National Institute for Health and Care Excellence

Final

# Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain

## [J] Evidence review for pharmacological management for chronic primary pain

*NICE guideline NG193*

*Intervention evidence review underpinning recommendations 1.2.7 to 1.2.15 and the research recommendation in the NICE guideline*

*April 2021*

*This evidence review was developed by the National Guideline Centre based at the Royal College of Physicians*

**Disclaimer**

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.



**ISBN**
978-1-4731-4066-0

# Contents

# 1 Pharmacological management

## 1.1 Review question: What is the clinical and cost effectiveness of pharmacological interventions for chronic primary pain?

## 1.2 Introduction

Medicines have been the mainstay of pain treatment for centuries. Products with an established role in the successful management of acute (short term and self-limiting) pain include paracetamol, non-steroidal anti-inflammatory drugs and opioids. These drugs are also prescribed and taken for longer periods when pain persists. The rapid expansion of our knowledge of the behaviour of the nervous system in preclinical models of longer-term pain, particularly nerve injury and inflammation, led to the exploration of novel molecular targets to try to improve the success of pharmacological treatments for chronic pain. There is a scientific rationale for the use of medicines for chronic pain already in use for other conditions involving the central nervous system, notably antidepressant and anti-epileptic drugs, as well as benzodiazepines and antipsychotic medicines. More recently developed compounds, including gabapentin, pregabalin and duloxetine were developed and promoted for both pain relieving and other indications. All medicines used for pain achieve their effects by interruption of fundamental systems involved in sensory processing, and as a group their use is associated with a range of central nervous system side effects.

Medicines are rarely the sole treatment of choice in chronic pain but they might be considered as adjuncts to other therapeutic interventions and self-management strategies. They are often prescribed with the aim of supporting maintenance of physical function but side effects can limit their usefulness.

When prescribing for pain it is important to reflect on not only the neurobiological rationale for their use but also the emotional, cultural and social determinants and personal consequences of the pain experience that can shape the likely response to medicines that have specific molecular targets in pain processing systems.

This review intends to explore the efficacy of a range of medicines that are prescribed for people with chronic primary pain.

## 1.3 PICO table

For full details see the review protocol in appendix A.

**Table 1: PICO characteristics of review question**

| | |
|---|---|
| **Population** | People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance). This includes chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain and chronic primary musculoskeletal pain other than orofacial pain. |
| **Intervention(s)** | • Oral paracetamol<br>• Non-steroidal anti-inflammatory drugs (by any route)<br>• Ketamine (by any route)<br>• Topical or intravenous local anaesthetics<br>• Local anaesthetics and/or corticosteroids by injection (trigger point)<br>• Oral or transdermal, intrathecal opioids (morphine, oxycodone, hydromorphone, buprenorphine, fentanyl, methadone, meptazinol, tapentadol, |

| | |
|---|---|
| | targinact, codeine, dihydrocodeine, tramadol, cocodamol, codydramol, naltrexone)<br>• Oral anti-epilepsy drugs (gabapentin, pregabalin, sodium valproate, carbamazepine, oxcarbazepine, topiramate, lamotrigine, lacosamide, levetiracetam)<br>• Oral anti-depressants<br>  ○ Tricyclic antidepressants (e.g. Amitriptyline, nortriptyline, clomipramine, imipramine)<br>  ○ Selective serotonin re-uptake inhibitors (e.g. Fluoxetine, citalopram)<br>  ○ Serotonin norepinephrine re-uptake inhibitors (e.g. Duloxetine, venlafaxine)<br>  ○ Tetracyclic antidepressants (mirtazapine)<br>• Oral cannabinoids (nabilone, nabiximols oromucosal spray)<br>• Antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole)<br>• Benzodiazepines (diazepam, oxazepam, lorazepam, temazepam, nitrazepam, clonazepam) |
| **Comparison(s)** | • Each other (drug class)*<br>• Placebo<br>*A stepped approach will be taken for within-class comparisons. If the evidence suggests superiority of a particular class after the class-comparison, within class comparison of that class will be explored. |
| **Outcomes** | Critical:<br>• Pain reduction<br>• Health related quality of life (including meaningful activity)<br>• Physical function<br>• Psychological distress (depression/ anxiety)<br>• Discontinuation due to adverse events<br><br>Important:<br>• Use of healthcare services<br>• Sleep<br><br>Outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months. |
| **Study design** | RCTs and systematic reviews of RCTs. Crossover RCTs will be considered if no non-crossover RCT evidence is identified. Enriched enrolment trials will be excluded. |

# 1.4 Clinical evidence

## 1.4.1 Included studies

34 studies were included in the review[2, 37, 39, 40, 45, 49, 50, 73, 112, 113, 123, 214, 215, 233, 275, 277, 311, 332, 336, 347, 350, 354, 403, 425, 471, 505, 507, 526, 537, 539, 549, 593, 633, 643]; and these are summarised in Table 3 below. The following comparisons were included in the review:

- 7 studies were identified that compared anti-epileptics with placebo
- 7 studies were identified that compared serotonin norepinephrine re-uptake inhibitors with placebo
- 6 studies were identified that compared selective serotonin re-uptake inhibitors with placebo
- 7 studies were identified that compared tricyclic antidepressants with placebo
- 1 study was identified that compared tetracyclic antidepressants with placebo

- 3 studies were identified that compared benzodiazepines with placebo
- 3 studies were identified that compared non-steroidal anti-inflammatory drugs with placebo
- 2 studies were identified that compared local anaesthetics with placebo
- 2 studies were identified that compared benzodiazepines with non-steroidal anti-inflammatory drugs
- 1 study was identified that compared cannabinoids with placebo
- 1 study was identified that compared serotonin norepinephrine re-uptake inhibitors with anti-epileptics.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

### 1.4.2 Excluded studies

49 Cochrane reviews were identified that were relevant to this review question, however none of these met the inclusion criteria for this review to enable them to be incorporated without further analysis (see Table 2 below). All Cochrane reviews were cross-referenced and checked for studies relevant to this review question.

**Table 2: Summary of Cochrane reviews identified**

| Cochrane review | Exclusion reason |
|---|---|
| Aboumarzouk 2012[3] | Different outcomes (some overlap) |
| Birse 2012[77] | Incorrect population (includes pain other than chronic primary pain) |
| Cepeda 2005[119] | Different outcomes (some overlap) |
| Cooper 2017[147] | Different outcomes (some overlap) |
| Cooper 2017[146] | Incorrect population (neuropathic pain) |
| Cording 2015[149] | Drug not available in the UK |
| Corrigan 2012[151] | Incorrect population (includes pain other than chronic primary pain) |
| Derry 2016[166] | Incorrect population (includes pain other than chronic primary pain) |
| Derry 2016[167] | Different outcomes (some overlap), minimum trial duration requirement of 8 weeks |
| Derry 2016[168] | Incorrect population (neuropathic pain) |
| Derry 2017[169] | Different outcomes (some overlap) |
| Derry 2017[170] | Incorrect population (includes pain other than chronic primary pain) |
| Duehmke 2017[183] | Incorrect population (neuropathic pain) |
| Els 2017[194] | Different outcomes (some overlap), incorrect population (includes pain other than chronic primary pain) |
| Els 2017[196] | Incorrect population (includes pain other than chronic primary pain), different outcomes (some overlap) |
| Furlan 2006[222] | Incorrect population (includes pain other than chronic primary pain), different outcomes (some overlap) |
| Gaskell 2014[227] | Incorrect population (neuropathic pain) |
| Gaskell 2016[228] | Different outcomes (some overlap) |
| Gaskell 2017[226] | Incorrect population (neuropathic pain) |
| Gill 2011[232] | Incorrect population (includes pain other than chronic primary pain) |

| Cochrane review | Exclusion reason |
|---|---|
| González 2007[242] | Protocol |
| Haroutounian 2012[264] | Incorrect population (included pain other than chronic primary pain) |
| Häuser 2013[270] | Minimum trial duration of 4 weeks, incorrect interventions (includes milnacipran) |
| Hauser 2015[266] | Different outcomes (some overlap) |
| Lunn 2014[346] | Incorrect population (includes pain other than chronic primary pain) |
| McMillan 2016[368] | Different outcomes (some overlap) |
| McNaughton 2001[369] | Incorrect interventions (includes non-pharmacological) |
| McNicol 2013[371] | Incorrect population (neuropathic pain) |
| McNicol 2017[370] | Incorrect population (neuropathic pain) |
| Moore 2005[393] | Not cochrane review |
| Moore 2009[394] | Different outcomes (some overlap), incorrect population (includes pain other than chronic primary pain) |
| Moore 2011[395] | Incorrect population (includes pain other than chronic primary pain) |
| Moore 2015[392] | Minimum trial duration of 4 weeks, different outcomes (some overlap) |
| Noble 2010[423] | Incorrect population (includes pain other than chronic primary pain) |
| O'Connell 2013[429] | Different outcomes (some overlap), incorrect interventions (includes non-pharmacological) |
| Santos 2015[512] | Different outcomes (some overlap), incorrect population (includes pain other than chronic primary pain) |
| Seidel 2013 [527] | Different outcomes (some overlap), incorrect population (includes pain other than chronic primary pain) |
| Stannard 2016[552] | Incorrect population (neuropathic pain) |
| Walitt 2015 [608] | Included crossover studies, minimum trial duration of 4 weeks |
| Walitt 2016 [606] | Included crossover studies, minimum trial duration of 4 weeks, different outcomes (no pain reduction outcome) |
| Walitt 2016 [607] | Included crossover studies, minimum trial duration of 4 weeks, different outcomes (no pain reduction outcome) |
| Wiffen 2005[624] | Incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2011 [629] | Incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2013[627] | Incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2013 [625] | Incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2013 [626] | Incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2014 [628] | Incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2016[631] | Incorrect population (neuropathic pain) |
| Zakrzewska 2005[646] | Different outcomes (some overlap), incorrect interventions (includes non-pharmacological) |

Although some studies were identified on the use of opiods for chronic pain, none of these met the eligibility criteria for this review. For example some studies included participants with pain caused by cancer, musculoskeletal diseases or neuropathic pain, rather than being specific to chronic primary pain. A number of systematic reviews related to opioid use for chronic pain were identified in this review and cross referenced for additional references. However, all of these reviews identified a limited amount of evidence. Further details are listed in the excluded studies list in appendix I.

See the excluded studies list in Appendix I:.

### 1.4.3 Summary of clinical studies included in the evidence review

**Table 3: Summary of studies included in the evidence review**

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| Abdelhafeez 2019[2] | Intervention: Gabapentin 900-2400mg/day (n=30)<br><br>Comparison: Placebo (n=30) | Women with chronic pelvic pain<br>Age mean 31.5 years<br>Mean pain duration: 16.5 months<br>N=60 | At 12 and 24 weeks:<br>• Pain reduction<br>• Discontinuation due to adverse events | Median maximum dose achieved was 2100mg per day. |
| Arnold 2002[40] | Intervention: Fluoxetine 10-80mg/day (n=30)<br><br>Comparison: Placebo (n=30) | Women with fibromyalgia<br>Age mean 46<br>Mean(SD) pain duration: 11(9) years<br>N=60 | At 12 weeks:<br>• Pain reduction<br>• Quality of life<br>• Physical function<br>• Psychological distress | 63% had history of major depression. |
| Arnold 2005[45] | Intervention: Duloxetine 60mg/day (QID or BID) (n=116)<br><br>Comparison: Placebo (n=120) | Women with fibromyalgia<br>Age mean 49.6 years<br>N=236 | At 12 weeks:<br>• Pain reduction<br>• Quality of life<br>• Psychological distress<br>• Discontinuation due to adverse events<br>• Sleep | 26% had major depressive disorder.<br>Duration of pain not stated. |
| Arnold 2007[39] | Intervention: Gabapentin (median dose 1800mg/day, n=75)<br><br>Comparison: Placebo (n=75) | Fibromyalgia<br>Aged over 18 years<br>N=150 | At 12 weeks:<br>• Quality of life<br>• Pain reduction<br>• Discontinuation due to adverse events<br>• Sleep | Inclusion criteria: score of >5 on average pain severity item of Brief Pain Inventory<br><br>Duration of pain not stated |
| Arnold 2010[37] | Intervention: Duloxetine 60-120mg/day (n=263) | Fibromyalgia | At 12 weeks: | 18% had major depressive disorder |

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Placebo (n=267) | Aged over 18 years<br>N=386 | • Pain reduction<br>• Quality of life<br>• Psychological distress<br>• Discontinuation due to adverse events | Duration of pain not stated |
| Arnold 2012[50] | Intervention: Duloxetine 30mg/day (n=155)<br>Comparison: Placebo (n=153) | Fibromyalgia<br>Age mean 51 years<br>Mean pain duration 6.5 years<br>N=308 | At 12 weeks:<br>• Pain reduction<br>• Quality of life<br>• Psychological distress<br>• Discontinuation due to adverse events | |
| Arnold 2019 [49] | Intervention: Pregabalin 150mg twice per day.(n=964)<br>Comparison: Placebo (n=966) | Fibromyalgia<br>Age mean 50 years<br>Mean pain duration 5.14 years<br>N=1930 | At 13 weeks:<br>• Pain reduction<br>• Quality of life<br>• Psychological distress<br>• Discontinuation due to adverse events<br>• Sleep | Washout period took place before randomisation whereby participants discontinued medicines that were not allowed in the study. Paracetamol and some non-pharmacological approaches (such as massage) were allowed for breakthrough fibromyalgia pain. |
| Bidari 2019 [73] | Intervention: Duloxetine 30mg/day (n=60)<br><br>Intervention: Pregabalin 75mg/day (n=39) | Fibromyalgia<br>Age mean (SD): Duloxetine group 41.6 (9.02), Pregabalin group 43.1 (7.78)<br>Duration of fibromyalgia in months, median (range):<br>Duloxetine group 24 (0-240)<br>Pregabalin group 36 (0-240)<br>N=99 | At 4 weeks:<br>• Pain reduction<br>• Quality of life<br>• Psychological distress<br>• Discontinuation due to adverse events | Range of months with fibromyalgia is reported as 0-240. It was assumed that this meant months since diagnosis with fibromyalgia, as 3 months pain/symptoms were required for inclusion as per the ACR 2010 fibromyalgia diagnosis criteria |
| Carette 1986[113] | Intervention: Amitriptyline 10-50mg/day (n=27) | Fibrositis | At 9 weeks:<br>• Pain reduction | |

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Placebo (n=32_ | Age mean (SD): Amitriptyline group 41.8 (10.4), Placebo group 40.1 (10.5)<br>Duration of pain (months): Amitriptyline group 75 (72), Placebo group 78 (71)<br>N=59 | | |
| Carette 1994[112] | Intervention: Amitriptyline 50mg/day (n=84)<br><br>Comparison: Placebo (n=42) | Fibromyalgia<br>Age mean 46 years<br>Mean pain duration: 7.5 years<br>N=126 | At 4 weeks and 6 months:<br>• Pain reduction<br>• Psychological distress<br>• Physical function | |
| Chappell 2008[123] | Intervention: Duloxetine 60mg/day (n=162)<br><br>Comparison: Placebo (n=168) | Fibromyalgia<br>Age mean 50 years<br>N=330 | At 27 weeks:<br>• Pain reduction<br>• Quality of life<br>• Physical function<br>• Psychological distress<br>• Discontinuation due to adverse events | 77% diagnosed with major depressive disorder.<br>43% had previously used antidepressants.<br><br>Pain duration not specified. |
| Foster 2010[214] | Intervention: Lidocaine, topical 5% cream (n=33)<br><br>Comparison: Placebo (n=33) | Vulvodynia<br>Women<br>Age mean 32 years<br>Pain duration: from 4.4 to 6.5 years<br>N=66 | At 12 weeks:<br>• Pain reduction<br>• Psychological distress | |
| Foster 2010[215] | Intervention: Amitriptyline 10-50mg/day (n=135)<br><br>Comparison: Placebo (n= 136) | Interstitial cystitis/painful bladder syndrome<br>Age 18 years and older<br>Mean(SD) pain duration: 6(9.5) years | At 12 weeks:<br>• Pain reduction<br>• Psychological distress<br>• Discontinuation due to adverse events | Treatment naïve |

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| | | N=271 | | |
| Ginsberg 1996[233] | Intervention: Amitriptyline 25mg/day (n=44)<br><br>Comparison: Placebo (n=22) | Fibromyalgia<br>Age mean 46 years<br>Mean(SD) pain duration: 3.3(4.1) years<br>N=66 | Pain reduction at 8 weeks | |
| Heckmann 2012[275] | Intervention: Clonazepam 0.5mg/day (n=10)<br><br>Comparison: Placebo (n=10) | Burning mouth syndrome<br>Age mean 65 years<br>Mean(SD) pain duration: 3.2 (2.2) years<br>N=20 | At 9 weeks:<br>• Pain reduction<br>• Psychological distress | |
| Heymann 2001[277] | Intervention: Amitriptyline 25mg/day (n=40)<br><br>Intervention: Nortriptyline 25mg/day(n=38)<br><br>Comparison: Placebo (n=40) | Fibromyalgia<br>Age mean 50 years<br>N=118 | At 8 weeks:<br>• Number of responders<br>• Quality of life | Pain duration not specified. |
| Kimos 2007 [311] | Intervention: Gabapentin; maximum dose 4200mg/day (n=25)<br><br>Comparison: Placebo (n=25) | Adults with masticatory muscle pain for at least 6 months not attributable to trauma, infection or inflammation<br>Age mean 33.58 years<br>N=50 | Pain reduction at 12 weeks | |
| Lee 2005[332] | Intervention: Sertraline 50mg/day (n=7)<br><br>Comparison: Placebo (n=7) | Men with chronic pelvic pain syndrome<br>Age 18 to 65 years<br>N=14 | At 13 weeks:<br>• Pain reduction<br>• Psychological distress<br>• Discontinuation due to adverse events | Pain duration not specified |

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| Lewis 2016 [336] | Intervention: Gabapentin 300-2700mg/day (n=22)<br><br>Comparison: Placebo (n=25) | Women with chronic pelvic pain for at least 6 months with no known pathology<br>Age 18 to 50 years<br>N=47 | At 12 weeks and 6 months:<br>• Pain reduction<br>• Physical function<br>• Psychological distress<br>• Discontinuation due to adverse events | |
| Luo 2009[347] | Intervention: Fluoxetine 20mg/day (n=40)<br><br>Comparison: Placebo (n=40) | Adults with persistent somatoform pain disorder (defined as a pain which cannot be fully explained by a physiological process or physical disorder).<br>Age 18 to 65 years<br>Mean(SD) pain duration: 21(18.7) months<br>N=80 | Pain reduction at 8 weeks | Participants with depressive symptoms of 17 or above on the HAMD were excluded |
| Maarrawi 2018[350] | Intervention: Amitriptyline 5mg/day (n=112)<br><br>Comparison: Placebo (n=108) | Idiopathic chronic neck pain<br>Mean age 44 years<br>Mean pain duration: 81.8% of participants had pain for more than 12 months<br>N=220 | At 8 weeks<br>• Pain reduction<br>• Physical function<br>• Psychological distress<br>• Discontinuation due to adverse events<br>• Sleep | |
| Mahagna 2016[354] | Intervention: Etoricoxib 90mg/day (n=32)<br><br>Comparison: Placebo (n=32) | Fibromyalgia<br>Mean age 50 years<br>Mean (SD) pain duration: 4.3(6.4) years<br>N=64 | At 6 weeks:<br>• Number of responders<br>• Quality of life<br>• Psychological distress<br>• Discontinuation due to adverse events | 45% on antidepressant treatment |

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| Murakami 2015[403] | Intervention: Duloxetine 60mg/day (n=196)<br><br>Comparison: Placebo (n=197) | Fibromyalgia<br>Mean age 48.7 years<br>Mean(D) pain duration: 5.6(6.3) years<br>N=393 | At 14 weeks:<br>• Pain reduction<br>• Quality of life<br>• Physical function<br>• Psychological distress<br>• Discontinuation due to adverse events<br>• Sleep | |
| Norregaard 1995[425] | Intervention: Citalopram 40mg/day (n=21)<br><br>Comparison: Placebo (n=21) | Fibromyalgia<br>Mean age 49 years<br>Mean(SD) pain duration: 10(9) years<br>N=42 | At 8 weeks:<br>• Physical function<br>• Psychological distress | 25% took daily paracetamol |
| Pontari 2010 [471] | Intervention: Pregabalin (150mg/day for 2 weeks, 300mg/day for 2 weeks, 600mg/day for 2 weeks, n=218)<br><br>Comparison: Placebo (n=106) | Men with pelvic pain for at least 3 months<br>Mean age 47 years<br>N=324 | At 6 weeks:<br>• Pain reduction<br>• Quality of life<br>• Psychological distress | Inclusion criteria: score of >16 on National Institute of Health Chronic Prostatitis Symptoms Index |
| Russell 1991[505] | Intervention: Ibuprofen 2400mg /day (n= 17)<br><br>Intervention: Alprazolam, maximum dose 3mg/day (n=17)<br><br>Comparison: placebo (n=14) | Fibromyalgia<br>Mean age: 47.3 years<br>Mean(SD) pain duration: 8.9(1) years<br>N=48 | At 6 weeks:<br>• Pain reduction<br>• Physical function<br>• Psychological distress | 60.2% had anxiety, 57.7% had chronic headache, 39.7% had irritable bowel syndrome |
| Russell 2008 [507] | Intervention: Duloxetine (20-120mg/day) (n=376) | Fibromyalgia<br>Mean age 51 years<br>N=520 | At 6 months:<br>• Pain reduction<br>• Quality of life | 25% had a diagnosis of major depressive disorder<br>Pain duration not specified |

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Placebo (n=144) | | • Physical function<br>• Discontinuation due to adverse events | |
| Scudds 1995[526] | Intervention: Topical lidocaine 4% (n=31)<br><br>Comparison: Placebo (n=30) | 42 adults with fibromyalgia and 19 with myofascial pain syndrome<br>Mean age 45 years.<br>Mean(SD) pain duration: 8.7(7.8) years N=61 | Number of responders at 3 weeks | |
| Singer 1997[537] | Intervention 1: Diazepam 5mg/day (n=16)<br><br>Intervention 2: Ibuprofen 2400mg/day (n=17)<br><br>Comparison: Placebo (n=16) | Chronic orofacial muscle pain<br>Mean age 36.1 years<br>Mean(SD) pain duration: at least 3 months<br>N=49 | At 4 weeks:<br>• Pain reduction<br>• Psychological distress | Clinical or radiographic evidence of TMJ pathology were exclusionary criteria |
| Skrabek 2008[539] | Intervention: Nabilone 2mg/day (n=20)<br><br>Comparison: Placebo (n=20) | Fibromyalgia<br>Mean age 48 years<br>N=40 | At 8 weeks:<br>• Pain reduction<br>• Quality of life<br>• Discontinuation due to adverse events | Pain duration not specified<br><br>Results for pain reduction and quality of life outcomes reported insufficiently to allow quality assessment or analysis. |
| Spinhoven 2010[549] | Paroxetine max dose 40mg/day (n=23)<br><br>Comparison: Placebo (n=23) | Non-cardiac chest pain<br>Mean age 57.4 years<br>Mean(SD) pain duration: 6(7.1)<br>N=46 | At 12 weeks:<br>• Pain reduction<br>• Psychological distress | Excluding major depression<br>28% had an anxiety disorder |
| van Ophoven 2004[593] | Intervention: Amitriptyline maximum dose 100mg/day (n=26) | Interstitial cystitis<br>Mean age 55 years | At 16 weeks:<br>• Pain reduction | Met the National institute of diabetes, digestive and kidney |

| Study | Interventions | Population | Outcomes | Comments |
|---|---|---|---|---|
| | Comparison: Placebo (n=26) | Mean(SD) pain duration: 3.8(5) years<br>N=52 | • Discontinuation due to adverse events | diseases definition of interstitial cystitis. |
| Wolfe 1994[633] | Intervention: Fluoxetine 20mg/day (n=21)<br><br>Comparison: Placebo (n=21) | Adults aged 21 to 70 years with fibromyalgia<br>Mean pain duration:13 years<br>N=42 | At 6 weeks:<br>• Pain reduction<br>• Physical function<br>• Psychological distress<br>• Discontinuation due to adverse events<br>• Sleep | |
| Yeephu 2013[643] (Suttiruksa 2016[563]) | Intervention: Mirtazapine 15-30mg/day (n=27)<br><br>Comparison: Placebo (n=13) | Fibromyalgia<br>Age 18 years and over<br>Mean(SD) pain duration: 19(9.5) years<br>N=40 | At 13 weeks:<br>• Quality of life<br>• Number of responders<br>• Discontinuation due to adverse events | |

See appendix D for full evidence tables.

### 1.4.4 Quality assessment of clinical studies included in the evidence review

**Table 4: Clinical evidence summary: Anti-epileptics (gabapentinoids) versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Anti-epileptics versus placebo (95% CI) |
| Pain reduction at ≤3 months (VAS, Brief Pain Inventory average pain severity score, range, McGill pain questionnaire, high is poor outcome, final values) | 508<br>(4 studies)<br>6-12 weeks | MODERATE[2] due to risk of bias | | - | The mean pain score in the intervention groups was 0.45 standard deviations lower<br>(0.63 to 0.27 lower) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Anti-epileptics versus placebo (95% CI) |
| Pain reduction at ≤3 months (VAS percentage reduction, change scores) | 44 (1 study) 12 weeks | VERY LOW[1,2] due to risk of bias, imprecision | | The mean pain reduction in the control groups was 24.3 | The mean pain reduction in the intervention groups was 27.1 higher (2.5 to 51.7 higher) |
| Pain reduction at >3 months (VAS, 0-10, high is poor outcome, final values); chronic pelvic pain subgroup | 59 (2 studies) 3-6 months | LOW[1.2] due to risk of bias, imprecision | | The mean pain score in the control groups was 5 | The mean pain score in the intervention groups was 1.68 lower (2.3 lower to 1.05 lower) |
| Pain reduction at >3 months (Average daily pain score, 0-10, high is poor outcome, change scores); fibromyalgia subgroup | 1902 (1 study) 13 weeks | MODERATE[2] due to risk of bias | | The mean change in pain score in the control group was -1.81 | The mean pain score in the intervention groups was 0.56 lower (0.77 lower to 0.35 lower) |
| Quality of life at ≤3 months (SF-12 physical component, high is good outcome, 0-100, final values) | 317 (1 study) 12 weeks | MODERATE[1] due to imprecision | | The mean quality of life in the control group was 44.3 | The mean quality of life in the intervention groups was 2.6 higher (0.14 higher to 5.06 higher) |
| Quality of life ≤3 months (SF-12 mental component, high is good outcome, 0-100, final values) | 317 (1 study) 12 weeks | HIGH | | The mean quality of life in the control group was 44.6 | The mean quality of life in the intervention groups was 0.4 higher (2.15 lower to 2.95 higher) |
| Quality of life at ≤3 months (Fibromyalgia impact questionnaire, 0-100, high is poor outcome, final values) | 119 (1 study) 12 weeks | LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control groups was 37.3 | The mean quality of life in the intervention groups was 11.1 lower (17.07 to 5.13 lower) |
| Quality of life at >3 months (EQ5D, 0-100, high is good outcome, change scores) | 1777 (1 study) 13 weeks | LOW[1,2] due to risk of bias, imprecision | | The mean change in quality of life in the control group was 0.08 | The mean quality of life in the intervention groups was 0.02 higher (0 to 0.04 lower) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Anti-epileptics versus placebo (95% CI) |
| Physical function at ≤3 months (Pain Disability Questionnaire function subscale, 0-90, high is poor outcome, final values) | 25 (1 study) 12 weeks | MODERATE[1] due to imprecision | | The mean physical function in the control group was 23 | The mean physical function in the intervention groups was 6.4 higher (8.35 lower to 21.15 higher) |
| Physical function at >3 months (Pain Disability Questionnaire function subscale, 0-90 high is poor outcome) | 25 (1 study) 6 months | LOW[1] due to imprecision | | The mean physical function in the control group was 20.3 | The mean physical function in the intervention groups was 3.6 higher (12.5 lower to 19.7 higher) |
| Psychological distress at ≤3 months (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, final values) | 25 (1 study) 12 weeks | VERY LOW[1,2] due to risk of bias, imprecision | | The mean psychological distress in the control group was 8.2 | The mean psychological distress in the intervention groups was 0.1 lower (3.91 lower to 3.71 higher) |
| Psychological distress at >3 months (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, change scores and final values) | 1804 (2 studies) 13 weeks - 6 months | MODERATE[2]due to risk of bias | | The mean psychological distress in the control group was 9.8 | The mean psychological distress in the intervention groups was 0.2 lower (0.52 lower to 0.12 higher) |
| Psychological distress at ≤3 months (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, final values) | 26 (1 study) 12 weeks | VERY LOW[1,2] due to risk of bias, imprecision | | The mean psychological distress in the control group was 4.7 | The mean psychological distress in the intervention groups was 0.8 higher (2.44 lower to 4.04 higher) |
| Psychological distress at >3 months (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, final values) | 1804 (2 studies) 13 weeks - 6 months | MODERATE[2] due to risk of bias | | The mean psychological distress in the control group was 4.9 | The mean psychological distress in the intervention groups was 0.42 lower (0.76 to 0.08 lower) |
| Psychological distress at ≤3 months (Hospital Anxiety and | 313 (1 study) 6 weeks | HIGH | | The mean psychological distress in the | The mean psychological distress in the intervention groups was 0.2 higher (1.64 lower to 2.04 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Anti-epileptics versus placebo (95% CI) |
| Depression scale, 0-21, high is poor outcome, final values) | | | | control group was 12.2 | |
| Discontinuation due to adverse events at ≤3 months (reasons not specified) | 119 (1 study) 12 weeks | LOW[1,2] due to risk of bias, imprecision | RR 1.86 (0.79 to 4.41) | 113 per 1000 | 97 more per 1000 (from 24 fewer to 385 more) |
| Discontinuation due to adverse events at >3 months (reasons not specified) | 2013 (3 studies) 3-6 months | LOW[1,2] due to risk of bias, imprecision | RR 1.52 (1.15 to 2) | 75 per 1000 | 39 more per 1000 (from 11 more to 75 more) |
| Sleep at ≤3 months (Medical Outcomes Study Sleep Problems index score, 0-100, high is poor outcome, final values) | 119 (1 study) 12 weeks | LOW[1,2] due to risk of bias, imprecision | | The mean sleep score in the control group was 47.8 | The mean sleep score in the intervention group was 14.4 lower (21.64 to 7.16 lower) |
| Sleep at >3 months (Average Daily Sleep Interference, 0-10, high is poor outcome, change scores) | 1905 (1 study) 13 weeks | MODERATE[,2] due to risk of bias | | The mean change in sleep score in the control group was -1.78 | The mean sleep score in the intervention group was 0.67 lower (0.86 to 0.48 lower) |

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias

**Table 5: Clinical evidence summary: SSRIs versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SSRIs versus placebo (95% CI) |
| Pain reduction final values (VAS , medical outcomes | 150 (3 studies) 6-8 weeks | ⊕⊖⊖⊖ VERY LOW[1,2,3] | | - | The mean pain score in the intervention groups was 0.41 standard deviations lower (1.08 lower to 0.27 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SSRIs versus placebo (95% CI) |
| study pain measure, high is poor outcome) ≤3 months | | due to risk of bias, imprecision, inconsistency | | | |
| Pain reduction change scores (McGill pain questionnaire, Prostatitis symptom severity scale, high is poor outcome) at >3 months | 65 (2 studies) 12-13 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | - | The mean pain score in the intervention groups was 0.65 standard deviations lower (1.16 to 0.15 lower) |
| Pain reduction (VAS final values, 0-10, high is poor outcome) at >3 months | 46 (1 study) 16 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean pain score in the control group was 2.35 | The mean pain score in the intervention groups was 0.25 lower (1.35 lower to 0.85 higher) |
| Quality of life at ≤3 months (FIQ total scores, 0-100, high is poor outcome, change scores) | 51 (1 study) 12 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean change in quality of life in the control group was +2.9 | The mean change in quality of life in the intervention groups was 11.5 lower (19.22 to 3.78 lower) |
| Physical function (HAQ total scores, FIQ physical function subscale, high is poor outcome, final values) at ≤3 months | 66 (2 studies) 6-8 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | - | The mean physical function in the intervention groups was 0.06 standard deviations lower (0.55 lower to 0.43 higher) |
| Physical function (physical impairment on Fibromyalgia impact questionnaire, 0-9.99, high is poor outcome, change scores) at ≤3 months | 51 (1 study) 12 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean change in physical function in the control group was -0.4 | The mean change in physical function in the intervention groups was 0.7 lower (1.91 lower to 0.51 higher) |
| Psychological distress (FIQ depression subscale, HADS-D, beck depression inventory, | 107 (3 studies) 12 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of | | - | The mean change in psychological distress in the intervention groups was 0.32 standard deviations |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SSRIs versus placebo (95% CI) |
| high is poor outcome) change scores ≤3 months | | bias, imprecision | | | lower (0.71 lower to 0.06 higher) |
| Psychological distress (FIQ anxiety subscale, AIMS anxiety, high is poor outcome) change scores at ≤3 months | 65 (2 studies) 12 weeks | ⊕⊕⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | - | The mean change in psychological distress in the intervention groups was 0.19 standard deviations lower (0.69 lower to 0.3 higher) |
| Psychological distress (Beck depression scale, HADS:A, high is poor outcome) final values at ≤3 months | 70 (2 studies) 6 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | - | The mean psychological distress in the intervention groups was 0.79 standard deviations lower (1.28 to 0.3 lower) |
| Psychological distress (HADS:A, 0-21, high is poor outcome, final values) at >3 months | 46 (1 study) 16 weeks | ⊕⊖⊖⊖ VERY LOW[2] due to risk of bias, imprecision | | The mean psychological distress in the control group was 7 | The mean psychological distress in the intervention groups was 2.3 lower (4.12 to 0.48 lower) |
| Discontinuation due to adverse events at ≤3 months (due to gastrointestinal problems) | 24 (1 study) 6 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | RR 0.6 (0.04 to 8.46) | 111 per 1000 | 44 fewer per 1000 (from 107 fewer to 829 more) |
| Discontinuation due to adverse events at >3 months (reasons not stated due to no events in intervention arm; placebo discontinuation due to feeling 'spaced out') | 14 (1 study) 13 weeks | ⊕⊕⊖⊖ LOW[2] due to imprecision | OR 0.14 (0.00 to 6.82) | 143 per 1000 | 100 fewer per 1000 (from 136 fewer to 107 more) |
| Sleep (VAS sleep outcome, 0-15, high is poor outcome) final values at ≤3 months | 24 (1 study) 6 weeks | ⊕⊖⊖⊖ VERY LOW[1,2] due to risk of | | The mean sleep in the control group was 7.6 | The mean sleep in the intervention groups was 0 higher (2.95 lower to 2.95 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SSRIs versus placebo (95% CI) |
| | | bias, imprecision | | | |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded due to heterogeneity, unexplained by subgroup analysis

**Table 6: Clinical evidence summary: SNRIs versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SNRIs versus placebo (95% CI) |
| Pain reduction (Brief Pain Inventory average pain severity, VAS, high is poor outcome) change scores at ≥3 months | 2194 (6 studies) 12-28 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in pain reduction in the control groups was -1.59 | The mean pain in the intervention groups was 0.69 lower (0.91 to 0.47 lower) |
| Quality of life (SF-36 mental component, 0-100, high is good outcome) change scores and final scores at ≤3 months | 1112 (3 studies) 7-12 weeks | ⊕⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision | | The mean quality of life in the control groups was 1.22 | The mean quality of life in the intervention groups was 3.17 higher (2.15 to 4.18 higher) |
| Quality of life (SF-36 physical component, 0-100, high is good outcome) change scores at ≤3 months | 1112 (3 studies) 7-12 weeks | ⊕⊖⊖⊖ LOW[1,2] due to risk of bias, inconsistency | | The mean quality of life in the control groups was 3.62 | The mean quality of life in the intervention groups was 1.01 higher (0.68 to 1.35 higher) |
| Quality of life (SF-36 physical functioning subscale, 0-100, | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] | | The mean change in quality of life in the control groups was 3.04 | The mean change in quality of life in the intervention groups was |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SNRIs versus placebo (95% CI) |
| high is good outcome) change score at >3 months | | due to risk of bias | | | 4.36 higher (3.93 to 4.79 higher) |
| Quality of life (SF-36 physical role limitations subscale, 0-100, high is good outcome) change score at>≥3 months | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in quality of life in the control groups was 0.44 | The mean change in quality of life in the intervention groups was 7.76 higher (7.17 to 8.35 higher) |
| Quality of life (SF-36 bodily pain subscale, 0-100, high is good outcome) change score at >3 months | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in quality of life in the control groups was 5.28 | The mean change in quality of life in the intervention groups was 5.67 higher (5.26 to 6.08 higher) |
| Quality of life (SF-36 vitality subscale, 0-100, high is good outcome) change score at >3 months | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in quality of life in the control groups was 3.35 | The mean change in quality of life in the intervention groups was 6.7 higher (6.2 to 7.2 higher) |
| Quality of life (SF-36 general health perceptions subscale, 0-100, high is good outcome) change score at >3 months | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in quality of life in the control groups was 3.31 | The mean change in quality of life in the intervention groups was 3.24 higher (2.86 to 3.63 higher) |
| Quality of life (SF-36 social functioning subscale, 0-100, high is good outcome) change score at >3 months | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in quality of life in the control groups was 3.28 | The mean change in quality of life in the intervention groups was 7.04 higher (6.43 to 7.65 higher) |
| Quality of life (SF-36 mental health subscale, 0-100, high is good outcome) change score at >3 months | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in quality of life in the control groups was -2 | The mean change in quality of life in the intervention groups was 7.91 higher (7.41 to 8.41 higher) |
| Quality of life (SF-36 emotional role limitations subscale, 0-100, high is good outcome) change score at >3 months | 386 (1 study) 14 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean change in quality of life in the control groups was -3.63 | The mean change in quality of life in the intervention groups was 9.13 higher (8.46 to 9.8 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SNRIs versus placebo (95% CI) |
| Quality of life (EQ-5D, 0-1 high is good outcome) change scores at >3 months | 520 (1 study) 28 weeks | ⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision | | The mean change in quality of life score in the control group was 0.12 | The mean change in quality of life in the intervention groups was 0.03 higher (0.04 lower to 0.1 higher) |
| Quality of life (Fibromyalgia impact questionnaire, 0-100, high is poor outcome) change scores at >3 months | 347 (1 study) 12 weeks | ⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision | | The mean quality of life change score in the control group was -8.35 | The mean quality of life in the intervention groups was 8.42 lower (12.08 to 4.76 lower) |
| Physical function (FIQ physical function subscale, Sheehan disability scale global functioning, high is poor outcome) change scores at >3 months | 1231 (3 studies) 12-27 weeks | ⨁⨁⊖⊖ LOW[1] due to risk of bias | | | The mean change in physical function in the intervention groups was 0.02 standard deviations lower (0.14 lower to 0.1 higher) |
| Psychological distress (Beck depression inventory, Hamilton rating scale for depression, high is poor outcome) change scores at >3 months | 1731 (5 studies) 12-27 weeks | ⨁⊖⊖⊖ VERY LOW[1,2,3] due to risk of bias, inconsistency, imprecision | | | The mean psychological distress in the intervention groups was 2.02 standard deviations lower (3.62 to 0.41 lower) |
| Discontinuation due to adverse events at ≥3 months; multiple reasons, 1 serious adverse event in placebo arm (irritable bowel syndrome) | 2367 (6 studies) 12-28 weeks | ⨁⊖⊖⊖ LOW[1] due to risk of bias | RR 1.71 (1.35 to 2.09) | 88 per 1000 | 60 more per 1000 (from 42 more to 92 more) |
| Sleep (Jenkins composite score, MOS-Sleep Index I, Brief pain inventory interference score for | 734 (2 studies) 12-14 weeks | ⨁⊖⊖⊖ VERY LOW[1,3] due to risk of | | | The mean sleep in the intervention groups was 0.53 standard deviations lower (0.68 to 0.38 lower) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SNRIs versus placebo (95% CI) |
| sleep, high is poor outcome, change scores) at ≥3 months | | bias, imprecision | | | |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment for heterogeneity, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 7: Clinical evidence summary: Tricyclic antidepressants versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Tricyclics versus placebo (95% CI) |
| Pain reduction (VAS and McGill pain questionnaire, final values, high is poor outcome) at ≤3 months | 430 (4 studies) 4-9 weeks | ⨁⨁⨁⨀ VERY LOW[1,3] due to risk of bias, inconsistency | | - | The mean pain in the intervention groups was 0.99 standard deviations lower (2.18 lower to 0.19 higher) |
| Pain reduction (VAS 0-10, high is poor outcome) change scores at ≤3 months | 131 (1 study) 12 weeks | ⨁⨁⨀⨀ MODERATE[1] due to risk of bias | | The mean change in pain score in the control group was -2.3 | The mean change in pain in the interventions groups was 0.30 lower (0.93 lower to 0.33 higher) |
| Pain reduction change scores (VAS 0-100, high is poor outcome) at >3 months | 48 (1 study) 16 weeks | ⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision | | The mean pain change in the control group was 1 | The mean pain in the intervention groups was 23.8 lower (35.82 to 11.78 lower) |
| Pain final values (McGill pain questionnaire, 0-78, high is poor outcome) at >3 months | 114 (1 study) 28 weeks | ⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision | | The mean pain in the control group was 21.6 | The mean pain in the intervention groups was 2.1 lower (7.68 lower to 3.48 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Tricyclics versus placebo (95% CI) |
| Number of responders (Scale of global improvement, great or moderate improvement) at ≤3 months | 106 (1 study) 8 weeks | ⨁⨁⨁⨀ MODERATE[2] due to imprecision | RR 1.56 (0.99 to 2.48) | 394 per 1000 | 220 more per 1000 (from 4 fewer to 583 more) |
| Quality of life final values (FIQ, 0-100, high is poor outcome) at ≤3 months | 106 (1 study) 8 weeks | ⨁⨁⨁⨀ MODERATE[2] due to imprecision | | The mean quality of life in the control group was 51.68 | The mean quality of life in the intervention groups was 7.37 lower (10.68 to 4.06 lower) |
| Physical functioning (NPDI, % improvement) at ≤3 months | 212 (1 study) 8 weeks | ⨁⨁⨁⨁ HIGH | | The mean physical functioning % improvement in the control group was 13.69 | The mean physical functioning % improvement in the intervention groups was 28.53 higher (25.05 to 32.01 higher) |
| Physical function final values (HAQ disability index, 0-3, high is poor outcome) at ≤3 months | 122 (1 study) 4 weeks | ⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision | | The mean physical function in the control group was 0.77 | The mean physical function in the intervention groups was 0.17 lower (0.37 lower to 0.03 higher) |
| Physical function final values (HAQ disability index, 0-3, high is poor outcome,) at >3 months | 114 (1 study) 28 weeks | ⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision | | The mean physical function in the control group was 0.7 | The mean physical function in the intervention groups was 0.17 lower (0.4 lower to 0.06 higher) |
| Psychological distress (HAD-D, % improvement) at ≤3 months | 212 (1 study) 8 weeks | ⨁⨁⨁⨀ MODERATE[2] due to imprecision | | The mean % improvement in psychological distress in the control group was 5.04 | The mean % improvement in psychological distress in the intervention groups was 5.32 higher (1.77 to 8.87 higher) |
| Psychological distress final values (Arthritis Impact Measurement Scale [AIMS] | 122 (1 study) 4 weeks | ⨁⨁⨀⨀ LOW[1] due to risk of bias | | The mean psychological distress in the control group was 2.97 | The mean psychological distress in the intervention groups was 0.12 lower (0.82 lower to 0.58 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Tricyclics versus placebo (95% CI) |
| depression component, high is poor outcome) at ≤3 months | | | | | |
| Psychological distress final values (Arthritis Impact Measurement Scale depression component [AIMS], 0-10, high is poor outcome) at >3 months | 114 (1 study) 28 weeks | ⨁⨁⊖⊖ LOW[1] due to risk of bias | | The mean psychological distress in the control group was 2.57 | The mean psychological distress in the intervention groups was 0.16 lower (0.89 lower to 0.57 higher) |
| Discontinuation due to adverse events at ≤3 months (due to drowsiness, palpitations, insomnia, panic attack) | 332 (1 study) 8 weeks | ⨁⨁⨁⊖ MODERATE[1] due to risk of bias | OR 7.72 (1.9 to 31.31) | 0 events in the control arm | 50 more per 1000 (from 10 more to 80 more) |
| Discontinuation due to adverse events at ≥3 months (reasons not specified, no serious adverse events reported) | 319 (2 studies) 12-16 weeks | ⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision | RR 2.68 (0.72 to 9.93) | 28 per 1000 | 47 more per 1000 (from 8 fewer to 250 more) |
| Sleep disturbance (Bisprectal index scale, % improvement) at ≤3 months | 212 (1 study) 8 weeks | ⨁⨁⨁⨁ HIGH | | The mean % improvement in sleep disturbance in the control group was 6.02 | The mean % improvement in sleep disturbance in the intervention groups was 28.87 higher (23.87 to 33.87 higher) |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded by 1 or 2 increments for heterogeneity, unexplained by subgroup analysis

**Table 8: Clinical evidence summary: Tetracyclic antidepressants versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Tetracyclic antidepressant versus placebo (95% CI) |
| Number of responders (VAS total score, VAS 24h morning recall, 30% improvement) at >3 months | 40 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | RR 1.54 (0.72 to 3.28) | 385 per 1000 | 208 more per 1000 (from 108 fewer to 878 more) |
| Quality of life (SF-36 physical functioning subscale, 0-100, high is good outcome, final values) at >3 months | 32 (1 study) 13 weeks | ⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 58 | The mean quality of life in the intervention groups was 20.35 higher (2.09 to 38.61 higher) |
| Quality of life (SF-36 physical role limitations subscale, 0-100, high is good outcome , final values) at >3 months | 32 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 57 | The mean quality of life in the intervention groups was 7 higher (114.81 lower to 128.81 higher) |
| Quality of life (SF-36 bodily pain subscale, 0-100, high is good outcome outcome , final values) at >3 months | 32 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 49 | The mean quality of life in the intervention groups was 8.5 higher (41.58 lower to 58.58 higher) |
| Quality of life (SF-36 general health perceptions subscale, 0-100, high is good outcome outcome , final values) at >3 months | 32 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 47 | The mean quality of life in the intervention groups was intervention groups was 9 higher (41.23 lower to 59.23 higher) |
| Quality of life (SF-36 vitality subscale, 0-100, high is good outcom outcome , final values e) at >3 months | 32 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 59 | The mean quality of life in the intervention groups was 6 higher (30.8 lower to 42.8 higher) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Tetracyclic antidepressant versus placebo (95% CI) |
| Quality of life (SF-36 social functioning subscale, 0-100, high is good outcome outcome , final values) at >3 months | 32 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 53 | The mean quality of life in the intervention groups was 3 lower (27.51 lower to 21.51 higher) |
| Quality of life (SF-36 mental health subscale, 0-100, high is good outcome outcome , final values) at >3 months | 32 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 72 | The mean quality of life in the intervention groups was 9 higher (23.77 lower to 41.77 higher) |
| Quality of life (SF-36 emotional role limitations subscale, 0-100, high is good outcome outcome , final values) at >3 months | 32 (1 study) 13 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | | The mean quality of life in the control group was 64 | The mean quality of life in the intervention groups was 17.95 higher (83.79 lower to 119.69 higher) |
| Discontinuation due to adverse events at >3 months | 32 (1 study) 13 weeks | ⨁⨁⊖⊖ LOW[2] due to imprecision | RR 0.81 (0.15 to 4.28) | 148 per 1000 | 28 fewer per 1000 (from 112 fewer to 219 more) |

1 Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Note: the study informing these outcomes reported means and SEM. This was assumed to be standard error and has been converted to standard deviation in this analysis. However, confidence intervals are very wide. Reasons for this are unclear but this could be a result of incorrect analysis within the study. The study was therefore downgraded for outcome reporting bias within the risk of bias assessment.

**Table 9: Clinical evidence summary: Benzodiazepines versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Benzodiazepines versus placebo (95% CI) |
| Pain reduction final values and change scores (VAS, 0-10, high is poor outcome) at ≤3 months | 74 (3 studies) 4-9 weeks | ⊕⊕⊕⊖ MODERATE[1] due to risk of bias | | The mean pain in the control groups was 3.41 | The mean pain in the intervention groups was 0.38 lower (0.82 lower to 0.06 higher) |
| Physical function (HAQ disability index, 0-3 high is poor outcome, change scores) at ≤3 months | 31 (1 study) 6 weeks | ⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision | | The mean change in physical function in the control group was -0.2 | The mean change in physical function in the intervention groups was 0.1 higher (0.03 to 0.17 higher) |
| Psychological distress (Centre for epidemiological studies depression scale, 0-30, high is poor outcome, change scores) at ≤3 months | 31 (1 study) 6 weeks | ⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision | | The mean change in psychological distress in the control group was -2.2 | The mean change in psychological distress in the intervention groups was 0.2 higher (0.01 lower to 0.41 higher) |
| Psychological distress (BDI, depression adjective checklist, high is poor outcome, final values) at ≤3 months | 43 (2 studies) 4-9 weeks | ⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision | | - | The mean psychological distress in the intervention groups was 0.51 lower standard deviations lower (1.12 lower to 0.11 higher) |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 10: Clinical evidence summary: NSAIDs versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with NSAIDs versus placebo (95% CI) |
| Pain reduction at ≤3 months (VAS, 0-10, high is poor | 55 (2 studies) 4-6 weeks | ⊕⊕⊕⊖ MODERATE [1] | | The mean change in pain in the control groups was 2.32 | The mean pain in the intervention groups was |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with NSAIDs versus placebo (95% CI) |
| outcome, change scores and final values) | | due to risk of bias | | | 0.28 lower<br>(0.66 lower to 0.1 higher) |
| Number of responders (Brief pain inventory, decrease of >30%) at ≤3 months | 64<br>(1 study)<br>6 weeks | ⨁⨁⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | RR 1<br>(0.46 to 2.19) | 281 per 1000 | 0 fewer per 1000<br>(from 220 fewer to 220 more) |
| Quality of life at ≤3 months (SF-36 mental component, 0-100, high is good outcome, final values) | 64<br>(1 study)<br>6 weeks | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean quality of life in the control group was<br>48.4 | The mean quality of life in the intervention groups was<br>1.9 lower<br>(11.71 lower to 7.91 higher) |
| Quality of life at ≤3 months (SF-36 physical component, 0-100, high is good outcome, final values) | 64<br>(1 study)<br>6 weeks | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean quality of life in the control group was<br>35.6 | The mean quality of life in the intervention groups was<br>0.4 lower<br>(9.19 lower to 8.39 higher) |
| Physical function at ≤3 months (HAQ disability index, 0-3 high is poor outcome, change scores) | 31<br>(1 study)<br>6 weeks | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to risk of bias | | The mean change in physical function in the control group was<br>-0.2 | The mean change in physical function in the intervention groups was<br>0.1 higher<br>(0.03 to 0.17 higher) |
| Psychological distress at ≤3 months (Centre for epidemiological studies depression scale, 0-30, high is poor outcome, change scores) | 31<br>(1 study)<br>6 weeks | ⨁⨁⨁⊖<br>MODERATE[1]<br>due to risk of bias | | The mean change in psychological distress in the control group was<br>-2.2 | The mean change in psychological distress in the intervention groups was<br>0.6 lower<br>(0.81 to 0.39 lower) |
| Psychological distress at ≤3 months (HAM-D, depression | 88<br>(2 studies)<br>6 weeks | ⨁⨁⊖⊖<br>LOW[1,2]<br>due to risk of | | - | The mean psychological distress in the intervention groups was |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with NSAIDs versus placebo (95% CI) |
| adjective checklist, high is poor outcome, final values) | | bias, imprecision | | | 0.09 standard deviations lower (0.51 lower to 0.33 higher) |
| Discontinuation due to adverse events at ≤3 months (reasons not specified, no serious adverse events) | 64 (1 study) 6 weeks | ⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision | OR 7.63 (0.47 to 124.75) | 0 per 1000 | 6 more per 1000 (from 4 fewer to 16 more) |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 11: Clinical evidence summary: Cannabinoids versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with Cannabinoids versus placebo (95% CI) |
| Discontinuation due to adverse events at ≤3 months (dizziness, disorientation, nausea, poor coordination, headache, drowsiness and fatigue ) | 40 (1 study)[3] 4 weeks | ⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision | RR 3 (0.34 to 26.45) | 50 per 1000 | 100 more per 1000 (from 33 fewer to 1000 more) |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Study also reported quality of life and pain reduction outcomes but these were reported in insufficient detail for quality assessment or inclusion in the analysis. See clinical evidence tables for further details.

**Table 12: Clinical evidence summary: Local anaesthetics versus placebo**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with local anaesthetics versus placebo (95% CI) |
| Pain reduction change scores (VAS score 0-10, high is poor outcomes) at ≤3 months | 58<br>(1 study)<br>12 weeks | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in pain score in the control group was<br>-4.57 | The mean pain in the intervention groups was<br>1.47 higher<br>(1.82 lower to 4.75 higher) |
| Number of responders (100mm VAS score, 30% reduction) at ≤3 months | 61<br>(1 study)<br>7 weeks | ⨁⊖⊖⊖<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | RR 0.88<br>(0.44 to 1.76) | 367 per 1000 | 44 fewer per 1000<br>(from 206 fewer to 279 more) |
| Psychological distress (Beck depression inventory 0-63, change score; high is poor outcome) at ≤3 months | 59<br>(1 study)<br>12 weeks | ⨁⨁⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in psychological distress in the control groups was -1.92 | The mean change in psychological distress in the intervention groups was<br>1.06 higher<br>(-1.85 lower to 3.97 higher) |
| Discontinuation due to adverse events at <3 months (reasons not stated) | 66<br>(1 study)<br>4 weeks | ⨁⨁⊖⊖<br>LOW[1,2]<br>due to risk of bias, imprecision | RR 1<br>(0.07 to 15.33) | | 0 more per 1000<br>(from 8 fewer to 8 more) |

1Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2]Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 13: Clinical evidence summary: NSAIDs versus benzodiazepines**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with NSAIDs versus benzodiazepines (95% CI) |
| Pain reduction (VAS, 0-10, high is poor outcome, change scores and final values) at ≤3 months | 57<br>(2 studies)<br>4-6 weeks | ⨁⨁⨀⨀<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean pain in the control groups was 3.95 | The mean pain in the intervention groups was<br>0.13 higher<br>(0.33 lower to 0.6 higher) |
| Physical function change scores (HAQ disability index, 0-3, high is poor outcome) at ≤3 months | 34<br>(1 study)<br>6 weeks | ⨁⨁⨀⨀<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in physical function in the control group was -0.1 | The mean change in physical function in the intervention groups was<br>0 higher<br>(0.07 lower to 0.07 higher) |
| Psychological distress change scores (Centre for epidemiological studies depression scale, 0-30, high is poor outcome) at ≤3 months | 34<br>(1 study)<br>6 weeks | ⨁⨁⨀⨀<br>LOW[1,2]<br>due to risk of bias, imprecision | | The mean change in psychological distress in the control group was -2 | The mean change in psychological distress in the intervention groups was<br>0.8 lower<br>(1 to 0.6 lower) |
| Psychological distress final values (HAM-D, 0-21, high is poor outcome) at ≤3 months | 23<br>(1 study)<br>6 weeks | ⨁⨀⨀⨀<br>VERY LOW[1,2]<br>due to risk of bias, imprecision | | The mean psychological in the control group was 5.4 | The mean psychological distress in the intervention groups was<br>1 higher<br>(2.26 lower to 4.26 higher) |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

**Table 14: Clinical evidence summary: SNRIs versus anti-epileptics**

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SNRIs versus anti-epileptics (95% CI) |
| Pain reduction at <3 months (Widespread Pain Index, 0-19, final value, high is poor outcome) | 66 (1 study) 4 weeks | ⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision | | The mean pain reduction in the control group was 6.32 | The mean pain in the intervention groups was 2.63 lower (4.60 to 0.66 lower) |
| Quality of life at <3 months (SF-12 Physical component, 0-100, final value, high is good outcome) | 66 (1 study) 4 weeks | ⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision | | The mean quality of life in the control group was 47.98 | The mean quality of life in the intervention groups was 6.98 higher (3.15 lower to 17.11 higher) |
| Quality of life at <3 months (SF-12 Mental component, 0-100, final value, high is good outcome) | 65 (1 study) 4 weeks | ⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision | | The mean quality of life in the control group was 56.53 | The mean quality of life in the intervention groups was 7.44 higher (3.36 lower to 18.24 higher) [3] |
| Psychological distress at <3 months (Beck Depression Inventory-II, 0-63, final value, high is poor outcome) | 66 (1 study) 4 weeks | ⊕⊖⊖⊖ VERY LOW2 due to risk of bias, imprecision | | The mean psychological distress in the control group was 13.48 | The mean psychological distress in the intervention groups was 1.83 lower (6.38 lower to 2.72 higher) |
| Discontinuation due to adverse events at <3 months | 99 (1 study) 4 weeks | ⊕⊖⊖⊖ VERY LOW1,2,4 due to risk of bias, indirectness, imprecision | RR 2.03 (1.02 to 4.04) | 205 per 1000 | 212 more per 1000 (from 14 more to 440 more) |

| Outcomes | No of Participants (studies) Follow up | Quality of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with Control | Risk difference with SNRIs versus anti-epileptics (95% CI) |

1 Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
3 Significant difference in outcome at baseline may affect final values and between-group effect direction. Baselines, mean (SD): SNRI group 56.69 (24.33), anti-epileptics group 45.77 (27.31)
4 Downgraded for outcome indirectness

See appendix F for full GRADE tables.

