no RCTs that compare CBD (either as a pure product or containing traces of THC) with standard treatment to standard treatment for fibromyalgia or for persistent treatment-resistant neuropathic pain. Cannabis could be a cost-effective treatment for these conditions because it could reduce resource use.

The committee agreed that a follow-up period of 6 months is a realistic duration for assessing chronic pain treatments.

PICO	<p>Population: Adults with fibromyalgia or persistent treatment-resistant neuropathic pain being managed by a pain specialist using standard treatment</p> <p>Intervention: CBD (either as a pure product or containing traces of THC)</p> <p>Comparator: usual care as defined by the researchers</p> <p>Outcomes should be measured at 6 months follow-up</p> <ul style="list-style-type: none">• Cost effectiveness• Participant reported pain relief of 30% or greater• Participant reported pain relief of 50% or greater (to assist the economic analysis)• Reduction in analgesics required• Change in pain intensity using Numerical Rating Scale¹, or Visual Analogue Scale²• A validated pain measurement tool• Participant/Patient/Subject Global Impression of Change (PGIC or SGIG) scale• Quality of life score using SF-36 or EQ-5D.• Mood• Serious adverse events• Adverse events including but not limited to: respiratory depression, sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment• Withdrawals due to adverse events• Complications due to adverse events• Substance abuse due to the use of cannabis-based medicinal product.• Misuse/diversion• Hepatic and renal failure <p>Outcomes requiring a narrative synthesis:</p>
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	<ul style="list-style-type: none"> Contraindications as listed in exclusion criteria <p>Monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn stopped as discussed in the methods of individual RCTs</p>
Current evidence base	No RCTs were identified which compare CBD with standard treatment to standard treatment for fibromyalgia or for persistent treatment-resistant neuropathic pain.
Study design	Randomised controlled trial
Other comments	Study should be adequately powered and have an adequate follow up period (minimum of 6 months)

2. In children and young people with intractable cancer-related pain and pain associated with specific diseases (such as epidermolysis bullosa), what is the clinical and cost effectiveness of cannabis-based medicinal products as an add-on treatment to improve symptoms in comparison to treatment with standard care?

There is currently no evidence that explores whether the addition of cannabis-based medicinal products as an adjunct to standard care improves symptoms for children and young people with intractable cancer-related pain and pain associated with specific diseases, such as epidermolysis bullosa. The reason for the lack of research so far is probably because there are relatively few children and young people with these conditions. In addition, there is concern regarding the use of high dose opioids for children and young people because it often causes adverse events. Therefore, a research recommendation was made. The committee defined 'intractable cancer-related pain' as cancer-related pain that does not respond to multiple drugs sufficiently to enable a reasonable quality of life and/or the child to be discharged home. The committee defined standard care as tertiary specialist pain/palliative management. An additional benefit from such research could be a reduction in resource use.

PICO	<p>Population: Children with intractable cancer-related pain (intractable cancer-related pain was defined by the committee as cancer-related pain which does not respond to multiple interventions including non-pharmacological and drug therapies sufficiently to enable a reasonable quality of life).</p> <p>Intervention: Cannabis-based medicinal product (CBMP) as an adjunct to standard care (standard care is defined as tertiary specialist pain management). CBP is defined as:</p> <ol style="list-style-type: none"> 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: <ul style="list-style-type: none"> is or contains cannabis, cannabis resin, cannabidiol or a cannabidiol derivative (not being dronabinol or its stereoisomers) is produced for medicinal use in humans; and is a medicinal product, or
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	<ul style="list-style-type: none"> • a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations) <p>2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol</p> <p>3. Licensed products Sativex and nabilone</p> <p>4. Plant-derived cannabinoids such as pure cannabidiol</p> <p>Comparator: Standard care (tertiary specialist pain management)</p> <p>Outcomes:</p> <ul style="list-style-type: none"> • Participant reported pain relief of 30% or greater • Participant reported pain relief of 50% or greater (to assist the economic analysis) • Reduction in analgesics required • Change in pain intensity using Numerical Rating Scale', or Visual Analogue Scale' • A validated pain measurement tool • Participant/Patient/Subject Global Impression of Change (PGIC or SGIG) scale • Quality of life score using SF-36 or EQ-5D. • Serious adverse events • Adverse events including but not limited to: sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Misuse/diversion • Hepatic and renal failure <p>Outcomes requiring a narrative synthesis:</p> <ul style="list-style-type: none"> • Contraindications as listed in exclusion criteria <p>Monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn stopped as discussed in the methods of individual RCTs</p>
Current evidence base	No RCTs were identified which compare CBD with standard treatment to standard treatment for children with cancer-related pain and pain associated with specific conditions.
Study design	Randomised controlled trial
Other comments	Study should be adequately powered and have an adequate follow up period.