# 1.5 Economic evidence

## 1.5.1 Included studies

No relevant health economic studies were identified for this question.

## 1.5.2 Excluded studies

Two economic studies that were relevant to this question were excluded due to methodological limitations.

See also the health economic study selection flow chart in appendix G.

## 1.5.3 Unit costs

Below is an illustration of the costs of different types of drugs identified in the review, with doses being taken from typical doses in the included studies and discussion with the commitee.

**Table 15: UK costs of drugs for managing chronic pain**

| Drug class | Drug | Daily dose | Cost | Cost/month | Cost/year |
|---|---|---|---|---|---|
| | **Antidepressants** | | | | |
| SSRI | Fluoxetine | 40mg | 20mg capsules<br>30 capsules per pack<br>£1.15 | £2.33 | £27.98 |
| SNRI | Duloxetine | 60mg | 60mg capsules<br>28 capsules per pack<br>£2.39 | £2.60 | £31.16 |
| | Venlafaxine | 150mg | 75mg tablets<br>56 tablets per pack<br>£3.58 | £3.89 | £46.67 |
| Tricyclic | Amitriptyline | 50mg | 25mg tablets<br>28 tablets per pack<br>£0.87 | £1.89 | £22.68 |
| | **Antiepileptics** | | | | |
| | Gabapentin | 1800mg | 600mg tablets<br>100 tablets per pack<br>£7.11 | £6.49 | £77.85 |
| | Pregabalin | 600mg | 200mg capsules<br>84 capsules per pack<br>£5.22 | £5.67 | £68.05 |
| | **Benzodiazepines** | | | | |
| | Diazepam | 5mg | 5mg tablets<br>28 tablets per pack<br>£0.76 | £0.83 | £9.91 |
| | **Cannabinoid** | | | | |

| Drug class | Drug | Daily dose | Cost | Cost/month | Cost/year |
|---|---|---|---|---|---|
| | Nabilone | 2mg | 1mg capsule 20 capsules per pack £196 | £596.17 | £7,154 |
| | **Local anaesthetics** | | | | |
| | Topical lidocaine | 2mg (a) | 40mg/g 30g tube £14.90 | £30.21 | £362.57 |
| | 700mg Lidocaine plasters | 2 plasters per day | 50mg/g 30 plasters per pack £72.40 | £146.81 | £1,761.73 |
| | **NSAIDs** | | | | |
| | Ibuprofen | 1600mg | 400mg tablets 24 tablets per pack £1.04 | £5.27 | £63.27 |

*Source: BNF, November 2019*[296]
*(a) In order to assume that roughly two tubes a month are needed.*

# 1.6 Evidence statements

## 1.6.1 Clinical evidence statements

### 1.6.1.1 Anti-epileptics (gabapentinoids) versus placebo

**Pain reduction**

Low quality evidence from 4 studies with a total of 508 participants showed no clinically important difference between gabapentinoids and placebo at ≤3 months. Very low quality evidence from 1 study with a total of 44 participants showed a clinically important benefit of gabapentinoids compared to placebo at ≤3 months. Low quality evidence from 2 studies with a total of 59 participants showed a clinically important benefit of gabapentinoids compared to placebo at >3 months (chronic pelvic pain subgroup). Moderate quality evidence from 1 study with 1902 participants showed no clinically important difference between gabapentinoids and placebo at >3 months (fibromyalgia subgroup).

**Quality of life**

Moderate to high quality evidence from 1 study with a total of 317 participants showed no clinically important difference between gabapentinoids and placebo at ≤3 months. Low quality evidence from 1 study with a total of 119 participants showed a clinically important benefit of gabapentinoids compared to placebo at ≤3 months. Low quality evidence from 1 study with 1777 participants showed no clinically important difference between gabapentinoids and placebo at >3 months.

**Physical function**

Low to moderate quality evidence from 1 study with 25 participants showed no clinically important difference between gabapentinoids and placebo at ≤3 months or >3 months.

**Psychological distress**

Very low quality evidence from 1 study with 25 participants showed no clinically important difference between gabapentinoids and placebo at ≤3 months. High quality evidence from 1 study with 313 participants showed no clinically important difference between gabapentinoids and placebo at ≤3 months. Moderate quality evidence from 2 studies with 1804 participants showed no clinically important difference between gabapentinoids and placebo at >3 months.

**Discontinuation due to adverse events**

Low quality evidence from 1 study with 119 participants showed clinically important harm of gabapentinoids compared to placebo at ≤3 months. Moderate quality evidence from 3 studies with 1905 participants showed no clinically important difference between gabapentinoids and placebo at >3 months.

**Sleep**

Low quality evidence from 1 study with 119 participants showed a clinically important benefit of gabapentinoids compared to placebo at ≤3 months. Moderate quality evidence from1 study with 1905 participants showed no clinically important difference between gabapentinoids and placebo at >3 months.

#### 1.6.1.2 SSRIs versus placebo

**Pain reduction**

Very low quality evidence from 3 studies with 150 participants showed a clinically important benefit of SSRIs compared to placebo at ≤3 months. Very low quality evidence from 2 studies with 65 participants showed a clinically important benefit of SSRIs compared to placebo at >3 months. Very low quality evidence from 1 study with 46 participants showed no clinically important difference between SSRIs and placebo at >3 months.

**Quality of life**

Very low quality evidence from 1 study with 51 participants showed a clinically important benefit of SSRIs compared to placebo at ≤3 months.

**Physical function**

Very low quality evidence from 1 study with 51 participants showed no clinically important difference between SSRIs and placebo at ≤3 months. Very low quality evidence from 2 studies with 66 participants showed no clinically important difference between SSRIs and placebo at ≤3 months.

**Psychological distress**

Very low quality evidence from 3 studies with 107 participants showed no clinically important difference between SSRIs and placebo at ≤3 months. Very low quality evidence from 1 study with 65 participants showed no clinically important difference between SSRIs and placebo at ≤3 months. Very low quality evidence from 2 studies with 70 participants showed no clinically important difference between SSRIs and placebo at ≤3 months. Very low quality evidence from 1 study with 46 participants showed a clinically important benefit of SSRIs compared to placebo at >3 months.

**Discontinuation due to adverse events**

Very low quality evidence from 1 study with 24 participants showed a clinically important benefit of SSRIs compared to placebo at ≤3 months. Low quality evidence from 1 study with 14 participants showed a clinically important benefit of SSRIs compared to placebo at >3 months.

**Sleep**

Very low quality evidence from 1 study with 24 participants showed no clinically important difference between SSRIs and placebo at ≤3 months.

#### 1.6.1.3 SNRIs versus placebo

**Pain reduction**

Moderate quality evidence from 6 studies with 2194 participants showed no clinically important difference between SNRIs and placebo at >3 months.

**Quality of life**

Very low quality evidence from 3 studies with 1112 participants showed a clinically important benefit of SNRIs compared to placebo at ≤3 months. Low quality evidence from the same 3 studies showed no clinically important difference between SNRIs and placebo at ≤3 months. Moderate quality evidence from 1 study with 386 participants showed a clinically important benefit of SNRIs compared to placebo at >3 months. Very low quality evidence from 1 study with 520 participants showed no clinically important difference between SNRIs and placebo at >3 months. Very low quality evidence from 1 study with 347 participants showed a clinically important benefit of SNRIs compared to placebo at >3 months.

**Physical function**

Low quality evidence from 3 studies with 1231 participants showed no clinically important difference between SNRIs and placebo at >3 months.

**Psychological distress**

Very low quality evidence from 5 studies with 1731 participants showed a clinically important benefit of SNRIs compared to placebo at >3 months.

**Discontinuation due to adverse events**

Low quality evidence from 6 studies with 2367 participants demonstrated that more people discontinued from SNRIs compared to placebo at >3 months.

**Sleep**

Very low quality evidence from 2 studies with 734 participants showed a clinically important benefit of SNRIs compared to placebo at >3 months.

#### 1.6.1.4 Tricyclic antidepressants versus placebo

**Pain reduction**

Very low quality evidence from 4 studies with 430 participants showed a clinically important benefit of tricyclic antidepressants compared to placebo at ≤3 months. Moderate quality evidence from 1 study with 131 participants showed no clinically important difference between tricyclic antidepressants and placebo at ≤3 months. Low quality evidence from 1 study with 48 participants showed a clinically important benefit of tricyclic antidepressants

compared to placebo at >3 months. Very low quality evidence from 1 study with 114 participants showed no clinically important difference between tricyclic antidepressants and placebo at >3 months. Moderate quality evidence from 1 study with 106 participants showed a clinically important benefit of tricyclic antidepressants compared to placebo at ≤3 months.

**Quality of life**

Moderate quality evidence from 1 study with 106 participants showed a clinically important benefit of tricyclic antidepressants compared to placebo at ≤3 months.

**Physical function**

High quality evidence from 1 study with 212 participants showed a clinically important benefit of tricyclic antidepressants compared to placebo at ≤3 months. Very low quality evidence from 1 study with 122 participants showed no clinically important difference between tricyclic antidepressants and placebo at ≤3 months. Very low quality evidence from 1 study with 114 participants showed no clinically important difference between tricyclic antidepressants and placebo at >3 months.

**Psychological distress**

Moderate quality evidence from 1 study with 212 participants showed no clinically important difference between tricyclic antidepressants and placebo at ≤3 months. Low quality evidence from 1 study with 122 participants showed no clinically important difference between tricyclic antidepressants and placebo at ≤3 months. Low quality evidence from 1 study with 114 participants showed a clinically important benefit of tricyclic antidepressants compared to placebo at >3 months.

**Discontinuation due to adverse events**

Moderate quality evidence from 1 study with 332 participants demonstrated that more people discontinued from tricyclic antidepressants compared to placebo at ≤3 months. Low quality evidence from 2 studies with 319 participants demonstrated that more people discontinued from tricyclic antidepressants compared to placebo at >3 months.

**Sleep**

High quality evidence from 1 study with 212 participants showed a clinically important benefit of tricyclic antidepressants compared to placebo at ≤3 months.

#### 1.6.1.5 Tetracyclic antidepressants versus placebo

**Pain reduction**

Very low quality evidence from 1 study with 40 participants showed a clinically important benefit of tetracyclic antidepressants compared to placebo at >3 months.

**Quality of life**

Low quality evidence from 1 study with 32 participants showed a clinically important benefit of tetracyclic antidepressants compared to placebo at >3 months

**Physical function**

No evidence identified.

**Psychological distress**

No evidence identified.

**Discontinuation due to adverse events**

Low quality evidence from 1 study with 31 participants showed no clinically important difference between tetracyclic antidepressants and placebo at >3 months.

**Sleep**

No evidence identified.

#### 1.6.1.6 Benzodiazepines versus placebo

**Pain reduction**

Moderate quality evidence from 3 studies with 74 participants showed no clinically important difference between benzodiazepines and placebo at ≤3 months.

**Quality of life**

No evidence identified.

**Physical function**

Low quality evidence from 1 study with 31 participants showed clinically important harm of benzodiazepiness compared to placebo at ≤3 months.

**Psychological distress**

Low quality evidence from 1 study with 31 participants showed no clinically important difference between benzodiazepines and placebo at ≤3 months. Low quality evidence from 2 studies with 43 participants showed a clinically important benefit of benzodiazepines compared to placebo at ≤3 months

**Discontinuation due to adverse events**

No evidence identified.

**Sleep**

No evidence identified.

#### 1.6.1.7 NSAIDs versus placebo

**Pain reduction**

Moderate quality evidence from 2 studies with 55 participants showed no clinically important difference between NSAIDs and placebo at ≤3 months. Low quality evidence from 1 study with 64 participants showed no clinically important difference between NSAIDs and placebo at ≤3 months.

**Quality of life**

Very low quality evidence from 1 study with 64 participants showed no clinically important difference between NSAIDs and placebo at ≤3 months.

**Physical function**

Low quality evidence from 1 study with 31 participants showed clinically important harm of NSAIDs compared to placebo at ≤3 months.

**Psychological distress**

Moderate quality evidence from 1 study with 31 participants showed no clinically important difference between NSAIDs and placebo at ≤3 months. Low quality evidence from 2 studies with 88 participants showed no clinically important difference between NSAIDs and placebo at ≤3 months.

**Discontinuation due to adverse events**

Low quality evidence from 1 study with 64 participants showed no clinically important difference between NSAIDs and placebo at ≤3 months.

**Sleep**

No evidence identified.

### 1.6.1.8 Cannabinoids versus placebo

Low quality evidence from 1 study with 40 participants demonstrated that more people discontinued from cannabinoids compared to placebo at ≤3 months.

No other evidence identified.

### 1.6.1.9 Local anaesthetics versus placebo

**Pain reduction**

Low quality evidence from 1 study with 58 participants showed clinically important harm of local anaesthetics compared to placebo at ≤3 months. Very low quality evidence from 1 study with 61 participants showed no clinically important difference between local anaesthetics and placebo at ≤3 months.

**Quality of life**

No evidence identified.

**Physical function**

No evidence identified.

**Psychological distress**

Low quality evidence from 1 study with 59 participants showed no clinically important difference between local anaesthetics and placebo at ≤3 months.

**Discontinuation due to adverse events**

Low quality evidence from 1 study with 66 participants showed no clinically important difference between local anaesthetics and placebo at ≤3 months.

**Sleep**

No evidence identified.

#### 1.6.1.10 NSAIDs versus benzodiazepines

**Pain reduction**

Low quality evidence from 1 study with 57 participants showed no clinically important difference between NSAIDs and benzodiazepines at ≤3 months.

**Quality of life**

No evidence identified.

**Physical function**

Low quality evidence from 1 study with 34 participants showed no clinically important difference between NSAIDs and benzodiazepines at ≤3 months.

**Psychological distress**

Low quality evidence from 1 study with 34 participants showed no clinically important difference between NSAIDs and benzodiazepines at ≤3 months. Very low quality evidence from 1 study with 23 participants showed no clinically important difference between NSAIDs and benzodiazepines at ≤3 months.

**Discontinuation due to adverse events**

No evidence identified.

**Sleep**

No evidence identified.

#### 1.6.1.11 SNRIs versus anti-epileptics

**Pain reduction**

Very low quality evidence from 1 study with 66 participants showed a clinically important benefit of SNRIs compared to gabapentinoids at ≤3 months.

**Quality of life**

Very low quality evidence from 1 study with 66 participants showed no clinically important difference between SNRIs and gabapentinoids at ≤3 months.

**Physical function**

No evidence identified.

**Psychological distress**

Very low quality evidence from 1 study with 66 participants showed no clinically important difference between SNRIs and gabapentinoids at ≤3 months.

**Discontinuation due to adverse events**

No evidence identified.

**Sleep**

No evidence identified.

### 1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

# 2 Long term safety of opioids for chronic pain

## 2.1 Review question: What is the long-term safety of opioids for the management of chronic pain?

## 2.2 Introduction

Opioids are some of the oldest medicines used today. Their use in acute pain following surgery or trauma and for pain relief at the end of life is well accepted. By contrast their use for long-term chronic pain is relatively recent and much more controversial. Despite this, there has been a huge increase in opioid prescribing in many Western countries over the last decade. The public health crisis of misuse of prescription opioids in North America has led to a focus on the clinical use of these medicines, in particular their use over prolonged periods for chronic pain.

Many people stop taking opioids relatively soon after initiation either because they do not provide sufficient pain relief or cause intolerable side effects. There are concerns regarding dependence and misuse when a person is taking opioids for a long time. However, there are a range of other serious harms and problems, including cognitive impairment, falls and fracture, sexual dysfunction, endocrine changes, immune dysfunction, depression, sleep apnoea, and heart attacks, that have been suggested to be associated with opioid use.

Between 2000 and 2014 the average length of continuous opioid prescription in the UK increased from 64 days to 102 days. As people are taking opioids for longer periods of time there is a need to understand more about the long-term harms associated with opioids. This evidence review will increase understanding of the long-term safety of opioid medicines and associated harms. It will also allow healthcare professionals and people taking opioids to have an informed discussion about long-term safety and harms with opioid medicines.

## 2.3 PICO table

For full details see the review protocol in appendix A.

**Table 16: PICO characteristics of review question**

| | |
|---|---|
| **Population** | People, aged 16 years and over, with chronic pain (whose pain management is not addressed by existing NICE guidance).<br>*Pain that persists or recurs for longer than 3 months.* |
| **Intervention(s)** | Oral or transdermal opioids (morphine, oxycodone, hydromorphone, buprenorphine, fentanyl, methadone, meptazinol, tapentadol, targinact, codeine, dihydrocodeine, tramadol, cocodamol, codydramol, pethidine) prescribed for chronic pain management for ≥6 months. |
| **Comparison(s)** | • Placebo<br>• no treatment/usual care<br>• non-comparative data |
| **Outcomes** | Serious adverse events:<br>• cognitive impairment<br>• fractures and falls<br>• sexual dysfunction/endocrine impairment<br>• immune dysfunction<br>• sleep apnoea |

| | |
|---|---|
| | • cardiovascular events<br>• all-cause mortality<br>• self-harm/suicide<br>• dependence<br>• depressive symptoms/mood disturbances.<br><br>Outcomes will be extracted at the longest time point up to 6 months, at the longest time point up to 1 year and at the longest time point after 1 year. |
| **Study design** | Systematic reviews<br>Randomised controlled trials<br>Observational studies (including cohorts, case series and case-control if no cohorts or case series are identified). Initially limited to n>5000 people receiving the intervention. If insufficient evidence identified, sample size threshold will be lowered to n>1000 for comparative data. |

When agreeing the protocol, the committee agreed that although these recommendations would be for people with chronic primary pain, the evidence base specifically for harms in this population was likely to be small to inform recommendations. The search was therefore covering all types of chronic pain so that evidence could be extrapolated as there was no reason to expect that harms would differ according to type of chronic pain.

# 2.4 Clinical evidence

## 2.4.1 Included studies

No randomised controlled trial evidence comparing opioids with placebo, no treatment or usual care for six months or longer was identified.

Three observational studies reporting non-comparative data were included in the review;[189, 190, 484] these are summarised in Table 17 below. Quality assessment of these studies is summarised in the study limitations table below (Table 18).

An overview of Cochrane reviews on adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain[196] was assessed for eligibility. This was excluded from the review as long-term opioid use was defined as two months or longer. The individual Cochrane reviews included in the overview were also screened for eligibility, but none were included in this review.

See also the study selection flow chart in appendix C and study evidence tables in appendix D.

## 2.4.2 Excluded studies

See the excluded studies list in appendix I.

### 2.4.3 Summary of clinical studies included in the evidence review

**Table 17: Summary of studies included in the evidence review**

| Study | Data source | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|---|
| Edlund 2007[190]<br><br>Retrospective cohort study<br><br>USA | South Central Veterans Affairs Health Care Network data warehouse | Chronic opioid use defined as ≥91 days' supply of prescribed opioid summed over one year (those with ≥151 days' supply were included in this review; n=10,387)<br><br>No comparator | N=15,160 veterans with chronic use of opioids for chronic non-cancer pain (majority arthritis and back pain)<br><br>Age:<br><40 years 4.2%<br>40-49 years 16.1%<br>50-59 years 35%<br>60+ years 44.6% | Abuse/dependence (ICD-9-CM codes 304.00-304.03, 304.70-304.73 and 305.50-305.53 within inpatient and outpatient records)<br><br>Follow up: 3 years<br><br>151-210 days' supply: 43/3275 (1.3%)<br>≥211 days' supply: 196/7112 (2.8%) | Days' supply of opioids during the year were not necessarily consecutive<br><br>1148 out of the total cohort had non-opioid substance abuse/ dependence during the year that they were recruited<br><br>People with opioid substance abuse disorder at baseline were excluded |
| Edlund 2010 (the Trends and Risks of Opioid Use for Pain TROUP study)[189]<br><br>Retrospective cohort study | Arkansas Medicaid files (serving a disadvantaged and vulnerable population) n=9,651<br><br>HealthCore Integrated | Chronic opioid use defined as at least 90 days' continuous use of opioids within a six-month period (those with >185 days' supply were included in this review; n=11,884)<br><br>No comparator | N=46,256 enrollees with chronic use of opioids for chronic non-cancer pain (majority back, joint, head and neck pain)<br><br>Age:<br>18-30 years 5.4%<br>31-40 years 17%<br>41-50 years 30.7% | Abuse/dependence derived from ICD-9-CM codes<br><br>Follow up: 12-54 months (HealthCore the mean of the post-index period was 818 days, and 1212 days in Arkansas Medicaid)<br><br>>185 days' supply: 696/11,884 (5.86%) | Data for Arkanas Medicaid files and HealthCore Integrated Research Database are combined<br><br>317 out of the total cohort had |

| Study | Data source | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|---|
| USA | Research Database (medical and pharmacy administrative claims and health plan eligibility data from five commercial health plans representing the West, Mid-West, and South-East) n=36,605 | | 51-64 years 32.3%<br>≥65 years 14.6% | | pre-index opioid substance abuse diagnosis and 1375 had non-opioid substance abuse diagnosis<br><br>Total days' supply exceeding the number of days in the period (183 days) suggested concurrent use of different opioid types |
| Ray 2016[484]<br><br>Retrospective cohort study<br><br>USA | Tennessee Medicaid files | Long-acting opioids (sustained release morphine, controlled release oxycodone, transdermal fentanyl and methadone) for >180 days; n=5584<br><br>Vs.<br><br>Anticonvulsants indicated for chronic pain (gabapentin, pregabalin, carbamazepine) or low-dose cyclic antidepressants | N=22,912 episodes of opioid therapy with a diagnosis of chronic pain (back, other musculoskeletal, abdominal, headache, other neurologic pain) in the past 90 days (majority back pain and other musculoskeletal pain)<br><br>Age 30-74 years<br>Mean (SD) = 47.9 (10.5) years | All-cause mortality<br><br>Follow up: patients left the cohort after 1 year without filling prescription, prescription for a different drug class, dying, not meeting inclusion-exclusion criteria or the end of study (14 years)<br><br>>180 days: 62/5584 (1.1%) | Patients could re-enter the cohort. 22,912 episodes of therapy: 20,405 unique patients<br><br>Data extracted for the opioids arm only, as the other drugs were not listed in the protocol as comparators. Studies comparing opioids to usual care where usual care involved |

| Study | Data source | Intervention and comparison | Population | Outcomes | Comments |
|---|---|---|---|---|---|
| | | | | | pharmacological therapy would be considered, but here patients taking anticonvulsants/ cyclic antidepressants were specifically selected as controls. |

See appendix D for full evidence tables.

### 2.4.4 Quality assessment of clinical studies included in the evidence review

**Table 18: Study limitations [Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist]**

| Study | Study objective | Study design | Study population | Intervention and co-intervention | Outcome measure | Statistical analysis | Results and conclusions | Competing interests and sources of support | Overall[a] |
|---|---|---|---|---|---|---|---|---|---|
| Edlund 2007[190] | Objective clearly stated | Retrospective cohort[b]<br><br>Data collected in >1 centre<br><br>Patients meeting the inclusion/ exclusion criteria were | Patient characteristics were described<br><br>Eligibility criteria were clearly stated<br><br>Unclear whether patients entered the | Intervention of interest reported but not clearly described (no description of which opioids were included/ routes of administration etc.) | Relevant outcome measures were established a priori<br><br>Unclear whether outcome assessors were blinded | Statistical tests were appropriate for the objectives of the study, but inappropriate for the purpose of this review (>151 days compared | Follow-up was long enough for outcome to occur<br><br>Losses to follow up not reported<br><br>The conclusions of the study | Sources of support for the study were reported but competing interests were not reported | HIGH |

| Study | Study objective | Study design | Study population | Intervention and co-intervention | Outcome measure | Statistical analysis | Results and conclusions | Competing interests and sources of support | Overall[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | recruited consecutively | study at a similar point in the disease (duration of pain not reported) | Additional interventions were not reported | to the intervention<br><br>Relevant outcomes were measured using partially appropriate objective methods | with 91-150 days rather than no opioid use) | were supported by the results but not relevant to this review | | |
| Edlund 2010[189] | Objective clearly stated | Retrospective cohort[b]<br><br>Data collected in >1 centre<br><br>Patients meeting the inclusion/exclusion criteria were recruited consecutively | Patient characteristics were described<br><br>Eligibility criteria were clearly stated<br><br>Unclear whether patients entered the study at a similar point in the disease (duration of pain not reported) | Intervention of interest was clearly described<br><br>Additional interventions were not clearly described (use of sedative/hypnotics only) | Relevant outcome measures were established a priori<br><br>Unclear whether outcome assessors were blinded to the intervention<br><br>Relevant outcomes were measured using | Statistical tests were appropriate for the objectives of the study, but inappropriate for the purpose of this review (>185 days compared with 91-160 days rather than no opioid use) | Follow-up was long enough for outcome to occur<br><br>Losses to follow up not reported<br><br>The conclusions of the study were supported by the results but not relevant to this review | Competing interests and sources of support were not reported | HIGH |

| Study | Study objective | Study design | Study population | Intervention and co-intervention | Outcome measure | Statistical analysis | Results and conclusions | Competing interests and sources of support | Overall[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | partially appropriate objective methods | | | | |
| Ray 2016[484] | Objective clearly stated | Retrospective cohort[b]<br><br>Data collected in >1 centre<br><br>Patients meeting the inclusion/exclusion criteria were recruited consecutively | Patient characteristics were described<br><br>Eligibility criteria were clearly stated but method of assessment inadequate (>90 days prescribed opioid use used to infer chronic pain)<br><br>Unclear whether patients entered the study at a similar point in the disease (duration of pain not reported) | Intervention of interest was clearly described<br><br>Additional interventions were not reported but patients left the cohort if they were prescribed a drug in a different class | Relevant outcome measures were established a priori<br><br>Unclear whether outcome assessors were blinded to the intervention<br><br>Relevant outcomes were measured using appropriate objective methods | Statistical tests were appropriate for the objectives of the study, but inappropriate for the purpose of this review (opioids compared with anticonvulsant/cyclic antidepressants rather than no opioid use) | Follow up was long enough for the outcome to occur<br><br>Losses to follow up not reported<br><br>The conclusions of the study were supported by the results but not relevant to this review | Competing interests and sources of support were reported | HIGH |

*(a) Options for risk of bias are low, moderate or high*

*(b) Data were extracted from a single arm, therefore studies were treated as case series for quality assessment*

## 2.5 Economic evidence

The committee agreed that health economic studies would not be relevant to this review question, and so were not sought.

## 2.6 Evidence statements

### 2.6.1 Clinical evidence statements

Evidence from three cohort studies reported long-term safety outcomes of opioids for chronic pain. Non-comparative data showed that the risk of opioid abuse/dependence ranged from 1.3% in those taking opioids for 151-210 days and 5.9% in those taking opioids for more than 185 days. The all-cause mortality risk in those taking opioids for more than 180 days was 1.1%. The evidence was considered to be at high risk of bias. One outcome was considered to be indirect as it was a composite measure of both abuse and dependence and the review outcome was dependence.

No evidence was identified for the outcomes of cognitive impairment, fractures and falls, sexual dysfunction/endocrine impairment, immune dysfunction, sleep apnoea, cardiovascular events, self-harm/suicide or depressive symptoms/mood disturbances.

# 3 Safety of gabapentinoids

## 3.1 Review question: What is the long-term safety of gabapentinoids for the management of chronic pain?

## 3.2 Introduction

Gabapentin and pregabalin are medicines that are used to treat epilepsy. The neural mechanisms of epilepsy and nerve damage pain have some commonality so the medicines are also prescribed for the treatment of neuropathic (nerve damage) pain such as pain after shingles, diabetes nerve pain and sciatica. They often considered together as 'gabapentinoids'.

There has been a large increase in prescribing of gabapentinoids in the UK over the last decade. Gabapentinoids affect fundamental neural processes. Central nervous system side effects are to be expected and include drowsiness, dizziness, unsteadiness and weight gain. There have been increasing concerns about the potential for misuse and abuse. Gabapentinoids, especially pregabalin, can produce feelings of relaxation, calmness and euphoria and they can enhance the euphoric effects of other drugs, especially opioids. In the UK, there has also been a large increase in the number of deaths in which use of pregabalin and gabapentin have been recorded on the death certificate. The Home Office has recently reclassified gabapentin and pregabalin as Schedule 3 controlled drugs.

In order to maintain appropriate access for those patients who do obtain substantial pain relief and to minimise misuse and abuse there is a need for a comprehensive understanding of the safety and harms of gabapentinoids. This review considers serious side effects and harms that have been reported with gabapentinoids. This information will allow healthcare professionals and people taking gabapentinoids to have an informed discussion about the long-term safety and harms associated with gabapentinoid medicines.

## 3.3 PICO table

For full details see the review protocol in appendix A.

**Table 19: PICO characteristics of review question**

| | |
|---|---|
| **Population** | People, aged 16 years and over, with chronic pain (whose pain management is not addressed by existing NICE guidance). Pain that persists or recurs for longer than 3 months. |
| **Interventions** | Gabapentinoids (gabapentin, pregabalin) prescribed for pain management. |
| **Comparisons** | Comparators:<br>• placebo<br>• each other<br>• non-comparative data |
| **Outcomes** | • serious adverse events:<br>• cognitive impairment<br>• gait disturbance/ataxia<br>• loss of balance<br>• all-cause mortality<br>• dependence<br>• weight gain<br>• rash |

| | |
|---|---|
| | • peripheral oedema<br>• tremor<br>• somnolence<br>Outcomes will be extracted at the longest time point up to 6 months, at the longest time point up to 1 year and at the longest time point after 1 year |
| **Study design** | Systematic reviews<br>Randomised controlled trials<br>Observational studies |

When agreeing the protocol, the committee agreed that although these recommendations would be for people with chronic primary pain, the evidence base specifically for harms in this population was likely to be small to inform recommendations. The search was therefore covering all types of chronic pain so that evidence could be extrapolated as there was no reason to expect that harms would differ according to type of chronic pain.

## 3.4 Clinical evidence

### 3.4.1 Included studies

No relevant clinical studies were identified.

See also the study selection flow chart in appendix C.

### 3.4.2 Excluded studies

See the excluded studies list in appendix I.

### 3.4.3 Summary of clinical studies included in the evidence review

No evidence identified.

### 3.4.4 Quality assessment of clinical studies included in the evidence review

No evidence identified.

## 3.5 Economic evidence

The committee agreed that health economic studies would not be relevant to this review question, and so were not sought.

## 3.6 Evidence statements

### 3.6.1 Clinical evidence statements

No relevant published evidence was identified.

# 4 The committee's discussion of the evidence

## 4.1 Interpreting the evidence

### 4.1.1 The outcomes that matter most

***Effectiveness of pharmacological treatments***

The committee considered pain reduction, quality of life, physical function, psychological distress and discontinuation due to adverse events to be critical outcomes for decision-making. Sleep and use of healthcare services were also considered important outcomes for decision-making. The critical and important outcomes agreed by the committee were adapted by consensus from relevant core outcome sets registered under the Core Outcome Measures in Effectiveness Trials (COMET) Initiative. This included the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations.

The included studies rarely reported sleep and use of healthcare services as outcomes but frequently reported all of the critical outcomes identified within this protocol.

For some of the interventions specified in the protocol, no relevant evidence for any of the outcomes was identified, including: paracetamol, steroids, an anaesthetics/steroid combination, opioids, ketamine and anti-psychotics.

***Safety of long-term use of opioids and gabapentinoids***

The evidence on adverse events associated with long-term opioid and gabapentinoid use for chronic pain was reviewed. Although recommendations were being made for people with chronic primary pain, the committee agreed that safety aspects would apply equally to all types of chronic pain and evidence could be extrapolated from the broader population where it was likely more data would be available.

Cognitive impairment, fractures and falls, sexual dysfunction/endocrine impairment, immune dysfunction, sleep apnoea, cardiovascular events, all-cause mortality, self-harm/suicide, dependence and depressive symptoms/mood disturbances were all identified by the committee as critical outcomes for decision making in the opioid review.

Cognitive impairment, gait disturbance/ataxia, loss of balance, all-cause mortality, dependence, weight gain, rash, peripheral oedema, tremor and somnolence were all identified by the committee as critical outcomes for decision making in the gabapentinoid review.

Other less serious side effects such as nausea and constipation were not included in the review as they tend to occur soon after initiating therapy and if not tolerable, would be more likely to cause discontinuation before six months.

No evidence was identified for cognitive impairment, fractures and falls, sexual dysfunction/endocrine impairment, immune dysfunction, sleep apnoea, cardiovascular events, self-harm/suicide, or depressive symptoms/mood disturbances in relation to opioids.

No evidence was identified for any long-term safety outcomes for gabapentinoids in the chronic pain population.

### 4.1.2 The quality of the evidence

***Effectiveness of pharmacological treatments***

The quality of the evidence for this review varied considerably between interventions. The majority of the evidence was very low or low quality, mainly due to risk of bias and imprecision. The majority of studies included within this review had a large dropout rate, resulting in a high risk of attrition bias. The majority of the evidence compared medications to placebo and there were few head-to-head drug trials. This applied to all comparisons throughout the review.

There was more evidence available to inform discussion of the use of antidepressants. Evidence was identified for all critical and important outcomes, although the evidence for SSRIs and SNRIs was generally of low to very low quality due to risk of bias, imprecision and inconsistency (SNRIs only). There was some slightly higher quality evidence for tricyclic antidepressants, with most outcomes ranging from moderate to low quality due to risk of bias, imprecision and inconsistency.

Evidence to inform committee discussion on the use of cannabinoids in people with chronic primary pain was of very low quality due to risk of bias and imprecision, based on one small study (40 participants) and was therefore considered insufficient evidence to inform a recommendation for or against the use of cannabinoids in this population..

There was some evidence available for other interventions suggesting a lack of benefit for anti-epileptics (specifically gabapentinoids), local anaesthetics, benzodiazepines and NSAIDs compared to placebo for chronic primary pain, although the evidence base was limited. For anti-epileptics there was evidence for all outcomes other than use of healthcare services and the quality varied from high to very low quality due to risk of bias and imprecision, however it was noted that the only evidence identified was for gabapentinoids and not for any other anti-epileptics. There was a smaller amount of evidence for local anaesthetics versus placebo, with evidence of low to very low quality due to risk of bias and imprecision for pain reduction, psychological distress and discontinuation due to adverse events. The quality of evidence for both NSAIDs and benzodiazepines was similar, with evidence ranging from moderate to low quality due to risk of bias and imprecision. There was evidence for all critical and important outcomes for NSAIDs, whereas evidence for benzodiazepines was limited to pain reduction, physical function and psychological distress. A head-to-head comparison of NSAIDs versus benzodiazepines included evidence for pain reduction, physical function and quality of life, most of which were of moderate quality due to risk of bias.

Where evidence were available, it was further discussed that the majority was at short term follow up only, and so the effectiveness of these medications in the long term was uncertain. The committee discussed the generalisability of the evidence to all people with chronic primary pain as the majority of the evidence identified was for women with fibromyalgia. Types of chronic primary pain were pooled for analysis, but where heterogeneity was present this was explored with subgroup analysis. This did not explain the heterogeneity. The committee therefore agreed that there was no reason not to consider evidence to be relevant

for all types of chronic primary pain. Furthermore where there was evidence of harm, the committee agreed there was good reason that this would apply irrespective of the condition, and so recommendations could be made across all chronic primary pain conditions. Where the committee thought there was reason to distinguish between chronic primary pain conditions, this is reflected in the recommendations.

***Safety of long-term opioids***

Non-comparative data were available from 3 retrospective cohort studies in the wider chronic pain population. The evidence for long-term safety of opioids was considered to be at high risk of bias due to insufficient details of the study population, background interventions and attrition rate. The composite outcome of both abuse and dependence was considered to be indirect as the review outcome was dependence and it was unclear from this which aspect was more affected by opioid use. No evidence was identified for opioids compared with placebo or no treatment/usual care.

***Safety of long-term gabapentinoids***

No evidence was identified for any long-term safety outcomes for gabapentinoids.

### 4.1.3 Benefits and harms

**Effectiveness of pharmacological treatments**

The evidence base in general showed limited benefit and some harms associated with pharmacological treatment of chronic primary pain. The exception was antidepressants, for which a larger evidence base showed treatment to be beneficial compared to placebo.

***Antidepressants***

Evidence showed a benefit of SNRIs, SSRIs and tricylic antidepressants for chronic primary pain. A small amount of evidence from 1 study with 32 participants also showed a benefit of tetracyclic antidepressants compared to placebo (for pain reduction and quality of life). However, this evidence was low quality and insufficient to inform recommendations.

Evidence for SNRIs versus placebo was based on 7 studies comparing duloxetine with placebo and showed long-term (over 3 months) benefit of duloxetine mainly in terms of improved quality of life, reduced psychological distress and improved sleep. Evidence identified no difference in pain or physical function, and a harm due to adverse events resulting in discontinuation. The majority of the evidence identified for tricyclic antidepressants compared amitriptyline with placebo. Evidence from 6 studies showed a benefit of tricyclic antidepressants for quality of life, pain, sleep and physical function, but no difference for psychological distress, and harm due to adverse events resulting in discontinuation. Evidence was mainly available for short-term follow-up (less than 3 months), with limited evidence available for long-term effectiveness. Evidence comparing SSRIs with placebo was based on 7 studies and showed a clinically important benefit of SSRIs (fluoxetine, paroxetine, citalopram and sertraline) for reducing pain and psychological distress, improving quality of life, and the discontinuation rate due to adverse events was lower compared to placebo. Evidence showed no difference for physical function or sleep.

Similarly to tricyclic antidepressants, evidence was SSRIs was mainly limited to short-term follow-up, with limited long-term evidence available.

The committee agreed that the evidence suggested that duloxetine, amitriptyline and SSRIs (fluoxetine, paroxetine, citalopram and sertraline) could be beneficial for critical outcomes related to chronic pain, such as quality of life, pain, physical function and psychological distress. No evidence was identified that compared the different antidepressant classes to each other and the committee agreed they could not assume one class to be more or less effective than another. The committee noted that duloxetine had a larger amount of long-term evidence of effectiveness. However, evidence showed a benefit of amitriptyline and SSRIs for pain whereas duloxetine did not demonstrate a benefit for pain in the long-term compared to placebo. The committee agreed that it was not possible to weigh up the benefits of each antidepressant class without head-to-head comparisons, and they could not recommend one class over another.

The committee also acknowledged that some uncertainty existed across the effect sizes seen within the evidence, with some confidence intervals crossing the MID thresholds or line of no effect. However, despite the uncertainty, the committee considered that benefits were shown across most of the critical outcomes and the evidence base was large enough to justify a recommendation. The committee therefore agreed to recommend consideration of these treatments for managing chronic primary pain. The committee agreed that the decision of which class of antidepressants to try should be based on a fully informed discussion with the person with chronic primary pain, taking account of the person's additional symptoms and the side effect profiles of these drugs and that the risk of withdrawal symptoms should be considered when prescribing these drugs.

The committee noted that none of the antidepressants have marketing authorisations for chronic primary pain, however they noted that there were no licensed alternatives and agreed that in their experience, these medications were already used in practice. It was considered that doses for SNRIs and SSRIs should be as per the doses for depression. The doses used for amitriptyline in the review varied from as low as 5mg demonstrating benefit. Therefore the committee agreed that this should be started at the lowest possible dose and titrated up if required. They were aware of a number of precautions listed in the SPC, as well as the Medicines and Healthcare products Regulatory Agency safety guidance on SSRIs and SNRIs, including increased risk of suicide in those with a history of suicide-related events, or those with a significant degree of suicidal ideation, increased risk of withdrawal reactions and concerns regarding use during pregnancy. It was agreed that these factors should form part of the decision between risks and benefits and appropriateness for the individual when considering these drugs.The committee discussed that there was no evidence for young people aged 16-17. They considered that due to the risk of side effects from these medicines, if their use was being considered in this age group, specialist advice should be sought.

If antidepressants were not effective, it was agreed that in line with safe prescribing practice, their use should not be continued. A recommendation was included to cross refer to the NICE guideline for depression in adults for guidance on stopping or reducing antidepressants.

***Cannabis-based medicinal products***

Evidence from 1 small study comparing cannabinoids with placebo showed a clinically important harm of cannabinoids for chronic primary pain in terms of greater discontinuation due to adverse events. The committee did not consider the evidence sufficient to inform recommendations, with results for pain reduction and quality of life from the same study reported insufficiently to be included within the analysis. They agreed that further research on the clinical effectiveness of cannabinoids for chronic primary pain would be beneficial, however they were aware of NICE's guideline on cannabis-based medicinal products, which recommended further research for cannabidiol in people with fibromyalgia and recommended against the use of nabilone, dronabinol, THC (delta-9-tetrahydrocannabinol) and a combination of cannabidiol (CBD) with THC. It was decided that this sufficiently covered guidance and future research for people with chronic primary pain.

***Opioids***

No evidence was identified for the clinical effectiveness of opioids. Evidence from non-randomised studies on the long-term use (more than 6 months) of opioids for chronic pain suggested an increased risk of dependence. There were limitations in this evidence, but there was no evidence from randomised trials on the efficacy of opioids for chronic primary pain, and it was agreed a priori when setting the protocol that evidence could be extrapolated from the broader chronic pain population and that non-randomised evidence was the most likely study design reporting long-term harms. This non-comparative data reported the overall all-cause mortality risk in people with a wide range of chronic pain conditions taking opioids for more than 180 days. The committee noted that this study was based on a heterogeneous population. Without any background/expected mortality data reported they were unable to draw any meaningful conclusions about long-term opioid safety from this.

The long-term risk of opioid abuse/dependence was greater in those taking opioids for more than 185 days when compared to those taking for 151-210 days. The committee considered that the reported value was likely to be an underestimate of the true incidence, as dependence is not often coded as such when it is suspected, and some clinicians only confirm a diagnosis of dependence in collaboration with the person concerned.

Based on their experience, the committee agreed that even short-term use of opioids could be harmful for a chronic condition. The lack of evidence for effectiveness of opioids, along with evidence of long-term harm, persuaded the committee to recommend against opioid use for people with chronic primary pain.

***NSAIDs***

Evidence showed no difference in pain reduction, quality of life, psychological distress or discontinuation between NSAIDs and placebo. Evidence from one small study (31 participants) showed that people treated with NSAIDs reported more difficulty in physical function compared to placebo, consistent with the general trend of a lack of effect of NSAIDs in chronic primary pain. The committee agreed that the lack of evidence of the effectiveness of NSAIDs, coupled with evidence of harm, was sufficient to recommend against its use in clinical practice.

***Benzodiazepines***

Evidence comparing benzodiazepines with placebo showed a worse outcome in people receiving benzodiazepines in relation to physical function. The committee considered this

alongside evidence showing no difference in pain reduction or psychological distress, and the lack of evidence on long-term effectiveness. The committee also considered the addictive properties of this group of drugs in the long term taken alongside this evidence meant they recommended against the use of benzodiazepines for chronic primary pain.

***Antiepileptics***

All evidence identified was comparing gabapentinoids to placebo. Seven studies demonstrated mainly no clinically important difference between gabapentinoids and placebo for quality of life, pain reduction, psychological distress and physical function. Furthermore, evidence at less than 3 months showed a clinically important harm of gabapentinoids for discontinuation due to adverse events. No evidence was identified from non-randomised studies on the long-term safety of gabapentinoids.

In the short-term (less than 3 months), gabapentinoids generally showed no benefit in terms of pain reduction, quality of life, physical function and psychological distress. However, one outcome showed a benefit of gabapentinoids in the short-term for pain reduction, but this was very low quality evidence and was based on a much smaller sample size than other outcomes showing no benefit for pain.

Longer-term evidence (over 3 months) also showed no clinically important benefit of gabapentinoids in terms of pain reduction, quality of life, physical function, psychological distress and sleep. For pain reduction, moderate quality evidence from 1 study with 1,902 participants showed no benefit of gabapentinoids compared to placebo (in people with fibromyalgia). Conversely, low quality evidence from 2 studies with a total of 59 participants showed a benefit of gabapentinoids for chronic pelvic pain. The committee discussed that the authors of the large study report benefits in terms of pain in their study conclusions, however the magnitude of this change was small, and did not meet the MID for clinical importance. Nor did it meet any of the other published MID values that the committee discussed but discarded (see methods chapter for full discussion of MIDs). Analysis of other outcomes from this large study demonstrated no difference between gabapentinoids and placebo for quality of life, psychological distress and sleep.

The committee discussed the possibility that gabapentinoids may be beneficial in some subgroups of chronic primary pain such as chronic pelvic pain. However, the committee agreed that the evidence generally showed a similar effect of medicines across chronic primary pain conditions. They also noted that the risk of harm would not be specific to any particular type of chronic primary pain.

Evidence based on one study also compared gabapentinoids to SNRIs. This evidence was very low quality, based on a small sample size, and only had a follow up of 4 weeks. This evidence was therefore not sufficient to make strong conclusions about the effectiveness of each drug class compared to each other. However, the evidence showed a benefit of SNRIs for pain reduction and no clinically important difference between the two drugs for quality of life and psychological distress.

The committee agreed that overall, there was insufficient evidence to justify the routine use of gabapentinoids for chronic primary pain. Furthermore, there was no evidence identified for any other antiepileptics included in the review protocol. The committee took into account their own experience of harms related to use of gabapentinoids, along with drug monographs in the British National Formulary and the summary of product characteristics and the risk of

abuse and dependence highlighted by the MHRA notification of the reclassification of gabapentinoids as a class C substance controlled under the Misuse of Drugs Act 1971 and scheduled under the Misuse of Drugs Regulations 2001 as schedule 3. They were also aware of the risks of taking valproate during pregnancy. The committee therefore decided that the risk of harms alongside the lack of evidence for effectiveness for managing chronic primary pain were sufficient to recommend against the use of anti-epileptics, including gabapentinoids for this population. They were aware that gabapentinoids are recommended for neuropathic pain and expert opinion within the committee suggested that complex regional pain syndrome (CRPS) may have a neuropathic pain element. Based on the expert opinion of some members, the committee decided to make a research recommendation for the use of gabapentinoids for CRPS, a population that was underrepresented in RCTs, to inform future practice.

***Local anaesthetics***

Evidence from 2 small studies (both for topical lidocaine) showed no difference between local anaesthetics and placebo in psychological distress and discontinuation and harm of local anaesthetics in relation to pain reduction. Due to the lack of evidence on its effectiveness, the committee decided to recommend against the use of local anesthetics. They agreed by consensus that this should apply equally for topical and intravenous use, as there was no reason to suggest intravenous use would be more beneficial for chronic primary pain. However, the committee noted that evidence across the guideline for CRPS was limited, and the expert opinion of some committee members suggested that response to local anaesthetics in this population may vary due to the neuropathic element of the condition. The committee therefore agreed that an exception to this recommendation is the use of local anaesthetics in clinical trials for CRPS.

***Paracetamol, corticosteroids, local anaesthetics corticosteroid combinations, ketamine and antipsychotics***

No evidence was identified for paracetamol, ketamine, corticosteroids, anaesthetic corticosteroid combinations, or antipsychotics. The committee agreed that not commenting on these medicines could result in their continued use in practice, which would be inappropriate given the lack of evidence. From their own experience, and from the summaries of product characteristics, the committee agreed that these medicines have possible harms. They agreed that it was important to highlight both the lack of evidence and possible associated harms, and so recommended against the use of these treatments.

***Withdrawing medication***

The committee were aware of evidence to suggest that reducing dose or stopping of some medicines may result in withdrawal symptoms. In light of the 'do not use' recommendations for a number of medicines, the committee made a recommendation to highlight the need to be aware of the risk of withdrawal symptoms when stopping medicines (including opioids, gabapentinoids and benzodiazepines) and also when considering prescribing gabapentinoids as part of a clinical trial or antidepressants.

## 4.2 Cost effectiveness and resource use

No relevant economic evidence was included for this question. Two studies were identified but excluded due to methodological limitations.

Unit costs were presented to the committee for consideration, based on the interventions identified in the clinical review. Unit costs can vary depending on the drug. Examples of prescribable medications with lower costs include benzodiazepines or some types of antidepressants. The cost involved to the NHS is not just the cost of the drugs themselves, but the monitoring involved, as well as the potential for adverse events and even dependence.

Pharmacological management is just one of the many options that can be used in practice to help patients manage their chronic pain. The committee acknowledged the high level of expenditure currently attributable to the use of drug treatments. Following the clinical review, the committee were of the view that the use of such interventions should ideally be reduced from levels in current practice.

The main class of interventions for which there was a signal of clinical benefit was antidepressants. The commitee agreed that these showed benefit in reducing pain, and also other outcomes such as quality of life. The committee decided to make a recommendation to consider antidepressants for people with chronic primary pain. The recommendation could not be stronger because of the lack of health economic evidence.

The committee agreed that overall, there was insufficient clinical evidence to justify the routine use of gapabentinoids for managing chronic primary pain, and made a recommendation against the use of gapabentinoids, unless in a clinical trial for CRPS.

The committee discussed the use of opioids at length. No clinical evidence was identified on the effectiveness of opioids in chronic primary pain, but some evidence on the risk of dependence from long term use was identified. The committee discussed that longer term use can lead to high costs of treating associated side effects. The committee therefore concluded, taking into account the balance of benefits and harms based on their own experience and data they were aware of, that opioids should not be used for the management of chronic primary pain.

The committee also made 'do not use' recommendations for drugs where there was no or very little evidence in the chronic primary pain population, and where they agreed new research would not change conclusions given the drugs have been around for many years and new research is unlikely.

Overall, the resource impact from the recommendations made for antidepressants in combination with the recommendations on drugs that should not be used are still likely to have a resource impact in the short term, as it is acknowledged that short term resources may be increased whilst helping people to stop their long-term use of opioids and gabapentinoids. Furthermore, it may be difficult to get people to agree that they should discontinue medications, so the extent to which practice will change for drugs where 'do not use' recommendations were made is unclear. Additionally, there is variation in the unit costs of antidepressants, and SNRIs are slightly more expensive than other types such as trycyclic antidepressants. However this does depend on dose. Also new uptake may be modest as

there is already some use of antidepressants, and the recommendation is only a 'consider' recommendation. However in the longer term the recommendations made should reduce the use of pharmacological interventions in the management of chronic primary pain. It was also suggested that there could be further savings where potential harms are avoided through the reduced use of opioids and gabapentinoids. This could have wider benefits both to an individual and to other sectors outside healthcare, for example through people returning to the workforce.

## 4.3 Other factors the committee took into account

The committee agreed that where there was evidence of harm it is reasonable to consider that these consequences of the medicines will apply across chronic primary pain conditions.

It was noted that the medicines considered within this review do not have a UK marketing authorisation for chronic primary pain, and are used off license. The committee were cognisant of the British National Formulary (BNF) monographs for opioids, gabapentin and pregabalin, including the cautions and side effects reported in the general population. They were also aware of a recent review by Public Health England 'Dependence and withdrawal associated with some prescribed medicines' (2019). In particular, the report highlighted that apart from antidepressants, 'medications reviewed are all licensed and indicated for (usually) short-term treatment of acute conditions'. The report also highlighted the problems with inappropriate limiting of these medicines, and in conjuction with the BNF and summary of product characteristics (SPC) led the committee to recommend being aware of the problems associated with withdrawing opioids, gabapentinoids and benzodiazepines.

The committee were aware of a large body of cohort study literature which did not meet the criteria for inclusion in the review of opioid safety. They also acknowledged that the evidence base for harms is much more extensive where outcomes are measured at less than 6 months. However this review was intended to capture outcomes from long-term use of opioids, so studies which only reported outcomes at less than 6 months did not meet the inclusion criteria.

The committee noted the potential for toxicity in overdose with venlafaxine during consideration of the Medicines and Healthcare products Regulatory Agency safety guidance on SSRIs and SNRIs. No evidence was identified for venlafaxine in the review, therefore the committee made no specific recommendation related to this drug. However, it was determined that the recommendation to consider an antidepressant such as duloxetine would ensure that if an SNRI were the preferered class of antidepressant, it would be prescribed over venlafaxine.

The committee discussed that it is often reported that people with chronic primary pain may be more intolerant or sensitive to drugs, perhaps due to central sensitisation and it may be helpful to discuss this with the individual before the decision to prescribe.

The committee highlighted the importance of shared decision making, including discussion about the potential risk of dependence and monitoring. It was considered that good practice points from other guidelines such as NG46 Controlled drugs: safe use and management also inform the use of medications recommended in this guideline. The committee were also aware of the development of a NICE guideline on safe prescribing and withdrawal management.

# References

1. Abdel Shaheed C, Maher CG, Williams KA, Day R, McLachlan AJ. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: A systematic review and meta-analysis. JAMA Internal Medicine. 2016; 176(7):958-968

2. AbdelHafeez MA, Reda A, Elnaggar A, El-Zeneiny H, Mokhles JM. Gabapentin for the management of chronic pelvic pain in women. Archives of Gynecology and Obstetrics. 2019; 21:21

3. Aboumarzouk OM, Nelson RL. Pregabalin for chronic prostatitis. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD009063. DOI: 10.1002/14651858.CD009063.pub2.

4. Achariyapota V, Titapant V. Relieving perineal pain after perineorrhaphy by diclofenac rectal suppositories: a randomized double-blinded placebo controlled trial. Journal of the Medical Association of Thailand. 2008; 91(6):799-804

5. Acuna C. Duloxetine for the treatment of fibromyalgia. Drugs of Today. 2008; 44(10):725-734

6. Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. Journal of Pain and Symptom Management. 2006; 31(5):465-476

7. Afilalo M, Morlion B. Efficacy of tapentadol ER for managing moderate to severe chronic pain. Pain Physician. 2013; 16(1):27-40

8. Agarwal MM, Elsi Sy M. Gabapentenoids in pain management in urological chronic pelvic pain syndrome: Gabapentin or pregabalin? Neurourology and Urodynamics. 2017; 36(8):2028-2033

9. Ahmed M, Aamir R, Jishi Z, Scharf MB. The effects of milnacipran on sleep disturbance in fibromyalgia: A randomized, double-blind, placebo-controlled, two-way crossover study. Journal of Clinical Sleep Medicine. 2016; 12(1):79-86

10. Ahmedani BK, Peterson EL, Wells KE, Lanfear DE, Williams LK. Policies and events affecting prescription opioid use for non-cancer pain among an insured patient population. Pain Physician. 2014; 17(3):205-216

11. Aiyer R, Gulati A, Gungor S, Bhatia A, Mehta N. Treatment of chronic pain with various buprenorphine formulations: A systematic review of clinical studies. Anesthesia and Analgesia. 2018; 127(2):529-538

12. Albazaz R, Wong YT, Homer-Vanniasinkam S. Complex regional pain syndrome: A review. Annals of Vascular Surgery. 2008; 22(2):297-306

13. Albertoni Giraldes AL, Salomao R, Leal PD, Brunialti MK, Sakata RK. Effect of intravenous lidocaine combined with amitriptyline on pain intensity, clinical manifestations and the concentrations of IL-1, IL-6 and IL-8 in patients with

fibromyalgia: A randomized double-blind study. International Journal of Rheumatic Diseases. 2016; 19(10):946-953

14. Alford DP. Chronic back pain with possible prescription opioid misuse. JAMA. 2013; 309(9):919-925

15. Allan L, Hays H, Jensen NH, de Waroux BL, Bolt M, Donald R et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ. 2001; 322(7295):1154-1158

16. Allegri N, Mennuni S, Rulli E, Vanacore N, Corli O, Floriani I et al. Systematic Review and Meta-Analysis on Neuropsychological Effects of Long-Term Use of Opioids in Patients With Chronic Noncancer Pain. Pain Practice. 2019; 19(3):328-343

17. Altman RD, Smith HS. Opioid therapy for osteoarthritis and chronic low back pain. Postgraduate Medicine. 2010; 122(6):87-97

18. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia--a randomized, double-blind, placebo-controlled study. European Journal of Pain. 2000; 4(1):27-35

19. Andreae MH, Andreae DA. Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery. Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD007105. DOI: 10.1002/14651858.CD007105.pub2.

20. Andrews JC. Vulvodynia interventions-systematic review and evidence grading. Obstetrical and Gynecological Survey. 2011; 66(5):299-315

21. Annemans L. Pharmacoeconomic impact of adverse events of long-term opioid treatment for the management of persistent pain. Clinical Drug Investigation. 2011; 31(2):73-86

22. Anonymous. Complex regional pain syndrome type 1. Some treatments assessed versus placebo, limited efficacy. Prescrire International. 2009; 18(104):267-271

23. Anonymous. Duloxetine effective for fibromyalgia in some women. Journal of Family Practice. 2006; 55(5):382

24. Anonymous. Fentanyl (Fentora). CADTH Common drug review. Clinical review report. Ottawa. Canadian Agency for Drugs and Technologies in Health, 2017. Available from: https://www.cadth.ca/fentanyl-buccal

25. Anonymous. Oral morphine eases chronic non-cancer pain, with little risk of addiction. American Journal of Health-System Pharmacy. 1996; 53(8):836-838

26. Anonymous. Prednisolone effective short-term for complex regional pain syndrome. South African Family Practice. 2006; 48(6):12

27. Anothaisintawee T, Attia J, Nickel JC, Thammakraisorn S, Numthavaj P, McEvoy M et al. Management of chronic prostatitis/chronic pelvic pain syndrome: A systematic review and network meta-analysis. JAMA. 2011; 305(1):78-86

28. Apolone G, Corli O, Negri E, Mangano S, Montanari M, Greco MT et al. Effects of transdermal buprenorphine on patients-reported outcomes in cancer patients: results from the Cancer Pain Outcome Research (CPOR) Study Group. Clinical Journal of Pain. 2009; 25(8):671-682

29. Arai T, Kashimoto Y, Ukyo Y, Tominaga Y, Imanaka K. Two placebo-controlled, randomized withdrawal studies to evaluate the fentanyl 1 day patch in opioid-naive patients with chronic pain. Current Medical Research and Opinion. 2015; 31(12):2207-2218

30. Argoff C, Arnstein P, Stanos S, Robinson CY, Galer BS, Gould E et al. Relationship between change in pain intensity and functional outcomes in patients with chronic pain receiving twice daily extended-release hydrocodone bitartrate. Journal of Opioid Management. 2015; 11(5):417-424

31. Arnér S, Meyerson BA. Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. Pain. 1988; 33(1):11-23

32. Arnold L, Mease P, Silverman S. Pregabalin: an alpha2-delta (alpha2-delta) ligand for the management of fibromyalgia. American Journal of Managed Care. 2010; 16(5 Suppl.):S138-143

33. Arnold LM. Duloxetine and other antidepressants in the treatment of patients with fibromyalgia. Pain Medicine. 2007; 8(Suppl 2):S63-74

34. Arnold LM, Arsenault P, Huffman C, Patrick J, Messig M, Chew M et al. Corrections to: Once-daily controlled-release pregabalin in the treatment of patients with fibromyalgia: a phase III, double-blind, randomized withdrawal, placebo-controlled study. Current Medical Research and Opinion. 2017; 33(4):795-796

35. Arnold LM, Arsenault P, Huffman C, Patrick JL, Messig M, Chew ML et al. Once daily controlled-release pregabalin in the treatment of patients with fibromyalgia: a phase III, double-blind, randomized withdrawal, placebo-controlled study. Current Medical Research and Opinion. 2014; 30(10):2069-2083

36. Arnold LM, Choy E, Clauw DJ, Oka H, Whalen E, Semel D et al. An evidence-based review of pregabalin for the treatment of fibromyalgia. Current Medical Research and Opinion. 2018; 34(8):1397-1409

37. Arnold LM, Clauw D, Wang F, Ahl J, Gaynor PJ, Wohlreich MM. Flexible dosed duloxetine in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. Journal of Rheumatology. 2010; 37(12):2578-2586

38. Arnold LM, Clauw DJ, Wohlreich MM, Wang F, Ahl J, Gaynor PJ et al. Efficacy of duloxetine in patients with fibromyalgia: pooled analysis of 4 placebo-controlled clinical trials. Primary Care Companion to the Journal of Clinical Psychiatry. 2009; 11(5):237-244

39. Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE, Jr. et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis and Rheumatism. 2007; 56(4):1336-1344

40. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE, Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. American Journal of Medicine. 2002; 112(3):191-197

41. Arnold LM, Hudson JI, Wang F, Wohlreich MM, Prakash A, Kajdasz DK et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with versus without major depressive disorder. Clinical Journal of Pain. 2009; 25(6):461-468

42. Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis and Rheumatism. 2004; 50(9):2974-2984

43. Arnold LM, Michael Gendreau R, Palmer RH, Gendreau JF, Wang Y. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: Results of a randomized, double-blind, placebo-controlled trial. Arthritis and Rheumatism. 2010; 62(9):2745-2756

44. Arnold LM, Pritchett YL, D'Souza DN, Kajdasz DK, Iyengar S, Wernicke JF. Duloxetine for the treatment of fibromyalgia in women: pooled results from two randomized, placebo-controlled clinical trials. Journal of Women's Health. 2007; 16(8):1145-1156

45. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain. 2005; 119(1-3):5-15

46. Arnold LM, Russell IJ, Diri EW, Duan WR, Young JP, Jr., Sharma U et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. Journal of Pain. 2008; 9(9):792-805

47. Arnold LM, Sarzi-Puttini P, Arsenault P, Khan T, Bhadra Brown P, Clair A et al. Efficacy and safety of pregabalin in patients with fibromyalgia and comorbid depression taking concurrent antidepressant medication: A randomized, placebo-controlled study. Journal of Rheumatology. 2015; 42(7):1237-1244

48. Arnold LM, Schikler KN, Bateman L, Khan T, Pauer L, Bhadra-Brown P et al. Safety and efficacy of pregabalin in adolescents with fibromyalgia: a randomized, double-blind, placebo-controlled trial and a 6-month open-label extension study. Pediatric Rheumatology Online Journal. 2016; 14(1):46

49. Arnold LM, Whitaker S, Hsu C, Jacobs D, Merante D. Efficacy and safety of mirogabalin for the treatment of fibromyalgia: results from three 13-week randomized, double-blind, placebo- and active-controlled, parallel-group studies and a 52-week open-label extension study. Current Medical Research and Opinion. 2019; 35(10):1825-1835

50. Arnold LM, Zhang S, Pangallo BA. Efficacy and safety of duloxetine 30 mg/d in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. Clinical Journal of Pain. 2012; 28(9):775-781

51. Ataoglu S, Ataoglu A, Erdogan F, Sarac J. Comparison of paroxetine, amitriptyline in the treatment of fibromyalgia. Turkish Journal of Medical Sciences. 1997; 27(6):535-539

52. Atli A, Theodore BR, Turk DC, Loeser JD. Intrathecal opioid therapy for chronic nonmalignant pain: a retrospective cohort study with 3-year follow-up. Pain Medicine. 2010; 11(7):1010-1016

53. Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: A systematic review and meta-analysis of randomized controlled trials. Pain Physician. 2017; 20(6):E755-E796

54. Azari P, Lindsay DR, Briones D, Clarke C, Buchheit T, Pyati S. Efficacy and safety of ketamine in patients with complex regional pain syndrome: a systematic review. CNS Drugs. 2012; 26(3):215-228

55. Baillargeon J, Raji MA, Urban RJ, Lopez DS, Williams SB, Westra JR et al. Opioid-Induced Hypogonadism in the United States. Mayo Clinic Proceedings: Innovations, Quality and Outcomes. 2019; 3(3):276-284

56. Baldini A, Von Korff M, Lin EH. A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. Primary Care Companion to CNS Disorders. 2012; 14(3)

57. Banta-Green CJ, Von Korff M, Sullivan MD, Merrill JO, Doyle SR, Saunders K. The prescribed opioids difficulties scale: a patient-centered assessment of problems and concerns. Clinical Journal of Pain. 2010; 26(6):489-497

58. Bartoli A, Michna E, He E, Wen W. Efficacy and safety of once-daily, extended-release hydrocodone in individuals previously receiving hydrocodone/acetaminophen combination therapy for chronic pain. Postgraduate Medicine. 2015; 127(1):5-12

59. Barutell C, Camba A, Gonzalez-Escalada JR, Rodriguez M, Opioid Group of the Spanish Society for the Study of P. High dose transdermal buprenorphine for moderate to severe pain in spanish pain centres--a retrospective multicenter safety and efficacy study. Pain Practice. 2008; 8(5):355-361

60. Bateman L, Palmer RH, Trugman JM, Lin Y. Results of switching to milnacipran in fibromyalgia patients with an inadequate response to duloxetine: a phase IV pilot study. Journal of Pain Research. 2013; 6:311-318

61. Beaulieu AD, Peloso P, Bensen W, Clark AJ, Watson CP, Gardner-Nix J et al. A randomized, double-blind, 8-week crossover study of once-daily controlled-release tramadol versus immediate-release tramadol taken as needed for chronic noncancer pain. Clinical Therapeutics. 2007; 29(1):49-60

62. Bell GS, Mula M, Sander JW. Suicidality in people taking antiepileptic drugs: What is the evidence? CNS Drugs. 2009; 23(4):281-292

63. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. American Journal of Medicine. 2003; 114(7):537-545

64. Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis and Rheumatism. 2005; 53(4):519-527

65. Benyamin RM, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. Pain Physician. 2009; 12(1):137-157

66. Berger A, Dukes E, McCarberg B, Liss M, Oster G. Change in opioid use after the initiation of gabapentin therapy in patients with postherpetic neuralgia. Clinical Therapeutics. 2003; 25(11):2809-2821

67. Berger A, Sadosky A, Dukes E, Edelsberg J, Oster G. Use of pregabalin in patients with painful neuropathic disorders under the care of general practitioners in the U.K. Pain Practice. 2009; 9(1):18-34

68. Berger RE. Re: Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. Journal of Urology. 2011; 185(4):1302-1303

69. Berry H, Bloom B, Hamilton EB, Swinson DR. Naproxen sodium, diflunisal, and placebo in the treatment of chronic back pain. Annals of the Rheumatic Diseases. 1982; 41(2):129-132

70. Bhadra P, Petersel D. Medical conditions in fibromyalgia patients and their relationship to pregabalin efficacy: pooled analysis of Phase III clinical trials. Expert Opinion on Pharmacotherapy. 2010; 11(17):2805-2812

71. Bialas P, Maier C, Klose P, Hauser W. Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and meta-analysis of open-label extension trials with a study duration >=26 weeks. European Journal of Pain. 2020; 24(2):265-278

72. Biasi G, Manca S, Manganelli S, Marcolongo R. Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo. International Journal of Clinical Pharmacology Research. 1998; 18(1):13-19

73. Bidari A, Moazen-Zadeh E, Ghavidel-Parsa B, Rahmani S, Hosseini S, Hassankhani A. Comparing duloxetine and pregabalin for treatment of pain and depression in women with fibromyalgia: an open-label randomized clinical trial. Daru: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2019; 14:14

74. Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R. A randomized study to demonstrate noninferiority of once-daily OROS hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain. Pain Practice. 2010; 10(5):404-415

75. Birke H, Ekholm O, Hojsted J, Sjogren P, Kurita GP. Chronic Pain, Opioid Therapy, Sexual Desire, and Satisfaction in Sexual Life: A Population-Based Survey. Pain Medicine. 2018; 02:1132–1139

76. Birke H, Ekholm O, Sjogren P, Fredheim O, Clausen T, Skurtveit S. Tramadol use in Norway: A register-based population study. Pharmacoepidemiology and Drug Safety. 2019; 28(1):54-61

77. Birse F, Derry S, Moore RA. Phenytoin for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD009485. DOI: 10.1002/14651858.CD009485.pub2.

78. Birthi P, Nagar VR, Nickerson R, Sloan PA. Hypogonadism associated with long-term opioid therapy: A systematic review. Journal of Opioid Management. 2015; 11(3):255-278

79. Bogetto F, Ferro G, Maina G, Gandolfo S. Amisulpride vs paroxetine in the treatment of burning mouth syndrome (BMS). Biological Psychiatry. 1997; 42(Suppl 1):27s

80. Bohme K, Likar R. Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain. A randomised, double-blind, placebo-controlled study. The pain clinic. 2004; 15(2):193-202

81. Bohnert AS, Logan JE, Ganoczy D, Dowell D. A detailed exploration into the association of prescribed opioid dosage and overdose deaths among patients with chronic pain. Medical Care. 2016; 54(5):435-441

82. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011; 305(13):1315-1321

83. Boland JW, McWilliams K, Ahmedzai SH, Pockley AG. Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: A systematic literature review. British Journal of Cancer. 2014; 111(5):866-873

84. Bradley LA, Wohlreich MM, Wang F, Gaynor PJ, Robinson MJ, D'Souza DN et al. Pain response profile of patients with fibromyalgia treated with duloxetine. Clinical Journal of Pain. 2010; 26(6):498-504

85. Branco JC, Zachrisson O, Perrot S, Mainguy Y. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. Journal of Rheumatology. 2010; 37(4):851-859

86. Breuer AJ, Mainka T, Hansel N, Maier C, Krumova EK. Short-term treatment with parecoxib for complex regional pain syndrome: a randomized, placebo-controlled double-blind trial. Pain Physician. 2014; 17(2):127-137

87. Broglio K, Pergolizzi J, Kowalski M, Lynch SY, He E, Wen W. Efficacy and safety of once-daily extended-release (ER) hydrocodone in individuals previously receiving ER morphine for chronic pain. Pain Practice. 2017; 17(3):382-391

88. Brown CS, Bachmann GA, Bachour C, Rawlinson L, Wan J, Foster DC. A randomized controlled trial of gabapentin in provoked vulvodynia: Racial differences. Journal of Lower Genital Tract Disease. 2017; 21(4 Supplement 1):S25

89. Brown CS, Bachmann GA, Wan J, Foster DC. Gabapentin for the treatment of vulvodynia: A randomized controlled trial. Obstetrics and Gynecology. 2018; 131(6):1000-1007

90. Brown CS, Franks AS, Wan J, Ling FW. Citalopram in the treatment of women with chronic pelvic pain: an open-label trial. Journal of Reproductive Medicine. 2008; 53(3):191-195

91. Brown CS, Wan J, Bachmann G, Rosen R. Self-management, amitriptyline, and amitripyline plus triamcinolone in the management of vulvodynia. Journal of Women's Health. 2009; 18(2):163-169

92. Brown RL, Fleming MF, Patterson JJ. Chronic opioid analgesic therapy for chronic low back pain. Journal of the American Board of Family Practice. 1996; 9(3):191-204

93. Bruera E. Treatment for chronic pain in patients with advanced cancer [NCT00003687]. 2003. Available from: https://clinicaltrials.gov/ct2/show/record/NCT00003687 Last accessed: 09/07/2018.

94. Brutcher RE, Kurihara C, Bicket MC, Moussavian-Yousefi P, Reece DE, Solomon LM et al. Compounded topical pain creams to treat localized chronic pain: A randomized controlled trial. Annals of Internal Medicine. 2019; 170(5):309-318

95. Burgess FW. Opioid therapy for chronic painful conditions. Medicine and Health, Rhode Island. 2001; 84(10):323-326

96. Burgstaller JM, Jenni BF, Steurer J, Held U, Wertli MM. Treatment efficacy for non-cardiovascular chest pain: a systematic review and meta-analysis. PloS One. 2014; 9(8):e104722

97. Burkill SM, Montgomery S, Lofling L, Kockum I, Piehl F, Strid P et al. Pain and painkiller use among multiple sclerosis patients in Sweden. Pharmacoepidemiology and Drug Safety. 2017; 26(Suppl 2):634

98. Busse JW, Wang L, Kamaleldin M, Craigie S, Riva JJ, Montoya L et al. Opioids for chronic noncancer pain: A systematic review and meta-analysis. JAMA. 2018; 320(23):2448-2460

99. Buynak R, Rappaport SA, Rod K, Arsenault P, Heisig F, Rauschkolb C et al. Long-term safety and efficacy of tapentadol extended release following up to 2 years of treatment in patients with moderate to severe, chronic pain: Results of an open-label extension trial. Clinical Therapeutics. 2015; 37(11):2420-2438

100. Buynak R, Shapiro D, Okamoto A, Hove I, Etropolski M. Efficacy and safety of tapentadol ER for chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. Journal of Pain. 2009; 10(Suppl 4):s50

101. Buynak R, Shapiro D, Okamoto A, Lange C, Etropolski M. Efficacy, safety, and gastrointestinal tolerability of tapentadol ER in a randomized, double-blind, placebo- and active-controlled phase III study of patients with chronic low back pain. Journal of Pain. 2009; 10(4, Supplement 1):S48

102. Campbell CI, Kline-Simon AH, Von Korff M, Saunders KW, Weisner C. Alcohol and Drug Use and Aberrant Drug-Related Behavior Among Patients on Chronic Opioid Therapy. Substance Use and Misuse. 2017; 52(10):1283-1291

103. Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ. 2001; 323(7303):13-16

104. Campbell G, Bruno R, Darke S, Shand F, Hall W, Farrell M et al. Prevalence and correlates of suicidal thoughts and suicide attempts in people prescribed pharmaceutical opioids for chronic pain. Clinical Journal of Pain. 2016; 32(4):292-301

105. Campbell G, Nielsen S, Bruno R, Lintzeris N, Cohen M, Hall W et al. The Pain and Opioids IN Treatment study: characteristics of a cohort using opioids to manage chronic non-cancer pain. Pain. 2015; 156(2):231-242

106. Campbell G, Nielsen S, Larance B, Bruno R, Mattick R, Hall W et al. Pharmaceutical opioid use and dependence among people living with chronic pain: Associations observed within the Pain and Opioids in Treatment (POINT) cohort. Pain Medicine. 2015; 16(9):1745-1758

107. Campbell K, Kutz JW, Jr., Shoup A, Wen W, Lynch SY, He E et al. Evaluation of the ototoxicity potential of once-daily, single-entity hydrocodone in patients with chronic pain: Results of two phase-3 clinical studies. Pain Physician. 2017; 20(1):E183-E193

108. Candiotti KA, Gitlin MC. Review of the effect of opioid-related side effects on the undertreatment of moderate to severe chronic non-cancer pain: tapentadol, a step toward a solution? Current Medical Research and Opinion. 2010; 26(7):1677-1684

109. Cantini F, Niccoli L, Bellandi F, Di MO. Effectiveness of fluoxetine associated with cyclobenzaprine in the treatment of fibromyalgia: twelve-months-follow up results. Reumatismo. 1995; 47(2):103-108

110. Capaci K, Hepguler S. Comparison of the effects of amitriptyline and paroxetine in the treatment of fibromyalgia syndrome. Pain Clinic. 2002; 14(3):223-228

111. Cappelleri JC, Bushmakin AG, McDermott AM, Dukes E, Sadosky A, Petrie CD et al. Measurement properties of the Medical Outcomes Study Sleep Scale in patients with fibromyalgia. Sleep Medicine. 2009; 10(7):766-770

112. Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. Arthritis and Rheumatism. 1994; 37(1):32-40

113. Carette S, McCain GA, Bell DA, Fam AG. Evaluation of amitriptyline in primary fibrositis. A double-blind, placebo-controlled study. Arthritis and Rheumatism. 1986; 29(5):655-659

114. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiology and Drug Safety. 2011; 20(7):754-762

115. Carmona-Bayonas A, Jimenez-Fonseca P, Castanon E, Ramchandani-Vaswani A, Sanchez-Bayona R, Custodio A et al. Chronic opioid therapy in long-term cancer survivors. Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of Mexico. 2017; 19(2):236-250

116. Carson S, Thakurta S, Low A, Smith B, Chou R. Drug class review: Long-acting opioid analgesics: Final update 6 report. Prepared by the Oregon Evidence-based Practice Center for the Drug Effectiveness Review Project. Portland, OR. Oregon Health & Science University, 2011. Available from: http://derp.ohsu.edu/about/final-document-display.cfm

117. Caruso I, Sarzi Puttini PC, Boccassini L, Santandrea S, Locati M, Volpato R et al. Double-blind study of dothiepin versus placebo in the treatment of primary fibromyalgia syndrome. Journal of International Medical Research. 1987; 15(3):154-159

118. Castagnera L, Maurette P, Pointillart V, Vital JM, Erny P, Senegas J. Long-term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. Pain. 1994; 58(2):239-243

119. Cepeda MS, Carr DB, Lau J. Local anesthetic sympathetic blockade for complex regional pain syndrome. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD004598. DOI: 10.1002/14651858.CD004598.pub2.

120. Chamberlin KW, Cottle M, Neville R, Tan J. Oral oxymorphone for pain management. Annals of Pharmacotherapy. 2007; 41(7):1144-1152

121. Chan BK, Tam LK, Wat CY, Chung YF, Tsui SL, Cheung CW. Opioids in chronic non-cancer pain. Expert Opinion on Pharmacotherapy. 2011; 12(5):705-720

122. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD004959. DOI: 10.1002/14651858.CD004959.pub4.

123. Chappell AS, Bradley LA, Wiltse C, Detke MJ, D'Souza DN, Spaeth M. A six-month double-blind, placebo-controlled, randomized clinical trial of duloxetine for the treatment of fibromyalgia. International Journal of General Medicine. 2008; 1:91-102

124. Chen A, Ashburn MA. Cardiac effects of opioid therapy. Pain Medicine. 2015; 16(Suppl 1):S27-31

125. Chenaf C, Kabore JL, Delorme J, Pereira B, Mulliez A, Roche L et al. Codeine shopping behavior in a retrospective cohort of chronic noncancer pain patients: Incidence and risk factors. Journal of Pain. 2016; 17(12):1291-1301

126. Chenaf C, Kabore JL, Delorme J, Pereira B, Mulliez A, Roche L et al. Incidence of tramadol shopping behavior in a retrospective cohort of chronic non-cancer pain patients in France. Pharmacoepidemiology and Drug Safety. 2016; 25(9):1088-1098

127. Choi HG, Jung EJ, Lee WY, Kim H, Cha W, Hah JH. Comparison of pharmacological treatments for burning mouth syndrome. Korean journal of otorhinolaryngology-head and neck surgery. 2012; 55(11):707-711

128. Chou D, Abalos E, Gyte GM, Gülmezoglu AM. Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD008407. DOI: 10.1002/14651858.CD008407.pub2.

129. Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miaskowski C. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. Journal of Pain. 2009; 10(2):147-159

130. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. Journal of Pain and Symptom Management. 2003; 26(5):1026-1048

131. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Annals of Internal Medicine. 2015; 162(4):276-286

132. Chou R, Weimer MB, Dana T. Methadone overdose and cardiac arrhythmia potential: findings from a review of the evidence for an American Pain Society and College on Problems of Drug Dependence clinical practice guideline. Journal of Pain. 2014; 15(4):338-365

133. Choy E, Marshall D, Gabriel ZL, Mitchell SA, Gylee E, Dakin HA. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. Seminars in Arthritis and Rheumatism. 2011; 41(3):335-345.e336

134. Choy E, Richards S, Bowrin K, Watson P, Lloyd A, Sadosky A et al. Cost effectiveness of pregabalin in the treatment of fibromyalgia from a UK perspective. Current Medical Research and Opinion. 2010; 26(4):965-975

135. Chu LF, Rico T, Cornell E, Obasi H, Encisco EM, Vertelney H et al. Ondansetron does not prevent physical dependence in patients taking opioid medications chronically for pain control. Drug and Alcohol Dependence. 2018; 183:176-183

136. Chung CP, Dupont WD, Murray KT, Hall K, Stein CM, Ray WA. Comparative out-of-hospital mortality of long-acting opioids prescribed for non-cancer pain: A retrospective cohort study. Pharmacoepidemiology and Drug Safety. 2019; 28(1):48-53

137. Cichowski SB, Rogers RG, Komesu Y, Murata E, Qualls C, Murata A et al. A 10-yr Analysis of Chronic Pelvic Pain and Chronic Opioid Therapy in the Women Veteran Population. Military Medicine. 2018; 183(11-12):e635-e640

138. Citron ML, Kaplan R, Parris WCV, Croghan MK, Herbst LH, Rosenbluth RJ et al. Long-term administration of controlled-release oxycodone tablets for the treatment of cancer pain. Cancer Investigation. 1998; 16(8):562-571

139. Clair A, Emir B. The safety and efficacy of pregabalin for treating subjects with fibromyalgia and moderate or severe baseline widespread pain. Current Medical Research and Opinion. 2016; 32(3):601-609

140. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. Milnacipran for the treatment of fibromyalgia in adults: A 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clinical Therapeutics. 2008; 30(11):1988-2004

141. Clauw DJ, Mease PJ, Palmer RH, Trugman JM, Wang Y. Continuing efficacy of milnacipran following long-term treatment in fibromyalgia: A randomized trial. Arthritis Research & Therapy. 2013; 15:R88

142. Cohen JM, Fagin AP, Hariton E, Niska JR, Pierce MW, Kuriyama A et al. Therapeutic intervention for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): a systematic review and meta-analysis. PloS One. 2012; 7(8):e41941

143. Collett BJ. Chronic opioid therapy for non-cancer pain. British Journal of Anaesthesia. 2001; 87(1):133-143

144. Colson J, Koyyalagunta D, Falco FJ, Manchikanti L. A systematic review of observational studies on the effectiveness of opioid therapy for cancer pain. Pain Physician. 2011; 14(2):E85-102

145. Coluzzi F, Billeci D, Maggi M, Corona G. Testosterone deficiency in non-cancer opioid-treated patients. Journal of Endocrinological Investigation. 2018; 41(12):1377-1388

146. Cooper TE, Chen J, Wiffen PJ, Derry S, Carr DB, Aldington D et al. Morphine for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD011669. DOI: 10.1002/14651858.CD011669.pub2.

147. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD012188. DOI: 10.1002/14651858.CD012188.pub2.

148. Coplan PM, Sessler NE, Harikrishnan V, Singh R, Perkel C. Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analgesics in the National Poison Data System. Postgraduate Medicine. 2017; 129(1):55-61

149. Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD008244. DOI: 10.1002/14651858.CD008244.pub3.

150. Corli O, Roberto A. Pharmacological and clinical differences among transmucosal fentanyl formulations for the treatment of breakthrough cancer pain: a review article. Minerva Anestesiologica. 2014; 80(10):1123-1134

151. Corrigan R, Derry S, Wiffen PJ, Moore RA. Clonazepam for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2012, Issue 5. Art. No.: CD009486. DOI: 10.1002/14651858.CD009486.pub2.

152. Cossins L, Okell RW, Cameron H, Simpson B, Poole HM, Goebel A. Treatment of complex regional pain syndrome in adults: A systematic review of randomized controlled trials published from June 2000 to February 2012. European Journal of Pain. 2013; 17(2):158-173

153. Coutinho AD, Gandhi K, Fuldeore RM, Landsman-Blumberg PB, Gandhi S. Long-term opioid users with chronic noncancer pain: Assessment of opioid abuse risk and relationship with healthcare resource use. Journal of Opioid Management. 2018; 14(2):131-141

154. Crofford LJ, Mease PJ, Simpson SL, Young JP, Jr., Martin SA, Haig GM et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. Pain. 2008; 136(3):419-431

155. Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis and Rheumatism. 2005; 52(4):1264-1273

156. Currow DC, Quinn S, Ekstrom M, Kaasa S, Johnson MJ, Somogyi AA et al. Can variability in the effect of opioids on refractory breathlessness be explained by genetic factors? BMJ Open. 2015; 5(5):e006818

157. da CBR, Nüesch E, Kasteler R, Husni E, Welch V, Rutjes AW et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD003115. DOI: 10.1002/14651858.CD003115.pub4.

158. Dauri M, Lazzari M, Casali M, Tufaro G, Sabato E, Sabato AF. Long-term efficacy of OROS hydromorphone combined with pregabalin for chronic non-cancer neuropathic pain. Clinical Drug Investigation. 2014; 34(5):309-316

159. de Moraes M, do Amaral Bezerra BA, da Rocha Neto PC, de Oliveira Soares AC, Pinto LP, de Lisboa Lopes Costa A. Randomized trials for the treatment of burning mouth syndrome: an evidence-based review of the literature. Journal of Oral Pathology and Medicine. 2012; 41(4):281-287

160. de Vries F, Bruin M, Lobatto DJ, Dekkers OM, Schoones JW, van Furth WR et al. Opioids and their endocrine effects: A systematic review and meta-analysis. Journal of Clinical Endocrinology and Metabolism. 2019; 12:12

161. de Vries M, Van Rijckevorsel DC, Vissers KC, Wilder-Smith OH, Van Goor H. Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy,

pharmacokinetics and tolerability. British Journal of Clinical Pharmacology. 2016; 81(3):525-537

162. de Vries M, van Rijckevorsel DCM, Vissers KCP, Wilder-Smith OHG, van Goor H, Pain et al. Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. Clinical Gastroenterology and Hepatology. 2017; 15(7):1079-1086.e1074

163. Deer TR, Pope JE, Hanes MC, McDowell GC. Intrathecal therapy for chronic pain: A review of morphine and ziconotide as firstline options. Pain medicine (Malden, Mass). 2019; 20(4):784-798

164. Degenhardt L, Bruno R, Lintzeris N, Hall W, Nielsen S, Larance B et al. Agreement between definitions of pharmaceutical opioid use disorders and dependence in people taking opioids for chronic non-cancer pain (POINT): a cohort study. The Lancet Psychiatry. 2015; 2(4):314-322

165. Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug and Alcohol Dependence. 2015; 147:144-150

166. Derry S, Conaghan P, Da SJAP, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD007400. DOI: 10.1002/14651858.CD007400.pub3.

167. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD011790. DOI: 10.1002/14651858.CD011790.pub2.

168. Derry S, Stannard C, Cole P, Wiffen PJ, Knaggs R, Aldington D et al. Fentanyl for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD011605. DOI: 10.1002/14651858.CD011605.pub2.

169. Derry S, Wiffen PJ, Häuser W, Mücke M, Tölle TR, Bell RF et al. Oral nonsteroidal anti-inflammatory drugs for fibromyalgia in adults. Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD012332. DOI: 10.1002/14651858.CD012332.pub2.

170. Derry S, Wiffen PJ, Kalso EA, Bell RF, Aldington D, Phillips T et al. Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD008609. DOI: 10.1002/14651858.CD008609.pub2.

171. Dersh J, Mayer TG, Gatchel RJ, Polatin PB, Theodore BR, Mayer EA. Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders. Spine. 2008; 33(20):2219-2227

172. Desai MJ, Saini V, Saini S. Myofascial pain syndrome: A treatment review. Pain and Therapy. 2013; 2(1):21-36

173. Desai R, Hong YR, Huo J. Utilization of pain medications and its effect on quality of life, health care utilization and associated costs in individuals with chronic back pain. Journal of Pain Research. 2019; 12:557-569

174. Deyo RA, Smith DH, Johnson ES, Tillotson CJ, Donovan M, Yang X et al. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine. 2013; 38(11):909-915

175. Diasso PDK, Birke H, Nielsen SD, Main KM, Hojsted J, Sjogren P et al. The effects of long-term opioid treatment on the immune system in chronic non-cancer pain patients: A systematic review. European Journal of Pain. 2020; 24(3):481-496

176. Distler O, Eich W, Dokoupilova E, Dvorak Z, Fleck M, Gaubitz M et al. Evaluation of the efficacy and safety of terguride in patients with fibromyalgia syndrome: Results of a twelve-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis and Rheumatism. 2010; 62(1):291-300

177. Domzal T. Epidural morphine xylocaine and 0.9% NaCl in chronic pain. a comparative study. Journal of Neurology. 1985; 232(Suppl 1):306

178. Doraiswamy PM, Varia I, Hellegers C, Wagner HR, Clary GL, Beyer JL et al. A randomized controlled trial of paroxetine for noncardiac chest pain. Psychopharmacology Bulletin. 2006; 39(1):15-24

179. Drewes AM, Andreasen A, Poulsen LH. Injection therapy for treatment of chronic myofascial pain: A double- blind study comparing corticosteroid versus diclofenac injections. Journal of Musculoskeletal Pain. 1993; 1(3-4):289-294

180. Driessens M, Famaey JP, Orloff S, Chochrad I, Cleppe D, De Brabanter G et al. Efficacy and tolerability of sustained-release ibuprofen in the treatment of patients with chronic back pain. Current Therapeutic Research - Clinical and Experimental. 1994; 55(11):1283-1292

181. Dublin S, Walker RL, Gray SL, Hubbard RA, Anderson ML, Yu O et al. Prescription opioids and risk of dementia or cognitive decline: A prospective cohort study. Journal of the American Geriatrics Society. 2015; 63(8):1519-1526

182. Dublin S, Walker RL, Shortreed SM, Ludman EJ, Sherman KJ, Hansen RN et al. Impact of initiatives to reduce prescription opioid risks on medically attended injuries in people using chronic opioid therapy. Pharmacoepidemiology and Drug Safety. 2019; 28(1):90-96

183. Duehmke RM, Derry S, Wiffen PJ, Bell RF, Aldington D, Moore RA. Tramadol for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD003726. DOI: 10.1002/14651858.CD003726.pub4.

184. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Annals of Internal Medicine. 2010; 152(2):85-92

185. Dupoiron D, Stachowiak A, Loewenstein O, Ellery A, Kremers W, Bosse B et al. Long-term efficacy and safety of oxycodone-naloxone prolonged-release formulation

(up to 180/90 mg daily) - results of the open-label extension phase of a phase III multicenter, multiple-dose, randomized, controlled study. European Journal of Pain. 2017; 21(9):1485-1494

186. Dwight MM, Arnold LM, O'Brien H, Metzger R, Morris-Park E, Keck PE, Jr. An open clinical trial of venlafaxine treatment of fibromyalgia. Psychosomatics. 1998; 39(1):14-17

187. Eckmann MS, Ramamurthy S, Griffin JG. Intravenous regional ketorolac and lidocaine in the treatment of complex regional pain syndrome of the lower extremity: a randomized, double-blinded, crossover study. Clinical Journal of Pain. 2011; 27(3):203-206

188. Edelbroek PM, Linssen AC, Zitman FG, Rooymans HG, de Wolff FA. Analgesic and antidepressive effects of low-dose amitriptyline in relation to its metabolism in patients with chronic pain. Clinical Pharmacology and Therapeutics. 1986; 39(2):156-162

189. Edlund MJ, Martin BC, Fan MY, Devries A, Braden JB, Sullivan MD. Risks for opioid abuse and dependence among recipients of chronic opioid therapy: results from the TROUP study. Drug and Alcohol Dependence. 2010; 112(1-2):90-98

190. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain. 2007; 129(3):355-362

191. Edlund MJ, Sullivan M, Steffick D, Harris KM, Wells KB. Do users of regularly prescribed opioids have higher rates of substance use problems than nonusers? Pain Medicine. 2007; 8(8):647-656

192. Ekholm O, Kurita GP, Hojsted J, Juel K, Sjogren P. Chronic pain, opioid prescriptions, and mortality in Denmark: A population-based cohort study. Pain. 2014; 155(12):2486-2490

193. Elrashidi MY, Philpot LM, Ramar P, Leasure WB, Ebbert JO. Depression and Anxiety Among Patients on Chronic Opioid Therapy. Health Services Research & Managerial Epidemiology. 2018; 5:1-7

194. Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012299. DOI: 10.1002/14651858.CD012299.pub2.

195. Els C, Jackson TD, Hagtvedt R, Kunyk D, Sonnenberg B, Lappi VG et al. High-dose opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews. 2017; 10:CD012299

196. Els C, Jackson TD, Kunyk D, Lappi VG, Sonnenberg B, Hagtvedt R et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD012509. DOI: 10.1002/14651858.CD012509.pub2.

197. Engel CC, Jr., Walker EA, Engel AL, Bullis J, Armstrong A. A randomized, double-blind crossover trial of sertraline in women with chronic pelvic pain. Journal of Psychosomatic Research. 1998; 44(2):203-207

198. Erhan E, Uyar M, Turan S, Yegul I, Tuglular I, Gokce Doering B et al. Fluvoxamine versus amitriptyline in the treatment of fibromyalgia. Journal of the Turkish Society of Algology. 2000; 12(1):32-36

199. Eroglu PK, Yilmaz O, Bodur H, Ates C. A comparison of the efficacy of dry needling, lidocaine injection, and oral flurbiprofen treatments in patients with myofascial pain syndrome: A double-blind (For Injection, Groups Only), randomized clinical trial. Turkish Journal of Rheumatology. 2013; 28(1):38-46

200. Esteve JLC, Acosta R, Perez Y, Rodriguez B, Seigler I, Sanchez C et al. Mifepristone versus placebo to treat uterine myoma: A double-blind, randomized clinical trial. International Journal of Women's Health. 2013; 5(1):361-369

201. Etropolski M, Kuperwasser B, Flugel M, Haufel T, Lange B, Rauschkolb C. Safety and tolerability of tapentadol extended release in moderate to severe chronic osteoarthritis or low back pain management: pooled analysis of randomized controlled trials. Advances in Therapy. 2014; 31(6):604-620

202. Etropolski M, Lange B, Kuperwasser B, Kelly K, Okamoto A, Steup A. Efficacy and safety of tapentadol extended release versus oxycodone controlled release in opioid-naive and opioid-experienced patients with chronic pain associated with osteoarthritis of the knee. Osteoarthritis and Cartilage. 2009; 17(Suppl 1 ):S175

203. Etropolski M, Rauschkolb-Loffler C, Shapiro D, Okamoto A, Lange C. A randomized, double-blind, placebo- and active-controlled phase III study of tapentadol ER for chronic low back pain: analysis of efficacy endpoint sensitivity. Journal of Pain. 2009; 10(Suppl 4):S51

204. Etropolski MS, Shapiro D, Leslie H, Okamoto A, Hove I, Lange C. Analysis of efficacy and safety of tapentadol extended release (ER) for chronic low back pain based on prior opioid experience. European Journal of Pain. 2009; 13(Suppl 1):S203-204

205. Eyigor C, Eyigor S, Korkmaz OK, Uyar M. Intra-articular corticosteroid injections versus pulsed radiofrequency in painful shoulder: a prospective, randomized, single-blinded study. Clinical Journal of Pain. 2010; 26(5):386-392

206. Feingold D, Brill S, Goor-Aryeh I, Delayahu Y, Lev-Ran S. The association between severity of depression and prescription opioid misuse among chronic pain patients with and without anxiety: A cross-sectional study. Journal of Affective Disorders. 2018; 235:293-302

207. Felden L, Walter C, Harder S, Treede RD, Kayser H, Drover D et al. Comparative clinical effects of hydromorphone and morphine: A meta-analysis. British Journal of Anaesthesia. 2011; 107(3):319-328

208. Finch PM, Knudsen L, Drummond PD. Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. Pain. 2009; 146(1-2):18-25

209. Fleet JL, Dixon SN, Kuwornu PJ, Dev VK, Montero-Odasso M, Burneo J et al. Gabapentin dose and the 30-day risk of altered mental status in older adults: A retrospective population-based study. PloS One. 2018; 13(3):e0193134

210. Fleuret C, Le Toux G, Morvan J, Ferreira F, Chastaing M, Guillet G et al. Use of selective serotonin reuptake inhibitors in the treatment of burning mouth syndrome. Dermatology. 2014; 228(2):172-176

211. Foley KM. Opioids and chronic neuropathic pain. New England Journal of Medicine. 2003; 348(13):1279-1281

212. Fonda JR, Gradus JL, Brogly SB, McGlinchey RE, Milberg WP, Fredman L. Traumatic Brain Injury and Opioid Overdose Among Post-9/11 Veterans With Long-Term Opioid Treatment of Chronic Pain. Journal of Head Trauma Rehabilitation. 2020; 35(3):209-217

213. Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. Journal of Orofacial Pain. 2004; 18(2):131-137

214. Foster DC, Kotok MB, Huang LS, Watts A, Oakes D, Howard FM et al. Oral desipramine and topical lidocaine for vulvodynia: a randomized controlled trial. Obstetrics and Gynecology. 2010; 116(3):583-593

215. Foster HE, Hanno PM, Nickel JC, Payne CK, Mayer RD, Burks DA et al. Effect of amitriptyline on symptoms in treatment naïve patients with interstitial cystitis/painful bladder syndrome. Journal of Urology. 2010; 183(5):1853-1858

216. Fragoso YD, Carrazana EJ. Low doses of gabapentin may be helpful in the management of chronic daily headache. Medscape General Medicine. 2000; 2(3):E52

217. Franco JV, Tirapegui FI, Turk T, Garrote V, Vietto V. Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD012552. DOI: 10.1002/14651858.CD012552.

218. Franco ML, Jesus Berro M, Calvo I, Pezonaga L, Sulleiro R, Seoane A et al. Usefulness of transdermal fentanyl in the management of nonmalignant chronic pain: A prospective, observational, multicenter study. Pain Clinic. 2002; 14(2):99-112

219. Freynhagen R, Muth-Selbach U, Lipfert P, Stevens MF, Zacharowski K, Tolle TR et al. The effect of mirtazapine in patients with chronic pain and concomitant depression. Current Medical Research and Opinion. 2006; 22(2):257-264

220. Frost A. Diclofenac versus lidocaine as injection therapy in myofascial pain. Scandinavian Journal of Rheumatology. 1986; 15(2):153-156

221. Furlan AD, Irvin E, Kim J, Van ED, Carnide N, Munhall C et al. Impact of long-term opioid use for chronic non-cancer pain on misuse, abuse or addiction, overdose, falls and fractures. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD011062. DOI: 10.1002/14651858.CD011062.

222. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ Canadian Medical Association Journal. 2006; 174(11):1589-1594

223. Gabrielle Page M, Saidi H, Ware MA, Choiniere M. Risk of opioid abuse and biopsychosocial characteristics associated with this risk among chronic pain patients attending a multidisciplinary pain treatment facility. Clinical Journal of Pain. 2016; 32(10):859-869

224. Gallagher AM, Leighton-Scott J, van Staa TP. Utilization characteristics and treatment persistence in patients prescribed low-dose buprenorphine patches in primary care in the United Kingdom: a retrospective cohort study. Clinical Therapeutics. 2009; 31(8):1707-1715

225. Garg RK, Fulton-Kehoe D, Franklin GM. Patterns of opioid use and risk of opioid overdose death among medicaid patients. Medical Care. 2017; 55(7):661-668

226. Gaskell H, Derry S, Stannard C, Moore RA. Oxycodone for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD010692. DOI: dx.doi.org/10.1002/14651858.CD010692.pub3.

227. Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2014, Issue 6. Art. No.: CD010692. DOI: dx.doi.org/10.1002/14651858.CD010692.pub2.

228. Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for pain in fibromyalgia in adults. Cochrane Database of Systematic Reviews 2016, Issue 9. Art. No.: CD012329. DOI: 10.1002/14651858.CD012329.

229. Gatti A, Longo G, Sabato E, Sabato AF. Long-term controlled-release oxycodone and pregabalin in the treatment of non-cancer pain: an observational study. European Neurology. 2011; 65(6):317-322

230. Gehling M, Hermann B, Tryba M. Meta-analysis of dropout rates in randomized controlled clinical trials: opioid analgesia for osteoarthritis pain. Der Schmerz. 2011; 25(3):296-305

231. Geisser ME, Palmer RH, Gendreau RM, Wang Y, Clauw DJ. A pooled analysis of two randomized, double-blind, placebo-controlled trials of milnacipran monotherapy in the treatment of fibromyalgia. Pain Practice. 2011; 11(2):120-131

232. Gill D, Derry S, Wiffen PJ, Moore RA. Valproic acid and sodium valproate for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2011, Issue 10. Art. No.: CD009183. DOI: 10.1002/14651858.CD009183.pub2.

233. Ginsberg F, Mancaux A, Joos E, Vanhove P, Famaey JP. A randomized placebo-controlled trial of sustained-release amitriptyline in primary fibromyalgia. Journal of Musculoskeletal Pain. 1996; 4(3):37-47

234. Giordano N, Geraci S, Santacroce C, Mattii G, Battisti E, Gennari C. Efficacy and tolerability of paroxetine in patients with fibromyalgia syndrome: A single-blind study. Current Therapeutic Research - Clinical and Experimental. 1999; 60(12):696-702

235. Gisev N, Nielsen S, Campbell G, Santo T, Mant A, Bruno R et al. Antidepressant use among people prescribed opioids for chronic noncancer pain. Pain Medicine. 2019; 12:12

236. Goesling J, Henry MJ, Moser SE, Rastogi M, Hassett AL, Clauw DJ et al. Symptoms of depression are associated with opioid use regardless of pain severity and physical functioning among treatment-seeking patients with chronic pain. Journal of Pain. 2015; 16(9):844-851

237. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis and Rheumatism. 1996; 39(11):1852-1859

238. Goldenberg DL, Clauw DJ, Palmer RE, Clair AG. Opioid use in fibromyalgia: A cautionary tale. Mayo Clinic Proceedings. 2016; 91(5):640-648

239. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis and Rheumatism. 1986; 29(11):1371-1377

240. Gomes T, Juurlink DN, Dhalla IA, Mailis-Gagnon A, Paterson JM, Mamdani MM. Trends in opioid use and dosing among socio-economically disadvantaged patients. Open Medicine : A Peer-reviewed, Independent, Open-access Journal. 2011; 5(1):e13-22

241. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. Archives of Internal Medicine. 2011; 171(7):686-691

242. González LE, Nishishinya MB, Carmona L, Peloso PMJ, Walitt B, Darko G et al. NSAIDs, analgesics and opioids agents for fibromyalgia syndrome. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD006554. DOI: 10.1002/14651858.CD006554.

243. Gordon DB. Oral transmucosal fentanyl citrate for cancer breakthrough pain: a review. Oncology Nursing Forum. 2006; 33(2):257-264

244. Gourlay GK, Cherry DA, Cousins MJ, Love BL, Graham JR, McLachlan MO. A controlled study of a serotonin reuptake blocker, zimelidine, in the treatment of chronic pain. Pain. 1986; 25(1):35-52

245. Graham NA, Merlo LJ, Goldberger BA, Gold MS. Methadone- and heroin-related deaths in Florida. American Journal of Drug and Alcohol Abuse. 2008; 34(3):347-353

246. Green TC, Black R, Serrano JM, Budman SH, Butler SF. Typologies of prescription opioid use in a large sample of adults assessed for substance abuse treatment. PloS One. 2011; 6(11):e27244

247. Griessinger N, Sittl R, Likar R. Transdermal buprenorphine in clinical practice--a post-marketing surveillance study in 13,179 patients. Current Medical Research and Opinion. 2005; 21(8):1147-1156

248. Grond S, Radbruch L, Meuser T, Loick G, Sabatowski R, Lehmann KA. High-dose tramadol in comparison to low-dose morphine for cancer pain relief. Journal of Pain and Symptom Management. 1999; 18(3):174-179

249. Grosset AB, Roberts MS, Woodson ME, Shi M, Swanton RE, Reder RF et al. Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials. Journal of Pain and Symptom Management. 2005; 29(6):584-594

250. Grünenthal GmbH. A study to evaluate the effectiveness and safety of tapentadol (CG5503) extended release (ER) in patients with moderate to severe chronic low back pain [NCT00449176]. 2010. Available from: https://clinicaltrials.gov/ct2/show/NCT00449176 Last accessed: 09/07/2018.

251. Guay DR. Is tapentadol an advance on tramadol? Consultant Pharmacist. 2009; 24(11):833-840

252. Guay DR. Oral hydromorphone extended-release. Consultant Pharmacist. 2010; 25(12):816-828

253. Guay DR. Use of oral oxymorphone in the elderly. Consultant Pharmacist. 2007; 22(5):417-430

254. Gudin J, Rauck R, Argoff C, Agaiby E, Gimbel J, Katz N et al. Long-term Safety and Tolerability of NKTR-181 in Patients with Moderate to Severe Chronic Low Back Pain or Chronic Noncancer Pain: A Phase 3 Multicenter, Open-Label, 52-Week Study (SUMMIT-08 LTS). Pain Medicine. 2019; 30:30

255. Guerriero F, Sgarlata C, Marcassa C, Ricevuti G, Rollone M. Efficacy and tolerability of low-dose oral prolonged-release oxycodone/naloxone for chronic nononcological pain in older patients. Clinical Interventions in Aging. 2015; 10:1-11

256. Gulec H, Capkin E, Sayar K, Ak I. The evaluation of the effectiveness of amitriptyline versus venlafaxine in female patients diagnosed with fibromyalgia syndrome. Klinik psikofarmakoloji bulteni. 2007; 17(2):68-73

257. Hadley G, Derry S, Moore RA, Wiffen PJ. Transdermal fentanyl for cancer pain. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD010270. DOI: 10.1002/14651858.CD010270.pub2.

258. Haggman-Henrikson B, Alstergren P, Davidson T, Hogestatt ED, Ostlund P, Tranaeus S et al. Pharmacological treatment of oro-facial pain - health technology assessment including a systematic review with network meta-analysis. Journal of Oral Rehabilitation. 2017; 44(10):800-826

259. Hale ME, Fleischmann R, Salzman R, Wild J, Iwan T, Swanton RE et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized,

double-blind evaluation in patients with chronic back pain. Clinical Journal of Pain. 1999; 15(3):179-183

260. Hale ME, Ma Y, Malamut R. Six-month, open-label study of hydrocodone extended release formulated with abuse-deterrence technology: Safety, maintenance of analgesia, and abuse potential. Journal of Opioid Management. 2016; 12(2):139-147

261. Hale ME, Speight KL, Harsanyi Z, Iwan T, Slagle NS, Lacouture PG. Efficacy of 12 hourly controlled-release codeine compared with as required dosing of acetaminophen plus codeine in patients with chronic low back pain. Pain Research & Management. 1997; 2(1):33-38

262. Hale ME, Zimmerman TR, Jr., Ma Y, Malamut R. Evaluation of quality of life, functioning, disability, and work/school productivity following treatment with an extended-release hydrocodone tablet formulated with abuse-deterrence technology: A 12-month open-label study in patients with chronic pain. Pain Practice. 2017; 17(2):229-238

263. Hale ME, Zimmerman TR, Ma Y, Malamut R. Twelve-month, open-label assessment of long-term safety and abuse potential of hydrocodone extended-release formulated with abuse-deterrence technology in patients with chronic pain. Journal of Opioid Management. 2015; 11(5):425-434

264. Haroutounian S, McNicol ED, Lipman AG. Methadone for chronic non-cancer pain in adults. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008025. DOI: 10.1002/14651858.CD008025.pub2.

265. Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J et al. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. Anesthesiology. 2013; 119(6):1453-1464

266. Hauser W, Klose P, Uceyler N, Walitt B. Antipsychotics for fibromyalgia. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD011804. DOI: dx.doi.org/10.1002/14651858.CD011804.

267. Hauser W, Petzke F, Fitzcharles MA. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. European Journal of Pain. 2018; 22(3):455-470

268. Hauser W, Schubert T, Scherbaum N, Tolle T. Guideline-recommended vs high-dose long-term opioid therapy for chronic noncancer pain is associated with better health outcomes: data from a representative sample of the German population. Pain. 2018; 159(1):85-91

269. Hauser W, Urrutia G, Tort S, Uceyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database of Systematic Reviews 2013, Issue CD010292. Art. No.: 620645129. DOI: http://dx.doi.org/10.1002/14651858.CD010292.

270. Häuser W, Urrútia G, Tort S, Üçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database of

Systematic Reviews 2013, Issue 1. Art. No.: CD010292. DOI: 10.1002/14651858.CD010292.

271. Hauser W, Walitt B, Klose P, Fitzcharles MA. Cannabinoids for fibromyalgia. Cochrane Database of Systematic Reviews 2015, Issue CD011694. Art. No.: 620561360. DOI: http://dx.doi.org/10.1002/14651858.CD011694.

272. Hayes CJ, Krebs EE, Hudson T, Brown J, Li C, Martin BC. Impact of opioid dose escalation on the development of substance use disorders, accidents, self-inflicted injuries, opioid overdoses and alcohol and non-opioid drug-related overdoses: a retrospective cohort study. Addiction. 2020; 115(6):1098-1112

273. Hearn L, Derry S, Moore RA. Lacosamide for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD009318. DOI: 10.1002/14651858.CD009318.pub2.

274. Hearn L, Wiffen PJ, Moore RA, Derry S. Imipramine for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD010769. DOI: dx.doi.org/10.1002/14651858.CD010769.

275. Heckmann SM, Kirchner E, Grushka M, Wichmann MG, Hummel T. A double-blind study on clonazepam in patients with burning mouth syndrome. Laryngoscope. 2012; 122(4):813-816

276. Hedayati H, Parsons J, Crowther CA. Topically applied anaesthetics for treating perineal pain after childbirth. Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD004223. DOI: 10.1002/14651858.CD004223.pub2.

277. Heymann RE, Helfenstein M, Feldman D. A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. Clinical and Experimental Rheumatology. 2001; 19(6):697-702

278. Higgins C, Smith BH, Matthews K. Evidence of opioid-induced hyperalgesia in clinical populations after chronic opioid exposure: a systematic review and meta-analysis. British Journal of Anaesthesia. 2019; 122(6):e114-e126

279. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. British Journal of Anaesthesia. 2018; 120(6):1335-1344

280. Hitzeman N, Athale N. Opioids for osteoarthritis of the knee or hip. American Family Physician. 2010; 81(9):1094-1096

281. Hoffman EM, Watson JC, St Sauver J, Staff NP, Klein CJ. Association of long-term opioid therapy with functional status, adverse outcomes, and mortality among patients with polyneuropathy. JAMA Neurology. 2017; 74(7):773-779

282. Hofmann JF, Lal A, Steffens M, Boettger R. Patient-relevant outcomes and health-related quality of life in patients with chronic, severe, noncancer pain treated with

tapentadol prolonged release-Using criteria of health technology assessment. Journal of Opioid Management. 2016; 12(5):323-331

283. Howe CQ, Sullivan MD, Saunders KW, Merrill JO, Banta-Green CJ, Weisner C et al. Depression and ambivalence toward chronic opioid therapy for chronic noncancer pain. Clinical Journal of Pain. 2012; 28(7):561-566

284. Hsu SK, Yeh CC, Lin CJ, Hsieh YJ. An open label trial of the effects and safety profile of extended-release tramadol in the management of chronic pain. Acta Anaesthesiologica Taiwanica. 2012; 50(3):101-105

285. Huang L, Zhou JG, Zhang Y, Wang F, Wang Y, Liu DH et al. Opioid-induced constipation relief from fixed-ratio combination prolonged-release oxycodone/naloxone compared with oxycodone and morphine for chronic nonmalignant pain: A systematic review and meta-analysis of randomized controlled trials. Journal of Pain and Symptom Management. 2017; 54(5):737-748.e733

286. Ilgen MA, Bohnert AS, Ganoczy D, Bair MJ, McCarthy JF, Blow FC. Opioid dose and risk of suicide. Pain. 2016; 157(5):1079-1084

287. Im JJ, Shachter RD, Oliva EM, Henderson PT, Paik MC, Trafton JA et al. Association of care practices with suicide attempts in US veterans prescribed opioid medications for chronic pain management. Journal of General Internal Medicine. 2015; 30(7):979-991

288. Imanaka K, Tominaga Y, Etropolski M, van Hove I, Ohsaka M, Wanibe M et al. Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain. Current Medical Research and Opinion. 2013; 29(10):1399-1409

289. Jafarinia M, Afarideh M, Tafakhori A, Arbabi M, Ghajar A, Noorbala AA et al. Efficacy and safety of oral ketamine versus diclofenac to alleviate mild to moderate depression in chronic pain patients: A double-blind, randomized, controlled trial. Journal of Affective Disorders. 2016; 204:1-8

290. James JR, Scott JM, Klein JW, Jackson S, McKinney C, Novack M et al. Mortality After Discontinuation of Primary Care-Based Chronic Opioid Therapy for Pain: a Retrospective Cohort Study. Journal of General Internal Medicine. 2019; 29:29

291. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine. 1998; 23(23):2591-2600

292. Janssen Pharmaceutical K. K. A confirmatory study of fentanyl in participants with post-herpetic neuralgia, complex regional pain syndrome or postoperative pain syndrome [NCT01008553]. 2009. Available from: https://clinicaltrials.gov/ct2/show/NCT01008553 Last accessed: 10/09/2018.

293. Jassal M, Egan G, Dahri K. Opioid Prescribing in the Elderly: A Systematic Review. Journal of Pharmacy Technology. 2019;

294. Jayawardhana J, Abraham AJ, Perri M. Deaths among opioid users: Impact of potential inappropriate prescribing practices. American Journal of Managed Care. 2019; 25(4):E98-E103

295. Johansson F, von Knorring L. A double-blind controlled study of seratonin uptake inhibitor (Zimelidine) versus placebo in chronic pain patients. Pain. 1979; 7(1):69-78

296. Joint Formulary Committee. British National Formulary (BNF). 2019. Available from: http://www.bnf.org.uk Last accessed: 11/11/2019.