Appendix L – Reference list of included studies

- Blake, D. R., Robson, P., Ho, M. et al. (2006) Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford, England)* 45(1): 50-2
- de Vries, Marjan, Van Rijckevorsel, Dagmar C. M., Vissers, Kris C. P. et al. (2016) Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability. *British journal of clinical pharmacology* 81(3): 525-37
- de Vries, Marjan, van Rijckevorsel, Dagmar C. M., Vissers, Kris C. P. et al. (2017) Tetrahydrocannabinol Does Not Reduce Pain in Patients with Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. *Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association* 15(7): 1079-1086.e4
- Fallon, Marie T., Albert Lux, Eberhard, McQuade, Robert et al. (2017) Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *British journal of pain* 11(3): 119-133
- Johnson, Jeremy R., Burnell-Nugent, Mary, Lossignol, Dominique et al. (2010) Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *Journal of pain and symptom management* 39(2): 167-79
- Langford, R. M., Mares, J., Novotna, A. et al. (2013) A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *Journal of neurology* 260(4): 984-97
- Lichtman, Aron H., Lux, Eberhard Albert, McQuade, Robert et al. (2018) Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. *Journal of pain and symptom management* 55(2): 179-188.e1
- Lynch, Mary E.; Cesar-Rittenberg, Paula; Hohmann, Andrea G. (2014) A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *Journal of pain and symptom management* 47(1): 166-73
- Malik, Z., Bayman, L., Valestin, J. et al. (2017) Dronabinol increases pain threshold in patients with functional chest pain: a pilot double-blind placebo-controlled trial. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus* 30(2): 1-8

Nurmikko, Turo J., Serpell, Mick G., Hoggart, Barbara et al. (2007) Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 133(13): 210-20

Portenoy, Russell K., Ganae-Motan, Elena Doina, Allende, Silvia et al. (2012) Nabiximols for opioid-treated cancer patients with poorly controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *The journal of Pain: Official journal of the American Pain Society* 13(5): 438-49

Rog, David J., Nurmikko, Turo J., Friede, Tim et al. (2005) Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 65(6): 812-9

Schimrigk, Sebastian, Marziniak, Martin, Neubauer, Christine et al. (2017) Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients. *European neurology* 78(56): 320-329

Serpell, M., Ratcliffe, S., Hovorka, J. et al. (2014) A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *European journal of pain (London, England)* 18(7): 999-1012

Skrabek, Ryan Quinlan, Galimova, Lena, Ethans, Karen et al. (2008) Nabilone for the treatment of pain in fibromyalgia. *The journal of Pain: official journal of the American Pain Society* 9(2): 164-73

Svendsen, Kristina B.; Jensen, Troels S.; Bach, Flemming W. (2004) Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double-blind placebo-controlled crossover trial. *BMJ (Clinical research ed.)* 329(7460): 253

van de Donk, Tine, Niesters, Marieke, Kowal, Mikael A. et al. (2019) An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain*

Wade, Derick T., Makela, Petra, Robson, Philip et al. (2004) Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Multiple sclerosis (Houndmills, Basingstoke, England)* 10(4): 434-41

Weber, M.; Goldman, B.; Truniger, S. (2010) Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: a randomised, double-blind crossover trial. *Journal of neurology, neurosurgery, and psychiatry* 81(10): 1135-40

Wissel, Jorg, Haydn, Tanja, Muller, Jorg et al. (2006) Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. *Journal of neurology* 253(10): 1337-41

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Dworkin, Robert H., et al. (2005) Core outcome measures for chronic pain clinical trials: IMMPACT recommendations." *Pain* 113(1): 9-19.

Dworkin, Robert H., et al. (2009) Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. *Pain* 146(3): 238-244.

References used solely in the economic model

Farrar, J et al (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 94: 149-158

Messina, S. et al., 2017. Sativex in resistant multiple sclerosis spasticity: Discontinuation study in a large population of Italian patients (SA.FE. study).. *PloS one*, 12(8), p. e0180651

Hoggart et al. 2015. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. *Journal of Neurology* 262(1)

Torrance et al 2006. The Epidemiology of Chronic Pain of Predominantly Neuropathic Origin. Results From a General Population Survey. *The Journal of Pain* 7(4)

Wang, T., Collet, J.-P., Shapiro, S. & Ware, M. A., 2008. Adverse effects of medical cannabinoids: a systematic review. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 6, 178(13), pp. 1669-1678.

Gu et al 2012. Estimating Preference-Based EQ-5D Health State Utilities or Item Responses from Neuropathic Pain Scores. *Patient* 5(3)