297. Juel J, Olesen SS, Olesen AE, Poulsen JL, Dahan A, Wilder-Smith O et al. Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial). BMJ Open. 2015; 5(3):e007087

298. Kalita J, Kohat AK, Misra UK, Bhoi SK. An open labeled randomized controlled trial of pregabalin versus amitriptyline in chronic low backache. Journal of the Neurological Sciences. 2014; 342(1-2):127-132

299. Kalita J, Vajpayee A, Misra UK. Comparison of prednisolone with piroxicam in complex regional pain syndrome following stroke: a randomized controlled trial. QJM: An International Journal of Medicine. 2006; 99(2):89-95

300. Kang SK, Lee YH, Park H, Ro JY, Auh QS. Effects of intramuscular morphine in men and women with temporomandibular disorder with myofascial pain. Oral Diseases. 2018; 24(8):1591-1598

301. Kapil RP, Friedman K, Cipriano A, Michels G, Shet M, Mondal SA et al. Effects of paroxetine, a CYP2D6 inhibitor, on the pharmacokinetic properties of hydrocodone after coadministration with a single-entity, once-daily, extended-release hydrocodone tablet. Clinical Therapeutics. 2015; 37(10):2286-2296

302. Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN. Sex differences in dose escalation and overdose death during chronic opioid therapy: A population-based cohort study. PloS One. 2015; 10(8):e0134550

303. Kater RM. Double-blind evaluation of the analgesic and toxic effects of flufenamic acid and mefenamic acid in patients with chronic pain. Medical Journal of Australia. 1968; 1(20):848-851

304. Katz N, Mazer NA. The impact of opioids on the endocrine system. Clinical Journal of Pain. 2009; 25(2):170-175

305. Kay C, Fergestrom N, Spanbauer C, Jackson JL. Opioid Dose and Benzodiazepine Use Among Commercially Insured Individuals on Chronic Opioid Therapy. Pain Medicine. 2019; 05

306. Khodneva Y, Muntner P, Kertesz S, Kissela B, Safford MM. Prescription opioid use and risk of coronary heart disease, stroke, and cardiovascular death among adults from a prospective cohort (REGARDS study). Pain Medicine. 2016; 17(3):444-455

307. Khodneva Y, Richman J, Kertesz S, Safford MM. Gender differences in association of prescription opioid use and mortality: A propensity-matched analysis from the REasons for Geographic And Racial Differences in Stroke (REGARDS) prospective cohort. Substance Abuse. 2019:1-10

308. Kiefer RT, Rohr P, Ploppa A, Dieterich HJ, Grothusen J, Koffler S et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. Pain Medicine. 2008; 9(8):1173-1201

309. Kim JL, Rele S, Marks DM, Masand PS, Yerramsetty P, Millet RA et al. Effects of milnacipran on neurocognition, pain, and fatigue in fibromyalgia: A 13-week, randomized, placebo-controlled, crossover trial. Primary Care Companion for CNS Disorders. 2013; 15(6)

310. Kim YC, Castaneda AM, Lee CS, Jin HS, Park KS, Moon JY. Efficacy and Safety of Lidocaine Infusion Treatment for Neuropathic Pain: A Randomized, Double-Blind, and Placebo-Controlled Study. Regional Anesthesia and Pain Medicine. 2018; 43(4):415-424

311. Kimos P, Biggs C, Mah J, Heo G, Rashiq S, Thie NM et al. Analgesic action of gabapentin on chronic pain in the masticatory muscles: a randomized controlled trial. Pain. 2007; 127(1-2):151-160

312. Kisely S, Forbes M, Sawyer E, Black E, Lalloo R. A systematic review of randomized trials for the treatment of burning mouth syndrome. Journal of Psychosomatic Research. 2016; 86:39-46

313. Kissin I. Long-term opioid treatment of chronic nonmalignant pain: unproven efficacy and neglected safety? Journal of Pain Research. 2013; 6:513-529

314. Kleinstäuber M, Witthöft M, Steffanowski A, van MH, Hiller W, Lambert MJ. Pharmacological interventions for somatoform disorders in adults. Cochrane Database of Systematic Reviews 2014, Issue 11. Art. No.: CD010628. DOI: 10.1002/14651858.CD010628.pub2.

315. Korting GE, Smith SD, Wheeler MA, Weiss RM, Foster HE, Jr. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. Journal of Urology. 1999; 161(2):558-565

316. Krebs EE, Becker WC, Zerzan J, Bair MJ, McCoy K, Hui S. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain. 2011; 152(8):1789-1795

317. Krebs EE, Clothier B, Nugent S, Jensen AC, Martinson BC, Goldsmith ES et al. The evaluating prescription opioid changes in veterans (EPOCH) study: Design, survey response, and baseline characteristics. PloS One. 2020; 15(4):e0230751

318. Kuo YF, Raji MA, Goodwin JS. Association of Disability With Mortality From Opioid Overdose Among US Medicare Adults. JAMA Network Open. 2019; 2(11):e1915638

319. Kuperwasser B, Häufel T, Kelly K, Etropolski M, Laschewski F, Okamoto A. Incidence and severity of gastrointestinal treatment-emergent adverse events in patients treated

with tapentadol extended release (ER) or oxycodone controlled release (CR) for relief of chronic osteoarthritis knee pain. Osteoarthritis and Cartilage. 2009; 17(Suppl 1):S178

320. Kurian R, Raza K, Shanthanna H. A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. European Journal of Pain. 2019; 23(7):1234-1250

321. Landau CJ, Carr WD, Razzetti AJ, Sessler NE, Munera C, Ripa SR. Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study. Clinical Therapeutics. 2007; 29(10):2179-2193

322. Landsman-Blumberg PB, Katz N, Gajria K, Coutinho AD, Yeung PP, White R. Burden of Alcohol Abuse or Dependence Among Long-Term Opioid Users with Chronic Noncancer Pain. Journal of Managed Care & Specialty Pharmacy. 2017; 23(7):718-724

323. Landsman-Blumberg PB, Katz N, Gajria K, D'Souza AO, Chaudhari SL, Yeung PP et al. Health care resource use and cost differences by opioid therapy type among chronic noncancer pain patients. Journal of Pain Research. 2017; 10:1713-1722

324. Lange A, Lasser KE, Xuan Z, Khalid L, Beers D, Heymann OD et al. Variability in opioid prescription monitoring and evidence of aberrant medication taking behaviors in urban safety-net clinics. Pain. 2015; 156(2):335-340

325. Lange B, Sohns M, Tempero J, Elling C. Efficacy and safety of tapentadol prolonged release formulation in the treatment of elderly patients with moderate-to-severe chronic osteoarthritis knee pain: a pooled analysis of two double-blind, randomized, placebo-, and active-controlled trials. Current Medical Research and Opinion. 2018; 34(12):2113-2123

326. Lanier RK, Henningfield JE, Gudin J, Rauck R, Elder H, Erpelding N et al. Assessment of potentially abuse-related events in two phase 3 studies of NKTR-181, a novel opioid analgesic, using the MADDERS system (Misuse, Abuse, and Diversion Drug Event Reporting System). Current Medical Research and Opinion. 2019; 35(9):1513-1522

327. Lawson K. Potential drug therapies for the treatment of fibromyalgia. Expert Opinion on Investigational Drugs. 2016; 25(9):1071-1081

328. Le Marshall KF, Littlejohn GO. Management strategies for fibromyalgia. Open Access Rheumatology. 2011; 3:47-51

329. Learman LA. Chronic pelvic pain - Part 2: An integrated management approach. Advanced Studies in Medicine. 2005; 5(7):360-366

330. Lee CB, Ha US, Lee SJ, Kim SW, Cho YH. Preliminary experience with a terpene mixture versus ibuprofen for treatment of category III chronic prostatitis/chronic pelvic pain syndrome. World Journal of Urology. 2006; 24(1):55-60

331. Lee J, Yoon JS, Lee JH, Chung SH, Lee KY, Kim YY et al. Clinical usefulness of long-term application of fentanyl matrix in chronic non-cancer pain: improvement of pain and physical and emotional functions. Cios clinics in orthopedic surgery. 2016; 8(4):465-474

332. Lee RA, West RM, Wilson JD. The response to sertraline in men with chronic pelvic pain syndrome. Sexually Transmitted Infections. 2005; 81(2):147-149

333. Lee SK, Yang DS, Lee JW, Choy WS. Four treatment strategies for complex regional pain syndrome type 1. Orthopedics. 2012; 35(6):e834-842

334. Lee YH, Song GG. Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: a Bayesian network meta-analysis of randomized controlled trials. Rheumatology International. 2016; 36(5):663-672

335. Leo RJ, Dewani S. A systematic review of the utility of antidepressant pharmacotherapy in the treatment of vulvodynia pain. Journal of Sexual Medicine. 2013; 10(10):2497-2505

336. Lewis SC, Bhattacharya S, Wu O, Vincent K, Jack SA, Critchley HO et al. Gabapentin for the management of chronic pelvic pain in women (GaPP1): A pilot randomised controlled trial. PloS One. 2016; 11(4):e0153037

337. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. Journal of Internal Medicine. 2013; 273(5):511-526

338. Lin YC, Kuan TS, Hsieh PC, Yen WJ, Chang WC, Chen SM. Therapeutic effects of lidocaine patch on myofascial pain syndrome of the upper trapezius: a randomized, double-blind, placebo-controlled study. American Journal of Physical Medicine and Rehabilitation. 2012; 91(10):871-882

339. Lintzeris N, Moodley R, Campbell G, Larance B, Bruno R, Nielsen S et al. Sleep quality among people living with chronic noncancer pain: Findings from the pain and opioids in treatment (POINT) cohort. Clinical Journal of Pain. 2016; 32(5):380-387

340. Lipkovich IA, Choy EH, Van Wambeke P, Deberdt W, Sagman D. Typology of patients with fibromyalgia: cluster analysis of duloxetine study patients. BMC Musculoskeletal Disorders. 2014; 15:450

341. List T, Axelsson S, Leijon G. Pharmacologic interventions in the treatment of temporomandibular disorders, atypical facial pain, and burning mouth syndrome. A qualitative systematic review. Journal of Orofacial Pain. 2003; 17(4):301-310

342. Liu YF, Kim Y, Yoo T, Han P, Inman JC. Burning mouth syndrome: a systematic review of treatments. Oral Diseases. 2018; 24(3):325-334

343. Loldrup D, Langemark M, Hansen HJ, Kastrup M, Jeppesen K, Bonnevie O et al. The validity of the Melancholia Scale (MES) in predicting outcome of antidepressants in chronic idiopathic pain disorders. European Psychiatry. 1991; 6(3):119-125

344. Loldrup D, Langemark M, Hansen HJ, Olesen J, Bech P. Clomipramine and mianserin in chronic idiopathic pain syndrome. A placebo controlled study. Psychopharmacology. 1989; 99(1):1-7

345. Lopez-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of Burning Mouth Syndrome: a randomized, double-blind, placebo controlled trial. Medicina Oral, Patología Oral y Cirugía Bucal. 2011; 16(5):e635-640

346. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD007115. DOI: 10.1002/14651858.CD007115.pub3.

347. Luo YL, Zhang MY, Wu WY, Li CB, Lu Z, Li QW. A randomized double-blind clinical trial on analgesic efficacy of fluoxetine for persistent somatoform pain disorder. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009; 33(8):1522-1525

348. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. British Journal of Clinical Pharmacology. 2011; 72(5):735-744

349. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. Journal Of Neuroimmune Pharmacology: The Official Journal Of The Society On NeuroImmune Pharmacology. 2015; 10(2):293-301

350. Maarrawi J, Abdel Hay J, Kobaiter-Maarrawi S, Tabet P, Peyron R, Garcia-Larrea L. Randomized double-blind controlled study of bedtime low dose amitriptyline in chronic neck pain. European Journal of Pain. 2018; 22(6):1180-1187

351. Macfarlane GJ, Beasley M, Jones GT, Stannard C. The epidemiology of regular opioid use and its association with mortality: Prospective cohort study of 466 486 UK biobank participants. EClinicalMedicine. 2020; 21:100321

352. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Hauser W, Flub E et al. EULAR revised recommendations for the management of fibromyalgia. Annals of the Rheumatic Diseases. 2017; 76(2):318-328

353. Magistro G, Wagenlehner FME, Grabe M, Weidner W, Stief CG, Nickel JC. Contemporary management of chronic prostatitis/chronic pelvic pain syndrome. European Urology. 2016; 69(2):286-297

354. Mahagna H, Amital D, Amital H. A randomised, double-blinded study comparing giving etoricoxib vs. placebo to female patients with fibromyalgia. International Journal of Clinical Practice. 2016; 70(2):163-170

355. Mailis-Gagnon A, Lakha SF, Furlan A, Nicholson K, Yegneswaran B, Sabatowski R. Systematic review of the quality and generalizability of studies on the effects of opioids on driving and cognitive/psychomotor performance. Clinical Journal of Pain. 2012; 28(6):542-555

356. Maina G, Vitalucci A, Gandolfo S, Bogetto F. Comparative efficacy of SSRIs and amisulpride in burning mouth syndrome: a single-blind study. Journal of Clinical Psychiatry. 2002; 63(1):38-43

357. Makris UE, Pugh MJ, Alvarez CA, Berlowitz DR, Turner BJ, Aung K et al. Exposure to high-risk medications is associated with worse outcomes in older veterans with chronic pain. American Journal of the Medical Sciences. 2015; 350(4):279-285

358. 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. 2017; 30(2):1-8

359. Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. Pain Physician. 2011; 14(2):91-121

360. Manchikanti L, Vallejo R, Manchikanti KN, Benyamin RM, Datta S, Christo PJ. Effectiveness of long-term opioid therapy for chronic non-cancer pain. Pain Physician. 2011; 14(2):E133-156

361. Marangell LB, Clauw DJ, Choy E, Wang F, Shoemaker S, Bradley L et al. Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. Pain. 2011; 152(1):31-37

362. Marschall U, L'Hoest H, Radbruch L, Hauser W. Long-term opioid therapy for chronic non-cancer pain in Germany.[Erratum appears in Eur J Pain. 2017 Nov;21(10 ):1774; PMID: 28990730]. European Journal of Pain. 2016; 20(5):767-776

363. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Medicine. 2009; 10(8):1353-1368

364. Matthey A, Cedraschi C, Piguet V, Besson M, Chabert J, Daali Y et al. Dual reuptake inhibitor milnacipran and spinal pain pathways in fibromyalgia patients: a randomized, double-blind, placebo-controlled trial. Pain Physician. 2013; 16(5):E553-562

365. McIntyre A, Paisley D, Kouassi E, Gendron A. Quetiapine fumarate extended-release for the treatment of major depression with comorbid fibromyalgia syndrome: a double-blind, randomized, placebo-controlled study. Arthritis & Rheumatology. 2014; 66(2):451-461

366. McIntyre A, Paisley D, Kuoassi E. A double-blind, randomized, placebocontrolled study of quetiapine XR for the treatment of major depression and fibromyalgia. European Neuropsychopharmacology. 2013; 23(Suppl 2):S415

367. McMillan AS, Nolan A, Kelly PJ. The efficacy of dry needling and procaine in the treatment of myofascial pain in the jaw muscles. Journal of Orofacial Pain. 1997; 11(4):307-314

368. McMillan R, Forssell H, Buchanan JA, Glenny A-M, Weldon JC, Zakrzewska JM. Interventions for treating burning mouth syndrome. Cochrane Database of Systematic

Reviews 2016, Issue 11. Art. No.: CD002779. DOI: 10.1002/14651858.CD002779.pub3.

369. McNaughton C, Mac Donald R, Wilt T. Interventions for chronic abacterial prostatitis. Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.: CD002080. DOI: 10.1002/14651858.CD002080.

370. McNicol ED, Ferguson MC, Schumann R. Methadone for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD012499. DOI: 10.1002/14651858.CD012499.pub2.

371. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD006146. DOI: 10.1002/14651858.CD006146.pub2.

372. McQuay HJ, Carroll D, Glynn CJ. Low dose amitriptyline in the treatment of chronic pain. Anaesthesia. 1992; 47(8):646-652

373. Mease P, Arnold L, Wang F, Ahl J, Mohs R, Gaynor P et al. The effect of duloxetine on cognition in patients with fibromyalgia. Arthritis and Rheumatism. 2010; 62(S10):S46

374. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. Journal of Rheumatology. 2009; 36(2):398-409

375. Mease PJ, Clauw DJ, Trugman JM, Hpalmer R, Wang Y. Efficacy of long-term milnacipran treatment in patients meeting different thresholds of clinically relevant pain relief: Subgroup analysis of a randomized, double-blind, placebo-controlled withdrawal study. Journal of Pain Research. 2014; 7:679-687

376. Mease PJ, Palmer RH, Wang Y. Effects of milnacipran on the multidimensional aspects of fatigue and the relationship of fatigue to pain and function: Pooled analysis of 3 fibromyalgia trials. Journal of Clinical Rheumatology. 2014; 20(4):195-202

377. Mease PJ, Russell IJ, Arnold LM, Florian H, Young JP, Jr., Martin SA et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. Journal of Rheumatology. 2008; 35(3):502-514

378. Mease PJ, Russell IJ, Kajdasz DK, Wiltse CG, Detke MJ, Wohlreich MM et al. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. Seminars in Arthritis and Rheumatism. 2010; 39(6):454-464

379. Mease PJ, Spaeth M, Clauw DJ, Arnold LM, Bradley LA, Russell IJ et al. Estimation of minimum clinically important difference for pain in fibromyalgia. Arthritis Care and Research. 2011; 63(6):821-826

380. Mejjad O, Serrie A, Ganry H, Legout V. Observational study in general practice of a paracetamol (325mg)-tramadol (37.5mg) fixed combination in the treatment of acute or chronic, moderate to severe pain in patients aged 65 years and over (SALZA study). Journal of Applied Therapeutic Research. 2011; 8(3):83-93

381. Meng Z, Yu J, Acuff M, Luo C, Wang S, Yu L et al. Tolerability of Opioid Analgesia for Chronic Pain: A Network Meta-Analysis. Scientific Reports. 2017; 7(1):1995

382. Menzies V, Thacker LR, 2nd, Mayer SD, Young AM, Evans S, Barstow L. Polypharmacy, opioid use, and fibromyalgia: A secondary analysis of clinical trial data. Biological Research for Nursing. 2017; 19(1):97-105

383. Merchant S, Provenzano D, Mody S, Ho KF, Etropolski M. Composite measure to assess efficacy/gastrointestinal tolerability of tapentadol ER versus oxycodone CR for chronic pain: pooled analysis of randomized studies. Journal of Opioid Management. 2013; 9(1):51-61

384. Meske DS, Lawal OD, Elder H, Langberg V, Paillard F, Katz N. Efficacy of opioids versus placebo in chronic pain: A systematic review and meta-analysis of enriched enrollment randomized withdrawal trials. Journal of Pain Research. 2018; 11:923-934

385. Michelet D, Brasher C, Horlin AL, Bellon M, Julien-Marsollier F, Vacher T et al. Ketamine for chronic non-cancer pain: A meta-analysis and trial sequential analysis of randomized controlled trials. European Journal of Pain. 2018; 22(4):632-646

386. Miki K, Murakami M, Oka H, Onozawa K, Yoshida S, Osada K. Efficacy of mirtazapine for the treatment of fibromyalgia without concomitant depression: a randomized, double-blind, placebo-controlled phase IIa study in Japan. Pain. 2016; 157(9):2089-2096

387. Miller LJ, Kubes KL. Serotonergic agents in the treatment of fibromyalgia syndrome. Annals of Pharmacotherapy. 2002; 36(4):707-712

388. Miller M, Barber CW, Leatherman S, Fonda J, Hermos JA, Cho K et al. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. JAMA Internal Medicine. 2015; 175(4):608-615

389. Minguez Serra MP, Salort Llorca C, Silvestre Donat FJ. Pharmacological treatment of burning mouth syndrome: A review and update. Medicina Oral, Patología Oral y Cirugía Bucal. 2007; 12(4):E299-304

390. Mohs R, Mease P, Arnold LM, Wang F, Ahl J, Gaynor PJ et al. The effect of duloxetine treatment on cognition in patients with fibromyalgia. Psychosomatic Medicine. 2012; 74(6):628-634

391. Moore RA, Cai N, Skljarevski V, Tolle TR. Duloxetine use in chronic painful conditions--individual patient data responder analysis. European Journal of Pain. 2014; 18(1):67-75

392. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for fibromyalgia in adults. Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD011824. DOI: 10.1002/14651858.CD011824.

393. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Research & Therapy. 2005; 7(5):R1046-1051

394. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD007076. DOI: 10.1002/14651858.CD007076.pub2.

395. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2011, Issue 3. Art. No.: CD007938. DOI: 10.1002/14651858.CD007938.pub2.

396. Morgan CL, Jenkins-Jones S, Currie C, Baxter G. Outcomes Associated with Treatment of Chronic Pain with Tapentadol Compared with Morphine and Oxycodone: A UK Primary Care Observational Study. Advances in Therapy. 2019; 08:08

397. Mosher HJ, Jiang L, Vaughan Sarrazin MS, Cram P, Kaboli PJ, Vander Weg MW. Prevalence and characteristics of hospitalized adults on chronic opioid therapy. Journal of Hospital Medicine (Online). 2014; 9(2):82-87

398. Moulin DE, Richarz U, Wallace M, Jacobs A, Thipphawong J. Efficacy of the sustained-release hydromorphone in neuropathic pain management: pooled analysis of three open-label studies. Journal of Pain & Palliative Care Pharmacotherapy. 2010; 24(3):200-212

399. Mubashir T, Nagappa M, Esfahanian N, Botros J, Arif AA, Suen C et al. Prevalence of Sleep Disordered Breathing in Opioid Users With Chronic Pain: A Systematic Review and Meta-Analysis. Journal of Clinical Sleep Medicine. 2020; 24:24

400. Muller W, Stratz T. Local treatment of tendinopathies and myofascial pain syndromes with the 5-HT3 receptor antagonist tropisetron. Scandinavian Journal of Rheumatology - Supplement. 2004; 119:44-48

401. Muller W, Stratz T. The use of the 5-$HT_3$ receptor antagonist tropisetron in trigger point therapy: A pilot study. Journal of Musculoskeletal Pain. 2005; 13(2):43-48

402. Murakami M, Osada K, Ichibayashi H, Mizuno H, Ochiai T, Ishida M et al. An open-label, long-term, phase III extension trial of duloxetine in Japanese patients with fibromyalgia. Modern Rheumatology. 2017; 27(4):688-695

403. Murakami M, Osada K, Mizuno H, Ochiai T, Alev L, Nishioka K. A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese fibromyalgia patients. Arthritis Research & Therapy. 2015; 17:224

404. Murray HW, Patkar AA, Peindl K, Krulewicz S, Dube E, Masand PS. Personality profiles as predictors of response for fibromyalgia. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA. 2005:NR150

405. Mystakidou K, Parpa E, Tsilika E, Katsouda E, Kouloulias V, Kouvaris J et al. Pain management of cancer patients with transdermal fentanyl: a study of 1828 step I, II, & III transfers.[Erratum appears in J Pain. 2004 Nov;5(9):528]. Journal of Pain. 2004; 5(2):119-132

406. Nalamachu SR, Kutch M, Hale ME. Safety and Tolerability of Once-Daily OROS() hydromorphone extended-release in opioid-tolerant adults with moderate-to-severe

chronic cancer and noncancer pain: pooled analysis of 11 clinical studies. Journal of Pain and Symptom Management. 2012; 44(6):852-865

407. Nalamachu SR, Narayana A, Janka L. Long-term dosing, safety, and tolerability of fentanyl buccal tablet in the management of noncancer-related breakthrough pain in opioid-tolerant patients. Current Medical Research and Opinion. 2011; 27(4):751-760

408. Narayana A, Katz N, Shillington AC, Stephenson JJ, Harshaw Q, Frye CB et al. National Breakthrough Pain Study: prevalence, characteristics, and associations with health outcomes. Pain. 2015; 156(2):252-259

409. Nasser K, Kivitz AJ, Maricic MJ, Silver DS, Silverman SL. Twice daily versus once nightly dosing of pregabalin for fibromyalgia: a double-blind randomized clinical trial of efficacy and safety. Arthritis Care and Research. 2014; 66(2):293-300

410. Natelson BH, Vu D, Mao X, Weiduschat N, Togo F, Lange G et al. Effect of milnacipran treatment on ventricular lactate in fibromyalgia: A randomized, double-blind, placebo-controlled trial. Journal of Pain. 2015; 16(11):1211-1219

411. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

412. NCT. An exploratory, randomised, double-blind, placebo-controlled, parallel group, pilot study to assess the analgesic efficacy of oxycodone/naloxone prolonged release tablets (OXN PR) compared to placebo in opioid-naive subjects suffering from severe pain due to bladder pain syndrome. 2010. Available from: Https://clinicaltrials.gov/show/nct01197261 Last accessed: 10/12/2019.

413. Nguyen TM, Eslick GD. Systematic review: the treatment of noncardiac chest pain with antidepressants. Alimentary Pharmacology and Therapeutics. 2012; 35(5):493-500

414. Nicholson AB. Methadone for cancer pain. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003971. DOI: 10.1002/14651858.CD003971.pub4.

415. Nickel JC. Interstitial cystitis. Etiology, diagnosis, and treatment. Canadian Family Physician. 2000; 46:2430-2434, 2437-2440

416. Nickel JC. Treatment of chronic prostatitis/chronic pelvic pain syndrome. International Journal of Antimicrobial Agents. 2008; 31(SUPPL. 1):112-116

417. Nickel JC, Atkinson G, Krieger JN, Mills IW, Pontari M, Shoskes DA et al. Preliminary assessment of safety and efficacy in proof-of-concept, randomized clinical trial of tanezumab for chronic prostatitis/chronic pelvic pain syndrome. Urology. 2012; 80(5):1105-1110

418. Nickel JC, Pontari M, Moon T, Gittelman M, Malek G, Farrington J et al. A randomized, placebo controlled, multicenter study to evaluate the safety and efficacy

of rofecoxib in the treatment of chronic nonbacterial prostatitis. Journal of Urology. 2003; 169(4):1401-1405

419. Niimi A. Safety and efficacy of tramadol in the treatment of refractory pain of interstitial cystitis: a double-blind, placebo-controlled, randomized prospective study. 2012. Available from: Http://www.umin.ac.jp/ctr/index.htm Last accessed:

420. Nishishinya B, Urrutia G, Walitt B, Rodriguez A, Bonfill X, Alegre C et al. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. Rheumatology. 2008; 47(12):1741-1746

421. Nishishinya MB, Walitt B, Urrútia G, Mease PJ, Rodríguez A, Riera LRJ et al. Anti-depressants and centrally active agents for fibromyalgia syndrome. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD006192. DOI: 10.1002/14651858.CD006192.

422. Nitecka-Buchta A, Nowak-Wachol A, Wachol K, Walczynska-Dragon K, Olczyk P, Batoryna O et al. Myorelaxant effect of transdermal cannabidiol application in patients with TMD: A randomized, double-blind trial. Journal of Clinical Medicine. 2019; 8 (11) (no pagination)(1886)

423. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C et al. Long-term opioid management for chronic noncancer pain. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD006605. DOI: 10.1002/14651858.CD006605.pub2.

424. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: A systematic review and meta-analysis of efficacy and safety. Journal of Pain and Symptom Management. 2008; 35(2):214-228

425. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain. 1995; 61(3):445-449

426. Novick TK, Surapaneni A, Shin JI, Alexander GC, Inker LA, Wright EA et al. Associations of opioid prescriptions with death and hospitalization across the spectrum of estimated gfr. Clinical Journal of the American Society of Nephrology. 2019; 14(11):1581-1589

427. Nuesch E, Hauser W, Bernardy K, Barth J, Juni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Annals of the Rheumatic Diseases. 2013; 72(6):955-962

428. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K et al. The effects of cannabis among adults with chronic painandan overview of general harms a systematic review. Annals of Internal Medicine. 2017; 167(5):319-331

429. O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome- an overview of systematic reviews. Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD009416. DOI: 10.1002/14651858.CD009416.pub2.

430. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. Journal of General Internal Medicine. 2000; 15(9):659-666

431. O'Malley PG, Jackson JL, Santoro J, Tomkins G, Balden E, Kroenke K. Antidepressant therapy for unexplained symptoms and symptom syndromes. Journal of Family Practice. 1999; 48(12):980-990

432. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. American Journal of Geriatric Pharmacotherapy. 2012; 10(6):331-342

433. Offiah I, McMahon SB, O'Reilly BA. Interstitial cystitis/bladder pain syndrome: Diagnosis and management. International Urogynecology Journal. 2013; 24(8):1243-1256

434. Oh TK, Jeon YT, Choi JW. Trends in chronic opioid use and association with five-year survival in South Korea: a population-based cohort study. British Journal of Anaesthesia. 2019; 123(5):655-663

435. Ohta H, Ohkura M, Suzuki M, Oka H, Usui C, Nishioka K. Efficacy and safety of pregabalin in Japanese patients with fibromyalgia: A randomized, double-blind, multicenter, placebo-controlled phase iii trial and open-label extension study. Arthritis and Rheumatism. 2012; 64(S10):S792

436. Ohta H, Oka H, Usui C, Ohkura M, Suzuki M, Nishioka K. An open-label long-term phase III extension trial to evaluate the safety and efficacy of pregabalin in Japanese patients with fibromyalgia. Modern Rheumatology. 2013; 23(6):1108-1115

437. Ohta H, Oka H, Usui C, Ohkura M, Suzuki M, Nishioka K. A randomized, double-blind, multicenter, placebo-controlled phase III trial to evaluate the efficacy and safety of pregabalin in Japanese patients with fibromyalgia. Arthritis Research & Therapy. 2012; 14(5):R217

438. Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. Pain. 1992; 49(2):205-219

439. Ortman HA, Siegel JA. The effect of methadone on the hypothalamic pituitary gonadal axis and sexual function: A systematic review. Drug and Alcohol Dependence. 2020; 207:107823

440. Ottman AA, Warner CB, Brown JN. The role of mirtazapine in patients with fibromyalgia: a systematic review. Rheumatology International. 2018; 38(12):2217-2224

441. Ozerbil O, Okudan N, Gokbel H, Levendoglu F. Comparison of the effects of two antidepressants on exercise performance of the female patients with fibromyalgia. Clinical Rheumatology. 2006; 25(4):495-497

442. Pace MC, Passavanti MB, Grella E, Mazzariello L, Maisto M, Barbarisi M et al. Buprenorphine in long-term control of chronic pain in cancer patients. Frontiers in Bioscience. 2007; 12:1291-1299

443. Padilla M, Clark GT, Merrill RL. Topical medications for orofacial neuropathic pain: a review. Journal of the American Dental Association (1939). 2000; 131(2):184-195

444. Pae CU, Masand PS, Marks DM, Krulewicz S, Han C, Peindl K et al. History of early abuse as a predictor of treatment response in patients with fibromyalgia: a post-hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release. World Journal of Biological Psychiatry. 2009; 10(4 Pt 2):435-441

445. Pae CU, Masand PS, Marks DM, Krulewicz S, Peindl K, Mannelli P et al. History of depressive and/or anxiety disorders as a predictor of treatment response: a post hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release in patients with fibromyalgia. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2009; 33(6):996-1002

446. Pampati S, Manchikanti L. What is the prevalence of symptomatic obstructive sleep apnea syndrome in chronic spinal pain patients? An assessment of the correlation of OSAS with chronic opioid therapy, obesity, and smoking. Pain Physician. 2016; 19(4):E569-579

447. Papadopoulou D, Fassoulaki A, Tsoulas C, Siafaka I, Vadalouca A. A meta-analysis to determine the effect of pharmacological and non-pharmacological treatments on fibromyalgia symptoms comprising OMERACT-10 response criteria. Clinical Rheumatology. 2016; 35(3):573-586

448. Papandreou C, Skapinakis P, Giannakis D, Sofikitis N, Mavreas V. Antidepressant drugs for chronic urological pelvic pain: an evidence-based review. Advances in Urology. 2009; 2009:797031

449. Papazisis G, Tzellos T, Toulis K, Goulis D, Sardeli C, Chourdakis M et al. Safety/tolerability of alpha2delta ligand pregabalin in the treatment of fibromyalgia: An evidence based evaluation. Review of Clinical Pharmacology and Pharmacokinetics. 2010; 24(2):181-182

450. Parsons B, Argoff CE, Clair A, Emir B. Improvement in pain severity category in clinical trials of pregabalin. Journal of Pain Research. 2016; 9:779-785

451. Parsons B, Emir B, Clair A. Temporal analysis of pain responders and common adverse events: when do these first appear following treatment with pregabalin. Journal of Pain Research. 2015; 8:303-309

452. Pascual ML, Fleming RR, Gana TJ, Vorsanger GJ. Open-label study of the safety and effectiveness of long-term therapy with extended-release tramadol in the management of chronic nonmalignant pain. Current Medical Research and Opinion. 2007; 23(10):2531-2542

453. Pask S, Dell'Olio M, Murtagh FEM, Boland JW. The Effects of Opioids on Cognition in Older Adults With Cancer and Chronic Noncancer Pain: A Systematic Review. Journal of Pain and Symptom Management. 2020; 59(4):871-893.e871

454. Passik SD, Messina J, Golsorkhi A, Xie F. Aberrant drug-related behavior observed during clinical studies involving patients taking chronic opioid therapy for persistent pain and fentanyl buccal tablet for breakthrough pain. Journal of Pain and Symptom Management. 2011; 41(1):116-125

455. Patkar AA, Masand PS, Krulewicz S, Mannelli P, Peindl K, Beebe KL et al. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. American Journal of Medicine. 2007; 120(5):448-454

456. Patkar AA, Peindl K, Krulewicz S, Mannelli P, Lindsay A, Masand PS. History of depressive and anxiety disorders as predictors of response in fibromyalgia. 158th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta, GA. 2005:NR382

457. Patton LL, Siegel MA, Benoliel R, De Laat A. Management of burning mouth syndrome: systematic review and management recommendations. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics. 2007; 103 (Suppl):S39.e31-13

458. Pauer L, Winkelmann A, Arsenault P, Jespersen A, Whelan L, Atkinson G et al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. Journal of Rheumatology. 2011; 38(12):2643-2652

459. Paulus DJ, Rogers AH, Bakhshaie J, Vowles KE, Zvolensky MJ. Pain severity and prescription opioid misuse among individuals with chronic pain: The moderating role of alcohol use severity. Drug and Alcohol Dependence. 2019; 204:107456

460. Pazin C, de Souza Mitidieri AM, Silva AP, Gurian MB, Poli-Neto OB, Rosa ESJC. Treatment of bladder pain syndrome and interstitial cystitis: a systematic review. International Urogynecology Journal. 2016; 27(5):697-708

461. Peacock A, Degenhardt L, Campbell G, Larance B, Nielsen S, Hall W et al. A typology of predictive risk factors for non-adherent medication-related behaviors among chronic non-cancer pain patients prescribed opioids: A cohort study. Pain Physician. 2016; 19(3):E421-434

462. Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. Journal of Pain and Symptom Management. 2001; 21(6):511-526

463. Pergolizzi JV, Jr., Raffa RB. Safety And Efficacy Of The Unique Opioid Buprenorphine For The Treatment Of Chronic Pain. Journal of Pain Research. 2019; 12:3299-3317

464. Pergolizzi JV, Raffa RB, Marcum Z, Colucci S, Ripa SR. Safety of buprenorphine transdermal system in the management of pain in older adults. Postgraduate Medicine. 2017; 129(1):92-101

465. Pergolizzi JV, Raffa RB, Taylor R, Rodriguez G, Nalamachu S, Langley P. A review of duloxetine 60mg once-daily dosing for the management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain due to chronic osteoarthritis pain and low back pain. Pain Practice. 2013; 13(3):239-252

466. Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. European Journal of Pain. 2014; 18(8):1067-1080

467. Petzke F, Jensen KB, Kosek E, Choy E, Carville S, Fransson P et al. Using fMRI to evaluate the effects of milnacipran on central pain processing in patients with fibromyalgia. Scandinavian Journal of Pain. 2013; 4(2):65-74

468. Pickering G, Macian N, Delage N, Picard P, Cardot JM, Sickout-Arondo S et al. Milnacipran poorly modulates pain in patients suffering from fibromyalgia: a randomized double-blind controlled study. Drug Design, Development and Therapy. 2018; 12:2485-2496

469. Pilowsky I, Barrow CG. A controlled study of psychotherapy and amitriptyline used individually and in combination in the treatment of chronic intractable, 'psychogenic' pain. Pain. 1990; 40(1):3-19

470. Polackwich AS, Shoskes DA. Chronic prostatitis/chronic pelvic pain syndrome: A review of evaluation and therapy. Prostate Cancer and Prostatic Diseases. 2016; 19(2):132-138

471. Pontari MA, Krieger JN, Litwin MS, White PC, Anderson RU, McNaughton-Collins M et al. Pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. Archives of Internal Medicine. 2010; 170(17):1586-1593

472. Pontari MA, Krieger JN, Litwin MS, White PC, Anderson RU, McNaughton-Collins M et al. A randomized placebo-controlled multicenter trial of pregabalin for the treatment of men with chronic prostatitis/chronic pelvic pain syndrome. Journal of Urology. 2009; 181(4):123

473. Porucznik CA, Johnson EM, Sauer B, Crook J, Rolfs RT. Studying adverse events related to prescription opioids: The Utah experience. Pain Medicine. 2011; 12(SUPPL. 2):S16-S25

474. Posner IA. Treatment of fibromyalgia syndrome with intravenous lidocaine: A prospective, randomized pilot study. Journal of Musculoskeletal Pain. 1994; 2(4):55-65

475. Potvin S, Morin M, Cloutier C, Gendron A, Bissonnette A, Marchand S. Add-on treatment of quetiapine for fibromyalgia: a pilot, randomized, double-blind, placebo-controlled 12-week trial. Journal of Clinical Psychopharmacology. 2012; 32(5):684-687

476. Przeklasa-Muszynska A, Dobrogowski J. Transdermal buprenorphine for the treatment of moderate to severe chronic pain: results from a large multicenter, non-

interventional post-marketing study in Poland. Current Medical Research and Opinion. 2011; 27(6):1109-1117

477. Purcell C, Patkar AA, Masand PS, Jiang W, Krulewicz S, Dube E et al. Predictors of response to a placebo-controlled, double-blind trial of paroxetine controlled release in fibromyalgia. 157th Annual Meeting of the American Psychiatric Association; 2004 May 1-6; New York, NY. 2004:NR361

478. Quijada-Carrera J, Valenzuela-Castano A, Povedano-Gomez J, Fernandez-Rodriguez A, Hernanz-Mediano W, Gutierrez-Rubio A et al. Comparison of tenoxicam and bromazepan in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. Pain. 1996; 65(2-3):221-225

479. Quijada J, Valenzuela A, Povedano J, Hernanz W, Fernández A, Gutiérrez A et al. Controlled clinical trial of tenoxicam and bromazepam in primary fibromyalgia. Revista Española de Reumatología. 1994; 21(5):195

480. Radbruch L, Sabatowski R, Petzke F, Brunsch-Radbruch A, Grond S, Lehmann KA. Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. Palliative Medicine. 2001; 15(4):309-321

481. Radbruch L, Vielvoye-Kerkmeer A. Buprenorphine TDS: The clinical development - Rationale and results. International Journal of Clinical Practice, Supplement. 2003; (133):15-18

482. Rasmussen P, Riishede J. Facial pain treated with carbamazepin (Tegretol). Acta Neurologica Scandinavica. 1970; 46(4):385-408

483. Rauck R, Coffey RJ, Schultz DM, Wallace MS, Webster LR, McCarville SE et al. Intrathecal gabapentin to treat chronic intractable noncancer pain. Anesthesiology. 2013; 119(3):675-686

484. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of long-acting opioids and mortality in patients with chronic noncancer pain. JAMA. 2016; 315(22):2415-2423

485. Reichenbach ZW, Sloan J, Rizvi-Toner A, Bayman L, Valestin J, Schey R. A 4-week pilot study with the cannabinoid receptor agonist dronabinol and its effect on metabolic parameters in a randomized trial. Clinical Therapeutics. 2015; 37(10):2267-2274

486. Reinecke H, Weber C, Lange K, Simon M, Stein C, Sorgatz H. Analgesic efficacy of opioids in chronic pain: recent meta-analyses. British Journal of Pharmacology. 2015; 172(2):324-333

487. Ren WW, Zhou ZY, Xu MM, Long S, Tang GZ, Mao HJ et al. Treatment of persistent somatoform pain disorder by floating needle therapy and duloxetine. Chinese Journal of Integrated Traditional and Western Medicine. 2016; 36(2):166-171

488. Rentsch CT, Edelman EJ, Justice AC, Marshall BDL, Xu K, Smith AH et al. Patterns and Correlates of Prescription Opioid Receipt Among US Veterans: A National, 18-Year Observational Cohort Study. AIDS and Behavior. 2019; 23(12):3340-3349

489. Reps JM, Cepeda MS, Ryan PB. Wisdom of the CROUD: Development and validation of a patient-level prediction model for opioid use disorder using population-level claims data. PloS One. 2020; 15(2):e0228632

490. Richardson E, Bedson J, Chen Y, Lacey R, Dunn KM. Increased risk of reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain: A matched cohort study in the Clinical Practice Research Datalink. European Journal of Pain. 2018; 22(9):1701-1708

491. Riediger C, Schuster T, Barlinn K, Maier S, Weitz J, Siepmann T. Adverse effects of antidepressants for chronic pain: A systematic review and meta-analysis. Frontiers in Neurology. 2017; 8:307

492. Riera R. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. Sao Paulo Medical Journal. 2015; 133(5):454

493. Rizzatti-Barbosa CM, Nogueira MT, de Andrade ED, Ambrosano GM, de Barbosa JR. Clinical evaluation of amitriptyline for the control of chronic pain caused by temporomandibular joint disorders. Cranio. 2003; 21(3):221-225

494. Rodriguez De Rivera-Campillo ME, Lopez-Lopez J, Chimenos-Kustner E. Treatment of burning mouth syndrome with topical clonazepam. Piel. 2011; 26(6):263-268

495. Rodriguez de Rivera Campillo E, Lopez-Lopez J, Chimenos-Kustner E. Response to topical clonazepam in patients with burning mouth syndrome: a clinical study. Bulletin du Groupement International pour la Recherche Scientifique en Stomatologie et Odontologie. 2010; 49(1):19-29

496. Roldan OV, Maglione H, Carreira R, Mainieri S. Piroxicam, diazepam and placebo in the treatment of temporomandibular joint dysfunction. Double blind study. Revista de la Asociación Odontológica Argentina. 1990; 78(2):83-85

497. Roskell NS, Beard SM, Zhao Y, Le TK. A meta-analysis of pain response in the treatment of fibromyalgia. Pain Practice. 2011; 11(6):516-527

498. Rossi E, Gallardo F, Weil MW. Prazepam as the initial treatment of myofascial pain-dysfunction syndrome. IRCS Medical Science. 1983; 11(7):637-638

499. Roth T, Bhadra-Brown P, Pitman VW, Resnick EM. Pregabalin improves fibromyalgia-related sleep disturbance. Clinical Journal of Pain. 2016; 32(4):308-312

500. Roth T, Lankford DA, Bhadra P, Whalen E, Resnick EM. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis Care and Research. 2012; 64(4):597-606

501. Roxburgh A, Bruno R, Larance B, Burns L. Prescription of opioid analgesics and related harms in Australia. Medical Journal of Australia. 2011; 195(5):280-284

502. Ruan X. Drug-related side effects of long-term intrathecal morphine therapy. Pain Physician. 2007; 10(2):357-366

503. Rubinstein AL, Carpenter DM. Association between commonly prescribed opioids and androgen deficiency in men: A retrospective cohort analysis. Pain Medicine. 2017; 18(4):637-644

504. Russell IJ, Crofford LJ, Leon T, Cappelleri JC, Bushmakin AG, Whalen E et al. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Medicine. 2009; 10(6):604-610

505. Russell IJ, Fletcher EM, Michalek JE, McBroom PC, Hester GG. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. A double-blind, placebo-controlled study. Arthritis and Rheumatism. 1991; 34(5):552-560

506. Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. JCR: Journal of Clinical Rheumatology. 2000; 6(5):250-257

507. Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain. 2008; 136(3):432-444

508. Salas J, Scherrer JF, Ahmedani BK, Copeland LA, Bucholz KK, Sullivan MD et al. Gender and the association between long-term prescription opioid use and new-onset depression. Journal of Pain. 2018; 19(1):88-98

509. Salas J, Scherrer JF, Schneider FD, Sullivan MD, Bucholz KK, Burroughs T et al. New-onset depression following stable, slow, and rapid rate of prescription opioid dose escalation. Pain. 2017; 158(2):306-312

510. Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. Archives of Internal Medicine. 2002; 162(1):19-24

511. Samborski W, Lezanska-Szpera M, Rybakowski JK. Effects of antidepressant mirtazapine on fibromyalgia symptoms. Roczniki Akademii Medycznej W Bialymstoku. 2004; 49:265-269

512. Santos J, Alarcão J, Fareleira F, Vaz-Carneiro A, Costa J. Tapentadol for chronic musculoskeletal pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD009923. DOI: 10.1002/14651858.CD009923.pub2.

513. Santos TGD, Miranda IAS, Nygaard CC, Schreiner L, Castro RA, Haddad JM. Systematic review of oral therapy for the treatment of symptoms of bladder pain syndrome: The Brazilian guidelines Revista Brasileira de Ginecologia e Obstetricia. 2018; 40(2):96-102

514. Sarzi-Puttini P, Buskila D, Carrabba M, Doria A, Atzeni F. Treatment strategy in fibromyalgia syndrome: where are we now? Seminars in Arthritis and Rheumatism. 2008; 37(6):353-365

515. Sator-Katzenschlager SM, Scharbert G, Kress HG, Frickey N, Ellend A, Gleiss A et al. Chronic pelvic pain treated with gabapentin and amitriptyline: a randomized controlled pilot study. Wiener Klinische Wochenschrift. 2005; 117(21-22):761-768

516. Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB et al. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. Journal of General Internal Medicine. 2010; 25(4):310-315

517. Schaeffer EM. Re: Preliminary assessment of safety and efficacy in proof-of-concept, randomized clinical trial of tanezumab for chronic prostatitis/chronic pelvic pain syndrome. Journal of Urology. 2013; 190(1):138

518. Scherrer JF, Salas J, Copeland LA, Stock EM, Ahmedani BK, Sullivan MD et al. Prescription opioid duration, dose, and increased risk of depression in 3 large patient populations. Annals of Family Medicine. 2016; 14(1):54-62

519. Scherrer JF, Salas J, Sullivan MD, Schneider FD, Bucholz KK, Burroughs T et al. The influence of prescription opioid use duration and dose on development of treatment resistant depression. Preventive Medicine. 2016; 91:110-116

520. Scherrer JF, Svrakic DM, Freedland KE, Chrusciel T, Balasubramanian S, Bucholz KK et al. Prescription opioid analgesics increase the risk of depression. Journal of General Internal Medicine. 2014; 29(3):491-499

521. Schilder JC, Sigtermans MJ, Schouten AC, Putter H, Dahan A, Noldus LP et al. Pain relief is associated with improvement in motor function in complex regional pain syndrome type 1: secondary analysis of a placebo-controlled study on the effects of ketamine. Journal of Pain. 2013; 14(11):1514-1521

522. Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD003870. DOI: 10.1002/14651858.CD003870.pub6.

523. Schoevers RA, Chaves TV, Balukova SM, Rot MA, Kortekaas R. Oral ketamine for the treatment of pain and treatment-resistant depression+. British Journal of Psychiatry. 2016; 208(2):108-113

524. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain. 2009; 147(1-3):107-115

525. Scrivani SJ, Chaudry A, Maciewicz RJ, Keith DA. Chronic neurogenic facial pain: lack of response to intravenous phentolamine. Journal of Orofacial Pain. 1999; 13(2):89-96

526. Scudds RA, Janzen V, Delaney G, Heck C, McCain GA, Russell AL et al. The use of topical 4% lidocaine in spheno-palatine ganglion blocks for the treatment of chronic muscle pain syndromes: a randomized, controlled trial. Pain. 1995; 62(1):69-77

527. Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD004844. DOI: 10.1002/14651858.CD004844.pub3.

528. Sencan S, Ak S, Karan A, Muslumanoglu L, Ozcan E, Berker E. A study to compare the therapeutic efficacy of aerobic exercise and paroxetine in fibromyalgia syndrome. Journal of Back and Musculoskeletal Rehabilitation. 2004; 17(2):57-61

529. Senye M, Mir CF, Morton S, Thie NM. Topical nonsteroidal anti-inflammatory medications for treatment of temporomandibular joint degenerative pain: a systematic review. Journal of Orofacial Pain. 2012; 26(1):26-32

530. Setnik B, Pixton GC, Webster LR. Safety profile of extended-release morphine sulfate with sequestered naltrexone hydrochloride in older patients: Pooled analysis of three clinical trials. Current Medical Research and Opinion. 2016; 32(3):563-572

531. Setnik B, Roland CL, Pixton GC, Sommerville KW. Prescription opioid abuse and misuse: gap between primary-care investigator assessment and actual extent of these behaviors among patients with chronic pain. Postgraduate Medicine. 2017; 129(1):5-11

532. Shen C, Zhao X, Dwibedi N, Wiener RC, Findley PA, Sambamoorthi U. Opioid use and the presence of Alzheimer's disease and related dementias among elderly Medicare beneficiaries diagnosed with chronic pain conditions. Alzheimer's & Dementia : Translational Research & Clinical Interventions. 2018; 4:661-668

533. Shipton EE, Shipton AJ, Williman JA, Shipton EA. Deaths from opioid overdosing: Implications of Coroners' Inquest Reports 2008-2012 and annual rise in opioid prescription rates: A population-based cohort study. Pain and Therapy. 2017; 6(2):203-215

534. Sigtermans MJ, van Hilten JJ, Bauer MC, Arbous MS, Marinus J, Sarton EY et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain. 2009; 145(3):304-311

535. Siler AC, Gardner H, Yanit K, Cushman T, McDonagh M. Systematic review of the comparative effectiveness of antiepileptic drugs for fibromyalgia. Journal of Pain. 2011; 12(4):407-415

536. Silverman SL, Backonja M, Pauer L, Landen J, Bhadra Brown P, Scavone JM et al. Effect of baseline characteristics on the pain response to pregabalin in fibromyalgia patients with comorbid depression. Pain Medicine. 2017; 19(3):419-428

537. Singer E, Dionne R. A controlled evaluation of ibuprofen and diazepam for chronic orofacial muscle pain. Journal of Orofacial Pain. 1997; 11(2):139-146

538. Sjogren P, Gronbaek M, Peuckmann V, Ekholm O. A population-based cohort study on chronic pain: the role of opioids. Clinical Journal of Pain. 2010; 26(9):763-769

539. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. Journal of Pain. 2008; 9(2):164-173

540. Skurtveit S, Furu K, Borchgrevink P, Handal M, Fredheim O. To what extent does a cohort of new users of weak opioids develop persistent or probable problematic opioid use? Pain. 2011; 152(7):1555-1561

541. Smith B, Peterson K, Fu R, McDonagh M, Thakurta S. Drug class review: Drugs for fibromyalgia: Final original evidence tables. Portland, OR. Oregon Health & Science University, 2011.

542. Smith CP. Male chronic pelvic pain: An update. Indian Journal of Urology. 2016; 32(1):34-39

543. Smith DM, Weitzel KW, Elsey AR, Langaee T, Gong Y, Wake DT et al. CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. Genetics in Medicine. 2019; 21(8):1842-1850

544. Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J et al. The comparative safety of opioids for nonmalignant pain in older adults. Archives of Internal Medicine. 2010; 170(22):1979-1986

545. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Archives of Internal Medicine. 2010; 170(22):1968-1976

546. Sorensen J, Bengtsson A, Backman E, Henriksson KG, Bengtsson M. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. Scandinavian Journal of Rheumatology. 1995; 24(6):360-365

547. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. Clinical Therapeutics. 2004; 26(11):1808-1820

548. Spaeth M. Arnold LM, Rosen A, Pritchett YL, D'Souza DN, Goldstein DJ, Iyengar S, Wernicke JF. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 119: 5-15, 2005 - Commentary. Journal of Musculoskeletal Pain. 2006; 14(2):55

549. Spinhoven P, Van der Does AJ, Van Dijk E, Van Rood YR. Heart-focused anxiety as a mediating variable in the treatment of noncardiac chest pain by cognitive-behavioral therapy and paroxetine. Journal of Psychosomatic Research. 2010; 69(3):227-235

550. Spoelstra SK, Borg C, Weijmar Schultz WC. Anticonvulsant pharmacotherapy for generalized and localized vulvodynia: a critical review of the literature. Journal of Psychosomatic Obstetrics & Gynecology. 2013; 34(3):133-138

551. Stacey BR, Dworkin RH, Murphy K, Sharma U, Emir B, Griesing T. Pregabalin in the treatment of refractory neuropathic pain: results of a 15-month open-label trial. Pain Medicine. 2008; 9(8):1202-1208

552. Stannard C, Gaskell H, Derry S, Aldington D, Cole P, Cooper TE et al. Hydromorphone for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD011604. DOI: 10.1002/14651858.CD011604.pub2.

553. Staud R, Lucas YE, Price DD, Robinson ME. Effects of milnacipran on clinical pain and hyperalgesia of patients with fibromyalgia: results of a 6-week randomized controlled trial. Journal of Pain. 2015; 16(8):750-759

554. Staud R, Weyl EE, Bartley E, Price DD, Robinson ME. Analgesic and anti-hyperalgesic effects of muscle injections with lidocaine or saline in patients with fibromyalgia syndrome. European Journal of Pain. 2014; 18(6):803-812

555. Sternbach RA, Deems LM, Timmermans G, Huey LY. On the sensitivity of the tourniquet pain test. Pain. 1977; 3(2):105-110

556. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018; 159(10):1932-1954

557. Stollenwerk A, Sohns M, Heisig F, Elling C, von Zabern D. Review of Post-Marketing Safety Data on Tapentadol, a Centrally Acting Analgesic. Advances in Therapy. 2018; 35(1):12-30

558. Straube S, Derry S, Moore RA, Paine J, McQuay HJ. Pregabalin in fibromyalgia--responder analysis from individual patient data. BMC Musculoskeletal Disorders. 2010; 11:150

559. Straube S, Moore RA, Paine J, Derry S, Phillips CJ, Hallier E et al. Interference with work in fibromyalgia: effect of treatment with pregabalin and relation to pain response. BMC Musculoskeletal Disorders. 2011; 12:125

560. Strauss S, Grothe M, Usichenko T, Neumann N, Byblow WD, Lotze M. Inhibition of the primary sensorimotor cortex by topical anesthesia of the forearm in patients with complex regional pain syndrome. Pain. 2015; 156(12):2556-2561

561. Sullivan M. Depression effects on long-term prescription opioid use, abuse, and addiction. Clinical Journal of Pain. 2018; Epublication

562. Sultan A, Gaskell H, Derry S, Moore RA. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials. BMC Neurology. 2008; 8:29

563. Suttiruksa S, Yeephu S, Prateepavanich P, Suthisisang C. Effects of mirtazapine on quality of life of Thai patients with fibromyalgia syndrome: A double-blind, randomized, placebo-controlled trial. Asian Biomedicine. 2016; 10(5):435-445

564. Ta LE, Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: A randomized placebo-controlled comparison of celecoxib to naproxen. Pain. 2004; 111(1-2):13-21

565. Tagarro I, Herrera J, Barutell C, Diez MC, Marin M, Samper D et al. Effect of a simple dose-escalation schedule on tramadol tolerability : assessment in the clinical setting. Clinical Drug Investigation. 2005; 25(1):23-31

566. Tammiala-Salonen T, Forssell H. Trazodone in burning mouth pain: a placebo-controlled, double-blind study. Journal of Orofacial Pain. 1999; 13(2):83-88

567. Tang NKY, Stella MT, Banks PDW, Sandhu HK, Berna C. The effect of opioid therapy on sleep quality in patients with chronic non-malignant pain: A systematic review and exploratory meta-analysis. Sleep Medicine Reviews. 2019; 45:105-126

568. Tanum L, Malt U. Mianserin Treatment of Idiopathic Abdominal Pain. Gut. 1994; 35 (Suppl 4):A169

569. Taskaynatan MA, Ozgul A, Tan AK, Dincer K, Kalyon TA. Bier block with methylprednisolone and lidocaine in CRPS type I: a randomized, double-blinded, placebo-controlled study. Regional Anesthesia and Pain Medicine. 2004; 29(5):408-412

570. Taylor R, Pergolizzi JV, Raffa RB. Tapentadol extended release for chronic pain patients. Advances in Therapy. 2013; 30(1):14-27

571. Thakral M, Walker RL, Saunders K, Shortreed SM, Dublin S, Parchman M et al. Impact of Opioid Dose Reduction and Risk Mitigation Initiatives on Chronic Opioid Therapy Patients at Higher Risk for Opioid-Related Adverse Outcomes. Pain Medicine. 2018; 19(12):2450-2458

572. Thakur D, Dickerson S, Kumar Bhutani M, Junor R. Impact of prolonged-release oxycodone/naloxone on outcomes affecting patients' daily functioning in comparison with extended-release tapentadol: a systematic review. Clinical Therapeutics. 2015; 37(1):212-224

573. Theoharides TC, Whitmore K, Stanford E, Moldwin R, O'Leary MP. Interstitial cystitis: bladder pain and beyond. Expert Opinion on Pharmacotherapy. 2008; 9(17):2979-2994

574. Tkacz J, Pesa J, Vo L, Kardel PG, Un H, Volpicelli JR et al. Opioid analgesic-treated chronic pain patients at risk for problematic use. American Journal of Managed Care. 2013; 19(11):871-880

575. Todorov AA, Kolchev CB, Todorov AB. Tiagabine and gabapentin for the management of chronic pain. Clinical Journal of Pain. 2005; 21(4):358-361

576. Trugman JM, Palmer RH, Ma Y. Milnacipran effects on 24-hour ambulatory blood pressure and heart rate in fibromyalgia patients: A randomized, placebo-controlled, dose-escalation study. Current Medical Research and Opinion. 2014; 30(4):589-597

577. Tsang CC, Giudice MG. Nabilone for the management of pain. Pharmacotherapy. 2016; 36(3):273-286

578. Tschopp KP, Gysin C. Local injection therapy in 107 patients with myofascial pain syndrome of the head and neck. ORL: Journal of Oto-Rhino-Laryngology and Its Related Specialties. 1996; 58(6):306-310

579. Turkington D, Grant JB, Ferrier IN, Rao NS, Linsley KR, Young AH. A randomized controlled trial of fluvoxamine in prostatodynia, a male somatoform pain disorder. Journal of Clinical Psychiatry. 2002; 63(9):778-781

580. Turner BJ, Liang Y. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: Interactions with mental health disorders. Journal of General Internal Medicine. 2015; 30(8):1081-1096

581. Turner JA, Shortreed SM, Saunders KW, LeResche L, Thielke S, Von Korff M. Does association of opioid use with pain and function differ by fibromyalgia or widespread pain status? Pain. 2016; 157(10):2208-2216

582. Turner JA, Shortreed SM, Saunders KW, LeResche L, Von Korff M. Association of levels of opioid use with pain and activity interference among patients initiating chronic opioid therapy: a longitudinal study. Pain. 2016; 157(4):849-857

583. Tyrer S, Lauder J, Michie M, Griffiths H, Charlton J. The effect of trazodone in depressed and non-depressed patients in chronic pain. 8th Congress of the Association of European Psychiatrists London, UK 7-12th July. 1996;

584. Tzellos T, Toulis K, Papazisis G, Zampeli V, Kouvelas D. Efficacy and safety/tolerability of gabapentin and pregabalin in the treatment of fibromyalgia: An evidence-based evaluation. Basic and Clinical Pharmacology and Toxicology. 2009; 104(6):493-494

585. Tzellos TG, Toulis KA, Goulis DG, Papazisis G, Zampeli VA, Vakfari A et al. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. Journal of Clinical Pharmacy and Therapeutics. 2010; 35(6):639-656

586. Uceyler N, Hauser W, Sommer C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. Arthritis and Rheumatism. 2008; 59(9):1279-1298

587. Üçeyler N, Sommer C, Walitt B, Häuser W. Anticonvulsants for fibromyalgia. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD010782. DOI: 10.1002/14651858.CD010782.pub2.

588. Usha PR, Naidu MUR, Kumar TR, Shobha JC, Kumar TV, Prasad VBN. A comparative study of the effects of fluoxetine, amitriptyline and placebo on salivary flow and haemodynamic parameters in patients with chronic pain. Asia Pacific Journal of Pharmacology. 1995; 10(1):21-24

589. Vaisman MA, Gantsev SK, Gazilov AA, Rudoi SV. Comparative assessment of chronic pain syndrome treatment methods in patients with small pelvis neoplasms. Anesteziologiia i Reanimatologiia. 1996; (4):31-35

590. 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; 160(4):860-869

591. van de Vusse AC, Stomp-van den Berg SG, Kessels AH, Weber WE. Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1 [ISRCTN84121379]. BMC Neurology. 2004; 4:13

592. Van Houdenhove B, Verstraeten D, Onghena P, De Cuyper H. Chronic idiopathic pain, mianserin and 'masked' depression. Psychotherapy and Psychosomatics. 1992; 58(1):46-53

593. van Ophoven A, Pokupic S, Heinecke A, Hertle L. A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. Journal of Urology. 2004; 172(2):533-536

594. VanderWeide LA, Smith SM, Trinkley KE. A systematic review of the efficacy of venlafaxine for the treatment of fibromyalgia. Journal of Clinical Pharmacy and Therapeutics. 2015; 40(1):1-6

595. Varia I, Logue E, O'Connor C, Newby K, Wagner HR, Davenport C et al. Randomized trial of sertraline in patients with unexplained chest pain of noncardiac origin. American Heart Journal. 2000; 140(3):367-372

596. Varma A, Sapra M, Iranmanesh A. Impact of opioid therapy on gonadal hormones: focus on buprenorphine. Hormone Molecular Biology and Clinical Investigation. 2018; Epublication

597. Veiga DR, Mendonca L, Sampaio R, Lopes JC, Azevedo LF. Incidence and Health Related Quality of Life of Opioid-Induced Constipation in Chronic Noncancer Pain Patients: A Prospective Multicentre Cohort Study. Pain Research and Treatment. 2018; 2018:5704627

598. Venâncio Rde A, Alencar FG, Zamperini C. Different substances and dry-needling injections in patients with myofascial pain and headaches. Cranio. 2008; 26(2):96-103

599. Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, Conno F. A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. Journal of Pain and Symptom Management. 1986; 1(4):203-207

600. Vincent K, Baranowski A, Bhattacharya S, Birch J, Cheong Y, Cregg R et al. GaPP2, a multicentre randomised controlled trial of the efficacy of gabapentin for the management of chronic pelvic pain in wome: study protocol. BMJ Open. 2018; 8(1):e014924

601. Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Human Psychopharmacology. 2004; 19(Suppl 1):S27-35

602. Von Korff M, Shortreed SM, LeResche L, Saunders K, Thielke S, Thakral M et al. A longitudinal study of depression among middle-aged and senior patients initiating chronic opioid therapy. Journal of Affective Disorders. 2017; 211:136-143

603. Voon P, Karamouzian M, Kerr T. Chronic pain and opioid misuse: a review of reviews. Substance Abuse Treatment, Prevention, & Policy. 2017; 12(1):36

604. Vosburg SK, Severtson SG, Dart RC, Cicero TJ, Kurtz SP, Parrino MW et al. Assessment of Tapentadol API Abuse Liability with the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System. Journal of Pain. 2018; 19(4):439-453

605. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015; 156(4):569-576

606. Walitt B, Klose P, Fitzcharles M-A, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD011694. DOI: 10.1002/14651858.CD011694.pub2.

607. Walitt B, Klose P, Uceyler N, Phillips T, Hauser W. Antipsychotics for fibromyalgia in adults. Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD011804. DOI: dx.doi.org/10.1002/14651858.CD011804.pub2.

608. Walitt B, Urrútia G, Nishishinya MB, Cantrell SE, Häuser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD011735. DOI: 10.1002/14651858.CD011735.

609. Wallace MS, Ridgeway BM, Leung AY, Gerayli A, Yaksh TL. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. Anesthesiology. 2000; 92(1):75-83

610. Wang D. Opioid medications in the management of chronic abdominal pain. Current Pain and Headache Reports. 2017; 21:40

611. Wang F, Ruberg SJ, Gaynor PJ, Heinloth AN, Arnold LM. Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia. Journal of Pain. 2011; 12(10):1088-1094

612. Wang W, Sun YH, Wang YY, Wang YT, Wang W, Li YQ et al. Treatment of functional chest pain with antidepressants: a meta-analysis. Pain Physician. 2012; 15(2):E131-142

613. Wang YX, Ren ZH, Wang SJ. A double-blind study on trazodone in the treatment of persistent somatoform pain disorder. Chinese journal of pain medicine. 2003; 9(2):70-72

614. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesthesia and Analgesia. 2010; 110(2):604-610

615. Warfield CA. Controlled-release morphine tablets in patients with chronic cancer pain: A narrative review of controlled clinical trials. Cancer. 1998; 82(12):2299-2306

616. Weber H, Lange R, Kuperwasser B, McCann B, Okamoto A, Steup A. Tolerability of tapentadol extended release (ER) based on discontinuations because of adverse events in patients with moderate-to-severe chronic pain. European Journal of Pain. 2009; 13(Suppl 1):S205

617. Weber H, Lange R, Kuperwasser B, McCann B, Okamoto A, Steup A. Tolerability of tapentadol extended release (ER) based on discontinuations because of adverse events in patients with moderate to severe chronic pain: results of a 1-year randomized phase 3 safety study. Rheumatology. 2010; 49(Suppl 1):i78-i80

618. Wei J, Lane NE, Bolster MB, Dubreuil M, Zeng C, Misra D et al. Association of Tramadol Use With Risk of Hip Fracture. Journal of Bone and Mineral Research. 2020; 35(4):631-640

619. Welsch P, Petzke F, Klose P, Hauser W. Opioids for chronic osteoarthritis pain: An updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. European Journal of Pain. 2020; 24(4):685-703

620. Wen W, Lynch SY, Munera C, Swanton R, Ripa SR, Maibach H. Application site adverse events associated with the buprenorphine transdermal system: a pooled analysis. Expert Opinion on Drug Safety. 2013; 12(3):309-319

621. Wersocki E, Bedson J, Chen Y, LeResche L, Dunn KM. Comprehensive systematic review of long-term opioids in women with chronic noncancer pain and associated reproductive dysfunction (hypothalamic-pituitary-gonadal axis disruption). Pain. 2017; 158(1):8-16

622. Wertli MM, Kessels AG, Perez RS, Bachmann LM, Brunner F. Rational pain management in complex regional pain syndrome 1 (CRPS 1)--a network meta-analysis. Pain Medicine. 2014; 15(9):1575-1589

623. Wieckiewicz M, Boening K, Wiland P, Shiau YY, Paradowska-Stolarz A. Reported concepts for the treatment modalities and pain management of temporomandibular disorders. Journal of Headache and Pain. 2015; 16(1):1-12

624. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD001133. DOI: 10.1002/14651858.CD001133.pub2.

625. Wiffen PJ, Derry S, Lunn MP, Moore RA. Topiramate for neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD008314. DOI: 10.1002/14651858.CD008314.pub3.

626. Wiffen PJ, Derry S, Moore RA. Lamotrigine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD006044. DOI: 10.1002/14651858.CD006044.pub4.

627. Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice AS et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD010567. DOI: 10.1002/14651858.CD010567.pub2.

628. Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD005451. DOI: 10.1002/14651858.CD005451.pub3.

629. Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD005451. DOI: 10.1002/14651858.CD005451.pub2.

630. Wiffen PJ, Derry S, Moore RA, Stannard C, Aldington D, Cole P et al. Buprenorphine for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD011603. DOI: 10.1002/14651858.CD011603.pub2.

631. Wiffen PJ, Knaggs R, Derry S, Cole P, Phillips T, Moore RA. Paracetamol (acetaminophen) with or without codeine or dihydrocodeine for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD012227. DOI: 10.1002/14651858.CD012227.pub2.

632. Wild JE, Grond S, Kuperwasser B, Gilbert J, McCann B, Lange B et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Practice. 2010; 10(5):416-427

633. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scandinavian Journal of Rheumatology. 1994; 23(5):255-259

634. Wolff RF, Reid K, di Nisio M, Aune D, Truyers C, Hernandez AV et al. Systematic review of adverse events of buprenorphine patch versus fentanyl patch in patients with chronic moderate-to-severe pain. Pain Management. 2012; 2(4):351-362

635. Won A, Lapane KL, Vallow S, Schein J, Morris JN, Lipsitz LA. Long-term effects of analgesics in a population of elderly nursing home residents with persistent nonmalignant pain. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2006; 61(2):165-169

636. Worley MJ, Heinzerling KG, Shoptaw S, Ling W. Volatility and change in chronic pain severity predict outcomes of treatment for prescription opioid addiction. Addiction. 2017; 112(7):1202-1209

637. Wu Z, Xia S, Geng H, Zhu H, Tang J, Zhang T et al. Combined therapy for chronic prostatitis chronic pelvic pain syndrome with doxazosin and diclofenac. Chinese journal of andrology. 2008; 22(7):20-25

638. Xu J, Cheng YQ, Lv SP, Li XZ, Feng R, Cui RM. A controlled study of paroxetine and amitriptyline in the treatment of primary fibromyalgia syndrome. Chinese mental health journal. 2006; 20(8):542-544

639. Xu J, Yang J, Lin P, Rosenquist E, Cheng J. Intravenous therapies for complex regional pain syndrome: A systematic review. Anesthesia and Analgesia. 2016; 122(3):843-856

640. Yang W, Propert KJ, Landis JR. Estimating the efficacy of an interstitial cystitis/painful bladder syndrome medication in a randomized trial with both non-adherence and loss to follow-up. Statistics in Medicine. 2014; 33(20):3547-3555

641. Yarborough BJH, Stumbo SP, Stoneburner A, Smith N, Dobscha SK, Deyo RA et al. Correlates of Benzodiazepine Use and Adverse Outcomes among Patients with Chronic Pain Prescribed Long-term Opioid Therapy. Pain Medicine (United States). 2019; 20(6):1148-1155

642. Yee LY, Lopez JR. Transdermal fentanyl. Annals of Pharmacotherapy. 1992; 26(11):1393-1399

643. Yeephu S, Suthisisang C, Suttiruksa S, Prateepavanich P, Limampai P, Russell IJ. Efficacy and safety of mirtazapine in fibromyalgia syndrome patients: a randomized placebo-controlled pilot study. Annals of Pharmacotherapy. 2013; 47(7-8):921-932

644. Yue Q, Ma Y, Teng Y, Zhu Y, Liu H, Xu S et al. An updated analysis of opioids increasing the risk of fractures. PloS One. 2020; 15(4):e0220216

645. Yunus MB, Masi AT, Aldag JC. Short term effects of ibuprofen in primary fibromyalgia syndrome: a double blind, placebo controlled trial. Journal of Rheumatology. 1989; 16(4):527-532

646. Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome. Cochrane Database of Systematic Reviews 2005, Issue 1. Art. No.: CD002779. DOI: 10.1002/14651858.CD002779.pub2.

647. Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome: a systematic review. Journal of Orofacial Pain. 2003; 17(4):293-300

648. Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: A systemic review and meta-analysis. Current Pain & Headache Reports. 2018; 22(2):12

649. Zhao S, Deng T, Luo L, Wang J, Li E, Liu L et al. Association between opioid use and risk of erectile dysfunction: A systematic review and meta-analysis. Journal of Sexual Medicine. 2017; 14(10):1209-1219

650. Zhao WP, Zhang ZG, Li XD, Yu D, Rui XF, Li GH et al. Celecoxib reduces symptoms in men with difficult chronic pelvic pain syndrome (Category IIIA). Brazilian Journal of Medical and Biological Research. 2009; 42(10):963-967

651. Ziegler CM, Wiechnik J, Muhling J. Analgesic effects of intra-articular morphine in patients with temporomandibular joint disorders: A prospective, double-blind, placebo-controlled clinical trial. Journal of Oral and Maxillofacial Surgery. 2010; 68(3):622-627

652. Zitman FG, Linssen AC, Edelbroek PM, Stijnen T. Low dose amitriptyline in chronic pain: the gain is modest. Pain. 1990; 42(1):35-42

653. Zoppi M, Grossi E, Signorini M, Vaiani G, Zamponi A. Analgesic activity of nabumetone vs placebo in myofascial pain syndromes (MPS). Clinical and Experimental Rheumatology. 1990; 8 (Suppl. 4):Abstr P 76

654. Zorba Paster R. Chronic pain management issues in the primary care setting and the utility of long-acting opioids. Expert Opinion on Pharmacotherapy. 2010; 11(11):1823-1833

# Appendices

# Appendix A: Review protocols

## Review protocol for pharmacological treatment

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | Not registered. |
| 1. | Review title | What is the clinical and cost effectiveness of pharmacological interventions for chronic primary pain? |
| 2. | Review question | What is the clinical and cost effectiveness of pharmacological interventions for chronic primary pain? |
| 3. | Objective | To determine the most clinically and cost effective pharmacological intervention for chronic primary pain. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• CINAHL, Current Nursing and Allied Health Literature<br><br>Searches will be restricted by:<br>• English language<br>• Human studies<br>• Letters and comments are excluded. |

| | | |
|---|---|---|
| | | Other searches:<br>• Inclusion lists of relevant systematic reviews will be checked by the reviewer.<br>The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.<br>The full search strategies will be published in the final review. |
| 5. | Condition or domain being studied | Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) and functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms. |
| 6. | Population | Inclusion: People, aged 16 years and over, with chronic primary pain (whose pain management is not addressed by existing NICE guidance) (chronic widespread pain, complex regional pain syndrome, chronic visceral pain, chronic orofacial pain , chronic primary musculoskeletal pain other than orofacial)<br><br>Exclusion: Those whose pain management is addressed by existing NICE guidance. |
| 7. | Intervention/Exposure/Test | Interventions:<br>• oral paracetamol<br>• non-steroidal anti-inflammatory drugs (by any route)<br>• ketamine (by any route)<br>• topical or intravenous local anaesthetics<br>• local anaesthetics and/or corticosteroids by injection (trigger point)<br>• oral or transdermal, intrathecal opioids (morphine, oxycodone, hydromorphone, buprenorphine, fentanyl, methadone, meptazinol, tapentadol, targinact, codeine, dihydrocodeine, tramadol, cocodamol, codydramol, naltrexone)<br>• oral anti-epilepsy drugs (gabapentin, pregabalin, sodium valproate, carbamazepine, oxcarbazepine, topiramate, lamotrigine, lacosamide, levetiracetam)<br>• oral anti-depressants<br>  ○ tricyclic antidepressants (e.g. amitriptyline, nortriptyline, clomipramine, imipramine) |

| | | |
|---|---|---|
| | | ○ selective serotonin re-uptake inhibitors (e.g. fluoxetine, citalopram)<br>○ serotonin norepinephrine re-uptake inhibitors (e.g. duloxetine, venlafaxine)<br>○ tetracyclic antidepressants (mirtazapine)<br>• oral cannabinoids (nabilone, nabixamols oromucosal spray)<br>• antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole)<br>• benzodiazepines (diazepam, oxazepam, lorazepam, temazepam, nitrazepam, clonazepam) |
| 8. | Comparator/Reference standard/Confounding factors | Comparators:<br>• each other (drug class)[a]<br>• placebo |
| 9. | Types of study to be included | Randomised controlled trials and systematic reviews of randomised controlled trials<br>Cross-over randomised controlled trials will be considered if no non-cross-over randomised controlled trial evidence is identified.<br>Enriched enrolment trials will be excluded as evidence from trials employing this methodology was considered to be of lower quality due to the increased risk of participant blinding/performance bias and the limited applicability to the wider review population.<br>[a] A stepped approach will be taken for within-class comparisons. If the evidence suggests superiority of a particular class after the class-comparison, within class comparison of that class will be explored. |
| 10. | Other exclusion criteria | Non-English language studies.<br>Within-class comparison |
| 11. | Context | A clear understanding of the evidence for the effectiveness of chronic primary pain treatments:<br>• improves the confidence of healthcare professionals in their conversations about pain, and<br>• helps healthcare professionals and patients to have realistic expectations about outcomes of treatment. |
| 12. | Primary outcomes (critical outcomes) | • Pain reduction (any validated scale) at ≤3 months, >3 months*<br>• health related quality of life (including meaningful activity) at ≤3 months, >3 months* |

| | | |
|---|---|---|
| | | • physical function (5 minute walk, sit to stand, Roland Morris Disability Questionnaire, Oswestry Disability Index, Canadian Occupational Performance Measure) at ≤3 months, >3 months*<br>• psychological distress (depression/ anxiety) (preferably Hospital Anxiety and Depression Scale) at ≤3 months, >3 months*<br>• discontinuation due to adverse events at ≤3 months, >3 months*<br>* outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months |
| 13. | Secondary outcomes (important outcomes) | • use of healthcare services at ≤3 months, >3 months*<br>• sleep at ≤3 months, >3 months*<br>* outcomes will be extracted at the longest time point up to 3 months and at the longest time point after 3 months |
| 14. | Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br>EviBASE will be used for data extraction.<br>Study investigators may be contacted for missing data where time and resources allow. |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the Cochrane Risk of Bias (2.0) tool. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. |
| 16. | Strategy for data synthesis | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. |

| | | | |
|---|---|---|---|
| 17. | Analysis of sub-groups | Proposed sensitivity / subgroup analysis to be explored where there is heterogeneity:<br>• chronic widespread pain<br>• complex regional pain<br>• visceral pain<br>• orofacial pain<br>• chronic primary musculoskeletal pain | |
| 18. | Type and method of review | ☒ | Intervention |
| | | ☐ | Diagnostic |
| | | ☐ | Prognostic |
| | | ☐ | Qualitative |
| | | ☐ | Epidemiologic |
| | | ☐ | Service Delivery |
| | | ☐ | Other (please specify) |
| 19. | Language | English | |
| 20. | Country | England | |
| 21. | Anticipated or actual start date | NA – not registered on PROSPERO | |
| 22. | Anticipated completion date | 19/08/2020 | |
| 23. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>Chronicpain@nice.org.uk | |

| | | |
|---|---|---|
| | | 5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre |
| 24. | Review team members | From the National Guideline Centre:<br>Serena Carville, Guideline Lead<br>Maria Smyth, Senior Systematic Reviewer<br>Rebecca Boffa, Senior Systematic Reviewer<br>Margaret Constanti, Senior Health Economist<br>Joseph Runicles, Information Specialist<br>Katie Broomfield, Project Manager |
| 25. | Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. |
| 26. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| 27. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10069 |
| 28. | Other registration details | - |

| | | |
|---|---|---|
| 29. | Reference/URL for published protocol | - |
| 30. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 31. | Keywords | - |
| 32. | Details of existing review of same topic by same authors | - |
| 33. | Additional information | - |
| 34. | Details of final publication | www.nice.org.uk |

# Review protocol for long term safety of opioids for chronic pain

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | Not registered. |
| 1. | Review title | What is the long-term safety of opioids for the management of chronic pain? |
| 2. | Review question | What is the long-term safety of opioids for the management of chronic pain? |
| 3. | Objective | To determine the long-term safety of opioids for the management of chronic pain. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR) |

| | | |
|---|---|---|
| | | • Embase<br>• MEDLINE<br>• CINAHL, Current Nursing and Allied Health Literature<br><br>Searches will be restricted by:<br>• English language<br>• Human studies<br>• Letters and comments are excluded.<br><br>Other searches:<br>• Inclusion lists of relevant systematic reviews will be checked by the reviewer.<br><br>The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review. |
| 5. | Condition or domain being studied | Pain that persists or recurs for longer than 3 months. |
| 6. | Population | Inclusion: People, aged 16 years and over, with chronic pain.<br><br>Exclusion: None |
| 7. | Intervention/Exposure/Test | Interventions:<br>• oral or transdermal opioids (morphine, oxycodone, hydromorphone, buprenorphine, fentanyl, methadone, meptazinol, tapentadol, targinact, codeine, dihydrocodeine, tramadol, cocodamol, codydramol, pethidine) prescribed for chronic pain management for ≥6 months |
| 8. | Comparator/Reference standard/Confounding factors | Comparators:<br>• placebo<br>• no treatment/usual care<br>• non-comparative data |
| 9. | Types of study to be included | Systematic reviews |

| | | |
|---|---|---|
| | | Randomised controlled trials<br>Observational studies<br>We will use a minimum sample size to select studies for inclusion for observational studies. Where a large amount of evidence is identified for an intervention, we will preferentially extract the largest studies until the committee are satisfied that a sufficient amount of evidence has been identified.<br><br>We will extract data according to the following hierarchy:<br>1.Randomised controlled trials<br>2.Large observational studies (including cohorts, case series and case-control if no cohorts or case series are identified). Initially limited to n>5000. If insufficient evidence identified, sample size threshold will be lowered to n>1000 for comparative data. |
| 10. | Other exclusion criteria | Non-English language studies<br>Within-class comparison<br>Case reports<br>Observational studies where <5,000 participants receive the intervention, in the first instance (see note above re. hierarchy).<br>Studies where the participants receive the intervention for <6 months |
| 11. | Context | A clear understanding of the evidence for the effectiveness of chronic pain treatments:<br>• improves the confidence of healthcare professionals in their conversations about pain, and<br>• helps healthcare professionals and patients to have realistic expectations about outcomes of treatment. |
| 12. | Primary outcomes (critical outcomes) | Serious adverse events:<br>• cognitive impairment<br>• fractures and falls<br>• sexual dysfunction/endocrine impairment<br>• immune dysfunction<br>• sleep apnoea<br>• cardiovascular events |

| | | | |
|---|---|---|---|
| | | • all-cause mortality<br>• self-harm/suicide<br>• dependence<br>• depressive symptoms/mood disturbances<br><br>outcomes will be extracted at the longest time point up to 6 months, at the longest time point up to 1 year and at the longest time point after 1 year | |
| 13. | Secondary outcomes (important outcomes) | None | |
| 14. | Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br>EviBASE will be used for data extraction.<br>Study investigators may be contacted for missing data where time and resources allow. | |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the Cochrane Risk of Bias (2.0) tool. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. | |
| 16. | Strategy for data synthesis | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. | |
| 17. | Analysis of sub-groups | Proposed sensitivity/subgroup analysis to be explored where there is heterogeneity:<br>• age (16-25, 25-65, 65 and over)<br>• co-prescribing | |
| 18. | Type and method of review | ☒ | Intervention |

| | | | |
|---|---|---|---|
| | | ☐ | Diagnostic |
| | | ☐ | Prognostic |
| | | ☐ | Qualitative |
| | | ☐ | Epidemiologic |
| | | ☐ | Service Delivery |
| | | ☐ | Other (please specify) |
| 19. | Language | English | |
| 20. | Country | England | |
| 21. | Anticipated or actual start date | NA – not registered on PROSPERO | |
| 22. | Anticipated completion date | 19/08/2020 | |
| 23. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>Chronicpain@nice.org.uk<br><br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | |
| 24. | Review team members | From the National Guideline Centre:<br>Serena Carville, Guideline Lead<br>Maria Smyth, Senior Systematic Reviewer | |

| | | |
|---|---|---|
| | | Rebecca Boffa, Senior Systematic Reviewer<br>Margaret Constanti, Senior Health Economist<br>Joseph Runicles, Information Specialist<br>Katie Broomfield, Project Manager |
| 25. | Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. |
| 26. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| 27. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10069 |
| 28. | Other registration details | - |
| 29. | Reference/URL for published protocol | - |
| 30. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 31. | Keywords | - |

| | | |
|---|---|---|
| 32. | Details of existing review of same topic by same authors | - |
| 33. | Additional information | - |
| 34. | Details of final publication | www.nice.org.uk |

## Review protocol for safety of gabapentinoids

| ID | Field | Content |
|---|---|---|
| 0. | PROSPERO registration number | Not registered. |
| 1. | Review title | What is the long-term safety of gabapentinoids for the management of chronic pain? |
| 2. | Review question | What is the long-term safety of gabapentinoids for the management of chronic pain? |
| 3. | Objective | To determine the long-term safety of gabapentinoids for the management of chronic pain. |
| 4. | Searches | The following databases will be searched:<br>• Cochrane Central Register of Controlled Trials (CENTRAL)<br>• Cochrane Database of Systematic Reviews (CDSR)<br>• Embase<br>• MEDLINE<br>• CINAHL, Current Nursing and Allied Health Literature<br><br>Searches will be restricted by: |

| | | |
|---|---|---|
| | | • English language<br>• Human studies<br>• Letters and comments are excluded.<br><br>Other searches:<br>• Inclusion lists of relevant systematic reviews will be checked by the reviewer.<br><br>The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.<br><br>The full search strategies will be published in the final review. |
| 5. | Condition or domain being studied | Pain that persists or recurs for longer than 3 months. |
| 6. | Population | Inclusion: People, aged 16 years and over, with chronic pain.<br><br>Exclusion: None |
| 7. | Intervention/Exposure/Test | Interventions:<br>• gabapentin<br>• pregabalin<br>prescribed for pain management. |
| 8. | Comparator/Reference standard/Confounding factors | Comparators:<br>• placebo<br>• each other<br>• non-comparative data |
| 9. | Types of study to be included | Systematic reviews |

| | | |
|---|---|---|
| | | Randomised controlled trials<br>Observational studies<br>We will use a minimum sample size to select studies for inclusion for observational studies. Where a large amount of evidence is identified for an intervention, we will preferentially extract the largest studies until the committee are satisfied that a sufficient amount of evidence has been identified.<br><br>We will extract data according to the following hierarchy:<br>1.Large observational studies (including cohorts, case series and case-control if no cohorts or case series are identified). Initially limited to n>5000. If insufficient evidence identified, sample size threshold will be lowered to n>1000.<br>2.Randomised controlled trials |
| 10. | Other exclusion criteria | Non-English language studies<br>Case reports<br>Observational studies where <5,000 participants receive the intervention, in the first instance (see note above re. hierarchy).<br>Studies where the participants receive the intervention for <6 months |
| 11. | Context | A clear understanding of the evidence for the effectiveness of chronic pain treatments:<br>• improves the confidence of healthcare professionals in their conversations about pain, and<br>• helps healthcare professionals and patients to have realistic expectations about outcomes of treatment. |
| 12. | Primary outcomes (critical outcomes) | Serious adverse events:<br>• cognitive impairment<br>• gait disturbance/ataxia<br>• loss of balance<br>• all-cause mortality<br>• dependence<br>• weight gain<br>• rash<br>• peripheral oedema |

| | | | |
|---|---|---|---|
| | | • tremor<br>• somnolence<br><br>Outcomes will be extracted at the longest time point up to 6 months, at the longest time point up to 1 year and at the longest time point after 1 year | |
| 13. | Secondary outcomes (important outcomes) | None | |
| 14. | Data extraction (selection and coding) | EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.<br>EviBASE will be used for data extraction.<br>Study investigators may be contacted for missing data where time and resources allow. | |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the Cochrane Risk of Bias (2.0) tool. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. | |
| 16. | Strategy for data synthesis | Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. | |
| 17. | Analysis of sub-groups | Proposed sensitivity/subgroup analysis to be explored where there is heterogeneity:<br>• age (16-25, 25-65, 65 and over)<br>• co-prescribing | |
| 18. | Type and method of review | ☒ | Intervention |
| | | ☐ | Diagnostic |
| | | ☐ | Prognostic |

| | | | |
|---|---|---|---|
| | | ☐ | Qualitative |
| | | ☐ | Epidemiologic |
| | | ☐ | Service Delivery |
| | | ☐ | Other (please specify) |
| 19. | Language | English | |
| 20. | Country | England | |
| 21. | Anticipated or actual start date | NA – not registered on PROSPERO | |
| 22. | Anticipated completion date | 19/08/2020 | |
| 23. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br>Chronicpain@nice.org.uk<br><br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | |
| 24. | Review team members | From the National Guideline Centre:<br>Serena Carville, Guideline Lead<br>Maria Smyth, Senior Systematic Reviewer<br>Rebecca Boffa, Senior Systematic Reviewer<br>Margaret Constanti, Senior Health Economist | |

| | | |
|---|---|---|
| | | Joseph Runicles, Information Specialist<br><br>Katie Broomfield, Project Manager |
| 25. | Funding sources/sponsor | This systematic review is being completed by the National Guideline Centre which receives funding from NICE. |
| 26. | Conflicts of interest | All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline. |
| 27. | Collaborators | Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10069 |
| 28. | Other registration details | - |
| 29. | Reference/URL for published protocol | - |
| 30. | Dissemination plans | NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:<br>• notifying registered stakeholders of publication<br>• publicising the guideline through NICE's newsletter and alerts<br>• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. |
| 31. | Keywords | - |
| 32. | Details of existing review of same topic by same authors | - |

| | | |
|---|---|---|
| 33. | Additional information | - |
| 34. | Details of final publication | www.nice.org.uk |

**Table 20: Health economic review protocol**

| Review question | All questions – health economic evidence |
|---|---|
| **Objectives** | To identify health economic studies relevant to any of the review questions. |
| **Search criteria** | • Populations, interventions and comparators must be as specified in the clinical review protocol above.<br>• Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis).<br>• Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.)<br>• Unpublished reports will not be considered unless submitted as part of a call for evidence.<br>• Studies must be in English. |
| **Search strategy** | A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. |
| **Review strategy** | Studies not meeting any of the search criteria above will be excluded. Studies published before 2002. Abstract-only studies and studies from non-OECD countries or the USA will also be excluded.<br>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[411]<br><br>**Inclusion and exclusion criteria**<br>• If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile.<br>• If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion**<br>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.<br><br>The health economist will be guided by the following hierarchies.<br>*Setting:*<br>• UK NHS (most applicable).<br>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). |

| | |
|---|---|
| | • OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>*Health economic study type:*<br>• Cost–utility analysis (most applicable).<br>• Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).<br>• Comparative cost analysis.<br>• Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.<br>*Year of analysis:*<br>• The more recent the study, the more applicable it will be.<br>• Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'.<br>• Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations.<br>*Quality and relevance of effectiveness data used in the health economic analysis:*<br>• The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. |

# Appendix B: Literature search strategies

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[411]

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

## B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 20 May 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies |
| Embase (OVID) | 1974 – 20 May 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2020 Issue 5 of 12<br>CENTRAL to 2020 Issue 5 of 12 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | Chronic pain/ |
| 2. | ((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab. |
| 3. | exp Complex Regional Pain Syndromes/ |
| 4. | (complex regional pain syndrome* or CRPS or causalgia).ti,ab. |
| 5. | ((reflex or sympathetic) adj2 dystroph*).ti,ab. |
| 6. | fibromyalgia/ |
| 7. | (fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab. |
| 8. | vulvodynia/ |
| 9. | (vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab. |
| 10. | interstitial cystitis/ |
| 11. | (interstitial adj2 cystitis).ti,ab. |
| 12. | algodystrophy/ |
| 13. | (algodystroph* or sudek or sudeck*).ti,ab. |
| 14. | exp myofascial pain syndromes/ |
| 15. | cystitis, interstitial/ |
| 16. | (loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab. |
| 17. | (LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab. |
| 18. | ((pelvic or pelvis) adj pain syndrome*).ti,ab. |
| 19. | ((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab. |
| 20. | (temporomandibular adj3 joint adj3 pain).ti,ab. |
| 21. | ((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab. |
| 22. | (functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab. |
| 23. | ((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab. |
| 24. | or/1-23 |
| 25. | letter/ |
| 26. | editorial/ |
| 27. | news/ |
| 28. | exp historical article/ |
| 29. | Anecdotes as Topic/ |
| 30. | comment/ |
| 31. | case report/ |
| 32. | (letter or comment*).ti. |
| 33. | or/25-32 |
| 34. | randomized controlled trial/ or random*.ti,ab. |
| 35. | 33 not 34 |
| 36. | animals/ not humans/ |
| 37. | exp Animals, Laboratory/ |
| 38. | exp Animal Experimentation/ |
| 39. | exp Models, Animal/ |
| 40. | exp Rodentia/ |
| 41. | (rat or rats or mouse or mice).ti. |
| 42. | or/35-41 |
| 43. | 24 not 42 |
| 44. | limit 43 to English language |
| 45. | exp *paracetamol/ |

| | |
|---|---|
| 46. | (acetaminophen or paracetamol).ti,ab. |
| 47. | exp analgesics, opioid/ |
| 48. | (non-steroid* or non-narcotic* or analgesic* or pharmacolog*).ti,ab. |
| 49. | exp *nonsteroid antiinflammatory agent/ or exp *analgesic agent/ |
| 50. | (NSAID* or ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac).ti,ab. |
| 51. | (Opioid* or Opiate*).ti,ab. |
| 52. | (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).ti,ab. |
| 53. | exp morphinans/ |
| 54. | (opium or omnopon or pantopon or papaveretum).ti,ab. |
| 55. | (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph* or hydrostat or hymorphan or laudicon or novolauden or palladone).ti,ab. |
| 56. | (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).ti,ab. |
| 57. | (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).ti,ab. |
| 58. | (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).ti,ab. |
| 59. | (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).ti,ab. |
| 60. | Ketobemidone.ti,ab. |
| 61. | (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).ti,ab. |
| 62. | (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).ti,ab. |
| 63. | Dextromoramide.ti,ab. |
| 64. | (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).ti,ab. |
| 65. | (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).ti,ab. |
| 66. | (Bezitramide or Burgodin).ti,ab. |
| 67. | (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).ti,ab. |
| 68. | exp *pentazocine lactate/ or exp *pentazocine/ or exp *paracetamol plus pentazocine/ or exp *naloxone plus pentazocine/ |
| 69. | (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).ti,ab. |
| 70. | exp *phenazocine/ |
| 71. | (Phenazocine or Prinadol or Narphen).ti,ab. |
| 72. | Oripavine.ti,ab. |
| 73. | (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).ti,ab. |
| 74. | (Etorphine or Immobilon or M99).ti,ab. |

| | |
|---|---|
| 75. | exp *butorphanol tartrate/ or exp *butorphanol/ |
| 76. | (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).ti,ab. |
| 77. | (Tilidine or tilidate or Valoron or Valtran or Tilidin).ti,ab. |
| 78. | exp *tramadol/ or exp *paracetamol plus tramadol/ |
| 79. | (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal* or tramedo or ultram or zamadol or zydol).ti,ab. |
| 80. | (Dezocine or Dalgan or 'WY-16225').ti,ab. |
| 81. | targinact.ti,ab. |
| 82. | exp *meptazinol/ |
| 83. | (Meptazinol or Meptid).ti,ab. |
| 84. | (Tapentadol or cg5503 or nucynta).ti,ab. |
| 85. | (Remifentanil or 'gi 87084b' or remifentanyl or ultiva).ti,ab. |
| 86. | exp *penicillin G sodium plus procaine penicillin/ or exp *procaine/ or exp *adrenalin plus procaine/ or exp *penicillin G sodium plus procaine penicillin plus streptomycin sulfate/ or exp *penicillin G potassium plus procaine penicillin plus streptomycin sulfate/ or exp *procaine penicillin/ or exp *penicillin G potassium plus procaine penicillin/ or exp *benzathine penicillin plus procaine penicillin/ or exp *procaine penicillin plus streptomycin sulfate/ |
| 87. | (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).ti,ab. |
| 88. | alfentanil.ti,ab. |
| 89. | (Alfenta or alfentanyl or fanaxal or limifen or rapifen).ti,ab. |
| 90. | (Dipipanone or co-dydramol or co-codamaol).ti,ab. |
| 91. | naltrexone/ or naloxone plus oxycodone/ |
| 92. | naltrexone.ti,ab. |
| 93. | ketamine/ |
| 94. | (ketamine or inducmina or ketalar or ketanest or calypso or narkamon or keta or velonarcon or ketmin or ketava or ketalin or ketina or brevinaze or keta-hameln).ti,ab. |
| 95. | ((topical or intravenous or intra-venous or IV) adj3 (an?esthe* or lidocain* or lignocain* or tetracain* or amethocain* or benzocain* or butamben or dibucain* or pramoxin* or prilocain* or etidocian)).ti,ab. |
| 96. | (emla* or eutectic mixture of local an?esthe* or tetracaine?adrenaline?cocain* or tetracaine?epinephrine?cocain* or lidocaine?adrenaline?tetracain* or lidocaine?epinephrine?tetracain*).ti,ab. |
| 97. | exp anticonvulsive agent/ |
| 98. | (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).ti,ab. |
| 99. | (antidepress* or anti-depress*).ti,ab. |
| 100. | serotonin norepinephrine reuptake inhibitor*.ti,ab. |
| 101. | selective serotonin reuptake inhibitor*.ti,ab. |
| 102. | (SSRI or SNRI).ti,ab. |
| 103. | (amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline or clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine).ti,ab. |
| 104. | (cannabis or hemp or marijuana or ganja or hashish or marihuana or bhang or cannininoid or cannabinoids or marinol or dronabinol or nabilone or cesamet or dexanabinol or sativex or tetrahydrocannabinolor or nabixamols oromucosal spray).ti,ab. |

| | |
|---|---|
| 105. | (neurolept* or antipsychotic*).ti,ab. |
| 106. | neuroleptanalgesia/ |
| 107. | exp neuroleptic agent/ |
| 108. | (diazepam or oxazepam or lorazepam or temazepam or nitrazepam or cloazepam).ti,ab. |
| 109. | or/45-108 |
| 110. | 44 and 109 |
| 111. | randomized controlled trial.pt. |
| 112. | controlled clinical trial.pt. |
| 113. | randomi#ed.ti,ab. |
| 114. | placebo.ab. |
| 115. | randomly.ti,ab. |
| 116. | Clinical Trials as topic.sh. |
| 117. | trial.ti. |
| 118. | or/111-117 |
| 119. | Meta-Analysis/ |
| 120. | exp Meta-Analysis as Topic/ |
| 121. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 122. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 123. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 124. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 125. | (search* adj4 literature).ab. |
| 126. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 127. | cochrane.jw. |
| 128. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 129. | or/119-128 |
| 130. | 110 and (118 or 129) |

**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | Chronic pain/ |
| 2. | ((chronic or persist* or idiopathic or atypical or a-typical) adj4 pain).ti,ab. |
| 3. | exp Complex regional pain syndrome/ |
| 4. | (complex regional pain syndrome* or CRPS or causalgia).ti,ab. |
| 5. | ((reflex or sympathetic) adj2 dystroph*).ti,ab. |
| 6. | fibromyalgia/ |
| 7. | (fibromyalgia* or fibrositis or myofascial pain syndrome).ti,ab. |
| 8. | vulvodynia/ |
| 9. | (vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis).ti,ab. |
| 10. | interstitial cystitis/ |
| 11. | (interstitial adj2 cystitis).ti,ab. |
| 12. | algodystrophy/ |
| 13. | (algodystroph* or sudek or sudeck*).ti,ab. |
| 14. | myofascial pain/ |
| 15. | noncardiac chest pain/ |
| 16. | cystalgia/ |
| 17. | Pelvis pain syndrome/ |

| | |
|---|---|
| 18. | (loin pain adj (haematuria or hematuria) adj syndrome*).ti,ab. |
| 19. | (LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS).ti,ab. |
| 20. | ((pelvic or pelvis) adj pain syndrome*).ti,ab. |
| 21. | ((non-cardiac or noncardiac) adj3 chest adj3 pain).ti,ab. |
| 22. | (temporomandibular adj3 joint adj3 pain).ti,ab. |
| 23. | ((prostate or vulv* or bladder or perineal) adj3 pain).ti,ab. |
| 24. | (functional pain syndrome* or non-cancer pain or noncancer pain).ti,ab. |
| 25. | ((pelvic or pelvis or abdominal) adj3 pain adj3 (unknown or un-known or idiopathic or atypic* or a-typic*)).ti,ab. |
| 26. | or/1-25 |
| 27. | letter.pt. or letter/ |
| 28. | note.pt. |
| 29. | editorial.pt. |
| 30. | case report/ or case study/ |
| 31. | (letter or comment*).ti. |
| 32. | or/27-31 |
| 33. | randomized controlled trial/ or random*.ti,ab. |
| 34. | 32 not 33 |
| 35. | animal/ not human/ |
| 36. | nonhuman/ |
| 37. | exp Animal Experiment/ |
| 38. | exp Experimental Animal/ |
| 39. | animal model/ |
| 40. | exp Rodent/ |
| 41. | (rat or rats or mouse or mice).ti. |
| 42. | or/34-41 |
| 43. | 26 not 42 |
| 44. | limit 43 to English language |
| 45. | exp *paracetamol/ |
| 46. | (acetaminophen or paracetamol).ti,ab. |
| 47. | exp *narcotic analgesic agent/ |
| 48. | (non-steroid* or non-narcotic* or analgesic* or pharmacolog*).ti,ab. |
| 49. | exp *nonsteroid antiinflammatory agent/ or exp *analgesic agent/ |
| 50. | (NSAID* or ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac).ti,ab. |
| 51. | (Opioid* or Opiate*).ti,ab. |
| 52. | (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).ti,ab. |
| 53. | morphine/ |
| 54. | *opiate/ |
| 55. | (opium or omnopon or pantopon or papaveretum).ti,ab. |
| 56. | (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph* or hydrostat or hymorphan or laudicon or novolauden or palladone).ti,ab. |

| | |
|---|---|
| 57. | (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).ti,ab. |
| 58. | (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).ti,ab. |
| 59. | (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag).ti,ab. |
| 60. | (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).ti,ab. |
| 61. | Ketobemidone.ti,ab. |
| 62. | (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).ti,ab. |
| 63. | (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).ti,ab. |
| 64. | Dextromoramide.ti,ab. |
| 65. | (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium).ti,ab. |
| 66. | (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen).ti,ab. |
| 67. | (Bezitramide or Burgodin).ti,ab. |
| 68. | (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).ti,ab. |
| 69. | exp *benzomorphan derivative/ |
| 70. | exp *pentazocine lactate/ or exp *pentazocine/ or exp *paracetamol plus pentazocine/ or exp *naloxone plus pentazocine/ |
| 71. | (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin).ti,ab. |
| 72. | exp *phenazocine/ |
| 73. | (Phenazocine or Prinadol or Narphen).ti,ab. |
| 74. | Oripavine.ti,ab. |
| 75. | (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).ti,ab. |
| 76. | (Etorphine or Immobilon or M99).ti,ab. |
| 77. | exp *morphinan derivative/ |
| 78. | exp *butorphanol tartrate/ or exp *butorphanol/ |
| 79. | (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic).ti,ab. |
| 80. | (Tilidine or tilidate or Valoron or Valtran or Tilidin).ti,ab. |
| 81. | exp *tramadol/ or exp *paracetamol plus tramadol/ |
| 82. | (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal* or tramedo or ultram or zamadol or zydol).ti,ab. |
| 83. | (Dezocine or Dalgan or 'WY-16225').ti,ab. |
| 84. | targinact.ti,ab. |
| 85. | exp *meptazinol/ |
| 86. | (Meptazinol or Meptid).ti,ab. |
| 87. | (Tapentadol or cg5503 or nucynta).ti,ab. |
| 88. | (Remifentanil or 'gi 87084b' or remifentanyl or ultiva).ti,ab. |
| 89. | exp *penicillin G sodium plus procaine penicillin/ or exp *procaine/ or exp *adrenalin plus procaine/ or exp *penicillin G sodium plus procaine penicillin plus streptomycin sulfate/ or exp *penicillin G potassium plus procaine penicillin plus streptomycin sulfate/ or exp *procaine penicillin/ or exp *penicillin G potassium plus procaine penicillin/ or |

| | |
|---|---|
| | exp *benzathine penicillin plus procaine penicillin/ or exp *procaine penicillin plus streptomycin sulfate/ |
| 90. | (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra).ti,ab. |
| 91. | exp *cocodamol/ |
| 92. | alfentanil.ti,ab. |
| 93. | (Alfenta or alfentanyl or fanaxal or limifen or rapifen).ti,ab. |
| 94. | (Dipipanone or co-dydramol or co-codamaol).ti,ab. |
| 95. | naltrexone/ or naloxone plus oxycodone/ |
| 96. | naltrexone.ti,ab. |
| 97. | ketamine/ |
| 98. | (ketamine or inducmina or ketalar or ketanest or calypso or narkamon or keta or velonarcon or ketmin or ketava or ketalin or ketina or brevinaze or keta-hameln).ti,ab. |
| 99. | ((topical or intravenous or intra-venous or IV) adj3 (an?esthe* or lidocain* or lignocain* or tetracain* or amethocain* or benzocain* or butamben or dibucain* or pramoxin* or prilocain* or etidocian)).ti,ab. |
| 100. | (emla* or eutectic mixture of local an?esthe* or tetracaine?adrenaline?cocain* or tetracaine?epinephrine?cocain* or lidocaine?adrenaline?tetracain* or lidocaine?epinephrine?tetracain*).ti,ab. |
| 101. | exp anticonvulsive agent/ |
| 102. | (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide).ti,ab. |
| 103. | exp *antidepressant agent/ |
| 104. | (antidepress* or anti-depress*).ti,ab. |
| 105. | serotonin norepinephrine reuptake inhibitor*.ti,ab. |
| 106. | selective serotonin reuptake inhibitor*.ti,ab. |
| 107. | (SSRI or SNRI).ti,ab. |
| 108. | (amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline or clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine).ti,ab. |
| 109. | (cannabis or hemp or marijuana or ganja or hashish or marihuana or bhang or cannininoid or cannabinoids or marinol or dronabinol or nabilone or cesamet or dexanabinol or sativex or tetrahydrocannabinolor or nabixamols oromucosal spray).ti,ab. |
| 110. | (neurolept* or antipsychotic*).ti,ab. |
| 111. | neuroleptanalgesia/ |
| 112. | exp neuroleptic agent/ |
| 113. | exp benzodiazepine derivative/ |
| 114. | (diazepam or oxazepam or lorazepam or temazepam or nitrazepam or cloazepam).ti,ab. |
| 115. | or/45-114 |
| 116. | 44 and 115 |
| 117. | random*.ti,ab. |
| 118. | factorial*.ti,ab. |
| 119. | (crossover* or cross over*).ti,ab. |
| 120. | ((doubl* or singl*) adj blind*).ti,ab. |
| 121. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |

| | |
|---|---|
| 122. | crossover procedure/ |
| 123. | single blind procedure/ |
| 124. | randomized controlled trial/ |
| 125. | double blind procedure/ |
| 126. | or/117-125 |
| 127. | systematic review/ |
| 128. | meta-analysis/ |
| 129. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 130. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 131. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 132. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 133. | (search* adj4 literature).ab. |
| 134. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 135. | cochrane.jw. |
| 136. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 137. | or/127-136 |
| 138. | 116 and (126 or 137) |

**Cochrane Library (Wiley) search terms**

| | |
|---|---|
| #1. | MeSH descriptor: [Chronic Pain] explode all trees |
| #2. | ((chronic or persist* or idiopathic or atypical or a-typical) near/4 pain):ti,ab |
| #3. | MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees |
| #4. | (complex regional pain syndrome* or CRPS or causalgia):ti,ab |
| #5. | ((reflex or sympathetic) near/2 dystroph*):ti,ab |
| #6. | MeSH descriptor: [Fibromyalgia] explode all trees |
| #7. | (fibromyalgia* or fibrositis or myofascial pain syndrome):ti,ab |
| #8. | MeSH descriptor: [Vulvodynia] explode all trees |
| #9. | (vulvodynia or vestibulodynia or dyspareunia or vulvar vestibulitis or vulvitis):ti,ab |
| #10. | MeSH descriptor: [Cystitis, Interstitial] explode all trees |
| #11. | (interstitial near/2 cystitis):ti,ab |
| #12. | MeSH descriptor: [Reflex Sympathetic Dystrophy] explode all trees |
| #13. | (algodystroph* or sudek or sudeck*):ti,ab |
| #14. | MeSH descriptor: [Myofascial Pain Syndromes] explode all trees |
| #15. | (loin pain near (haematuria or hematuria) near syndrome*):ti,ab |
| #16. | (LPHS or prostatodynia or CPPS or atypic* odontalgia or a-typic* odontalgia or burning mouth syndrome* or phantom tooth pain or neuropathic orofacial pain or "myofascial pain" or MPS):ti,ab |
| #17. | ((pelvic or pelvis) near pain syndrome*):ti,ab |
| #18. | ((non-cardiac or noncardiac) near/3 chest near/3 pain):ti,ab |
| #19. | (temporomandibular near/3 joint near/3 pain):ti,ab |
| #20. | ((prostate or vulv* or bladder or perineal) near/3 pain):ti,ab |
| #21. | (functional pain syndrome* or non-cancer pain or noncancer pain):ti,ab |
| #22. | ((pelvic or pelvis or abdominal) near/3 pain near/3 (unknown or un-known or idiopathic or atypic* or a-typic*)):ti,ab |
| #23. | (or #1-#22) |
| #24. | MeSH descriptor: [Acetaminophen] explode all trees |

| | |
|---|---|
| #25. | (acetaminophen or paracetamol):ti,ab |
| #26. | MeSH descriptor: [Analgesics, Opioid] explode all trees |
| #27. | (non-steroid* or non-narcotic* or analgesic* or pharmacolog*):ti,ab |
| #28. | MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees |
| #29. | MeSH descriptor: [Analgesics] explode all trees |
| #30. | (NSAID* or ibuprofen or aspirin or naproxen or fenoprofen or flurbiprofen or ketoprofen or dexketoprofen or dexibuprofen or tiaprofenic acid or diclofenac or aceclofenac or indometacin or mefenamic acid or meloxicam or nabumetone or phenylbutazone or piroxicam or sulindac or tenoxicam or tolfenamic acid or ketorolac or celecoxib or etoricoxib or aceclofenac or acemetacin or diclofenac or etodolac):ti,ab |
| #31. | (Opioid* or Opiate*):ti,ab |
| #32. | (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph):ti,ab |
| #33. | MeSH descriptor: [Morphinans] explode all trees |
| #34. | (opium or omnopon or pantopon or papaveretum):ti,ab |
| #35. | (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph* or hydrostat or hymorphan or laudicon or novolauden or palladone):ti,ab |
| #36. | (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin):ti,ab |
| #37. | (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin):ti,ab |
| #38. | (Diamorphine or acetomorphine or diacetylmorphine or diagesil or diamorf or heroin or min-i-jet morphine sulfate or skag):ti,ab |
| #39. | (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup):ti,ab |
| #40. | Ketobemidone:ti,ab |
| #41. | (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan):ti,ab |
| #42. | (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze):ti,ab |
| #43. | Dextromoramide:ti,ab |
| #44. | (Piritramide or Dipidolor or dipydolor or Piridolan or Pirium):ti,ab |
| #45. | (Dextropropoxyphene or darvon or dolene or doloxene or levopropoxyphene or pp-cap or propoxyphene or proxyphen):ti,ab |
| #46. | (Bezitramide or Burgodin):ti,ab |
| #47. | (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron):ti,ab |
| #48. | MeSH descriptor: [Pentazocine] explode all trees |
| #49. | MeSH descriptor: [Naloxone] explode all trees |
| #50. | (Pentazocine or Fortral or Fortwin or lexir or Talacen or talwin):ti,ab |
| #51. | MeSH descriptor: [Phenazocine] explode all trees |
| #52. | (Phenazocine or Prinadol or Narphen):ti,ab |
| #53. | Oripavine:ti,ab |
| #54. | (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic):ti,ab |

| | |
|---|---|
| #55. | (Etorphine or Immobilon or M99):ti,ab |
| #56. | MeSH descriptor: [Butorphanol] explode all trees |
| #57. | (Butorphanol or 'bc2627' or beforal or dolorex or moradol or stadol or torbugesic):ti,ab |
| #58. | (Tilidine or tilidate or Valoron or Valtran or Tilidin):ti,ab |
| #59. | MeSH descriptor: [Tramadol] explode all trees |
| #60. | (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal* or tramedo or ultram or zamadol or zydol):ti,ab |
| #61. | (Dezocine or Dalgan or 'WY-16225'):ti,ab |
| #62. | targinact:ti,ab |
| #63. | MeSH descriptor: [Meptazinol] explode all trees |
| #64. | (Meptazinol or Meptid):ti,ab |
| #65. | (Tapentadol or cg5503 or nucynta):ti,ab |
| #66. | (Remifentanil or 'gi 87084b' or remifentanyl or ultiva):ti,ab |
| #67. | MeSH descriptor: [Penicillin G Procaine] explode all trees |
| #68. | MeSH descriptor: [Procaine] explode all trees |
| #69. | MeSH descriptor: [Penicillin G] explode all trees |
| #70. | MeSH descriptor: [Streptomycin] explode all trees |
| #71. | (Procaine or allocaine or anuject or gerokit or mericaine or novocaine or procaina serra):ti,ab |
| #72. | alfentanil:ti,ab |
| #73. | (Alfenta or alfentanyl or fanaxal or limifen or rapifen):ti,ab |
| #74. | (Dipipanone or co-dydramol or co-codamaol):ti,ab |
| #75. | MeSH descriptor: [Naltrexone] explode all trees |
| #76. | naltrexone:ti,ab |
| #77. | MeSH descriptor: [Ketamine] explode all trees |
| #78. | (ketamine or inducmina or ketalar or ketanest or calypso or narkamon or keta or velonarcon or ketmin or ketava or ketalin or ketina or brevinaze or keta-hameln):ti,ab |
| #79. | ((topical or intravenous or intra-venous or IV) near/3 (an?esthe* or lidocain* or lignocain* or tetracain* or amethocain* or benzocain* or butamben or dibucain* or pramoxin* or prilocain* or etidocian)):ti,ab |
| #80. | (emla* or eutectic mixture of local an?esthe* or tetracaine?adrenaline?cocain* or tetracaine?epinephrine?cocain* or lidocaine?adrenaline?tetracain* or lidocaine?epinephrine?tetracain*):ti,ab |
| #81. | MeSH descriptor: [Anticonvulsants] explode all trees |
| #82. | (carbamazepine or clobazam or clonazepam or ethosuximide or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or phenytoin or pregabalin or rufinamide or topiramate or valproate or vigabatrin or zonisamide):ti,ab |
| #83. | (antidepress* or anti-depress*):ti,ab |
| #84. | serotonin norepinephrine reuptake inhibitor*:ti,ab |
| #85. | selective serotonin reuptake inhibitor*:ti,ab |
| #86. | (SSRI or SNRI):ti,ab |
| #87. | (amoxapine or bupropion or citalopram or fluoxetine or fluvoxamine or maprotiline or mianserin or paroxetine or quipazine or ritanserin or sulpiride or trazodone or tryptophan or viloxazine or amitriptyline or clomipramine or desipramine or dothiepin or doxepin or imipramine or iprindole or lofepramine or nortriptyline or opipramol or protriptyline or trimipramine or nortriptyline or duloxetine or mirtazapine or venlafaxine):ti,ab |
| #88. | (cannabis or hemp or marijuana or ganja or hashish or marihuana or bhang or cannininoid or cannabinoids or marinol or dronabinol or nabilone or cesamet or dexanabinol or sativex or tetrahydrocannabinolor or nabixamols oromucosal spray):ti,ab |

| | |
|---|---|
| #89. | (neurolept* or antipsychotic*):ti,ab |
| #90. | MeSH descriptor: [Neuroleptanalgesia] explode all trees |
| #91. | MeSH descriptor: [Antipsychotic Agents] explode all trees |
| #92. | (diazepam or oxazepam or lorazepam or temazepam or nitrazepam or cloazepam):ti,ab |
| #93. | (or #24-#92) |
| #94. | #23 and #93 |

## B.2 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 20 May 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies<br>Observational studies |
| Embase (OVID) | 1974 – 20 May 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies<br>Observational studies |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2020 Issue 5 of 12<br>CENTRAL to 2020 Issue 5 of 12 | None |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | chronic pain/ or pain, intractable/ |
| 2. | ((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab. |
| 3. | or/1-2 |
| 4. | letter/ |
| 5. | editorial/ |
| 6. | news/ |
| 7. | exp historical article/ |
| 8. | Anecdotes as Topic/ |
| 9. | comment/ |
| 10. | case report/ |
| 11. | (letter or comment*).ti. |
| 12. | or/4-11 |

| | |
|---|---|
| 13. | randomized controlled trial/ or random*.ti,ab. |
| 14. | 12 not 13 |
| 15. | animals/ not humans/ |
| 16. | exp Animals, Laboratory/ |
| 17. | exp Animal Experimentation/ |
| 18. | exp Models, Animal/ |
| 19. | exp Rodentia/ |
| 20. | (rat or rats or mouse or mice).ti. |
| 21. | or/14-20 |
| 22. | 3 not 21 |
| 23. | limit 22 to English language |
| 24. | Pregabalin/ |
| 25. | (gabapentin* or 1 aminomethyl cyclohexaneacetic acid or neurontin or neurotonin or nupentin or gabagamma or gaba-gamma or gralise or horizant or phenibut or anvifen or fenibut or noofen or ci 945 or ci945 or dineurin or gabalept or gabaliquid geriasan or gabatin or go 3450 or go3450 or goe 3450 or goe3450 or kaptin or keneil or pregabalin or lyrica or 3 aminomethyl 5 methylhexanoic acid or 3 isobutyl 4 aminobutyric acid or 3 isobutyl GABA or 3 isobutylgaba or 4 amino 3 isobutylbutyric acid or ci 1008 or ci1008 or pd 144723 or pd144723).ti,ab. |
| 26. | (mirogabalin or atagabalin or 4-methylpregabalin or pd 200390 or pd200390 or ds 5565 or ds5565 or pd 217014 or pd217014).ti,ab. |
| 27. | or/24-26 |
| 28. | randomized controlled trial.pt. |
| 29. | controlled clinical trial.pt. |
| 30. | randomi#ed.ti,ab. |
| 31. | placebo.ab. |
| 32. | randomly.ti,ab. |
| 33. | Clinical Trials as topic.sh. |
| 34. | trial.ti. |
| 35. | or/28-34 |
| 36. | Meta-Analysis/ |
| 37. | exp Meta-Analysis as Topic/ |
| 38. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 39. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 40. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 41. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 42. | (search* adj4 literature).ab. |
| 43. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 44. | cochrane.jw. |
| 45. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 46. | or/36-45 |
| 47. | Epidemiologic studies/ |
| 48. | Observational study/ |
| 49. | exp Cohort studies/ |
| 50. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 51. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |

| | |
|---|---|
| 52. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 53. | Controlled Before-After Studies/ |
| 54. | Historically Controlled Study/ |
| 55. | Interrupted Time Series Analysis/ |
| 56. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 57. | or/47-56 |
| 58. | exp case control study/ |
| 59. | case control*.ti,ab. |
| 60. | or/58-59 |
| 61. | 57 or 60 |
| 62. | Cross-sectional studies/ |
| 63. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 64. | or/62-63 |
| 65. | 57 or 64 |
| 66. | 57 or 60 or 64 |
| 67. | 23 and 27 and (35 or 46 or 66) |

**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | chronic pain/ or pain, intractable/ |
| 2. | ((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab. |
| 3. | or/1-2 |
| 4. | letter.pt. or letter/ |
| 5. | note.pt. |
| 6. | editorial.pt. |
| 7. | case report/ or case study/ |
| 8. | (letter or comment*).ti. |
| 9. | or/4-8 |
| 10. | randomized controlled trial/ or random*.ti,ab. |
| 11. | 9 not 10 |
| 12. | animal/ not human/ |
| 13. | nonhuman/ |
| 14. | exp Animal Experiment/ |
| 15. | exp Experimental Animal/ |
| 16. | animal model/ |
| 17. | exp Rodent/ |
| 18. | (rat or rats or mouse or mice).ti. |
| 19. | or/11-18 |
| 20. | 3 not 19 |
| 21. | limit 20 to English language |
| 22. | pregabalin/ or gabapentin enacarbil/ or gabapentin/ |
| 23. | (gabapentin* or 1 aminomethyl cyclohexaneacetic acid or neurontin or neurotonin or nupentin or gabagamma or gaba-gamma or gralise or horizant or phenibut or anvifen or fenibut or noofen or ci 945 or ci945 or dineurin or gabalept or gabaliquid geriasan or gabatin or go 3450 or go3450 or goe 3450 or goe3450 or kaptin or keneil or pregabalin or lyrica or 3 aminomethyl 5 methylhexanoic acid or 3 isobutyl 4 aminobutyric acid or 3 isobutyl GABA or 3 isobutylgaba or 4 amino 3 isobutylbutyric acid or ci 1008 or ci1008 or pd 144723 or pd144723).ti,ab. |

| | |
|---|---|
| 24. | (mirogabalin or atagabalin or 4-methylpregabalin or pd 200390 or pd200390 or ds 5565 or ds5565 or pd 217014 or pd217014).ti,ab. |
| 25. | or/22-24 |
| 26. | random*.ti,ab. |
| 27. | factorial*.ti,ab. |
| 28. | (crossover* or cross over*).ti,ab. |
| 29. | ((doubl* or singl*) adj blind*).ti,ab. |
| 30. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 31. | crossover procedure/ |
| 32. | single blind procedure/ |
| 33. | randomized controlled trial/ |
| 34. | double blind procedure/ |
| 35. | or/26-34 |
| 36. | systematic review/ |
| 37. | meta-analysis/ |
| 38. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 39. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 40. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 41. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 42. | (search* adj4 literature).ab. |
| 43. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 44. | cochrane.jw. |
| 45. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 46. | or/36-45 |
| 47. | Clinical study/ |
| 48. | Observational study/ |
| 49. | family study/ |
| 50. | longitudinal study/ |
| 51. | retrospective study/ |
| 52. | prospective study/ |
| 53. | cohort analysis/ |
| 54. | follow-up/ |
| 55. | cohort*.ti,ab. |
| 56. | 54 and 55 |
| 57. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 58. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 59. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 60. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 61. | or/47-53,56-60 |
| 62. | exp case control study/ |
| 63. | case control*.ti,ab. |
| 64. | or/62-63 |
| 65. | 61 or 64 |

| | |
|---|---|
| 66. | cross-sectional study/ |
| 67. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 68. | or/66-67 |
| 69. | 61 or 68 |
| 70. | 61 or 64 or 68 |
| 71. | 21 and 25 and (35 or 46 or 70) |

**Cochrane Library (Wiley) search terms**

| | |
|---|---|
| #1. | MeSH descriptor: [Chronic Pain] explode all trees |
| #2. | MeSH descriptor: [Pain, Intractable] explode all trees |
| #3. | ((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) near/3 pain*):ti,ab |
| #4. | (or #1-#3) |
| #5. | MeSH descriptor: [Pregabalin] explode all trees |
| #6. | (gabapentin* or 1 aminomethyl cyclohexaneacetic acid or neurontin or neurotonin or nupentin or gabagamma or gaba-gamma or gralise or horizant or phenibut or anvifen or fenibut or noofen or ci 945 or ci945 or dineurin or gabalept or gabaliquid geriasan or gabatin or go 3450 or go3450 or goe 3450 or goe3450 or kaptin or keneil or pregabalin or lyrica or 3 aminomethyl 5 methylhexanoic acid or 3 isobutyl 4 aminobutyric acid or 3 isobutyl GABA or 3 isobutylgaba or 4 amino 3 isobutylbutyric acid or ci 1008 or ci1008 or pd 144723 or pd144723):ti,ab |
| #7. | (mirogabalin or atagabalin or 4-methylpregabalin or pd 200390 or pd200390 or ds 5565 or ds5565 or pd 217014 or pd217014):ti,ab |
| #8. | (or #6-#7) |
| #9. | #4 and #8 |

## B.3 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline (OVID) | 1946 – 20 May 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies<br>Observational studies |
| Embase (OVID) | 1974 – 20 May 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies<br>Observational studies |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2020 Issue 5 of 12<br>CENTRAL to 2020 Issue 5 of 12 | None |

| Database | Dates searched | Search filter used |
|---|---|---|
| | | |

**Medline (Ovid) search terms**

| | |
|---|---|
| 1. | chronic pain/ or pain, intractable/ |
| 2. | ((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab. |
| 3. | or/1-2 |
| 4. | letter/ |
| 5. | editorial/ |
| 6. | news/ |
| 7. | exp historical article/ |
| 8. | Anecdotes as Topic/ |
| 9. | comment/ |
| 10. | case report/ |
| 11. | (letter or comment*).ti. |
| 12. | or/4-11 |
| 13. | randomized controlled trial/ or random*.ti,ab. |
| 14. | 12 not 13 |
| 15. | animals/ not humans/ |
| 16. | exp Animals, Laboratory/ |
| 17. | exp Animal Experimentation/ |
| 18. | exp Models, Animal/ |
| 19. | exp Rodentia/ |
| 20. | (rat or rats or mouse or mice).ti. |
| 21. | or/14-20 |
| 22. | 3 not 21 |
| 23. | limit 22 to English language |
| 24. | exp Analgesics, Opioid/ |
| 25. | exp NARCOTICS/ |
| 26. | exp Opiate Alkaloids/ |
| 27. | (opiate* or opioid*).ti,ab. |
| 28. | (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).ti,ab. |
| 29. | exp morphinans/ |
| 30. | (opium or omnopon or pantopon or papaveretum).ti,ab. |
| 31. | (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph* or hydrostat or hymorphan or laudicon or novolauden or palladone).ti,ab. |
| 32. | (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).ti,ab. |
| 33. | (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).ti,ab. |
| 34. | (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).ti,ab. |

| | |
|---|---|
| 35. | (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).ti,ab. |
| 36. | exp *meptazinol/ |
| 37. | (Meptazinol or Meptid).ti,ab. |
| 38. | (Tapentadol or cg5503 or nucynta).ti,ab. |
| 39. | (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal* or tramedo or ultram or zamadol or zydol).ti,ab. |
| 40. | targinact.ti,ab. |
| 41. | (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).ti,ab. |
| 42. | (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).ti,ab. |
| 43. | exp *tramadol/ |
| 44. | (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).ti,ab. |
| 45. | (Dipipanone or co-dydramol or co-codamaol).ti,ab. |
| 46. | or/24-45 |
| 47. | randomized controlled trial.pt. |
| 48. | controlled clinical trial.pt. |
| 49. | randomi#ed.ti,ab. |
| 50. | placebo.ab. |
| 51. | randomly.ti,ab. |
| 52. | Clinical Trials as topic.sh. |
| 53. | trial.ti. |
| 54. | or/47-53 |
| 55. | Meta-Analysis/ |
| 56. | exp Meta-Analysis as Topic/ |
| 57. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 58. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 59. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 60. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 61. | (search* adj4 literature).ab. |
| 62. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 63. | cochrane.jw. |
| 64. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 65. | or/55-64 |
| 66. | Epidemiologic studies/ |
| 67. | Observational study/ |
| 68. | exp Cohort studies/ |
| 69. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 70. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 71. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |

| | |
|---|---|
| 72. | Controlled Before-After Studies/ |
| 73. | Historically Controlled Study/ |
| 74. | Interrupted Time Series Analysis/ |
| 75. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 76. | or/66-75 |
| 77. | exp case control study/ |
| 78. | case control*.ti,ab. |
| 79. | or/77-78 |
| 80. | 76 or 79 |
| 81. | Cross-sectional studies/ |
| 82. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 83. | or/81-82 |
| 84. | 76 or 83 |
| 85. | 76 or 79 or 83 |
| 86. | 23 and 46 and (54 or 65 or 85) |

**Embase (Ovid) search terms**

| | |
|---|---|
| 1. | chronic pain/ or intractable pain/ |
| 2. | ((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) adj3 pain*).ti,ab. |
| 3. | or/1-2 |
| 4. | letter.pt. or letter/ |
| 5. | note.pt. |
| 6. | editorial.pt. |
| 7. | case report/ or case study/ |
| 8. | (letter or comment*).ti. |
| 9. | or/4-8 |
| 10. | randomized controlled trial/ or random*.ti,ab. |
| 11. | 9 not 10 |
| 12. | animal/ not human/ |
| 13. | nonhuman/ |
| 14. | exp Animal Experiment/ |
| 15. | exp Experimental Animal/ |
| 16. | animal model/ |
| 17. | exp Rodent/ |
| 18. | (rat or rats or mouse or mice).ti. |
| 19. | or/11-18 |
| 20. | 3 not 19 |
| 21. | limit 20 to English language |
| 22. | exp narcotic analgesic agent/ |
| 23. | exp narcotic agent/ |
| 24. | exp opiate/ |
| 25. | (Opioid* or Opiate*).ti,ab. |
| 26. | (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph).ti,ab. |
| 27. | morphine/ |
| 28. | (opium or omnopon or pantopon or papaveretum).ti,ab. |

| | |
|---|---|
| 29. | (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph* or hydrostat or hymorphan or laudicon or novolauden or palladone).ti,ab. |
| 30. | (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin).ti,ab. |
| 31. | (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic).ti,ab. |
| 32. | (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze).ti,ab. |
| 33. | (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron).ti,ab. |
| 34. | exp *meptazinol/ |
| 35. | (Meptazinol or Meptid).ti,ab. |
| 36. | (Tapentadol or cg5503 or nucynta).ti,ab. |
| 37. | targinact.ti,ab. |
| 38. | (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup).ti,ab. |
| 39. | (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin).ti,ab. |
| 40. | exp *tramadol/ or exp *paracetamol plus tramadol/ |
| 41. | (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal* or tramedo or ultram or zamadol or zydol).ti,ab. |
| 42. | (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan).ti,ab. |
| 43. | (Dipipanone or co-dydramol or co-codamaol).ti,ab. |
| 44. | or/22-43 |
| 45. | random*.ti,ab. |
| 46. | factorial*.ti,ab. |
| 47. | (crossover* or cross over*).ti,ab. |
| 48. | ((doubl* or singl*) adj blind*).ti,ab. |
| 49. | (assign* or allocat* or volunteer* or placebo*).ti,ab. |
| 50. | crossover procedure/ |
| 51. | single blind procedure/ |
| 52. | randomized controlled trial/ |
| 53. | double blind procedure/ |
| 54. | or/45-53 |
| 55. | systematic review/ |
| 56. | meta-analysis/ |
| 57. | (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. |
| 58. | ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. |
| 59. | (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. |
| 60. | (search strategy or search criteria or systematic search or study selection or data extraction).ab. |
| 61. | (search* adj4 literature).ab. |

| | |
|---|---|
| 62. | (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. |
| 63. | cochrane.jw. |
| 64. | ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. |
| 65. | or/55-64 |
| 66. | Clinical study/ |
| 67. | Observational study/ |
| 68. | family study/ |
| 69. | longitudinal study/ |
| 70. | retrospective study/ |
| 71. | prospective study/ |
| 72. | cohort analysis/ |
| 73. | follow-up/ |
| 74. | cohort*.ti,ab. |
| 75. | 73 and 74 |
| 76. | (cohort adj (study or studies or analys* or data)).ti,ab. |
| 77. | ((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab. |
| 78. | ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 79. | (before adj2 after adj2 (study or studies or data)).ti,ab. |
| 80. | or/66-72,75-79 |
| 81. | exp case control study/ |
| 82. | case control*.ti,ab. |
| 83. | or/81-82 |
| 84. | 80 or 83 |
| 85. | cross-sectional study/ |
| 86. | (cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab. |
| 87. | or/85-86 |
| 88. | 80 or 87 |
| 89. | 80 or 83 or 87 |
| 90. | 21 and 44 and (54 or 65 or 89) |

**Cochrane Library (Wiley) search terms**

| | |
|---|---|
| #1. | MeSH descriptor: [Chronic Pain] this term only |
| #2. | MeSH descriptor: [Pain, Intractable] this term only |
| #3. | ((persist* or intract* or chronic or longstanding or long standing or longterm or long term or refractory or prolong* or long last* or sustain* or linger* or syndrome*) near/3 pain*):ti,ab |
| #4. | (or #1-#3) |
| #5. | MeSH descriptor: [Analgesics, Opioid] explode all trees |
| #6. | MeSH descriptor: [Narcotics] explode all trees |
| #7. | MeSH descriptor: [Opiate Alkaloids] explode all trees |
| #8. | (Opioid* or Opiate*):ti,ab |
| #9. | (morphine or Astramorph or avinza or depodur or duramorph or embeda or infumorph or kadian or m-eslon or morcap or morphia or ms contin or msir or mst or nepenthe or oramorph or rescudose or rms or roxanol or sevredol or statex or zomorph):ti,ab |
| #10. | MeSH descriptor: [Morphinans] explode all trees |
| #11. | (opium or omnopon or pantopon or papaveretum):ti,ab |

| | |
|---|---|
| #12. | (Hydromorphone or dihydromorphinone or dilaudid or dimorphone or exalgo or hydmrphn or hydromorph* or hydrostat or hymorphan or laudicon or novolauden or palladone):ti,ab |
| #13. | (oxycodone or Dazidox or dihydrohydroxycodeinone or dihydrone or dinarkon or endocodone or eth-oxydose or eucodal or hydroxycodeinon or m-oxy or oxiconum or oxycdn or oxycone or oxycontin or oxyfast or oxyir or pancodine or percocet or percolone or remoxy or roxicodone or theocodin):ti,ab |
| #14. | (Buprenorphine or '6029-m' or buprenex or buprex or prefin or Suboxone or subutex or temgesic):ti,ab |
| #15. | (Fentanyl or abstral or actiq or duragesic or fentanest or fentora or fentyl or ionsys or matrifen or nasalfent or onsolis or oralet or phentanyl or sublimaze):ti,ab |
| #16. | (methadone or adanon or althose or amidines or amidone or biodone or diskets or dolophine or Heptadon or metadol or metasedin or methaddict or metharose or Methadose or methdn or methex or phy or phymet or physeptone or pinadone or symoron):ti,ab |
| #17. | MeSH descriptor: [Meptazinol] explode all trees |
| #18. | (Meptazinol or Meptid):ti,ab |
| #19. | (Tapentadol or cg5503 or nucynta):ti,ab |
| #20. | targinact:ti,ab |
| #21. | (Codeine or ardinex or galcodine or isocodeine or methyl morphine or rx 336m or stanley-linctus or stanley-syrup):ti,ab |
| #22. | (Dihydrocodeine or contugesic or dhc mundipharma or dicodin or dihydcdn or paracodin or paramol or parzone or rikodeine or tiamon or tosidrin or tuscodin):ti,ab |
| #23. | MeSH descriptor: [Tramadol] explode all trees |
| #24. | (Tramadol or 'k-315' or ralivia or ryzolt or tramahexal or tramake insts or tramal* or tramedo or ultram or zamadol or zydol):ti,ab |
| #25. | (Pethidine or demerol or dolantin or dolargan or dolcontral or dolosal or dolsin or isonipecain or isonipecaine hydrochloride or lydol or meperidine or operidine epj or pethilorfan):ti,ab |
| #26. | (Dipipanone or co-dydramol or co-codamaol):ti,ab |
| #27. | (or #5-#26) |
| #28. | #4 and #27 |

# Appendix C: Clinical evidence selection

**Figure 1: Flow chart of clinical study selection for the review of Pharmacological management**

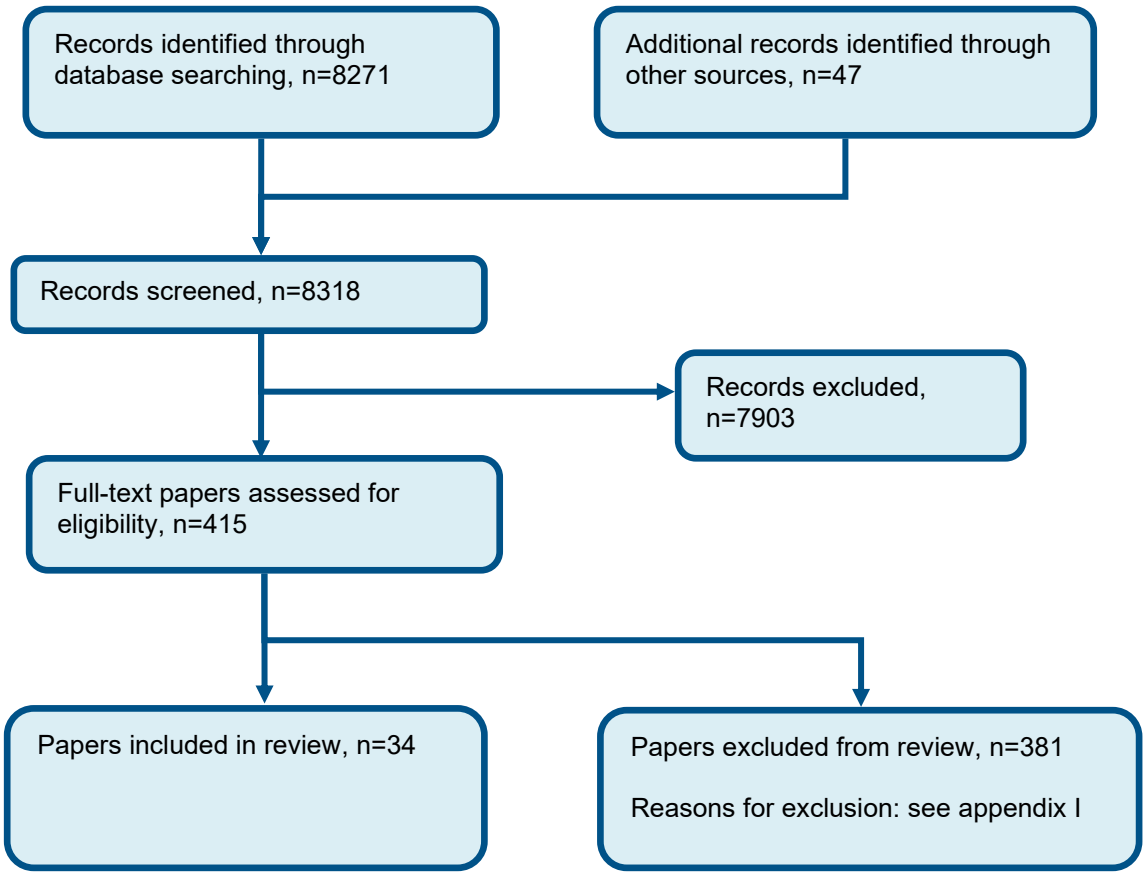


**Figure 2: Flow chart of clinical study selection for the review of long-term safety of opioids for chronic pain**

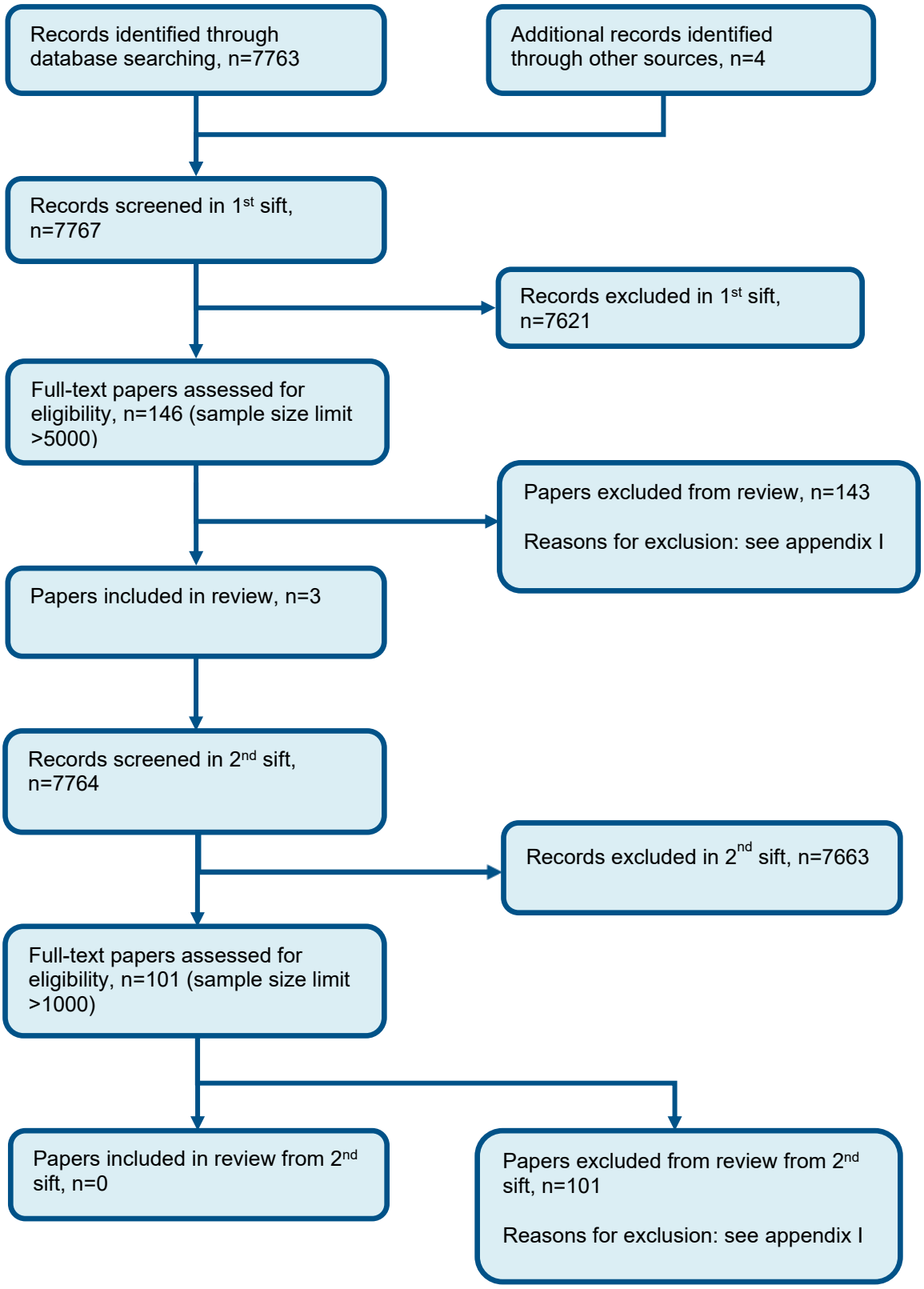
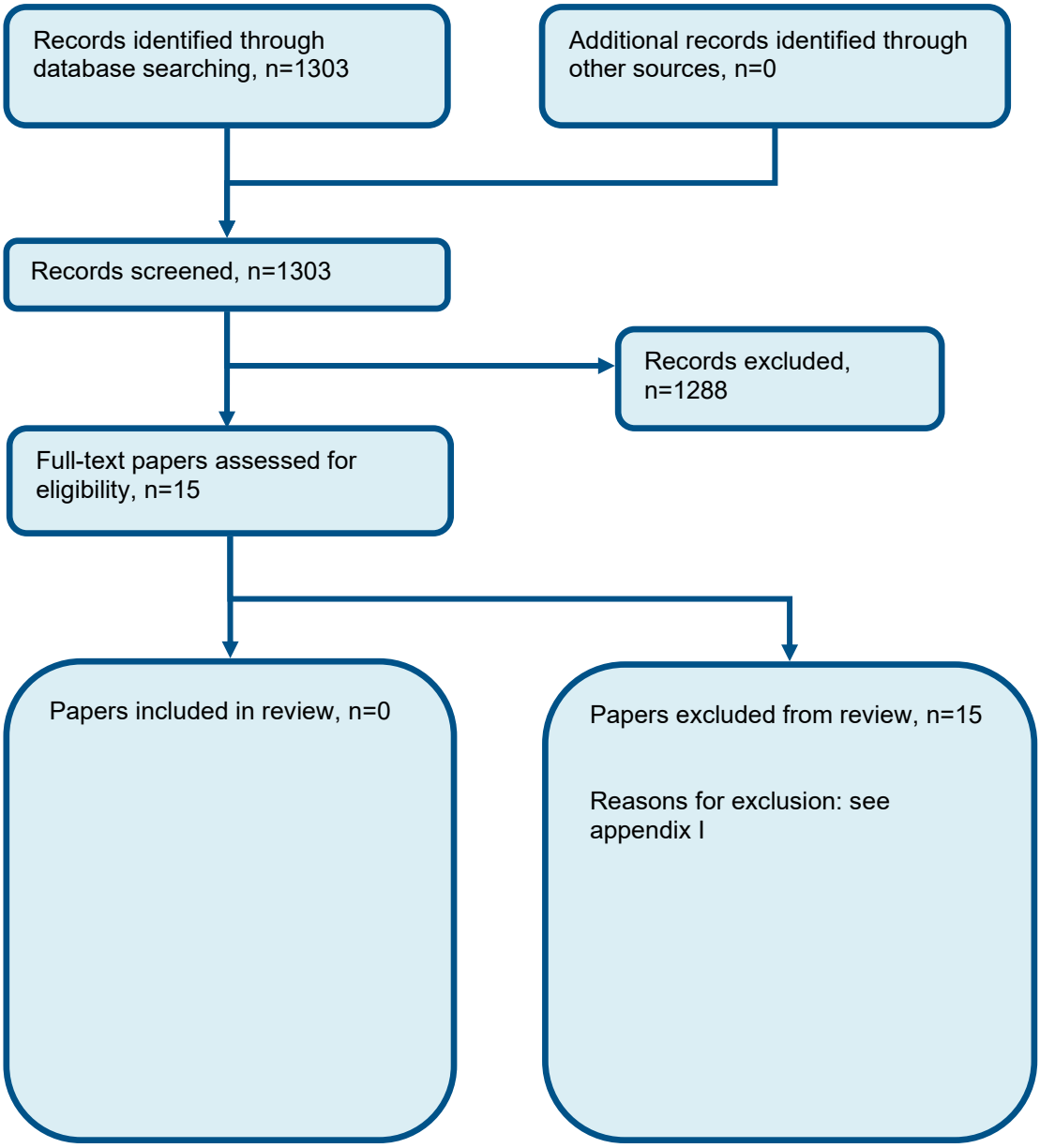


**Figure 3: Flow chart of clinical study selection for the review of gabapentinoid safety**



# Appendix D: Clinical evidence tables

## D.1 Pharmacological management

| Study | Abdelhafeez 2019[2] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=60) |
| Countries and setting | Conducted in Egypt; Setting: Ain Shams University, Cario |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 24 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: chronic pelvic pain in the absence of any known cause |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Aged between 25-45 years, moderate to severe chronic pelvic pain for longer than 6 months (not just exclusively with menstruation or intercourse and not associated with pregnancy), chronic pelvic pain incompletely relieved by NSAIDs, no obvious pelvic pathology |
| Exclusion criteria | Pregnancy, breast-feeding, active pelvic infection, hypersensitivity to gabapentin, endometriosis or adhesions, chronic or recurrent GI disease, renal or hepatic mpairment, previous diagnosis of malignancy, chronic alcohol use and tranquilizer use. |
| Recruitment/selection of patients | From 2016-2018; all women who attended the gynecology outpatient clinic complaining of chronic pelvic pain were approached. |
| Age, gender and ethnicity | Age - Mean (SD): 32.7(4.91); 30.27(5.32). Gender (M:F): All women. Ethnicity: Not reported |
| Further population details | People with chronic visceral pain |
| Extra comments | Mean duration of pain 15(11-21); 18(14-22) months |
| Indirectness of population | No indirectness |
| Interventions | (n=30) Intervention 1: anti-epileptics - gabapentin. Oral 300mg gabapentin tablets initially divided into 900mg per day (3 doses per day), increased by one capsule on a weekly basis (maximum dose 2700mg per day) until sufficient pain relief was achieved, or adverse effects occured. Women were followed up weekly at the outpatient clinic for 6 weeks to adjust dose and check adverse events. Duration 24 weeks. |

| Study | Abdelhafeez 2019[2] |
|---|---|
| | Concurrent medication/care: Not specified. Indirectness: No indirectness<br><br>(n=30) Intervention 2: placebo. Matching placebo. Duration 24 weeks. Concurrent medication/care: Not specified. Indirectness: No indirectness |
| Funding | No funding |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO<br><br>Protocol outcome 1: Pain reduction<br>- Actual outcome: 10cm VAS at 12 weeks; Group 1: mean 5.12 (SD 0.67); n=27, Group 2: mean 5.9 (SD 0.92); n=23; VAS 0-10 Top=High is poor outcome; Comments: Baseline 5.94(0.73); 6.09(0.54)<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: 6 due to adverse events, 4 unclear; Group 2 Number missing: 6, Reason: All due to lack of efficacy<br>- Actual outcome: 10cm VAS at 24 weeks; Group 1: mean 3.72 (SD 0.69); n=20, Group 2: mean 5.5 (SD 1.13); n=14; VAS 0-10 Top=High is poor outcome; Comments: Baseline: 5.94(0.73); 6.09(0.54)<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 10, Reason: 6 due to adverse events, 4 unclear; Group 2 Number missing: 6, Reason: All due to lack of efficacy<br><br>Protocol outcome 2: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events at 24 weeks; Group 1: 6/30, Group 2: 0/30<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Use of healthcare services; Sleep |

| Study | Arnold 2002[40] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=60) |
| Countries and setting | Conducted in USA; Setting: Not stated |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 12 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Aged ≥18; Fibromyalgia (ACR); |
| Exclusion criteria | History of trauma, stroke, seizure, rheumatic disease, arthropathy, psychosis, mania, dementia, drug/alcohol dependence. |
| Recruitment/selection of patients | Advertisements in rheumatology clinics |
| Age, gender and ethnicity | Age - Mean (SD): 46 ± 11. Gender (M:F): All female. Ethnicity: 95% white, no further details |
| Further population details | 1. Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=30) Intervention 1: selective serotonin reuptake inhibitors - fluoxetine. Started at 10mg/day and titrated in increments of 10-20mg every 2 weeks to maximum of 80mg/day. Duration 12 weeks. Concurrent medication/care: unreported. Indirectness: No indirectness<br><br>(n=30) Intervention 2: placebo. dose/quantity, brand name, extra details. Duration 12 weeks. Concurrent medication/care: Unreported. Indirectness: No indirectness |
| Funding | Study funded by industry (Eli Lilly) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUOXETINE versus PLACEBO

Protocol outcome 1: Pain reduction at 12 weeks
- Actual outcome: McGill Pain questionnaire: ITT mean change from baseline to endpoint at 12 weeks; Group 1: mean -10.8 Score points (SD 12.3); n=25, Group 2: mean -1.8 Score points (SD 11.9); n=26;  MIQ 0-78 Top=High is poor outcome; Comments: Mean baseline score:
Fluoxetine = 26 ± 13; Placebo = 27 ± 12

| | |
|---|---|
| Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Reasons not given for withdrawal in each arm (just overall); Indirectness of outcome: No indirectness ; Blinding details: Analyst funded by manufacturer of product; Group 1 Number missing: 11, Reason: Adverse events, lack of efficacy or lost to follow-up; Group 2 Number missing: 12, Reason: Predominantly lack of efficacy leading to withdrawal<br><br>Protocol outcome 2: Quality of life at 12 weeks<br>- Actual outcome: FIQ total score: ITT mean change from baseline to endpoint at 12 weeks; Group 1: mean -8.6 Total score (SD 14.5); n=25, Group 2: mean 2.9 Total score (SD 13.6); n=26; FIQ 0-100 Top=High is poor outcome; Comments: Baseline score: Fluoxetine = 42 ± 14; Placebo = 44 ± 14<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Analyst funded by manufacturer of product; Group 1 Number missing: 5, Reason: Adverse events, lack of efficacy or lost to follow-up; Group 2 Number missing: 4, Reason: Predominantly lack of efficacy leading to withdrawal<br><br>Protocol outcome 3: Physical function at 12 weeks<br>- Actual outcome: FIQ Physical impairment: ITT mean change from baseline to endpoint at 12 weeks; Group 1: mean -1.1 (SD 2.3); n=25, Group 2: mean -0.4 (SD 2.1); n=26; FIQ Physical impairment 0-9.99 Top=High is poor outcome; Comments: Baseline: 3.7 ± 2.7 : 3.7 ± 2.7<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: Analyst funded by manufacturer of product; Group 1 Number missing: 5, Reason: Adverse events, lack of efficacy or lost to follow-up; Group 2 Number missing: 4, Reason: Predominantly lack of efficacy leading to withdrawal<br><br>Protocol outcome 4: Psychological distress at 12 weeks<br>- Actual outcome: FIQ anxiety subscale mean change from baseline to endpoint at 12 weeks; Group 1: mean -0.3 (SD 2.5); n=25, Group 2: mean 0.7 (SD 2.9); n=26; Comments: Baseline: 4± 2.48 : 4.8 ± 2.25<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Adverse events, lack of efficacy or lost to follow-up; Group 2 Number missing: 4, Reason: Predominantly lack of efficacy leading to withdrawal<br><br>- Actual outcome: FIQ depression subscale change from baseline to endpoint at 12 weeks; Group 1: mean -0.9 (SD 3.7); n=25, Group 2: mean 1.1 (SD 2.5); n=26; Top=High is poor outcome; Comments: Baseline: F: 11.8 ± 7.6; P: 13.9 ± 8.86<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5, Reason: Adverse events, lack of efficacy or lost to follow-up; Group 2 Number missing: 4, Reason: Predominantly lack of efficacy leading to withdrawal | |
| Protocol outcomes not reported by the study | Discontinuation due to adverse events; Use of healthcare services ; Sleep |

| Study | Arnold 2005[45] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=354) |
| Countries and setting | Conducted in USA; Setting: Outpatient research centres |
| Line of therapy | Unclear line |
| Duration of study | Intervention time: 12 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Female outpatients >18; Fibromyalgia (ACR); BPI average pain severity ≥4 |
| Exclusion criteria | Trauma; rheumatism, arthritic inflammation; auto-immune disease; Mental health disorders other than MDD; treatment refractory in opinion of investigator; prior participation in same-intervention trial; Concomitant regular use of analgesia (excluding acetaminophen and aspirin); antiemetics, sedatives or alternative therapies. |
| Recruitment/selection of patients | Physician referral or advertisement |
| Age, gender and ethnicity | Age - Other: >18 (range or mean unreported). Gender (M:F): All women. Ethnicity: 89.5% Caucasian |
| Further population details | 1. Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=234) Intervention 1: serotonin norepinephrine reuptake inhibitors - duloxetine. 60 mg QD and BID. Duration 12 weeks. Concurrent medication/care: None except protocol-permitted interventions<br><br>(n=120) Intervention 2: placebo. None reported. Duration 12 weeks. Concurrent medication/care: None except protocol-permitted interventions |
| Funding | Study funded by industry (Eli Lilly) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE versus PLACEBO

Protocol outcome 1: Pain reduction at 12 weeks
- Actual outcome: BPI average intensity of pain at 12 weeks; Group 1: mean -2.4 Brief Pain Inventory (SD 2.4); n=230, Group 2: mean -1.16 Brief Pain Inventory (SD 2.3); n=118; Brief Pain Inventory 0-10 Top=High is poor outcome; Comments: Baseline: Duloxetine = 6.4 ± 1.5; Placebo = 6.5 ± 1.5
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data – Very high, Outcome reporting - High, Measurement

- High, Crossover - Low, Subgroups - Low, Comments - Used standard deviations for baseline results, and standard errors for endpoint results. Extracted results for duloxetine are means of two dosage groups: 60 mg QD (n=118) and 60 mg BID (n=116) ; Indirectness of outcome: --, Comments: 2 groups: 60 mg/day and 120 mg/day; Group 1 Number missing: 86, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation; Group 2 Number missing: 52, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation

Protocol outcome 2: Quality of life at 12 weeks
- Actual outcome: FIQ score at 12 weeks; Group 1: mean -16.77 (SD 16.3); n=226, Group 2: mean -8.35 (SD 16.4); n=115; Fibromyalgia Impact total 0-100 Top=High is poor outcome; Comments: Baseline: Duloxetine = 51.95 ± 12.5; Placebo = 53.1 ± 12.4
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data – Very high, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Comments - Used standard deviations for baseline results, and standard errors for endpoint results. Extracted results for duloxetine are means of two dosage groups: 60 mg QD (n=118) and 60 mg BID (n=116) ; Indirectness of outcome: --, Comments: 2 groups: 60 mg/day and 120 mg/day;; Group 1 Number missing: 86, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation; Group 2 Number missing: 52, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation

Protocol outcome 3: Psychological distress (depression/anxiety) at 12 weeks
- Actual outcome: Hamilton depression score at 12 weeks; Group 1: mean -3.38 (SD 4.6); n=221 Group 2: mean -2.24 (SD 4.7); n=120; Hamilton depression score, 0-52 Top=High is poor outcome; Comments: Baseline: Duloxetine = 11.3 ± 6.3; Placebo =11.5 ± 6.5
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data – Very high, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Comments - Used standard deviations for baseline results, and standard errors for endpoint results. Extracted results for duloxetine are means of two dosage groups: 60 mg QD (n=118) and 60 mg BID (n=116) ; Indirectness of outcome: --, Comments: 2 groups: 60 mg/day and 120 mg/day; Baseline details: Randomised to two different dosage groups; Group 1 Number missing: 86, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation; Group 2 Number missing: 52, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation

Protocol outcome 4: Discontinuation due to adverse events at 12 weeks
- Actual outcome: Number who discontinued due to adverse events at 12 weeks; Group 1: 52/234, Group 2: 14/120
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data – High, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Comments - No baseline value for this subscore was reported. Extracted results for duloxetine are means of two dosage groups: 60 mg QD (n=118) and 60 mg BID (n=116) ; Indirectness of outcome: Comments: 2 groups: 60 mg/day and 120 mg/day; Group 1 Number missing: 86, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation; Group 2 Number missing: 52, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation

Protocol outcome 5: Sleep at 12 weeks
- Actual outcome: BPI Sleep subscore at 12 weeks; Group 1: mean -2.68 (SD 3.1); n=230, Group 2: mean -1.71 (SD 3); n=118; BPI interference: Sleep subscore 0-10 Top=High is poor outcome; Comments: No baseline scores reported
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data – Very high, Outcome reporting – Very high, Measurement - High, Crossover - Low, Subgroups - Low, Comments - No baseline value for this subscore was reported. Extracted results for duloxetine are means of two dosage groups: 60 mg QD (n=118) and 60 mg BID (n=116) ; Indirectness of outcome: --, Comments: 2 groups: 60 mg/day and 120

| | |
|---|---|
| mg/day; Baseline details; Group 1 Number missing: 86, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation; Group 2 Number missing: 52, Reason: Adverse events, lack of efficacy, patient decision, non-compliance, protocol violation | |
| Protocol outcomes not reported by the study | Physical function; Use of healthcare services |

| Study | Arnold 2007[39] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=150) |
| Countries and setting | Conducted in USA; Setting: 3 research centres in the US |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 12 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | (1) 18 years of age or over and met the ACR criteria for fibromyalgia (2) score of 4 or more on the average pain severity item of the Brief Pain Inventory (BPI) at screening and randomisation. |
| Exclusion criteria | Pain from traumatic injury or structural or regional rheumatic disease; rheumatoid arthritis, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; lifetime history of psychosis, hypomania or mania, epilepsy, or dementia; substance abuse in the last 6 months; serious risk of suicide; pregnancy or breastfeeding; unacceptable contraception in those of childbearing potential; patients who, in the opinion of the investigator, were treatment refractory; prior treatment with gabapentin or pregabalin; and treatment with an investigational drug within 30 days of screening. Concomitant medication exclusions consisted of medications or herbal agents with CNS effects, with the exception of episodic use of sedating antihistamines (antidepressants required a 14-day washout period prior to beginning study medication except for fluoxetine, which required a 30-day washout period); analgesics, with the exception of acetaminophen or over-the-counter nonsteroidal anti-inflammatory drugs; and unconventional or alternative therapies. |
| Recruitment/selection of patients | Between 2003 and 2006, no further details |
| Age, gender and ethnicity | Age - Mean (SD): 48.25 (11.2). Gender (M:F): Define. Ethnicity: 97.3% White, 1.3% African American, 0.65% Asian, 0.65% other. |
| Further population details | 1. Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=75) Intervention 1: anti-epileptics - gabapentin. Gabapentin or matching placebo was titrated in the following manner: 300 mg once a day at bedtime for 1 week, 300 mg twice a day for 1 week,300 mg twice a day and 600 mg once a day at bedtime for 2 weeks, 600 mg 3 times a day for 2 weeks, and 600 mg twice a day and 1,200 mg once a day at bedtime(2,400 mg/day) for the remainder of the study beginning at week 6. If a patient could not tolerate 2,400 mg/day, the dosage was reduced to a minimum of 1,200mg/day, |

| | |
|---|---|
| | administered 3 times a day. The study medication dose was stable for at least the last 4 weeks of the therapy phase. During the tapering phase, the dosage was decreased by 300 mg/day until discontinuation. The median dosage at the end point for patients treated with gabapentin was 1,800 mg/day (interquartile range 1,200–2,400 mg/day).<br>Duration 12 weeks. Concurrent medication/care: Acetaminophen or over the counter NSAIDs allowed. Indirectness: No indirectness<br><br>(n=75) Intervention 2: placebo. Gabapentin or matching placebo was titrated in the following manner: 300 mg once a day at bedtime for 1 week, 300 mg twice a day for 1 week,300 mg twice a day and 600 mg once a day at bedtime for 2 weeks, 600 mg 3 times a day for 2 weeks, and 600 mg twice a day and 1,200 mg once a day at bedtime(2,400 mg/day) for the remainder of the study beginning at week 6. If a patient could not tolerate 2,400 mg/day, the dosage was reduced to a minimum of 1,200mg/day, administered 3 times a day. The study medication dose was stable for at least the last 4 weeks of the therapy phase. During the tapering phase, the dosage was decreased by 300 mg/day until discontinuation.<br>Duration 12 weeks. Concurrent medication/care: Acetaminophen or over the counter NSAIDs allowed. Indirectness: No indirectness |
| Funding | Academic or government funding (NIH grant (in addition to lead author receiving consulting fees from numerous pharmaceutical companies)) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: Brief pain inventory average pain severity score at 12 weeks; Group 1: mean 3.2 (SD 2); n=57, Group 2: mean 4.6 (SD 2.6) n=62; BPI, 0-10 Top=High is poor outcome; Comments: Baseline Gabapentin: 5.7 = 5.7 ±1.4; Placebo =6 ± 1.5

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Quality of life difference at baseline; Group 1 Number missing: 18; Group 2 Number missing: 13 (reasons not specified)

Protocol outcome 2: Quality of life
- Actual outcome: Fibromyalgia Impact Questionnaire at 12 weeks; Group 1: mean 26.2 (SD 15.1); n=56, Group 2: mean 37.3 (SD 18.1); n=62; FIQ 0-100 Top=High is poor outcome; Comments: Baseline Gabapentin: 46.3 ±11.5; Placebo = 47.7 ± 10.3

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Quality of life difference at baseline; Group 1 Number missing: 18; Group 2 Number missing: 13

Protocol outcome 4: Discontinuation due to adverse events

| | |
|---|---|
| - Actual outcome: Discontinuation due to adverse events at 12 weeks; Group 1: 12/75, Group 2: 7/75<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Quality of life difference at baseline; Group 1 Number missing: 18; Group 2 Number missing: 13<br><br>Protocol outcome 5: Sleep<br>- Actual outcome: Medical Outcomes Study Sleep Problems index score at 12 weeks; Group 1: mean 33.4 (SD 19.4); n=57, Group 2: mean 47.8 (SD 20.9); n=62; MOSSP index score 0-100 Top=High is poor outcome; Comments: Baseline: Gabapentin 56 ±16.3; Placebo = 55.8 ± 18.5<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Quality of life difference at baseline; Group 1 Number missing: 18; Group 2 Number missing: 13 | |
| Protocol outcomes not reported by the study | Physical function; Use of healthcare services |

| Study | Arnold 2010[37] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=530) |
| Countries and setting | Conducted in Puerto Rico, USA; Setting: 48 research centres |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 12 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | >18 years old; Fibromyalgia (ACR); BPI ≥4 |
| Exclusion criteria | Psychiatric disorder (other than MDD or GAD); any autoimmune disease; severe liver disease; pregnant/breast feeding; previously judged treatment-refractory in any former duloxetine trial. |
| Recruitment/selection of patients | Physician referral or public announcements |
| Age, gender and ethnicity | Age - Mean (SD): 50 (11). Gender (M:F): 36/494. Ethnicity: 77% Caucasian; 15.5% Hispanic |
| Further population details | 1. Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=263) Intervention 1: serotonin norepinephrine reuptake inhibitors - duloxetine. Week 1 = 30mg QD; Week 2 = 60mg QD; Weeks 4 and 8: increased by 30mg in patients with <50% pain reduction (BPI). Duration 12 weeks. Concurrent medication/care: None reported<br><br>(n=267) Intervention 2: placebo. Placebo. Duration 12 weeks. Concurrent medication/care: None reported |
| Funding | Study funded by industry (Lilly USA) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE versus PLACEBO

Protocol outcome 1: Pain reduction at 12 weeks
- Actual outcome: Brief Pain Inventory at 12 weeks; Group 1: mean -2.6 Scale points (SE 0.2); n=188, Group 2: mean -1.7 Scale points (SE 0.2); n=197; BPI average pain interference 0-10 Top=High is poor outcome; Comments: Baseline: Duloxetine = 6.0 (2.0); Placebo = 6.0 (2.1)
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: Balanced; Blinding details: Start day of intervention was double blinded; Group 1 Number missing: 87, Reason: Discontinuation (adverse events n = 41); Group 2 Number missing: 80, Reason: Discontinuation (adverse events n = 24)

| | |
|---|---|
| Protocol outcome 2: Quality of life at 12 weeks<br>- Actual outcome: SF-36 Mental component summary at 12 weeks; Group 1: mean 5.1 (SD 0.7); n=263, Group 2: mean 1.3 (SD 0.7); n=263<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: Balanced; Blinding details: Start day of intervention was double blinded; Group 1 Number missing: 87, Reason: Discontinuation (adverse events n = 41); Group 2 Number missing: 80, Reason: Discontinuation (adverse events n = 24)<br>- Actual outcome: SF-36 Physical component summary at 12 weeks; Group 1: mean 6; n=263, Group 2: mean 4.8 (0.6) n=267<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: Balanced; Blinding details: Start day of intervention was double blinded; Group 1 Number missing: 87, Reason: Discontinuation (adverse events n = 41); Group 2 Number missing: 80, Reason: Discontinuation (adverse events n = 24)<br><br>Protocol outcome 3: Psychological distress (depression/anxiety) at 12 weeks<br>- Actual outcome: Beck Depression Inventory at 12 weeks; Group 1: mean -5.5 (SD 0.5); n=263, Group 2: mean -3.6 (SD 0.5); n=267; Total score 0-63 Top=High is poor outcome; Comments: Baseline: Duloxetine = 16.2 ± 10.4; Placebo = 16.2 ± 10.4<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: Balanced; Blinding details: Start day of intervention was double blinded; Group 1 Number missing: 87, Reason: Discontinuation (adverse events n = 41); Group 2 Number missing: 80, Reason: Discontinuation (adverse events n = 24)<br><br>Protocol outcome 4: Discontinuation due to adverse events at 12 weeks<br>- Actual outcome: N who discontinued due to adverse events at 12 weeks; Group 1: 41/263, Group 2: 24/267<br>Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Baseline details: Balanced; Blinding details: Start day of intervention was double blinded; Group 1 Number missing: 0, Reason: Discontinuation (adverse events n = 41); Group 2 Number missing: 0, Reason: Discontinuation (adverse events n = 24) | |
| Protocol outcomes not reported by the study | Physical function; Use of healthcare services ; Sleep |

| Study | Arnold 2012[50] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=308) |
| Countries and setting | Conducted in Argentina, Israel, Mexico, USA; Setting: 29 outpatient research centres |
| Line of therapy | Unclear line |
| Duration of study | Intervention time: 12 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | >18; Fibromyalgia (ACR); BPI average pain score ≥4; with or without MDD or GAD. |
| Exclusion criteria | Prior treatment with duloxetine; substance abuse; psychiatric disorder other than MDD or GAD; arthritis; rheumatism; recent surgery. Use of CNS based medication or analgesics except aspirin and some NSAIDs. |
| Recruitment/selection of patients | Unreported |
| Age, gender and ethnicity | Age - Mean (SD): 50 ± 12. Gender (M:F): 95% women. Ethnicity: 87.4% White, the rest unspecified |
| Further population details | 1. Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=155) Intervention 1: serotonin norepinephrine reuptake inhibitors - duloxetine. 30 mg/day. Duration 12 weeks. Concurrent medication/care: None reported, though some concomitant NSAIDs allowed. Indirectness: No indirectness<br><br>(n=153) Intervention 2: placebo. Daily tablet. Duration 12 weeks. Concurrent medication/care: Unreported though some concomitant NSAIDs allowed. Indirectness: No indirectness |
| Funding | Study funded by industry (Eli Lilly) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE versus PLACEBO

Protocol outcome 1: Pain reduction at 12 weeks
- Actual outcome: BPI average pain severity at 12 weeks; Group 1: mean -2.14 Least squares mean LOCF (SD 2.4739); n=121, Group 2: mean -1.83 Least squares mean LOCF (SD 2.4739); n=110; BPI 0-10 Top=High is poor outcome; Comments: Baseline: Duloxetine = 6.50 ± 1.47 on scale; Placebo = 6.37 ± 1.67 on scale

| | |
|---|---|
| Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Indirectness of outcome: -- ; Group 1 Number missing: 34, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation, sponsor decision; Group 2 Number missing: 43, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation.<br><br>Protocol outcome 2: Quality of life at 12 weeks<br>- Actual outcome: SF-36 mental component score at 12 weeks; Group 1: mean 5.56 Least squares mean LOCF (SD 0.85); n=140, Group 2: mean 2.87 Least squares mean LOCF (SD 0.87); n=134; SF-36 Unreported Top=High is good outcome<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - High, Indirectness of outcome: -- ; Group 1 Number missing: 34, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation, sponsor decision ; Group 2 Number missing: 43, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation.<br>- Actual outcome: SF-36 physical component score at 12 weeks; Group 1: mean 4.75 least squares mean LOCF (SD 0.72); n=140, Group 2: mean 3.91 least squares mean LOCF (SD 0.73); n=134; SF-36 Unreported Top=High is good outcome<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low, Other 1 - High, Indirectness of outcome: -- ; Group 1 Number missing: 34, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation, sponsor decision ; Group 2 Number missing: 43, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation.<br><br>Protocol outcome 3: Psychological distress (depression/anxiety) at 12 weeks<br>- Actual outcome: BDI-II at 12 weeks; Group 1: mean -5.47 Least squares mean LOCF (SD 0.6); n=140, Group 2: mean -3.91 Least squares mean LOCF (SD 0.61); n=134; BDI 0-21 Top=High is poor outcome; Comments: Baseline: Duloxetine = 15.0 ± 9.64; Placebo = 16.84 ± 11.47<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Group 1 Number missing: 34, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation, sponsor decision ; Group 2 Number missing: 43, Reason: Adverse event, lack of efficacy, lost to follow-up, protocol violation.<br><br>Protocol outcome 4: Discontinuation due to adverse events at 12 weeks<br>- Actual outcome: N who discontinued due to adverse events at 12 weeks; Group 1: 14/135, Group 2: 9/119<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Group 1 Number missing: 22, Reason: lack of efficacy, lost to follow-up, protocol violation, sponsor decision ; Group 2 Number missing: 15, Reason: lack of efficacy, lost to follow-up, protocol violation. | |
| Protocol outcomes not reported by the study | Physical function; Use of healthcare services ; Sleep |

| Study | Arnold 2019[49] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 3 (3 identical multi-centre RCTs) (n=3864 (2 study arms not included in this report [both arms were for mirogabalin which is not licensed in the UK for any indication]. N=1930 included)) |
| Countries and setting | Conducted in Multiple countries; Setting: Multiple centre's worldwide from 2014-2016 (more than 150 sites in total) |
| Line of therapy | Unclear |
| Duration of study | Intervention + follow up: 13 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: Diagnosis of fibromyalgia |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Widespread pain for at least 3 months and met the ACR criteria for fibromalgia. (1990). Additional criteria from 2010 ACR must have been met (including WPI score of 7 or more, SSS score of 5 or more, or WPI 3-6 and SSS more than 9). ADPS of 4 or more over the 7 days prior to randomisation (during which time patients were titrated off of existing medication if present). Women of child-bearing potential were only included if they used adequate contraception |
| Exclusion criteria | Other conditions that explained pain,other conditions that could have interfered with study participation or assessment of safety. Abnormal ECG or lab values, severe or uncontrolled depression, hypersensitivity to study medications. |
| Recruitment/selection of patients | Not specified |
| Age, gender and ethnicity | Age - Mean (SD): 49.3(11.5); 50.1(11.3). Gender (M:F): 159:1774. Ethnicity: Majority white (86.8%) |
| Further population details | People with chronic widespread pain |
| Extra comments | Mean duration of pain 5.01(6.55); 5.3(6.89) years |
| Indirectness of population | No indirectness |
| Interventions | (n=964) Intervention 1: anti-epileptics - pregabalin. Pregabalin 150mg BID. Washout period before randomisation varied depending on medication that was discontinued. After completion of the washout period, participants entered a titration period aiming for pregabalin 150mg twice daily in the morning and at bedtime. . Duration 13 weeks. Concurrent medication/care: Multiple medicines prohibited. Paracetemol allowed for breakthrough fibromyalgia pain, non-pharmacological approaches such as massage also allowed.<br><br>(n=966) Intervention 2: placebo. Matching placebo. Duration 13 weeks. Concurrent medication/care: Multiple |

| | |
|---|---|
| | medicines prohibited. Paracetamol allowed for breakthrough fibromyalgia pain, non-pharmacological approaches such as massage also allowed. |
| Funding | Study funded by industry (Multiple pharmaceutical organisations) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: Average daily worst pain score at 13 weeks; Group 1: mean -2.37 (SD 2.39); n=947, Group 2: mean -1.81 (SD 2.39); n=955; ADPS, 0-10, Top=High is poor outcome
*Note: study reported change scores and SE separately for the 3 RCTs. SE was converted to SD and mean change scores +/- SD were pooled across the 3 RCTs. Raw data from study:*
Study A
Pregabalin (n=317): -1.9(0.13)
Placebo (n=317): -1.66(0.13)
Study B
Pregabalin (n=311): -2.47(0.13)
Placebo (n=315): -1.86(0.13)
Study C
Pregabalin (n=319): -2.64 (0.14)
Placebo (n=323): -1.9(0.14)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low,; Indirectness of outcome: No indirectness;
Duloxetine group 56.69 (24.33)
Pregabalin group 45.77 (27.31); Group 1 Number missing: Not reported , Reason: NA; Group 2 Number missing: Not reported, Reason: NA
Comments: Baseline scores: 7.08(1.35); 7.14(1.33)
Overall missing rate only (25.37%)

Protocol outcome 2: Quality of life at Define
- Actual outcome: EQ5D at 13 weeks; Group 1: mean 0.1 (SD 0.19); n=887, Group 2: mean 0.08 (SD 0.19); n=890; EQ5D 0-100 Top=High is good outcome; Comments: Outcomes from the three studies have been combined, baseline scores not reported
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 77; Group 2 Number missing: 76

Protocol outcome 3: Psychological distress (depression/anxiety) at Define
- Actual outcome: Depression at 13 weeks; Group 1: mean -1.23 (SD 3.75); n=889, Group 2: mean -0.8 (SD 3.62); n=890; HADS 0-21 Top=High is poor

| | |
|---|---|
| outcome; Comments: Outcomes from the three studies have been combined, baseline scores not reported<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 75; Group 2 Number missing: 76<br>- Actual outcome: Anxiety at 13 weeks; Group 1: mean -1.03 (SD 3.47); n=889, Group 2: mean -0.84 (SD 3.41); n=890; HADs 0-21 Top=High is poor outcome; Comments: Outcomes from the three studies have been combined, baseline scores not reported<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 75; Group 2 Number missing: 76<br><br>Protocol outcome 4: Discontinuation due to adverse events at Define<br>- Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 104/949, Group 2: 73/957<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 9<br><br>Protocol outcome 5: Sleep at Define<br>- Actual outcome: Sleep at 13 weeks; Group 1: mean -2.45 (SD 2.07); n=948, Group 2: mean -1.78 (SD 2.09); n=957; Average Daily Sleep Interference Score 0-10 Top=High is poor outcome; Comments: Outcomes from the three studies have been combined, baseline scores not reported<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 16; Group 2 Number missing: 9 | |
| Protocol outcomes not reported by the study | Physical function; Psychological distress (depression/anxiety); Discontinuation due to adverse events; Use of healthcare services ; Sleep |

| Study | Bidari 2019[73] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=99) |
| Countries and setting | Conducted in Switzerland; Setting: An academic outpatient rheumatology clinic, Razi Hospital, Guilan University of Medical Sciences, from May 2016 through March 2017. |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 4 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: Diagnosed with fibromyalgia based on the American College of Rheumatology (ACR) 2010 criteria. |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Women diagnosed with FM, based on the American College of Rheumatology (ACR) 2010 criteria were considered for study screening. Patients were eligible if they were aged between 18 and 65 and were willing to participate in the study. |
| Exclusion criteria | Patients were excluded if they had a history of taking certain drugs within a specified period prior to the study enrollment: duloxetine, pregabalin, gabapentin, or antidepressants within the last 12 weeks; monoamine oxidase inhibitors within the last 14 days; muscle relaxants, steroids, opioid analgesics, or benzodiazepines within the last week; injection of analgesics to painful areas within the last month. It was also required that patients: were not pregnant or breast feeding and did not intend to become pregnant during the trial; did not have other comorbid medical conditions that could provoke chronic pain such as malignancies, multiple major surgeries, recent traumatic injuries, or rheumatologic diseases other than FM; did not have concurrent neurological or psychiatric disorders except anxiety/depressive disorders; did not have occupations that demanded high level of concentration or alertness; were not known to have chronic liver diseases, severe renal failure, or uncontrolled narrow-angle glaucoma; and finally, had no history of hypersensitivity to trial medications. |
| Age, gender and ethnicity | Age - Mean (SD): Duloxetine group 41.6 (9.02), Pregabalin 43.1 (7.78). Gender (M:F): All women. Ethnicity: Not stated. |
| Further population details | 1. chronic orofacial pain: people with pain conditions other than chronic orofacial pain 2. chronic visceral pain: people with pain conditions other than chronic visceral pain 3. chronic widespread pain: people with pain conditions other than chronic widespread pain 4. complex regional pain syndrome: people with pain conditions other than complex regional pain syndrome |
| Extra comments | Duration of fibromyalgia, months, median (range):<br>Duloxetine group 24 (0-240)<br>Pregabalin group 36 (0-240) |

| | |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | (n=60) Intervention 1: serotonin norepinephrine reuptake inhibitors - duloxetine. Patients initially received duloxetine (30 mg per day). By the time of follow-up clinic visit at week 1, medication was titrated up to 60 mg duloxetine, once daily if the patient was tolerant and no serious adverse events were observed. During the next 3 weeks, there were no clinic visits planned; but, patients could come to the clinic in person for any concern. The study rheumatologist was available to answer patients' phone calls, and medication doses were titrated down in case of new adverse events or intolerance. To monitor adherence to treatment, pill counts were used and were checked with individual patients as well as their caregivers or companions. In case pill counts exceeded the expected numbers, or non-adherence was reported by the patient or caregivers, the issue was explored in detail. Duration 4 weeks. Concurrent medication/care: Psychoactive/sedative or pain medications other than trial medications, or cognitive behavioural therapy were not given during the trial. Indirectness: No indirectness<br><br>(n=39) Intervention 2: anti-epileptics - pregabalin. Patients initially received pregabalin (75 mg per day). By the time of follow-up clinic visit at week 1, medication was titrated up to 75 mg pregabalin, twice daily (150 mg per day) if the patient was tolerant and no serious adverse events were observed. During the next 3 weeks, there were no clinic visits planned; but, patients could come to the clinic in person for any concern. The study rheumatologist was available to answer patients' phone calls, and medication doses were titrated down in case of new adverse events or intolerance. To monitor adherence to treatment, pill counts were used and were checked with individual patients as well as their caregivers or companions. In case pill counts exceeded the expected numbers, or non-adherence was reported by the patient or caregivers, the issue was explored in detail. Duration 4 weeks. Concurrent medication/care: Psychoactive/sedative or pain medications other than trial medications, or cognitive behavioural therapy were not given during the trial. Indirectness: No indirectness |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE versus PREGABALIN

Protocol outcome 1: Pain reduction
- Actual outcome: Widespread Pain Index (WPI) score at 4 weeks (post-treatment); Group 1: mean 3.69 (SD 2.68); n=35, Group 2: mean 6.32 (SD 5.01); n=31; Widespread Pain Index (WPI) 0-19 Top=High is poor outcome; Comments: Baselines, mean (SD):
Duloxetine group 7.71 (3.67)
Pregabalin group 8.03 (3.74)
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25, Reason: Participants withdrew consent (mostly due to adverse events); Group 2 Number missing: 8, Reason: Participants withdrew consent (mostly due to adverse events)

Protocol outcome 2: Quality of life
- Actual outcome: 12-Item Short Form Survey (SF-12) Physical component at 4 weeks (post-treatment); Group 1: mean 54.96 (SD 22.07); n=35, Group 2: mean 47.98 (SD 19.92); n=31; SF-12 Physical component 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
Duloxetine group 36.96 (23.31)
Pregabalin group 34.88 (16.12)
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25, Reason: Participants withdrew consent (mostly due to adverse events); Group 2 Number missing: 8, Reason: Participants withdrew consent (mostly due to adverse events)
- Actual outcome: 12-Item Short Form Survey (SF-12) Mental component at 4 weeks (post-treatment); Group 1: mean 63.97 (SD 22.51); n=34, Group 2: mean 56.53 (SD 21.91); n=31; SF-12 Mental component 0-100 Top=High is good outcome; Comments: Baselines, mean (SD):
Duloxetine group 56.69 (24.33)
Pregabalin group 45.77 (27.31)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Baselines, mean (SD):
Duloxetine group 56.69 (24.33)
Pregabalin group 45.77 (27.31); Group 1 Number missing: 26, Reason: Participants withdrew consent (mostly due to adverse events); Group 2 Number missing: 8, Reason: Participants withdrew consent (mostly due to adverse events)

Protocol outcome 3: Psychological distress (depression/anxiety)
- Actual outcome: Beck Depression Inventory-II (BDI=II) score at 4 weeks (post-treatment); Group 1: mean 11.65 (SD 9.56); n=35, Group 2: mean 13.48 (SD 9.28); n=31; Beck Depression Inventory-II (BDI-II) 0-63 Top=High is poor outcome; Comments: Baselines, mean (SD):
Duloxetine group 17 (9.27)
Pregabalin group 20.10 (11.43)
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25, Reason: Participants withdrew consent (mostly due to adverse events); Group 2 Number missing: 8, Reason: Participants withdrew consent (mostly due to adverse events)

Protocol outcome 4: Discontinuation due to adverse events
- Actual outcome: Dropout (due primarily to adverse events) at 4 weeks (post-treatment); Group 1: 25/60, Group 2: 8/39; Comments: Dropouts occurred when participants withdrew consent; the study states that this was mostly due to adverse outcomes.
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Dropouts occurred when participants withdrew consent; the study states that this was mostly due to adverse outcomes. Numbers of various adverse events were reported as a separate outcome but were not explicitly linked to discontinuation. It should therefore be noted that a minority dropouts could also be due to reasons other than adverse events; Group 1 Number missing: 0; Group 2 Number missing: 0

| | |
|---|---|
| Protocol outcomes not reported by the study | Physical function ; Use of healthcare services ; Sleep |

| Study | Carette 1986[113] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=59) |
| Countries and setting | Conducted in Canada; Setting: Outpatient rheumatology clinics in three university centres |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 9 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Primary fibrositis defined as 1) widespread aching of more than 3 months duration, 2) local tenderness at 12 of 14 specified sites, 3) disturbed sleep with morning fatigue and stiffness, 4) absence of traumatic, neurologic, muscular, infectious, osseous, endocrine, or other rheumatic conditions, and 5) normal Westergren erythrocyte sedimation rate, creatine phosphokinase level, latex fixation result, antinuclear antibody factor, and thyroid stimulating hormone (TSH) level |
| Exclusion criteria | Patients treated with amitriptyline within the preceding year and those with previous hypersensitivity reaction to the drug were excluded. Patients with a history of glaucoma, urinary retention, ischemic heart disease, arrhythmia, or<br><br>congestive heart failure were also excluded. |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Mean (SD): Amitriptyline group: 41.8 (10.4); placebo group 40.1 (10.5). Gender (M:F): 5/54. Ethnicity: Not reported |
| Further population details | 1. chronic orofacial pain: Not applicable 2. chronic visceral pain: 3. chronic widespread pain: people with chronic widespread pain 4. complex regional pain syndrome: |

| | |
|---|---|
| Extra comments | Duration of pain (months): amitriptyline group 71 (58); placebo group 97 (87) |
| Indirectness of population | No indirectness |
| Interventions | (n=27) Intervention 1: tricyclic antidepressants - amitriptyline. 10 mg daily at bedtime for the first week, 25 mg for the second through the fourth weeks, and 50 mg for the last 5 weeks of the trial. The amitriptyline was in capsules that were identical to the placebo capsules<br><br>. Duration 9 weeks. Concurrent medication/care: Nonsteroidal antiinflammatory drugs, hypnotic drugs, and antidepressant agents were discontinued for a minimum of 3 weeks before entry into the trial. Only acetaminophen was permitted during the study, and each dose was recorded<br><br>. Indirectness: No indirectness<br><br>(n=32) Intervention 2: placebo. Placebo capsules identical to the amitriptyline capsules. Duration 9 weeks. Concurrent medication/care: Nonsteroidal antiinflammatory drugs, hypnotic drugs, and antidepressant agents were discontinued for a minimum of 3 weeks before entry into the trial. Only acetaminophen was permitted during the study, and each dose was recorded. Indirectness: No indirectness |
| Funding | Other (Supported by Arthritis Society<br>) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: Pain at End of study (9 weeks); Group 1: mean 4.3 (SD 3); n=27, Group 2: mean 5 (SD 3); n=32; VAS 0-10 Top=High is poor outcome; Comments: Baseline values: Amitriptyline 6.3 (2.3); placebo 5.8 (2.4)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

| | |
|---|---|
| Protocol outcomes not reported by the study | Quality of life at Define; Physical function at Define; Psychological distress (depression/anxiety) at Define; Discontinuation due to adverse events at Define; Use of healthcare services at Define; Sleep at Define |

| Study | Carette 1994[112] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=126) |
| Countries and setting | Conducted in Canada; Setting: Outpatient clinics |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 6 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Fibromyalgia (ACR); ≥4cm on at least 50% of VAS global fibromyalgia assessment; normal erythrocyte, phosphokinase and TSH tests. |
| Exclusion criteria | Rheumatism; endocrine or neurologic problems; infections; osseous disorder; previous treatment with study drugs; glaucoma; urinary retention; heart conditions. |
| Recruitment/selection of patients | Canadian university centres and 2 private practices. |
| Age, gender and ethnicity | Age - Mean (SD): 44.4 ± 9.97. Gender (M:F): Women: A = 78, C = 78, P = 39. Ethnicity: Not reported |
| Further population details | 1. Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=84) Intervention 1: tricyclic antidepressants - amitriptyline. 10 mg/day for 1st week, 25 mg/day for 2nd to 12th week, 50 mg/day thereafter. No further details. Duration 6 months. Concurrent medication/care: None<br><br>(n=42) Intervention 2: placebo. Sham pills. Duration 6 months. Concurrent medication/care: Sham cyclobenzaprine. Indirectness: No indirectness |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO

Protocol outcome 1: Pain reduction at 3 months
- Actual outcome: McGill Pain Score at 3 months; Group 1: mean 21.7 Pain scale (SD 15); n=76, Group 2: mean 22.8 Pain scale (SD 13.5); n=37; McGill Pain Questionnaire 0-78 Top=High is poor outcome; Comments: Baseline values: 28.2 ± 12.5 : 28.6 ± 12.42
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Completer results reported as analysed, but not reported; Indirectness of outcome: -- ; Baseline details: Placebo

group was half the size of the amitriptyline group; Group 1 Number missing: 14, Reason: Adverse events, lack of response, other; Group 2 Number missing: 14, Reason: Lack of response, other

Protocol outcome 3:Physical function at 3 months
- Actual outcome: HAQ disability index at 3 months; Group 1: mean 0.6(SD 0.48); n=76, Group 2: mean 0.76 (SD 0.62); n=37; Top=High is poor outcome; Comments: Baseline values: 3.55 ± 1.92 : 3.76 ± 1.98
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Completer results reported as analysed, but not reported; Indirectness of outcome: -- ; Baseline details: Placebo group was half the size of the amitriptyline group; Group 1 Number missing: 14, Reason: Adverse events, lack of response, other; Group 2 Number missing: 14, Reason: Lack of response, other

Protocol outcome 3: Psychological distress (depression/anxiety) at 3 months
- Actual outcome: AIMS Depression Scale at 3 months; Group 1: mean 2.55 (SD 1.61); n=78, Group 2: mean 2.93 (SD 1.89); n=36; Top=High is poor outcome; Comments: Baseline: 3.55 ± 1.92 : 3.76 ± 1.98
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Completer results reported as analysed, but not reported; Indirectness of outcome: -- ; Baseline details: Non comparable sample sizes; Group 1 Number missing: 14, Reason: Adverse events, lack of response, other; Group 2 Number missing: 14, Reason: Lack of response, other

Protocol outcome 1: Pain reduction at 6 months
- Actual outcome: McGill Pain Score at 6 months; Group 1: mean 19.5 Pain scale (SD 13.5); n=78, Group 2: mean 21.6 Pain scale (SD 14.4); n=36; McGill Pain Intensity 0-78 Top=High is poor outcome; Comments: Baseline values: 28.2 ± 12.5 : 28.6 ± 12.4
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Completer results reported as analysed, but not reported; Indirectness of outcome: -- ; Baseline details: Placebo group was half the size of the amitriptyline group: power imbalance; Group 1 Number missing: 14, Reason: Adverse events, lack of response, other; Group 2 Number missing: 14, Reason: Lack of response, other

Protocol outcome 3:Physical function at 6 months
- Actual outcome: HAQ disability index at 6 months; Group 1: mean 0.53(SD 0.4); n=78, Group 2: mean 0.7 (SD 0.65); n=36; Top=High is poor outcome; Comments: Baseline values: 3.55 ± 1.92 : 3.76 ± 1.98
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Completer results reported as analysed, but not reported; Indirectness of outcome: -- ; Baseline details: Placebo group was half the size of the amitriptyline group; Group 1 Number missing: 14, Reason: Adverse events, lack of response, other; Group 2 Number missing: 14, Reason: Lack of response, other

Protocol outcome 3: Psychological distress (depression/anxiety) at 6 months
- Actual outcome: AIMS Depression Scale at 6 months; Group 1: mean 2.41 (SD 1.86); n=78, Group 2: mean 2.57 (SD 1.84); n=36; Top=High is poor outcome; Comments: Baseline: 3.55 ± 1.92 : 3.76 ± 1.98

| | |
|---|---|
| Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Completer results reported as analysed, but not reported; Indirectness of outcome: -- ; Baseline details: Placebo group was half the size of the amitriptyline group; Group 1 Number missing: 14, Reason: Adverse events, lack of response, other; Group 2 Number missing: 14, Reason: Lack of response, other | |
| Protocol outcomes not reported by the study | Quality of life, Use of healthcare services ; Sleep |

| Study | Chappell 2008[123] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=330) |
| Countries and setting | Conducted in Germany, Spain, Sweden, United Kingdom, USA; Setting: Multi centre in different countries |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 27 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable: None |
| Inclusion criteria | >18 years; ACR diagnosis of fibromyalgia; With or without major depression |
| Exclusion criteria | Current/previous duloxetine treatment; Current primary axis 1 diagnosis other than major depression; trauma injury; rheumatism; regional pain syndrome; multiple surgeries; failed back syndrome; arthritis; serious medical illness. |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Mean (SD): 50 years. Gender (M:F): 22:308 Ethnicity: 91% Caucasian, 1% African, 7% Hispanic |
| Further population details | Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=162) Intervention 1: serotonin norepinephrine reuptake inhibitors - duloxetine. titration in which they received duloxetine 30 mg QD for one week before receiving duloxetine 60 mg QD for 12 weeks. If at Visit 8 (Week 13) the patient did not have 50% reduction in the Brief Pain Inventory-Modified Short Form (BPI) 27 average pain score, the patient was blindly escalated to 120 mg QD. Duration 27 weeks. Concurrent medication/care: None reported<br><br>(n=168) Intervention 2: placebo. Placebo. Duration 27 weeks. Concurrent medication/care: None reported. Indirectness: No indirectness |
| Funding | Study funded by industry (Eli Lilly) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE versus PLACEBO<br><br>Protocol outcome 1: Pain reduction at 27 weeks | |

- Actual outcome: Brief pain inventory average score at 27 weeks; Group 1: mean -1.62 Least squared means (converted from SE) (SD 2.5); n=101, Group 2: mean -1.13 Least squared means (converted from SE) (SD 2.5); n=103; BPI average severity and interference of pain in last 24 hours 0-10 Top=High is poor outcome; Comments: Baseline measures: Mean (SD): D group: 6.58 (1.52) Placebo: 6.43 (1.48)
Baseline reported with SD, and endpoint reported as LSM with SE

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness; Group 1 Number missing: 61, Reason: Dropout rate high, but balanced. Reasons given for attrition, but method of ITT not explained; Group 2 Number missing: 65, Reason: Patients did not necessarily answer all questions on questionnaires. Imputation data was calculated from existing values, but method not reported.

Protocol outcome 2: Quality of life at 27 weeks
- Actual outcome: SF-36 mental component summary at 27 weeks; Group 1: mean 3.37 Least squared means score (SD converted from SE) (SD 8.1); n=146, Group 2: mean 0.79 Least squared means score (SD converted from SE) (SD 8); n=162; SF-36 Unreported Top=High is good outcome; Comments: Baseline measure unreported

Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Very high, Crossover - Low, Other 1 - Very high, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 61, Reason: Dropout rate high, but balanced. Reasons given for attrition, but method of ITT not explained.
Group 2 Number missing: 65, Reason: Patients did not necessarily answer all questions on questionnaires.
Imputation data was calculated from existing values, but method not reported.

- Actual outcome: SF-36 physical component summary at 27 weeks; Group 1: mean 2.61 Least squared means score (SD converted from SE) (SD 8.1); n=146, Group 2: mean 2.06 Least squared means score (SD converted from SE) (SD 8); n=162; Comments: Baseline measures unreported
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Very high, Crossover - Low, Other 1 - Very high, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 61, Reason: Dropout rate high, but balanced. Reasons given for attrition, but method of ITT not explained.
Group 2 Number missing: 65, Reason: Patients did not necessarily answer all questions on questionnaires. Imputation data was calculated from existing values, but method not reported.

Protocol outcome 3: Psychological distress (depression/anxiety) at 27 weeks
- Actual outcome: Hamilton depression scale total score at 27 weeks; Group 1: mean -2.04(SD 4.8); n=101, Group 2: mean -1.7 (SD 4.6); n=103; HAMD 0 - 52 Top=High is poor outcome; Comments: Baseline mean not recorded
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: Baseline scores not reported; Baseline details: Patients with severe major depression disorder were equally distributed.; Group 1 Number missing: 61, Reason: Dropout rate high, but balanced. Reasons given for attrition, but method of ITT not explained.
Group 2 Number missing: 65, Reason: Patients did not necessarily answer all questions on questionnaires.
Imputation data was calculated from existing values, but method not reported.

| | |
|---|---|
| Protocol outcome 4: Physical function at 27 weeks<br>- Actual outcome: FIQ physical function subscale total score at 27 weeks; Group 1: mean -0.02 (SD 2.3); n=101, Group 2: mean -0.06 (SD 2.3); n=103. Comments: baseline scores not reported<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: Baseline scores not reported; Group 1 Number missing: 61, Reason: Dropout rate high, but balanced. Reasons given for attrition, but method of ITT not explained.<br>Group 2 Number missing: 65, Reason: Patients did not necessarily answer all questions on questionnaires.<br>Imputation data was calculated from existing values, but method not reported.<br><br>Protocol outcome 5: Discontinuation due to adverse events at 27 weeks<br>- Actual outcome: N who discontinued due to adverse events at 27 weeks; Group 1: 30/162, Group 2: 19/168<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness; Group 1 Number missing: 162, Reason: Dropout rate high, but balanced. Reasons given for attrition, but method of ITT not explained.<br>Group 2 Number missing: 168, Reason: Patients did not necessarily answer all questions on questionnaires.<br>Imputation data was calculated from existing values, but method not reported. | |
| Protocol outcomes not reported by the study | Use of healthcare services ; Sleep |

| Study | Foster 2010[214] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=66) |
| Countries and setting | Conducted in USA; Setting: Strong Memorial Hospital, University of Rochester (USA) |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 12 weeks (randomised phase) |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | >3 continuous months of insertional pain/dyspareunia; vulvodynia (Friedrich's criteria); vestibular tender points; age 18 - 50. 4 out of 10 pain intensity. |
| Exclusion criteria | Other neuropathology or infection of vagina |
| Recruitment/selection of patients | Unreported |
| Age, gender and ethnicity | Age - Mean (SD): placebo: 27.7 (6.3), lidocaine 31.6 (8.4). Gender (M:F): All female. Ethnicity: Predominantly white |
| Further population details | 1. Chronic visceral pain: people with chronic visceral pain |
| Indirectness of population | No indirectness |
| Interventions | (n=33) Intervention 1: topical/IV local anaesthetics - topical lidocaine. 5% cream. Duration 12 weeks. Concurrent medication/care: Desipramine placebo tablets. Indirectness: Serious indirectness; Indirectness comment: Concomitant with sham desipramine placebo tablets as part of a 4-arm trial of two interventions.<br><br>(n=33) Intervention 2: placebo. Sham 5% lidocaine cream. Duration 12 weeks. Concurrent medication/care: Desipramine placebo tablets. Indirectness: Serious indirectness; Indirectness comment: Concomitant with sham desipramine placebo tablets as part of a 4-arm trial of two interventions. |
| Funding | Academic or government funding (Eunice Kennedy Shriver National Institute of Child Health and Clinical Development) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TOPICAL LIDOCAINE versus PLACEBO

Protocol outcome 1: Pain reduction at 12 weeks
- Actual outcome: McGill short form, total score at 12 weeks; Group 1: mean -3.1 Absolute changes from baseline to endpoint (SD 6.77); n=27, Group 2:

| | |
|---|---|
| mean -4.57 (SD 5.86); n=31; McGill short form total score 0-78 Top=High is poor outcome; Comments: Baseline means: Lidocaine = 12.32; Placebo = 13.74 (no SD reported)<br><br>Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Lost to follow-up; dropped out; pregnancy; Group 2 Number missing: 2, Reason: Lost to follow-up; dropped out<br><br>Protocol outcome 2: Psychological distress (depression/anxiety) at 12 weeks<br>- Actual outcome: Beck Depression Inventory score at 12 weeks; Group 1: mean 0.86 (SD 5.9); n=28, Group 2: mean -1.92 (SD 5.44); n=31; BDI Unreported Top=High is poor outcome; Comments: Baseline means: Lidocaine = 21.37; Placebo = 20.9<br>Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 5, Reason: Lost to follow-up; dropped out; pregnancy; Group 2 Number missing: 2, Reason: Lost to follow-up; dropped out<br><br>Protocol outcome 3: Discontinuation due to adverse events at 12 weeks<br>- Actual outcome: Discontinuation due to adverse events at 12 weeks; Group 1: 1/33, Group 2: 1/33<br>Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: -- ; Group 1 Number missing: 5, Reason: Lost to follow-up; dropped out; pregnancy; Group 2 Number missing: 2, Reason: Lost to follow-up; dropped out | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Use of healthcare services ; Sleep |

| Study | Foster 2010[215] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=47) |
| Countries and setting | Conducted in USA; Setting: Gynaecology clinics in Lothian and Grampian |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 6 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Bladder pain/discomfort and urinary frequency; symptoms for >6 weeks; treatment naive. |
| Exclusion criteria | Heart, liver or neuralgic disease; glaucoma; cancer |
| Recruitment/selection of patients | Gynaecology clinics |
| Age, gender and ethnicity | Age - Mean (SD): 38. Gender (M:F): Women = 115 (85%) :111 (82%). Ethnicity: 100% Caucasian |
| Further population details | 1. Chronic visceral pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=135) Intervention 1: tricyclic antidepressants - amitriptyline. For three weeks: 10 - 25 mg/day stepped. Titrated to 50 mg if required. Thereafter: up to 75 mg/day. Duration 12 weeks. Concurrent medication/care: None reported. Indirectness: No indirectness<br><br>(n=136) Intervention 2: placebo. Once a day with sham titration. Duration 12 weeks. Concurrent medication/care: None reported. Indirectness: No indirectness |
| Funding | Other (Chief Scientist's Office of Scotland) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO

Protocol outcome 1: Pain reduction at 12 weeks
- Actual outcome: VAS pain score at 12 weeks; Group 1: mean -2.6 (SD 2.5); n=111, Group 2: mean -2.3 (SD 2.4); n=119; Pain score 0-10 Top=High is poor outcome; Comments: Baseline 5.8 ± 1.5 : 6.0 ± 1.8

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 23; Group 2 Number missing: 17, reasons not specified

| | |
|---|---|
| Protocol outcome 2: Discontinuation due to adverse events at 12 weeks<br>- Actual outcome: N discontinued adverse events at 12 weeks; Group 1: 7/135, Group 2: 2/136<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Use of healthcare services ; Sleep |

| Study | GaPP1 trial: Lewis 2016[336] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=47) |
| Countries and setting | Conducted in United Kingdom; Setting: 2 centres in Scotland |
| Line of therapy | Not applicable |
| Duration of study | Intervention time: 6 months |
| Method of assessment of guideline condition | Method of assessment /diagnosis not stated: NA |
| Stratum | Overall: NA |
| Subgroup analysis within study | Not applicable: NA |
| Inclusion criteria | Between 18-50 years old, pelvic pain that was located within the true pelvis or between and below anterior iliac crests for greater than 6 months, associated with functional disability and no obvious pelvic pathology at laparoscopy. Required to be using contraception |
| Exclusion criteria | Known pelvic pathology such as endometriosis or ovarian cyst, already taking gabapentin or pregabalin, due to undergo surgery, history of renal impairment, allergic to gabapentin, breast feeding or were pregnant of planning pregnancy in the next six months |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Range: 18-50 years . Gender (M:F): All women. Ethnicity: Caucasian |
| Further population details | 1. Chronic visceral pain: people with chronic visceral pain |
| Indirectness of population | No indirectness |
| Interventions | (n=22) Intervention 1: anti-epileptics - gabapentin. 300mg gabapentin daily increased in 300mg increments each week until 50% pain reduction or side effects, up to a maximum dose of 2700mg. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA<br><br>(n=25) Intervention 2: placebo. equivalent dose in placebo tablets. Duration 6 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA |
| Funding | Academic or government funding (project grant from the Chief Scientist's Office of Scotland ) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS (how strong was the pain during the past 4 weeks on average?) at 6 months ; Group 1: mean 3.6 (SD 2.4); n=13, Group 2: mean

4.5 (SD 2.3); n=12; VAS not reported Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 13, Reason: not reported
- Actual outcome: VAS (how strong was the pain during the past 4 weeks on average?) at 3 months ; Group 1: mean 4.2 (SD 2.7); n=13, Group 2: mean 5.1 (SD 2.3); n=13; VAS not reported Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 12, Reason: not reported

Protocol outcome 2: Physical function
- Actual outcome: Pain Disability Questionnaire (function) at 3 months ; Group 1: mean 29.4 (SD 21); n=13, Group 2: mean 23 (SD 16.5); n=12; Pain Disability Questionnaire (function) not reported Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 12, Reason: not reported
- Actual outcome: Pain Disability Questionnaire (function) at 6 months ; Group 1: mean 23.9 (SD 25.3); n=13, Group 2: mean 20.3 (SD 14.8); n=12; Pain Disability Questionnaire (function) not reported Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 13, Reason: not reported

Protocol outcome 3: Psychological distress (depression/anxiety)
- Actual outcome: Hospital Anxiety and Depression Scale (anxiety) at 3 months ; Group 1: mean 8.1 (SD 5.4); n=13, Group 2: mean 8.2 (SD 4.2); n=13; Hospital Anxiety and Depression Scale 0-21 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 12, Reason: not reported
- Actual outcome: Hospital Anxiety and Depression Scale (anxiety) at 6 months ; Group 1: mean 7.5 (SD 5.7); n=13, Group 2: mean 9.8 (SD 5.3); n=12; Hospital Anxiety and Depression Scale (anxiety) 0-21 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 13, Reason: not reported
- Actual outcome: Hospital Anxiety and Depression Scale (depression) at 3 months ; Group 1: mean 5.5 (SD 3.9); n=13, Group 2: mean 4.7 (SD 4.5); n=13; Hospital Anxiety and Depression Scale 0-21 Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 12, Reason: not reported

| | |
|---|---|
| - Actual outcome: Hospital Anxiety and Depression Scale (depression) at 6 months ; Group 1: mean 5.2 (SD 4.9); n=13, Group 2: mean 4.9 (SD 4); n=12; Hospital Anxiety and Depression Scale (depression) 0-21 Top=High is poor outcome<br>Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 9, Reason: not reported ; Group 2 Number missing: 13, Reason: not reported<br><br>Protocol outcome 4: Discontinuation due to adverse events<br>- Actual outcome: withdrawal due to side effects at 6 months ; Group 1: 4/22, Group 2: 3/25<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Quality of life; Use of healthcare services ; Sleep |

| Study | Ginsberg 1996[233] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=51) |
| Countries and setting | Conducted in Belgium; Setting: Outpatient clinics |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 8 weeks |
| Method of assessment of guideline condition | Unclear method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Fibromyalgia (ACR); history of widespread pain ≥3 months; 11-18 tender point sites. |
| Exclusion criteria | Rheumatism; pregnancy (or potential for); lactation; glaucoma; risk of urinary retention; history of heart disease; anti-depressants; sleeping medication; analgesics (except paracetamol); Receipt of study drug within 6 months prior to study; Vitamin D or magnesium drugs. |
| Recruitment/selection of patients | Rheumatology clinics in Belgium |
| Age, gender and ethnicity | Age - Mean (SD): 46 ± 1. Gender (M:F): 20:4; 18:4 (completers). Ethnicity: Caucasian 22:22; Black 1:0 |
| Further population details | 1. Chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=26) Intervention 1: tricyclic antidepressants - amitriptyline. Sustained release capsules 25 mg. Duration 8 weeks. Concurrent medication/care: None. Indirectness: No indirectness<br><br>(n=24) Intervention 2: placebo. Sham pills from same supplier as experimental drugs. Duration 8 weeks. Concurrent medication/care: None. Indirectness: No indirectness |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS evaluation of pain at 8 weeks; Group 1: mean 3.9 VAS pain score (SD 2.3); n=24, Group 2: mean 6.8 VAS pain score (SD 1.8); n=22; VAS pain score 0-10 Top=High is poor outcome; Comments: Baseline: 7.3 ± 1.4 : 7.1 ± 1.4
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness

| | |
|---|---|
| of outcome: No indirectness; Group 1 Number missing: 2, Reason: Lost to follow up; Group 2 Number missing: 3, Reason: Lost to follow up | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Discontinuation due to adverse events; Use of healthcare services , Sleep |

| Study | Heckmann 2012[275] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=20) |
| Countries and setting | Conducted in Germany; Setting: Dental surgery |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 6 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Burning mouth syndrome diagnosis |
| Exclusion criteria | Diabetes, hepatitis, jaundice, liver problems, vitamin B-12 deficiency, infections, sleep apnoea, glaucoma, asthma, Parkinson's, Mental health problems. |
| Recruitment/selection of patients | Erlangen University Dental School referrals. |
| Age, gender and ethnicity | Age - Mean (SD): 63.95 ± 10.76. Gender (M:F): Not reported. Ethnicity: Not reported |
| Further population details | 1. chronic orofacial pain |
| Indirectness of population | No indirectness |
| Interventions | (n=10) Intervention 1: Benzodiazepines - clonazepam. 0.5 mg/day. Duration 6 weeks. Concurrent medication/care: None reported<br><br>(n=10) Intervention 2: placebo. Supply of 63 tablets. Duration 6 weeks. Concurrent medication/care: None reported |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLONAZEPAM versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS pain rating at 6 weeks; Group 1: mean 4.5 (SD 2.4); n=10, Group 2: mean 4.5 (SD 1.8); n=10; VAS pain rating 0-10 Top=High is poor outcome; Comments: Baseline values: 7.4 ± 2.4 : 6.0 ± 2.2 :
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: no indirectness ; Group 1 Number missing: Not reported ; Group 2 Number missing: Not reported

| | |
|---|---|
| Protocol outcome 2: Psychological distress (depression/anxiety)<br>- Actual outcome: Beck Depression Index at 6 weeks; Group 1: mean 0.6 (SD 0.8); n=10, Group 2: mean 0.8 (SD 0.9); n=10; BDI 0-3 Top=High is poor outcome; Comments: Baseline values: 0.5 ± 0.8 : 0.6 ± 1.1<br>Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - ; Indirectness of outcome: no indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Use of healthcare services ; Sleep, Discontinuation due to adverse events |

| Study | Heymann 2001[277] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=118) |
| Countries and setting | Conducted in Brazil; Setting: San Paulo clinic |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 8 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Women with fibromyalgia (ACR) who were naive to the interventions; 6 months clear of any other study; 4 weeks clear of analgesic narcotics, anti-depressants, neuroleptics and anxiolytics. Acetaminophen was permitted. |
| Exclusion criteria | Pregnant, in physical rehab; heart arrhythmia; renal or hepatic disease; glaucoma; urinary retention; hyperthyroidism; inflammation. |
| Recruitment/selection of patients | Federal University of São Paulo outpatients |
| Age, gender and ethnicity | Age - Mean (range): 53.4 (31-75) : 48.8 (18-76) : 49.4 (22-75). Gender (M:F): All women. Ethnicity: Caucasian: n = 26 : n = 21 : n = 26 Remainder = 'non-Caucasian' |
| Further population details | 1. Chronic widespread pain subgroup |
| Extra comments | Fibromyalgia |
| Indirectness of population | No indirectness |
| Interventions | (n=40) Intervention 1: tricyclic antidepressants - amitriptyline. 25 mg QD. Duration 8 weeks. Concurrent medication/care: Some concomitant medication allowed<br><br>(n=38) Intervention 2: tricyclic antidepressants - nortriptyline. 25 mg QD. Duration 8 weeks. Concurrent medication/care: Some concomitant drugs allowed<br><br>(n=40) Intervention 3: placebo. Sham tablets. Duration 8 weeks. Concurrent medication/care: Some concomitant drugs allowed |
| Funding | Funding not stated |

| | |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO<br><br>Protocol outcome 1: Quality of life<br>- Actual outcome: FIQ at 8 weeks; Group 1: mean 39.97 (SD 4.16); n=37, Group 2: mean 67.45 (SD 4.34); n=36; Fibromyalgia questionnaire 0-100 Top=High is poor outcome; Comments: Baseline 63.17 ± 4.16; 67.45 ± 4.34<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: no indirectness ; Group 1 Number missing: 3; Group 2 Number missing: 7 (reasons not reported)<br><br>Protocol outcome 1: Pain reduction<br>- Actual outcome: Number of responders on scale of global improvement (score of great or moderate improvement) at 8 weeks; Group 1:25/40 Group 2: 13/33<br>Risk of bias: All domain - High, Selection - Low, Blinding -Low, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: no indirectness- ; Group 1 Number missing: 3; Group 2 Number missing: 7(reasons not reported)<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NORTRIPTYLINE versus PLACEBO<br><br>Protocol outcome 1: Quality of life<br>- Actual outcome: FIQ at 8 weeks; Group 1: mean 48.78 (SD 7.28); n=36, Group 2: mean 51.68 (SD 7.98); n=33; Fibromyalgia questionnaire 0-100 Top=High is poor outcome; Comments: Baseline: 67.30 ± 4.68 : 67.45 ± 4.34<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: no indirectness; Group 1 Number missing: 2; Group 2 Number missing: 7 (reasons not reported)<br><br>Protocol outcome 1: Pain reduction<br>- Actual outcome: Number of responders on scale of global improvement (score of great or moderate improvement) Group 1:20/38, Group 2: 13/33<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: no indirectness; Group 1 Number missing: 3; Group 2 Number missing: 7 (reasons not reported)<br><br>Note: nortriptyline and amitriptyline arms combined in review analysis | |
| Protocol outcomes not reported by the study | Physical function; Psychological distress (depression/anxiety); Use of healthcare services ; Sleep |

| Study | Kimos 2007[311] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=50) |
| Countries and setting | Conducted in Canada; Setting: TMD/Orofacial pain clinic, department of Dentistry at University of Alberta |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 12 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | (1) Masticatory muscle pain for at least 6 months (2) not attributable to recent acute trauma or previous infection or inflammation (3) moderate to severe baseline score of 50 mm or greater using a 100mm (4) Pain upon palpation in the temporalis and masseter. |
| Exclusion criteria | (1) inflammatory TMD (2) pregnant or nursing (3) epilepsy, cardiac, renal or hepatic disorders (4) history of intolerance to gabapentin or any of the components (5) dental or periodontal disease or neuropathic facial pain (6) patients wearing occlusal splint appliance for less than 6 months |
| Recruitment/selection of patients | Female subjects chosen because TMD are prevalent in this population |
| Age, gender and ethnicity | Age - Mean (SD): 33.58 years. Gender (M:F): All female. Ethnicity: Not stated |
| Further population details | 1. chronic orofacial pain: people with chronic orofacial pain (Masticatory muscle pain) subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=25) Intervention 1: anti-epileptics - gabapentin. Administered until adequate pain control was reached or unacceptable side effects limited titration. Patients were started on 300mg per day and the dose was increased by 300mg every 3 days until pain was controlled. The maximum dose was 4200mg per day. Duration 12 weeks. Concurrent medication/care: Acetaminophen 500mg was allowed as a rescue drug where subjects needed pain control between doses, or if the study medication was not having an analgesic effect. Maximum every 6 hours, 40000mg maximum daily dosage. Indirectness: No indirectness<br><br>(n=25) Intervention 2: placebo. Placebo. Duration 12 weeks. Concurrent medication/care: Acetaminophen 500mg as rescue therapy. Indirectness: No indirectness |
| Funding | Academic or government funding (University of Alberta. Pharmascience Inc. donated the gabapentin used in the study) |

| | |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GABAPENTIN versus PLACEBO<br><br>Protocol outcome 1: Pain reduction<br>- Actual outcome: VAS pain reduction (%) at 12 weeks; Group 1: mean 51.4 (SD 38.8); n=24, Group 2: mean 24.3 (SD 43.54); n=20<br>Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 33% vs 25% taking SSRIs; Group 1 Number missing: 6; Group 2 Number missing: 8 (reasons not reported) | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Discontinuation due to adverse events; Use of healthcare services ; Sleep |

| Study | Lee 2005[332] |
|---|---|
| Study type | RCT ( randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=14) |
| Countries and setting | Conducted in United Kingdom; Setting: Unspecified research centre |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 13 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Aged between 18-65 years, exclusion of bacterial prostatitis and chlamydia. |
| Exclusion criteria | Participants with urethritis, symptoms of benign prostatic hyperplasia or significant abnormalities on baseline bloods were excluded. Other exclusion criteria were current treatment with an antidepressant or anxiolytic drug, history of seizures, or any history of hypersensitivity or intolerance to SSRI |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Range: 18-65. Gender (M:F): All men. Ethnicity: Not reported |
| Further population details | 1. chronic visceral pain |
| Extra comments | Men with symptoms of chronic pelvic pain syndrome |
| Indirectness of population | No indirectness |
| Interventions | (n=7) Intervention 1: selective serotonin reuptake inhibitors - sertraline. 50 mg/day. Duration 13 weeks. Concurrent medication/care: None reported<br><br>(n=7) Intervention 2: placebo. 50mg. Duration 13 weeks. Concurrent medication/care: None reported |
| Funding | Academic or government funding (MSSVD paid for the drugs used) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SERTRALINE versus PLACEBO

Protocol outcome 1: Psychological distress (depression/anxiety)
- Actual outcome: HAD anxiety score at 13 weeks; Group 1: mean -0.9 'SD' calculated from p-value instead because no SDs reported. (SD 3.5); n=6, Group 2: mean -2.5 'SD' field is p-value instead because no SDs reported. (SD 3.5); n=7;  HAD anxiety 0-10 Top=High is poor outcome; Comments: Baseline: 7.6 : 8.2

| | |
|---|---|
| Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - high, Measurement - low, Crossover - Low, Comments - Indirectness of outcome: no indirectness; Baseline details: Inferred from Mann Whitney U test result; Group 1 Number missing: 1, Reason: Feeling 'spaced out'; Group 2 Number missing: 0, Reason: NA<br>- Actual outcome: HAD depression score at 13 weeks; Group 1: mean -1.6 'SD' calculated from p-value instead because no SDs reported. (SD 3); n=7, Group 2: mean -0.7 'SD' field is p-value instead because no SDs reported. (SD 3); n=7; HADS depression 0-100 Top=High is poor outcome; Comments: Baseline: 4.7 : 4.5<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - high, Measurement - low, Crossover - Low, Comments - Indirectness of outcome: no indirectness; Baseline details: Inferred from Mann Whitney U test result; Group 1 Number missing: 1, Reason: Feeling 'spaced out'; Group 2 Number missing: 0, Reason: NA | |
| Protocol outcome 2: Pain reduction<br>- Actual outcome: Prostatic symptom severity at 13 weeks; Group 1: mean -6.1 'SD' calculated from p-value instead because no SDs reported. (SD 10.05); n=7, Group 2: mean -2 'SD' field is p-value instead because no SDs reported. (SD 10.05); n=7; Baseline: SSRI: 23.4; Placebo: 28<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - high, Measurement - low, Crossover - Low, Comments - No SDs but study included as has been used in RM meta-analysis; Indirectness of outcome: no indirectness; Baseline details: Inferred from Mann Whitney U test result; Group 1 Number missing: 1, Reason: Feeling 'spaced out'; Group 2 Number missing: 0, Reason: NA | |
| Protocol outcome 3: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 0/7 Group 2: 1/7<br>Risk of bias: All domain – Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - No SDs but study included as has been used in RM meta-analysis.; Indirectness of outcome: no indirectness ; Baseline details: Inferred from Mann Whitney U test result; Group 1 Number missing: 1, Reason: Feeling 'spaced out'; Group 2 Number missing: 0, Reason: NA | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Use of healthcare services ; Sleep |

| Study | Luo 2009[347] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=80) |
| Countries and setting | Conducted in China; Setting: Outpatients clinic of Tonji University Hospital |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 8 weeks |
| Method of assessment of guideline condition | Partially adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | 6 month duration of disease (persistent somatoform pain disorder defined by pain which cannot be fully explained by a physiological process or physical disorder). |
| Exclusion criteria | Depressive symptoms prior to pain, unstable or severe illness, pregnant, taking anti-depressants. |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Range: 18-65. Gender (M:F): 34:46. Ethnicity: Chinese |
| Further population details | Subgroups unclear |
| Extra comments | Met ICD-10 diagnostic criteria for somatoform pain disorder |
| Indirectness of population | No indirectness |
| Interventions | (n=40) Intervention 1: selective serotonin reuptake inhibitors - fluoxetine. 20 mg/day. Duration 8 weeks. Concurrent medication/care: None reported<br><br>(n=40) Intervention 2: placebo. Manufactured by the hospital's pharmacy rather than by pharmaceutical firm. Duration 8 weeks. Concurrent medication/care: None reported |
| Funding | Other (Shanghai Science and Technology Committee) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUOXETINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: Medical Outcomes Study Pain Measures (MOSPM)
at 8 weeks; Group 1: mean 33.08 (SD 18.81); n=40, Group 2: mean 55.33 (SD 25.44); n=40; MOSPM 0-75 Top=High is poor outcome; Comments: Baseline values: 29.53 ± 22.76 : 55.33 ± 25.44

| | |
|---|---|
| Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - No attrition rate reported. Indirectness of outcome: no indirectness; Baseline details: Mann Whitney test; Blinding details: Placebo not manufactured by same firm as the intervention which may have 'unblinded' some participants; Group 1 Number missing, Reason: Unclear whether any data missing or not; Group 2 Number missing, Reason: Unclear whether any data missing or not | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Use of healthcare services ; Sleep |

| Study | Maarrawi 2018[350] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=220) |
| Countries and setting | Conducted in Lebanon; Setting: Hotel-Dieu de France Hospital, Beirut |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 2 months |
| Method of assessment of guideline condition | Partially adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Idiopathic chronic neck pain 15 days/month for ≥3 months; no previous trauma or neurologic disorder except tension headache, trismus or perturbed sleep. |
| Exclusion criteria | Neurologic disorder; cervical disc disease; migraine, trauma, major depression; analgesic abuse history; intolerance to study drug class; mental health problems; glaucoma; heart problems; constipation; drugs for CNP other than NSAIDs during month prior to study; pregnancy; prostatic symptoms. |
| Recruitment/selection of patients | From Hotel-Dieu de France |
| Age, gender and ethnicity | Age - Range: 18-75. Gender (M:F): Not reported. Ethnicity: Not reported, but infer Lebanese |
| Further population details | 1. chronic orofacial pain subgroup |
| Extra comments | Idiopathic chronic neck pain (CNP) |
| Indirectness of population | No indirectness |
| Interventions | (n=166) Intervention 1: tricyclic antidepressants - amitriptyline. 5 mg/day Duration 2 months. Concurrent medication/care: Allowed NSAIDs<br><br>(n=166) Intervention 2: placebo. Sham pill. Duration 2 months. Concurrent medication/care: Allowed NSAIDs |
| Funding | Academic or government funding (Saint Joseph Council of Research, Beirut University) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS pain scale at 2 months; Group 1: mean 33.08 (SD 18.81) Group 2: mean55.31 Percent change in ten-point VAS score (SD 25.44); n=108, Scale 0-10, high = poor outcome, baseline values not reported

| | |
|---|---|
| Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 3: Discontinuation due to adverse events<br>- Actual outcome: N who discontinued due to side effects at 2 months; Group 1: 8/162, Group 2: 0/158<br>Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 2: Physical function<br>- Actual outcome: Neck Pain Disability Index % improvement at 2 months; Group 1: mean 42.22 (SD 15.5); n=104, Group 2: mean 13.69 (SD 9.5); n=108, Comment: baseline values not reported<br>Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 2: Sleep<br>- Actual outcome: BIS % improvement at 2 months; Group 1: mean 34.89 (SD 22.98); n=104, Group 2: mean 6.02 (SD 12.38); n=108<br>Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Quality of life; Use of healthcare services |

| Study | Mahagna 2016[354] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=64) |
| Countries and setting | Conducted in Israel; Setting: Medical centres in Israel |
| Line of therapy | 2nd line |
| Duration of study | Intervention time: 6 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | FMS (ACR); women aged 18-75 years |
| Exclusion criteria | Pregnancy/breast-feeding; heart disease; neoplasticism; rheumatism, GI bleeding; renal failure; hypertension; significant disability. No other NSAID use. |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Mean (SD): 50 ± 11.57. Gender (M:F): All women. Ethnicity: Not reported |
| Further population details | 1. chronic widespread pain: subgroup |
| Extra comments | Taking established fibromyalgia treatments concomitantly: Anti-depressants (15:14); anti-epileptics (1:2); opiates (1:0). |
| Indirectness of population | No indirectness |
| Interventions | (n=32) Intervention 1: NSAID - etoricoxib. 90 mg/day. Duration 6 weeks. Concurrent medication/care: Patient's established treatment (except NSAIDs). Indirectness: No indirectness<br><br>(n=32) Intervention 2: placebo. Sham etoricoxib. Duration 6 weeks. Concurrent medication/care: Patient's established treatment (except NSAIDs). Indirectness: No indirectness |
| Funding | Study funded by industry (MSD) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ETORICOXIB versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: Brief Pain Inventory at 6 weeks; Group 1: 9/32, Group 2: 9/32; Comments: N with decrease in BPI score >30% at endpoint
Risk of bias: All domain - Very high, Selection - high, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low,

| | |
|---|---|
| Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: No baseline score reported.; Blinding details: More women in experimental group took concomitant opiates and anti-depressants than in placebo group; Group 1 Number missing: 6, Reason: Withdrawal, discontinuation, adverse events; Group 2 Number missing: 2, Reason: Discontinuation<br><br>Protocol outcome 2: Quality of life<br>- Actual outcome: SF-36 Physical component at 6 weeks; Group 1: mean 35.2 (SD 16.8); n=32, Group 2: mean 35.6 (SD 19); n=32<br>Risk of bias: All domain - Very high, Selection - high, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Blinding details: More women in experimental group took concomitant opiates and anti-depressants than in placebo group; Group 1 Number missing: 6, Reason: Withdrawal, discontinuation, adverse events; Group 2 Number missing: 2, Reason: Discontinuation<br>- Actual outcome: SF-36 Mental component at 6 weeks; Group 1: mean 46.5 (SD 21); n=32, Group 2: mean 48.4(SD 19); n=32<br>Risk of bias: All domain - Very high, Selection - high, Blinding - High, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Blinding details: More women in experimental group took concomitant opiates and anti-depressants than in placebo group; Group 1 Number missing: 6, Reason: Withdrawal, discontinuation, adverse events; Group 2 Number missing: 2, Reason: Discontinuation<br><br>Protocol outcome 3: Psychological distress<br>- Actual outcome: Hamilton Rating Scale for Depression at 6 weeks; Group 1: mean 10.6 (SD 6); n=32, Group 2: mean 9.9 (SD 6.2), n=32,<br>Risk of bias: All domain - Very high, Selection - high, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Blinding details: More women in experimental group took concomitant opiates and anti-depressants than in placebo group; Group 1 Number missing: 6, Reason: Withdrawal, discontinuation, adverse events; Group 2 Number missing: 2, Reason: Discontinuation<br><br>Protocol outcome 4: Discontinuation due to adverse events<br>- Actual outcome: N discontinued due to AEs at 6 weeks; Group 1: 2/32, Group 2: 0/32<br>Risk of bias: All domain - Very high, Selection - high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: No baseline score reported.; Blinding details: More women in experimental group took concomitant opiates and anti-depressants than in placebo group; Group 1 Number missing: 0, Reason: Withdrawal, discontinuation, adverse events; Group 2 Number missing: 0, Reason: Discontinuation |
| Protocol outcomes not reported by the study | Physical function; Use of healthcare services ; Sleep |

| Study | Murakami 2015[403] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=393) |
| Countries and setting | Conducted in Japan; Setting: 42 outpatient hospitals/clinics in Japan |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 14 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis: |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Male and female outpatients aged between 20 and 75 years who met the ACR 1990 criteria for fibromyalgia and had a Brief Pain Inventory (BPI) average pain score ≥4 at visits 1 and 2 were included |
| Exclusion criteria | Past duloxetine treatment; serious or medically unstable disease, clinically significant abnormal laboratory values, or abnormal electrocardiogram (ECG) findings; pain caused by non-fibromyalgia diseases; poorly controlled thyroid dysfunction; rheumatoid, inflammatory, or infectious arthritis; autoimmune disorders other than thyroid dysfunction; psychiatric disorders other than major depressive disorder within the past year; and suicidal tendencies as assessed using the Columbia-Suicide Severity Rating Scale |
| Recruitment/selection of patients | March 2012 to December 2013 |
| Age, gender and ethnicity | Age - Mean (SD): 48.7(11.9) Gender (M:F): 65:321. Ethnicity: Japanese |
| Further population details | 1. chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=196) Intervention 1: serotonin norepinephrine reuptake inhibitors - duloxetine. After a 1 to 2 week screening phase participants were randomised to duloxetine for 14 weeks. This was orally administered once daily after breakfast. Patients received 20mg per day for 1 week followed by 40mg per day for 1 week, and then 60mg per day for the duration of the study. Duration 14 weeks. Concurrent medication/care: Patients were prohibited from using analgesics and drugs with analgesic effects, including nonsteroidal anti-inflammatory drugs, anticonvulsants, pregabalin, neurotropin, anesthetics, opioids, and adrenocorticosteroids. The use of analgesics for up to 3 consecutive days and for up to a total of 10 days was permitted only for the treatment of adverse events (AEs). Coadministration of acetaminophen at doses up to 1500 mg/day was permitted to treat AEs and as rescue treatment for fibromyalgia, except on the day before efficacy was evaluated after visit 2 and until just before the evaluation. The use of prophylactic aspirin at doses up to 325 mg/day to prevent cardiac events was also permitted. Indirectness: No indirectness |

| | |
|---|---|
| | (n=197) Intervention 2: placebo. Placebo. Duration 14 weeks. Concurrent medication/care: patients were prohibited from using analgesics and drugs with analgesic effects, including nonsteroidal anti-inflammatory drugs, anticonvulsants, pregabalin, neurotropin, anesthetics, opioids, and adrenocorticosteroids. The use of analgesics for up to 3 consecutive days and for up to a total of 10 days was permitted only for the treatment of adverse events (AEs). Coadministration of acetaminophen at doses up to 1500 mg/day was permitted to treat AEs and as rescue treatment for fibromyalgia, except on the day before efficacy was evaluated after visit 2 and until just before the evaluation. The use of prophylactic aspirin at doses up to 325 mg/day to prevent cardiac events was also permitted. Indirectness: No indirectness |
| Funding | Study funded by industry (Shionogi & Co. Ltd., Eli Lilly Japan K.K., and Eli Lilly & Company) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: BPI total score average (change score) at 14 weeks; Group 1: mean -1.6 (SD 0.26); n=191, Group 2: mean -1.22 (SD 0.26); n=195; BPI 0-10 Top=High is poor outcome; Comments: Baseline D: 6.05 ± 1.29 P: 6.13 ± 1.35
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48

Protocol outcome 2: Quality of life
- Actual outcome: SF-36 physical functioning subscale (change score) at 14 weeks; Group 1: mean 7.4 (SD 2.13); n=191, Group 2: mean 3.04 (SD 2.15); n=195; SF-36 0-100 Top=High is good outcome; Comments: Baseline
D: 63.72 ± 18.75
P:62.51 ± 19.82
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48
- Actual outcome: SF-36 physical role limitations subscale (change score) at 14 weeks; Group 1: mean 8.2 (SD 2.96); n=191, Group 2: mean 0.44 (SD 2.98); n=195; Comments: Baseline:
D: 49.25 ± 25.57
P: 49.13 ± 25.60
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48
- Actual outcome: SF-36 bodily pain subscale (change score) at 14 weeks; Group 1: mean 10.95 (SD 2.07); n=191, Group 2: mean 5.28 (SD 2.08); n=195; SF-36 0-100 Top=High is good outcome; Comments: Baseline:
D: 36.53 ± 12.40
P: 36.60 ± 11.71
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48

- Actual outcome: SF-36 general health perceptions subscale (change score) at 14 weeks; Group 1: mean 6.55 (SD 1.92); n=191, Group 2: mean 3.31 (SD 1.94); n=195; SF-36 0-100 Top=High is good outcome; Comments: Baseline
39.37 ± 17.67
38.76 ± 14.77
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48
- Actual outcome: SF-36 vitality subscale (change score) at 14 weeks; Group 1: mean 10.05 (SD 2.51); n=191, Group 2: mean 3.35 (SD 2.53); n=195; SF-36 0-100 Top=High is good outcome; Comments: Baseline:
32.43 ± 21.03
31.96 ± 18.80
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48
- Actual outcome: SF-36 social functioning subscale (change score) at 14 weeks; Group 1: mean 10.32 (SD 3.04); n=191, Group 2: mean 3.28 (SD 3.06); n=195; sf-36 0-100 Top=High is good outcome; Comments: Baseline
55.71 ± 26.54
55.76 ± 27.53
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48
- Actual outcome: SF-36 mental health subscale (change score) at 14 weeks; Group 1: mean 5.91 (SD 2.51); n=191, Group 2: mean -2 (SD 2.52); n=195; SF-36 0-100 Top=High is good outcome; Comments: Baseline
56.10 ± 19.84
55.50 ± 18.85
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48
- Actual outcome: SF-36 emotional role limitations subscale (change score) at 14 weeks; Group 1: mean 5.5 (SD 3.35); n=191, Group 2: mean -3.63 (SD 3.36); n=195; SF-36 0-100 Top=High is good outcome; Comments: Baseline:
61.24 ± 26.80
60.34 ± 29.16
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48

Protocol outcome 3: Physical function
- Actual outcome: Fibromyalgia impact questionnaire physical function subscale at 14 weeks; Group 1: mean -0.37 (SD 2.35); n=191, Group 2: mean -0.37 (SD 0.26); n=195; FIQ 0-5 Top=High is poor outcome; Comments: Baseline
D: 3.36 ± 2.35
P: 3.85 ± 2.32
Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48

| | |
|---|---|
| Protocol outcome 4: Psychological distress (depression/anxiety)<br>- Actual outcome: Beck Depression Inventory II total change scores at 14 weeks; Group 1: mean -4.09 (SD 0.84); n=191, Group 2: mean -1.19 (SD 0.85); n=195; BDI-II 0-63 Top=High is poor outcome<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48<br><br>Protocol outcome 5: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events at 14 weeks; Group 1: 15/196, Group 2: 14/197<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48<br><br>Protocol outcome 6: Sleep<br>- Actual outcome: BPI interference score - sleep at 14 weeks; Group 1: mean -1.82 (SD 0.35); n=191, Group 2: mean -1.57 (SD 0.36); n=195; Comments: Baseline<br>D: 5.30 ± 2.81<br>P: 5.22 ± 2.91<br>Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 30; Group 2 Number missing: 48 | |
| Protocol outcomes not reported by the study | Use of healthcare services |

| Study | Norregaard 1995[425] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=42) |
| Countries and setting | Conducted in Denmark; Setting: Inferred: hospital clinic |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 4 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Fibromyalgia (ACR); stopped other drugs 2 weeks prior to study. Allowed NSAIDs. |
| Exclusion criteria | Heart, lung or liver disease; glaucoma; pregnant/lactating; history of endogenous depression; thyroid, rheumatoid or erythrocyte disorders. |
| Recruitment/selection of patients | Telephone, letter or personal contact |
| Age, gender and ethnicity | Age - Mean (SD): 49 ± 9. Gender (M:F): Not reported. Ethnicity: Not reported |
| Further population details | 1. chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=21) Intervention 1: selective serotonin reuptake inhibitors - citalopram. 20 mg/day stepped to 40 mg/day for last 4 weeks if unresponsive. Duration 8 weeks. Concurrent medication/care: NSAIDs allowed. Indirectness: No indirectness<br><br>(n=21) Intervention 2: placebo. Duration 8 weeks. Concurrent medication/care: Allowed NSAIDs. Indirectness: No indirectness |
| Funding | Other (H Lundbeck) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CITALOPRAM versus PLACEBO

Protocol outcome 1: Physical function
- Actual outcome: FIQ Physical Function component at 8 weeks; Group 1: mean 1.7 (SD 0.6); n=21, Group 2: mean 1.7 (SD 0.5); n=21; Not reported 68
Top=High is poor outcome; Comments: Baseline values: Same as final values (no change)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Very high because unclear which arm 8 of the withdrawals had been allocated to.; Indirectness of outcome: no

| | |
|---|---|
| indirectness ; Group 1 Number missing: 9, Reason: It is not clear in which arm eight of the withdrawals were in; Group 2 Number missing: 0, Reason: It is not clear in which arm eight of the withdrawals were in<br><br>Protocol outcome 2: Psychological distress (depression/anxiety)<br>- Actual outcome: Beck Depression Inventory at 8 weeks; Group 1: mean 1 (SD 6.1); n=21, Group 2: mean 0.9 (SD 7.9); n=21; BDI 0-63 Top=High is poor outcome; Comments: Baseline values: 16.4 ± 8.3 : 16.3 ± 8.3<br>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Very high because unclear which arm 8 of the withdrawals had been allocated to.; Indirectness of outcome: -- ; Group 1 Number missing: 9, Reason: It is not clear in which arm eight of the withdrawals were in; Group 2 Number missing: 0, Reason: It is not clear in which arm eight of the withdrawals were in | |
| Protocol outcomes not reported by the study | Pain reduction; Quality of life; Discontinuation due to adverse events; Use of healthcare services ; Sleep |

| Study | Pontari 2009[472] (Pontari 2010[471]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=324) |
| Countries and setting | Conducted in USA; Setting: 10 tertiary care clinics |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 6 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Discomfort or pain in the pelvic region during at least 3 of the previous 6 months, and they had a total score of at least 15 of 43 on the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI). Previous treatment with gabapentin or pregabalin was allowed if it was completed at least 2 weeks before study enrollment. |
| Exclusion criteria | Creatinine clearance less than 60 mL/min/1.73m2, a platelet count less than 100 000 103/μL, allergy to any anti-seizure medication, known sensitivity to pregabalin, treatment with thiazolidinedione or antidiabetic agents ,New York Heart Association class III or IV congestive heart failure, a history of thrombocytopenia or bleeding diathesis, and a history of alcohol abuse. Participants were not excluded if they had previous treatment for CP/CPPS or for taking analgesics for another condition if they continued to have pelvic pain despite the analgesic therapy and had a score of at least 15 on the NIH-CPSI. |
| Age, gender and ethnicity | Age - Mean (SD): 47 ± 13. Gender (M:F): All men. Ethnicity: White: 79% Black: 12% |
| Further population details | 1. chronic visceral pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=218) Intervention 1: anti-epileptics - pregabalin. 150mg/d (50mg orally 3 times daily) for 2 weeks, then 300mg/d (100mg orally 3 times daily) for 2 weeks, then 600mg/d (200mg orally 3 times daily) for 2 weeks. Duration 6 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA<br><br>(n=106) Intervention 2: placebo. placebo with similar escalation in capsules prescribed. Duration 6 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA |
| Funding | Academic or government funding (National Institutes of Health grant |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PREGABALIN versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: McGill Pain Questionnaire at 6 weeks; Group 1: mean 9.6 (SD 8.8); n=210, Group 2: mean 12.4 (SD 9.1); n=103; McGill pain reduction 0-45 Top=High is poor outcome; Comments: 13.8 ± 8.7 : 14.1 ± 8.5
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Asymmetric group sizes; Indirectness of outcome: -- ; Group 1 Number missing: 8; Group 2 Number missing: 3

Protocol outcome 2: Quality of life
- Actual outcome: Medical Outcomes Summary SF-12: Physical at 6 weeks; Group 1: mean 46.9 Score ≥50 = Better quality of life (SD 10.1); n=210, Group 2: mean 44.3 Score ≥50 = Better quality of life (SD 10.6); n=103; SF-12 Physical 0-100 Top=High is good outcome; Comments: 44.9 ± 10.1 : 43.9 ± 10.3Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Asymmetric group sizes; Indirectness of outcome: -- ; Group 1 Number missing: 8; Group 2 Number missing: 3
- Actual outcome: Medical Outcomes Summary SF-12: Mental at 6 weeks; Group 1: mean 45 Score ≥50 = Better quality of life (SD 11.2); n=210, Group 2: mean 44.6 Score ≥50 = Better quality of life (SD 10.6); n=103; SF-12 Mental 0-100 Top=High is good outcome; Comments: 41.8 ± 10.6 : 42.8 ± 10.6
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Asymmetric group sizes; Indirectness of outcome: -- ; Group 1 Number missing: 8; Group 2 Number missing: 3

Protocol outcome 3: Psychological distress (depression/anxiety) at 6 weeks
- Actual outcome: HADS score at 6 weeks; Group 1: mean 12.4 (SD 7.8); n=210, Group 2: mean 12.2 (SD 7.8); n=103; Hamilton anxiety and depression 0-42 Top=High is poor outcome; Comments: 14.8 ± 7.5 : 14.1 ± 7.3
±7.5 : 14.1 ± 7.3
±7.3)
Risk of bias: All domain - Hig Low h, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Asymmetric group sizes; Indirectness of outcome: -- ; Group 1 Number missing: 8; Group 2 Number missing: 3

Protocol outcome 4: Discontinuation due to adverse events at 6 weeks
- Actual outcome: Discontinuation due to adverse events: n at 6 weeks; Group 1: 0/218, Group 2: 0/106
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Asymmetric group sizes; Indirectness of outcome: -- ; Group 1 Number missing: 0; Group 2 Number missing: 0

| | |
|---|---|
| Protocol outcomes not reported by the study | Physical function; Use of healthcare services ; Sleep |

| Study | Russell 1991[505] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=102) |
| Countries and setting | Conducted in USA; Setting: Not reported |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 8 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Primary fibrositis/fibromyalgia (Russell 1986); 18-65 years old |
| Exclusion criteria | Other rheumatic conditions; chronic infections; untreated endocrine disorders; active peptic ulcers; mental health disorders; seizures. |
| Recruitment/selection of patients | Not reported: Infer Texas Health Science Center |
| Age, gender and ethnicity | Age - Mean (SD): 47.3 ± 1.2. Gender (M:F): 10:90. Ethnicity: 20% hispanic |
| Further population details | 1. chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=17) Intervention 1: benzodiazepines - alprazolam. Alprazolam 0.5 mg/day (titrated up to 3mg if no adverse effects). Step-down titration during week 8. Duration 8 weeks. Concurrent medication/care: Allowed to take hypertension/diabetes drugs if required. Indirectness: No indirectness<br><br>(n=17) Intervention 2: NSAID - ibuprofen. ibuprofen 600 mg x 4 times/day. Duration 8 weeks. Concurrent medication/care: Allowed to take hypertension/diabetes drugs if required. Indirectness: No indirectness<br><br>(n=14) Intervention 3: placebo. Coded placebo. Duration 8 weeks. Concurrent medication/care: Allowed to take hypertension/diabetes drugs if required. Indirectness: No indirectness |
| Funding | Study funded by industry (The Upjohn Company, Kalamazoo) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ALPRAZOLAM versus PLACEBO<br><br>Protocol outcome 1: Pain reduction | |

- Actual outcome: VAS Patient Self-assessment at 6 weeks; Group 1: mean -1.4 (SD 0.8); n=17, Group 2: mean -0.9 (SD 0.5); n=14; VAS pain assessment by patient 0-10 Top=High is poor outcome; Comments: Baseline values: 7.0 : 6.1
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - No SDs reported for baseline results. Attrition rate not logically reported; Indirectness of outcome: no indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Physical function
- Actual outcome: Health Assessment Questionnaire (HAQ): disability index at 6 weeks; Group 1: mean -0.1 (SD 0.1); n=17, Group 2: mean -0.2 (SD 0.1); n=14; HAQ Disability Index 0-3 Top=High is poor outcome; Comments: Baseline values: 1.3 : 1.4
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - No SDs reported for baseline results. Attrition rate not logically reported; Indirectness of outcome: no indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Psychological distress
- Actual outcome: Centre for epidemiological studies – depression scale at 6 weeks; Group 1: mean -2 (SD 0.3); n=17, Group 2: mean -2.2 (SD 0.3); n=14; Centre for epidemiological studies 0-100, Top=High is poor outcome; Comments: Baseline not reported
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - No SDs reported for baseline results. Attrition rate not logically reported; Indirectness of outcome: no indirectness ; Group 1 Number missing; Group 2 Number missing

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS self-assessment at 6 weeks; Group 1: mean -1.2 (SD 0.6); n=17, Group 2: mean -0.9 (SD 0.5); n=14; VAS ruler 0-10 Top=High is poor outcome, baseline not reported
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - No SDs reported for baseline results. Attrition rate not logically reported; Indirectness of outcome: no indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Physical function
- Actual outcome: Health Assessment Questionnaire disability index at 6 weeks; Group 1: mean -0.1 (SD 0.1); n=17, Group 2: mean -0.2 (SD 0.1); n=14; HAQ 0-3 Top=High is poor outcome, baseline not reported
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - No SDs reported for baseline results. Attrition rate not logically reported; Indirectness of outcome: no indirectness ; Group 1 Number missing; Group 2 Number missing

Protocol outcome 2: Psychological distress
- Actual outcome: Centre for epidemiological studies – depression scale at 6 weeks; Group 1: mean -2.8 (SD 0.3); n=17, Group 2: mean -2.2 (SD 0.3);

| | |
|---|---|
| n=14; Centre for epidemiological studies depression scale 0-100 Top=High is poor outcome; Comments: Baseline not reported<br>Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - No SDs reported for baseline results. Attrition rate not logically reported; Indirectness of outcome: no indirectness ;<br>Group 1 Number missing; Group 2 Number missing | |
| Protocol outcomes not reported by the study | Quality of life; Discontinuation due to adverse events; Use of healthcare services; Sleep |

| **Study** | **Russell 2008[507]** |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=520) |
| Countries and setting | Conducted in USA; Setting: 38 outpatient research centres in the USA and Puerto Rico between 2005 and 2007 |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 6 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | (1) At least 18 years of age (2) met fibromyalgia criteria defined by ACR (3) score of 4 or more on the average pain severity item of the BPI |
| Exclusion criteria | (1) Any primary psychiatric diagnosis other than major depression (2) pain symptoms unrelated to fibromyalgia (3) surgeries (4) failed back syndrome (5)other conditions such as RA, inflammatory arthritis, autoimmune diseases and any unstable or medical psychiatric disorder, severe liver disease (6) pregnancy or breast-feeding (7) history of substance abuse within the last year |
| Recruitment/selection of patients | Patients were identified by physician referral or advertisement for a fibromyalgia medication trial |
| Age, gender and ethnicity | Age - Mean (SD): 51(10.5) years. Gender (M:F): 27:493. Ethnicity: 84% English, 4% African, 11% Hispanic, 1% Other |
| Further population details | 1. chronic orofacial pain: people with pain conditions other than chronic orofacial pain 2. chronic visceral pain: people with pain conditions other than chronic visceral pain 3. chronic widespread pain: people with chronic widespread pain (Fibromyalgia). 4. complex regional pain syndrome: people with pain conditions other than complex regional pain syndrome |

| | |
|---|---|
| Indirectness of population | No indirectness |
| Interventions | (n=79) Intervention 1: serotonin norepinephrine reuptake inhibitors - duloxetine. 3 months double blind phase followed by an additional 13-week double blind phase. A 2-week taper occurred at the end of the additional 28 weeks for patients who discontinued after receiving at least 2 weeks of treatment. Participants starting on 20mg/day had their dosage titrated to 60mg/day after 3 months. Duration 6 months. Concurrent medication/care: Not specified. Indirectness: No indirectness<br><br>(n=150) Intervention 2: serotonin norepinephrine reuptake inhibitors - duloxetine. 3 months double blind phase followed by an additional 13-week double blind phase. A 2-week taper occurred at the end of the additional 28 weeks for patients who discontinued after receiving at least 2 weeks of treatment. Participants starting on 60mg/day were started on 30mg/day for 1 week, then to 120mg/day. Had their dosage titrated to 60mg/day after 3 months. Duration 6 months. Concurrent medication/care: Not specified. Indirectness: No indirectness<br><br>(n=147) Intervention 3: serotonin norepinephrine reuptake inhibitors - duloxetine. 3 months double blind phase followed by an additional 13-week double blind phase. A 2-week taper occurred at the end of the additional 28 weeks for patients who discontinued after receiving at least 2 weeks of treatment. Participants starting on 120mg/day were started on 30mgday for 1 week, then 60mg/day for 1 week, then 120mg/day. Duration 6 months. Concurrent medication/care: Not specified. Indirectness: No indirectness<br><br>(n=144) Intervention 4: placebo. Placebo. Duration 6 months. Concurrent medication/care: Not specified. Indirectness: No indirectness |
| Funding | Study funded by industry (Eli Lilly and Company and Boehringer Ingelheim GmbH) |

To note: review analysis combines duloxetine 20mg/day, 60mg/day and 120mg/day groups.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE 20MG/DAY versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: Pain reduction (BPI average pain severity) at 6 months; Group 1: mean -2.22 (SD 2.5); n=79, Group 2: mean -1.43 (SD 2.52); n=144; Brief pain inventory 0-10 Top=High is poor outcome
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporti-ng - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34; Group 2 Number missing: 72

Protocol outcome 2: Quality of life
- Actual outcome: Quality of life (EQ-5D) at 6 months; Group 1: mean -14.77 (SD 16.71); n=79, Group 2: mean -10.42 (SD 17.88); n=144; Baseline not reported

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34; Group 2 Number missing: 72

Protocol outcome 3: Physical function
- Actual outcome: Physical function (FIQ physical function subscale) at 6 months; Group 1 mean -5.63 (SD 7.64); n=79, Group 2: mean -4.85 (SD 8.24); n=144; Baseline not reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 34; Group 2 Number missing: 72

Protocol outcome 4: Discontinuation due to adverse events Group 1 35/79, Group 2: 72/144
- Actual outcome: Discontinuation due to adverse events at 6 months;
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 58

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE 60MG/DAY versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: Pain reduction (BPI average pain severity) at 6 months; Group 1: mean -1.98 (SD 2.57); n=150, Group 2: mean -1.43 (SD 2.52); n=144; Brief pain inventory 0-10 Top=High is poor outcome, Baseline not reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68; Group 2 Number missing: 72

Protocol outcome 2: Quality of life
- Actual outcome: Quality of life (EQ-5D) at 6 months; ; Group 1: mean -12.28 (SD 17.63); n=150, Group 2: mean -10.42 (SD 17.88); n=144, Baseline not reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68; Group 2 Number missing: 72

Protocol outcome 3: Physical function
- Actual outcome: Physical function (FIQ physical function subscale) at 6 months; Group 1: mean -5.38 (SD 8.08); n=150, Group 2: mean -4.85 (SD 8.24); n=144, Baseline not reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 91; Group 2 Number missing: 72

Protocol outcome 4: Discontinuation due to adverse events
- Actual outcome: Discontinuation due to adverse events at 6 months; Group 1 68/147 , Group 2: 72/144
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68; Group 2 Number missing: 58

| | |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DULOXETINE 120MG/DAY versus PLACEBO<br><br>Protocol outcome 1: Pain reduction<br>- Actual outcome: Pain reduction (BPI average pain severity) at 6 months; Group 1: mean -2.26 (SD 2.4); n=147, Group 2: mean -1.43 (SD 2.52); n=144<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68; Group 2 Number missing: 72<br><br>Protocol outcome 2: Quality of life<br>- Actual outcome: Quality of life (EQ-5D) at 6 months; Group 1: mean -13.86 (SD 17.09); n=147, Group 2: mean -10.42 (SD 17.88); n=144<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68; Group 2 Number missing: 72<br><br>Protocol outcome 3: Physical function<br>- Actual outcome: Physical function (FIQ physical function subscale) at 6 months; Group 1: mean -5.23 (SD 7.88); n=147, Group 2: mean --4.85 (SD 8.24); n=144<br>Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 68; Group 2 Number missing: 72<br><br>Protocol outcome 4: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events at 6 months; Group 1 68/147 , Group 2: 72/144<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 29; Group 2 Number missing: 58 | |
| Protocol outcomes not reported by the study | Psychological distress (depression/anxiety); Use of healthcare services ; Sleep |

| Study | Scudds 1995[526] |
|---|---|
| Study type | RCT ( randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=61) |
| Countries and setting | Conducted in Canada; Setting: Not reported |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 3 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Diagnosis of fibromyalgia or myofascial pain syndrome. Met ARA 1990 criteria for fibromyalgia or had generally accepted criteria for MPS. |
| Exclusion criteria | Previous or suspected hypersensitivity to lidocaine, significant concomitant disease, pregnant, participated in clinical study within 2 months, receiving concurrent treatments such as physical therapy or other medication. Other drugs were stopped 1 week before study entry. Stable medications such as amitriptyline were allowed if the dosage did not change. |
| Recruitment/selection of patients | Not reported |
| Age, gender and ethnicity | Age - Mean (SD): 45 ± 9.2. Gender (M:F): 8:53. Ethnicity: Not reported |
| Further population details | 1. chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=31) Intervention 1: local anaesthetic and/or steroid trigger point injection - lidocaine injection. 4%. Duration 3 weeks. Concurrent medication/care: Stable medications (flexeril, valium, amitriptyline) were allowed provided frequency did not change.<br><br>(n=30) Intervention 2: placebo. Sterile water. Duration 3 weeks. Concurrent medication/care: Stable medications (flexeril, valium, amitriptyline) were allowed provided frequency did not change. Indirectness: No indirectness |
| Funding | Study funded by industry (Astra Pharma (Canada)) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LIDOCAINE INJECTION versus PLACEBO<br><br>Protocol outcome 1: Pain reduction | |

| | |
|---|---|
| - Actual outcome: VAS: 100mm ruler at 3 weeks; Group 1: 10/31, Group 2: 11/30; Comments: Number of responders with score-decrease >30%<br>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Very high, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing, Reason: No attrition reported; Group 2 Number missing, Reason: No attrition reported | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Discontinuation due to adverse events; Use of healthcare services ; Sleep |

| Study | Singer 1997[537] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=49) |
| Countries and setting | Conducted in USA; Setting: National Institute of Dental Research |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 4 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Daily/near daily facial pain for ≥3 months (recorded in diary); muscle tenderness on palpation |
| Exclusion criteria | Suicidal ideation; mood disorders; substance abuse; TMJ pathology; facial trauma including surgery; systemic illness; allergy to study drugs. |
| Recruitment/selection of patients | Local doctors and dentists |
| Age, gender and ethnicity | Age - Mean (SD): 36.1 (no SD). Gender (M:F): 4:35. Ethnicity: NR |
| Further population details | 1. chronic orofacial pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=10) Intervention 1: benzodiazepines - diazepam. 2.5 mg/qid for 1 week, then 5 mg/qid for 3 weeks if no side effects. Duration 4 weeks. Concurrent medication/care: None reported. Indirectness: Very serious indirectness; Indirectness comment: No N<br><br>(n=10) Intervention 2: placebo. Same regimen as intervention. Duration 4 weeks. Concurrent medication/care: -. Indirectness: Very serious indirectness<br><br>(n=10) Intervention 3: NSAID - ibuprofen. 2400mg/day: 600 mg/qid. Duration 4 weeks. Concurrent medication/care: -. Indirectness: Very serious indirectness |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIAZEPAM versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS pain scale at 4 weeks; Group 1: mean 39.5 (SD 29.3); n=10, Group 2: mean 23.2 (SD 22.4); n=10; VAS Not reported Top=High

is poor outcome; Comments: Baseline values: 50.9 ± 21.6 : 38.7 ± 36.9. Note: converted to 0-10 scale for analysis
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Very high, Measurement - High, Crossover - Low, Comments - No n for each arm (just overall N reported).

Protocol outcome 2: Psychological distress (depression/anxiety)
- Actual outcome: Depression Adjective Checklist at 4 weeks; Group 1: mean 5.4 (SD 4.3); n=10, Group 2: mean 10.7 (SD 8.2); n=10; Depression Adjective Checklist Not reported Top=High is poor outcome; Comments: Baseline values: 8.7 ± 6.6 : 9.9 ± 6.1
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Very high, Measurement - High, Crossover - Low, Comments - No n for each arm (just overall N reported).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS pain scale at 4 weeks; Group 1: mean 25.9 (SD 24.4); n=10, Group 2: mean 23.2 (SD 22.4); n=10; VAS Pain Not reported Top=High is poor outcome; Comments: Baseline values: 37.7 ± 27.0 : 38.7 ± 36.9. Note: converted to 0-10 scale for analysis
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Very high, Measurement - High, Crossover - Low, Comments - No n for each arm (just overall N reported).

Protocol outcome 2: Psychological distress (depression/anxiety)
- Actual outcome: Depression Adjective Checklist at 4 weeks; Group 1: mean 6.4 (SD 3.6); n=10, Group 2: mean 10.7 (SD 8.2); n=10; Adjective check list Unclear Top=High is poor outcome; Comments: Baseline values: 8.1 ± 3.6 : 9.9 ± 6.1
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Very high, Measurement - High, Crossover - Low, Comments - No n for each arm (just overall N reported).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IBUPROFEN versus DIAZEPAM

Protocol outcome 1: Pain reduction
- Actual outcome: VAS pain scale at 4 weeks; Group 1: mean 25.9 (SD 24.4); n=10, Group 2: mean 39.5 (SD 29.3); n=10; VAS Pain Not reported Top=High is poor outcome; Comments: Baseline values: 37.7 ± 27.0 : 50.9 ± 21.6. Note: converted to 0-10 scale for analysis
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Very high, Measurement - High, Crossover - Low, Comments - No n for each arm (just overall N reported).

Protocol outcome 2: Psychological distress (depression/anxiety)
- Actual outcome: Depression Adjective Checklist at 4 weeks; Group 1: mean 6.4 (SD 3.6); n=10, Group 2: mean 5.4 (SD 4.3); n=10; Adjective check list Unclear Top=High is poor outcome; Comments: Baseline values: 8.1 ± 3.6 :8.7 ± 6.6
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Very high, Measurement - High, Crossover - Low, Comments - No n for each arm (just overall N reported).

| | |
|---|---|
| Protocol outcomes not reported by the study | Quality of life; Physical function; Discontinuation due to adverse events; Use of healthcare services ; Sleep |

| Study | Spinhoven 2010[549] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=69) |
| Countries and setting | Conducted in Netherlands; Setting: Outpatient centres |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 16 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | (1) nonspecific chest pain occurring at least once a week or once per month if accompanied by severe psychological distress (2) aged 18 to 75 years |
| Exclusion criteria | (1) conditions that could cause chest pain such as coronary artery disease or MI (2) current psychiatric treatment for the pain (3) psychiatric conditions such as major depression, bipolar, substance use disorder (4) pregnancy (5) use of psychotropic medications |
| Recruitment/selection of patients | Patients received letters by mail asking for participation |
| Age, gender and ethnicity | Age - Mean (SD): 57.4(9) years. Gender (M:F): 24:22. Ethnicity: Not specified |
| Further population details | 1. chronic orofacial pain: people with pain conditions other than chronic orofacial pain 2. chronic visceral pain: people with chronic visceral pain 3. chronic widespread pain: people with pain conditions other than chronic widespread pain 4. complex regional pain syndrome: people with pain conditions other than complex regional pain syndrome |
| Indirectness of population | No indirectness |
| Interventions | (n=23) Intervention 1: selective serotonin reuptake inhibitors - paroxetine. Paroxetine started on 10mg per day in the first week, increased weekly in increments of 10mg to a maximum daily dosage of 40mg/day. Dosage was decreased with intolerable side-effects. 12 medication control visits were scheduled during the 16 week treatment period. Duration 16 weeks. Concurrent medication/care: Psychotherapeutic or behavioural interventions not allowed. Indirectness: No indirectness<br><br>(n=23) Intervention 2: placebo. Placebo . Duration 16 weeks. Concurrent medication/care: Psychotherapeutic or behavioural interventions not allowed. Indirectness: No indirectness |
| Funding | Academic or government funding (Dutch Heart Foundation and Glaxo Smith Kline) |

| | |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PAROXETINE versus PLACEBO<br><br>Protocol outcome 1: Pain reduction<br>- Actual outcome: Pain reduction (VAS final values) at 16 weeks; Group 1: mean 20.9 (SD 19.4); n=23, Group 2: mean 23.5 (SD 18.5); n=23; VAS 0-100 Top=High is poor outcome<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 4<br>- Actual outcome: Pain reduction (VAS final values) at 8 weeks; Group 1: mean 22 (SD 19.3); n=23, Group 2: mean 23.8 (SD 17.9); n=23; VAS 0-100 Top=High is poor outcome<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 4<br><br>Protocol outcome 2: Psychological distress (depression/anxiety)<br>- Actual outcome: Hospital anxiety and depression scale (anxiety component) at 16 weeks; Group 1: mean 4.7 (SD 3); n=23, Group 2: mean 7 (SD 3.3); n=23; HASD:A Not stated Top=High is poor outcome<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 4<br>- Actual outcome: Hospital anxiety and depression scale (anxiety component) at 8 weeks; Group 1: mean 4.6 (SD 3); n=23, Group 2: mean 7.1 (SD 2.8); n=23; HADS:A Not reported Top=High is poor outcome<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 7; Group 2 Number missing: 4 | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Discontinuation due to adverse events; Use of healthcare services ; Sleep |

| Study | Skrabek 2008[539] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=44) |
| Countries and setting | Conducted in Canada; Setting: Muscular Skeletal outpatient clinic at Winnipeg. |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 4 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Fibromyalgia (ACR 1990); cannabinoid naive; continuing pain despite other medications. |
| Exclusion criteria | Psychotic disorders; non-idiopathic pain; routine blood test abnormalities; pregnant/lactating; serious illness; sensitivity to marijuana |
| Recruitment/selection of patients | NR |
| Age, gender and ethnicity | Age - Range: 18-70 (mostly aged 40 to early 50s). Gender (M:F): NR. Ethnicity: Not reported |
| Further population details | 1. chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=20) Intervention 1: cannabinoids - nabilone. 0.5 mg/day, then 1 mg (0.5 mg/bid) after 7 days. Duration 4 weeks. Concurrent medication/care: Subjects were asked to continue any current treatment for fibromyalgia, including breakthrough pain medications, but not to begin any new therapies. Indirectness: No indirectness<br><br>(n=20) Intervention 2: placebo. Identical pills. Duration 4 weeks. Concurrent medication/care: Subjects were asked to continue any current treatment for fibromyalgia, including breakthrough pain medications, but not to begin any new therapies. Indirectness: No indirectness |
| Funding | Other (Government funding and funding from Valeant Canada Ltd) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NABILONE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS Pain score at 4 weeks; Mean difference from baseline in Group 1 -2.04(p<.02), Comment: results were reported in insufficient detail for quality assessment or inclusion in the analysis. Baseline values: Group 1 6.86 (2.14), Group 2 6.2 (1.46)
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low,

| | |
|---|---|
| Crossover - Low, Comments; Indirectness of outcome: No indirectness, Comments: NA. Group 1 Number missing: unclear ; Group 2 Number missing: unclear<br><br>Protocol outcome 2: Quality of life<br>- Actual outcome: Fibromyalgia Impact Questionnaire at 4 weeks; Group 1: Mean difference from baseline in Group 1 -12.07 (<.02)Comment: results were reported in insufficient detail for quality assessment or inclusion in the analysis. Baseline values: Group 1 66.45 (12.76), Group 2 66.53 (16.21)<br>Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting -High, Measurement - Low, Crossover - Low, Comments Indirectness of outcome: No indirectness, Comments: Group 1 Number missing: unclear; Group 2 Number missing: unclear<br><br>Protocol outcome 3: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events at 4 weeks; Group 1: 3/20, Group 2: 1/20<br>Risk of bias: All domain - High, Selection - High, Blinding -Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Reasons for discontinuation: Group 1 dizziness, disorientation and nausea (n=1), poor coordination, dizziness , headache and nausea (n=1), drowsiness and fatigue (n=1); Group 2 headaches (n=1); Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 | |
| Protocol outcomes not reported by the study | Psychological distress; Physical function; Use of healthcare services ; Sleep |

| Study | Van Ophoven 2004[593] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=50) |
| Countries and setting | Conducted in Germany; Setting: Munster University Hospital |
| Line of therapy | 2nd line |
| Duration of study | Intervention time: 4 months |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Interstitial cystitis diagnosis (Hanno 1999); Had received previous conservative treatment resulting in, at best, short relief. |
| Exclusion criteria | None reported |
| Recruitment/selection of patients | Munster University Hospital, no further details |
| Age, gender and ethnicity | Age - Mean (SD): 55.35 ± 16.74. Gender (M:F): 44:6. Ethnicity: Not reported |
| Further population details | 1. chronic visceral pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=25) Intervention 1: tricyclic antidepressants - amitriptyline. 25-100 mg/day (stepped, unforced titration). Duration 4 months. Concurrent medication/care: None reported. Indirectness: No indirectness<br><br>(n=25) Intervention 2: placebo. Manufactured at hospital pharmacy. Duration 6 months. Concurrent medication/care: None reported. Indirectness: No indirectness |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMITRIPTYLINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS pain intensity at 6 months; Group 1: mean -22.8 (SD 26.1); n=25, Group 2: mean 1 (SD 14.8); n=25; Comments: Baseline values: 52.7 ± 24.6 : 52.6 ± 28.4
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Placebo pills were home-made: not made by the manufacturer of the experimental pills; Indirectness of outcome: no indirectness; Group 1 Number missing: 1; Group 2 Number missing: 1 (due to adverse events)

| | |
|---|---|
| Protocol outcome 2: Discontinuation due to adverse events<br>- Actual outcome: N discontinued due to adverse events at 6 months; Group 1: 1/25, Group 2: 1/25<br>Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High, Comments - Placebo pills were home-made: not made by the manufacturer of the experimental pills; Indirectness of outcome: no indirectness; Group 1 Number missing: 1; Group 2 Number missing: 1 (due to adverse events) | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Use of healthcare services ; Sleep |

| Study | Wolfe 1994[633] |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | 1 (n=42) |
| Countries and setting | Conducted in USA; Setting: Outpatient rheumatology clinics |
| Line of therapy | 1st line |
| Duration of study | Intervention time: 6 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Women with fibromyalgia (ACR) with 7-14 tender points and VAS pain score ≥1/3. Fluoxetine-naive. |
| Exclusion criteria | Other significant rheumatic disease; concomitant treatments other than NSAIDs and acetaminophen. |
| Recruitment/selection of patients | From a register of fibromyalgia patients |
| Age, gender and ethnicity | Age - Mean (SD): 50 ± 12. Gender (M:F): All women. Ethnicity: >95% white |
| Further population details | 1. chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=21) Intervention 1: selective serotonin reuptake inhibitors - fluoxetine. 20 mg/am. Duration 6 weeks. Concurrent medication/care: NSAIDs were allowed. Indirectness: No indirectness<br><br>(n=21) Intervention 2: placebo. 1 sham dose per day am. Duration 6 weeks. Concurrent medication/care: NSAIDs were allowed. Indirectness: No indirectness |
| Funding | Funding not stated |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUOXETINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS scale at 6 weeks; Group 1: mean 1.6 (SD 0.79); n=15, Group 2: mean 1.6 (SD 0.79); n=9; VAS pain 0-3 Top=High is poor outcome; Comments: Baseline values: 1.7 ± 0.48 : 1.8 ± 0.81
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no indirectness ; Group 1 Number missing: 6, Reason: Lack of efficacy; Loss to follow-up; Adverse event; Group 2 Number missing: 12, Reason: Lack of efficacy; Loss to follow-up; Adverse event

| | |
|---|---|
| | Protocol outcome 2: Physical function<br>- Actual outcome: HAQ total scores at 6 weeks; Group 1: mean 0.7 (SD 0.43); n=15, Group 2: mean 0.8 (SD 0.76); n=9; 0-3, Top=High is poor outcome; Comments: Baseline values: 0.9 ± 1.1 : 1.1 ± 0.66<br>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no indirectness ; Group 1 Number missing: 6, Reason: Lack of efficacy; Loss to follow-up; Adverse event; Group 2 Number missing: 12, Reason: Lack of efficacy; Loss to follow-up; Adverse event<br><br>Protocol outcome 3: Psychological distress (depression/anxiety)<br>- Actual outcome: Beck Depression Inventory at 6 weeks; Group 1: mean 8.3 (SD 5.86); n=15, Group 2: mean 13.9 (SD 10.82); n=9; Beck Depression Inventory 0-63 Top=High is poor outcome; Comments: Baseline values: 11.8 ± 7.65 : 13.9 ± 8.86<br>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no indirectness ; Group 1 Number missing: 6, Reason: Lack of efficacy; Loss to follow-up; Adverse event; Group 2 Number missing: 12, Reason: Lack of efficacy; Loss to follow-up; Adverse event<br><br>Protocol outcome 4: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events: n at 6 weeks; Group 1: 1/15, Group 2: 1/9<br>Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no indirectness ; Group 1 Number missing: 0, Reason: 0; Group 2 Number missing: 0, Reason: 0<br><br>Protocol outcome 5: Sleep at 6 weeks<br>- Actual outcome: VAS Sleep difficulty at 6 weeks; Group 1: mean 7.6 (SD 3.1); n=15, Group 2: mean 7.6 (SD 3.83); n=9; VAS sleep difficulty 0-15 Top=High is poor outcome; Comments: Baseline values: 9.6 ± 2.12 : 9.7 ± 4.09<br>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no indirectness ; Group 1 Number missing: 6, Reason: Lack of efficacy; Loss to follow-up; Adverse event; Group 2 Number missing: 12, Reason: Lack of efficacy; Loss to follow-up; Adverse event |
| Protocol outcomes not reported by the study | Quality of life; Use of healthcare services |

| Study | Yeephu 2013[643] (Suttiruksa 2016[563]) |
|---|---|
| Study type | RCT (Patient randomised; Parallel) |
| Number of studies (number of participants) | (n=40) |
| Countries and setting | Conducted in Thailand; Setting: Not stated |
| Line of therapy | Unclear |
| Duration of study | Intervention time: 13 weeks |
| Method of assessment of guideline condition | Adequate method of assessment/diagnosis |
| Stratum | Overall |
| Subgroup analysis within study | Not applicable |
| Inclusion criteria | Aged 18 years or older, descended from Thai parents, met FMS criteria as defined by the 1990 American College of Rheumatology Research Classification Criteria, 2 and had a current Pain Visual Analog Scale (PVAS) score of at least 40 mm at screening. Previously treated FMS patients were eligible if they had failed to respond adequately to previous medications and were willing to discontinue those medications for a period of at least 5 half-lives. |
| Exclusion criteria | Any severe or unstable physical or psychiatric disorder; inflammation, injury, or trauma in the previous month; substance abuse within the past year; serious suicide risk; comorbid inflammatory rheumatic diseases such as systemic lupus erythematosus or rheumatoid arthritis; were pregnant or breastfeeding; had allergic history to any constituent of investigational products; or had severe allergic reactions to multiple medications. Additional exclusion criteria were use of medications or herbal agents with CNS activity; regular use of analgesics, with the exception of acetaminophen up to 2 g/day; and chronic use of sedatives/ hypnotics. Individuals who were unable to discontinue medications that might affect the study results. |
| Recruitment/selection of patients | Not stated |
| Age, gender and ethnicity | Age - Mean (SD): 44.66(10.77). Gender (M:F): All females. Ethnicity: Not specified |
| Further population details | 1. chronic widespread pain subgroup |
| Indirectness of population | No indirectness |
| Interventions | (n=27) Intervention 1: Tetracyclic antidepressant - mirtazepine. Randomised to 15 or 30mg per day. Starting dose of 7.5 mg (half tablet) and titrated up to the randomised dose over 1 or 2 weeks and then continued with stable dosage for 13 weeks. During dose escalation participants were contacted every 1-3 days via telephone and every 1-2 weeks via clinic visit. The date on which the patient started the expected dose was counted as day 0 (week 0 or visit 1). After that, patients were followed at day 7 ± 2 (week 1 or visit 2), day 21 ± 2 (week 3 or visit 3), day 35 ± 2 (week 5 or visit 4), day 63 ± 7 (week 9 or visit 5), and day 91 ± 7 (week 13 or visit 6) |

| | |
|---|---|
| | Duration 13 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness<br><br>(n=13) Intervention 2: placebo. Placebo. Duration 13 weeks. Concurrent medication/care: Not stated. Indirectness: No indirectness |
| Funding | Academic or government funding (Commission on Higher Education Staff Development Project for the Joint PhD Program in Biopharmaceutical Sciences, Thailand) |

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIRTAZEPINE versus PLACEBO

Protocol outcome 1: Pain reduction
- Actual outcome: VAS responders (definition not specified) at 13 weeks; Group 1: 16/27, Group 2: 5/13
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 3

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIRTAZEPINE versus PLACEBO*

Protocol outcome 1: Quality of life
- Actual outcome: SF36 Bodily pain. Change from baseline at 13 weeks; Group 1: mean 58 (SD 65.62); n=11, Group 2: mean 49 (SD 66.34); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 33 (15.9); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence
- Actual outcome: SF36 General health. Change from baseline at 13 weeks; Group 1: mean 59 (SD 65.62); n=11, Group 2: mean 47 (SD 62.02); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM, baseline values not reported
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 36 (19.7); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence
- Actual outcome: SF36 Mental health. Change from baseline at 13 weeks; Group 1: mean 81 (SD 50.84); n=11, Group 2: mean 72 (SD 41.46); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 63 (17.1); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Physical functioning. Change from baseline at 13 weeks; Group 1: mean 80 (SD 18.39); n=11, Group 2: mean 58 (SD 25.96); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 59 (21.6); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Role limitations - emotional. Change from baseline at 13 weeks; Group 1: mean 88.9 (SD 59.13); n=11, Group 2: mean 64 (SD 146.75); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 41 (37.9); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Role limitations - physical. Change from baseline at 13 weeks; Group 1: mean 63 (SD 135.93); n=11, Group 2: mean 57 (SD 166.58); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 30 (37.0); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Social functioning. Change from baseline at 13 weeks; Group 1: mean 48 (SD 32.45); n=11, Group 2: mean 53 (SD 35.33); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 53 (12.3); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Vitality. Change from baseline at 13 weeks; Group 1: mean 64 (SD 62.02); n=11, Group 2: mean 59 (SD 40.38); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 48 (19.1); Group 1 Number missing: 2, Reason: 1 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIRTAZEPINE versus PLACEBO*

Protocol outcome 1: Quality of life

- Actual outcome: SF36 Bodily pain. Change from baseline at 13 weeks; Group 1: mean 57 (SD 71.09); n=11, Group 2: mean 49 (SD 66.02); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 33 (15.9); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 General health. Change from baseline at 13 weeks; Group 1: mean 53 (SD 87.55); n=11, Group 2: mean 47 (SD 62.02); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 36 (19.7); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Mental health. Change from baseline at 13 weeks; Group 1: mean 83 (SD 46.4); n=11, Group 2: mean 72 (SD 41.46); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 63 (17.1); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Physical functioning. Change from baseline at 13 weeks; Group 1: mean 76.7 (SD 22.45); n=11, Group 2: mean 58 (SD 25.96); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM baseline values not reported

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 59 (21.6); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Role limitations - emotional. Change from baseline at 13 weeks; Group 1: mean 75 (SD 142.18); n=11, Group 2: mean 64 (SD 146.75); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 41 (37.9); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Role limitations - physical. Change from baseline at 13 weeks; Group 1: mean 65 (SD 171.37); n=11, Group 2: mean 57 (SD 166.58); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 30 (37.0); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence

- Actual outcome: SF36 Social functioning. Change from baseline at 13 weeks; Group 1: mean 52.1 (SD 18.33); n=11, Group 2: mean 53 (SD 35.33); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported

| | |
|---|---|
| Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 53 (12.3); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence<br>- Actual outcome: SF36 Vitality. Change from baseline at 13 weeks; Group 1: mean 66 (SD 66.98); n=11, Group 2: mean 59 (SD 40.38); n=10; SF36 0-100 Top=High is good outcome; Comments: SD calculated from SEM , baseline values not reported<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 48 (19.1); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence<br><br>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MIRTAZEPINE versus PLACEBO<br><br>Protocol outcome 1: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events 13 weeks; Group 1:3/26, Group 2: 2/14<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Not reported separately per group for outcome: FMS 33 (15.9); Group 1 Number missing: 3, Reason: 2 due to adverse events, 1 lack of adherence; Group 2 Number missing: 2, Reason: 2 due to adverse events, 1 lack of adherence<br><br>*To not that results for mirtazapine 15mg/day and 30mg/day were pooled in the analysis<br><br>Protocol outcome 2: Discontinuation due to adverse events<br>- Actual outcome: Discontinuation due to adverse events at 13 weeks; Group 1: 3/27, Group 2: 2/13<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2; Group 2 Number missing: 1 | |
| Protocol outcomes not reported by the study | Quality of life; Physical function; Psychological distress (depression/anxiety); Use of healthcare services; Sleep |

## D.2 Opioid safety

| Study | Edlund 2007[190] |
|---|---|
| Study type | Retrospective cohort study |
| Number of studies (number of participants) | (n=15,160) |
| Countries and setting | USA, South Central Veterans Affairs Health Care Network data warehouse |
| Line of therapy | Not reported |
| Duration of study | 4 years (recruitment during 2002 and follow up during years 2003-2005) |
| Method of assessment of guideline condition | Partially adequate method of assessment/diagnosis: cut-off of ≥91 days opioid use during 12 months as it is 'unlikely that an individual would receive more than 90 days' supply of opioids for an acute condition' |
| Stratum | NA |
| Subgroup analysis within study | Age: majority were 25-65 or ≥65 years<br>Co-prescribing: not reported |
| Inclusion criteria | Veterans with at least 1 opioid prescription between January 1 2002 and December 30 2002; 91 or more days of opioid use during the 12 month period |
| Exclusion criteria | Any cancer diagnosis; opioid substance abuse disorder in years 2000, 2001 or 2002; prescriptions for methadone in 2001 or 2002 |
| Recruitment/selection of patients | Consecutive patients meeting the inclusion/exclusion criteria |
| Age, gender and ethnicity | Age - <40 years 4.2%<br>40-49 years 16.1%<br>50-59 years 35%<br>60+ years 44.6%<br>Gender: M:F 14,381:776<br>Ethnicity: white 70.6%, black 11.6%, other 1.6%, unknown 16.2% |
| Further population details | NA |
| Extra comments | 1148 out of the total cohort had non-opioid substance abuse/dependence during the year that they were recruited |
| Indirectness of population | No indirectness |

| Study | Edlund 2007[190] |
|---|---|
| Interventions | n=10,387 chronic opioid users with ≥151 days' supply of prescribed opioids summed over one year |
| Funding | Veterans Affairs Health Service Research and Development |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS: OPIOIDS<br><br>Protocol outcome: Dependence<br>- Actual outcome: abuse/dependence 151-210 days' supply: 43/3275 (1.3%); ≥211 days' supply: 196/7112 (2.8%) Risk of bias: High ; Indirectness of outcome: serious indirectness | |
| Protocol outcomes not reported by the study | cognitive impairment, fractures and falls, sexual dysfunction/endocrine impairment, immune dysfunction, sleep apnoea, cardiovascular events, all-cause mortality, self-harm/suicide, depressive symptoms/mood disturbances |
| Risk of bias details | See quality assessment |

| Study | Edlund 2010[189] |
|---|---|
| Study type | Retrospective cohort study |
| Number of studies (number of participants) | (n=46,256) |
| Countries and setting | USA, Arkansas Medicaid files (serving a disadvantaged and vulnerable population) n=9,651 and HealthCore Integrated Research Database (medical and pharmacy administrative claims and health plan eligibility data from five commercial health plans representing the West, Mid-West, and South-East) n=36,605 |
| Line of therapy | Not reported |
| Duration of study | 4 years |
| Method of assessment of guideline condition | Partially adequate method of assessment/diagnosis: cut-off of at least 90 days' continuous opioid use as it is 'unlikely that an individual would receive opioids for greater than 90 days (usually four prescriptions) in a six-month period for acute conditions' |
| Stratum | NA |
| Subgroup analysis within study | Age: majority were 25-65 or ≥65 years<br>Co-prescribing: unclear/not reported |
| Inclusion criteria | Adult enrolees (≥18 years) on chronic opioid therapy defined as at least 90 days' continuous use of opioids within a six-month period during the study period; 12 months of continuous enrolment before and after the index date |

| Study | Edlund 2010[189] |
|---|---|
| Exclusion criteria | Cancer diagnosis at any time in the year before or after the index date (other than non-melanoma skin cancer) residents of nursing homes; those receiving hospice benefits |
| Recruitment/selection of patients | Consecutive patients meeting the inclusion/exclusion criteria |
| Age, gender and ethnicity | Age - 18-30 years 5.4%<br>31-40 years 17%<br>41-50 years 30.7%<br>51-64 years 32.3%<br>≥65 years 14.6%<br>Gender: M:F 17,746:28,510<br>Ethnicity: not reported |
| Further population details | NA |
| Extra comments | 317 out of the total cohort had pre-index opioid substance abuse diagnosis and 1375 had non-opioid substance abuse diagnosis |
| Indirectness of population | No indirectness |
| Interventions | n=11,884 chronic opioid users with >185 days' supply of prescribed opioids |
| Funding | Not reported |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS: OPIOIDS<br><br>Protocol outcome: Dependence<br>- Actual outcome: abuse/dependence >185 days' supply: 696/11,884 (5.86%) Risk of bias: High ; Indirectness of outcome: serious indirectness | |
| Protocol outcomes not reported by the study | cognitive impairment, fractures and falls, sexual dysfunction/endocrine impairment, immune dysfunction, sleep apnoea, cardiovascular events, all-cause mortality, self-harm/suicide, depressive symptoms/mood disturbances |
| Risk of bias details | See quality assessment |

| Study | Ray 2016[484] |
|---|---|
| Study type | Retrospective cohort study |
| Number of studies (number of participants) | (n=22,912) |
| Countries and setting | USA, Tennessee Medicaid files |

| Study | Ray 2016[484] |
|---|---|
| Line of therapy | Not reported |
| Duration of study | 14 years |
| Method of assessment of guideline condition | Unclear method of assessment/diagnosis: diagnosis of chronic pain |
| Stratum | NA |
| Subgroup analysis within study | Age: 25-65 and ≥65 years<br>Co-prescribing: not reported |
| Inclusion criteria | Diagnosis of chronic pain (back, other musculoskeletal, abdominal, headache, other neurologic pain) in the past 90 days; filling a study drug prescription |
| Exclusion criteria | ≥75 years; patients with cancer, other life threatening diseases or evidence of hospice or other terminal care; nursing home residents; discharged from hospital within 30 days, evidence of drug abuse; prescription filled in the prior year for any study drugs; starting daily dose not recommended for chronic pain or unusually high |
| Recruitment/selection of patients | Consecutive patients meeting the inclusion/exclusion criteria |
| Age, gender and ethnicity | Age - Mean (SD): 47.9 (10.5) years<br>Gender: M:F 9174:13,738<br>Ethnicity: not reported |
| Further population details | NA |
| Extra comments | Patients could re-enter the cohort. 22,912 episodes of therapy: 20,405 unique patients |
| Indirectness of population | No indirectness |
| Interventions | n= 5584 receiving opioids for >180 days |
| Funding | Grant from the National Heart, Lung and Blood Institute, grant from the national Institute of Arthritis and Musculoskeletal and Skin Diseases and grant from the Rheumatology Research Foundation |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS: OPIOIDS<br><br>Protocol outcome: all-cause mortality<br>- Actual outcome: all-cause mortality >180 days: 62/5584 (1.1%) Risk of bias: High ; Indirectness of outcome: no indirectness | |
| Protocol outcomes not reported by the study | cognitive impairment, fractures and falls, sexual dysfunction/endocrine impairment, immune dysfunction, sleep apnoea, cardiovascular events, self-harm/suicide, dependence, depressive symptoms/mood disturbances |
| Risk of bias details | See quality assessment |

## D.3 Gabapentinoid safety

None

# Appendix E: Forest plots

## E.1 Pharmacological management

### E.1.1 Anti-epileptics versus placebo

**Figure 4: Pain final values (VAS, Brief Pain Inventory average severity score, McGill pain questionnaire score, final values, high is poor outcome) at ≤ 3 months**

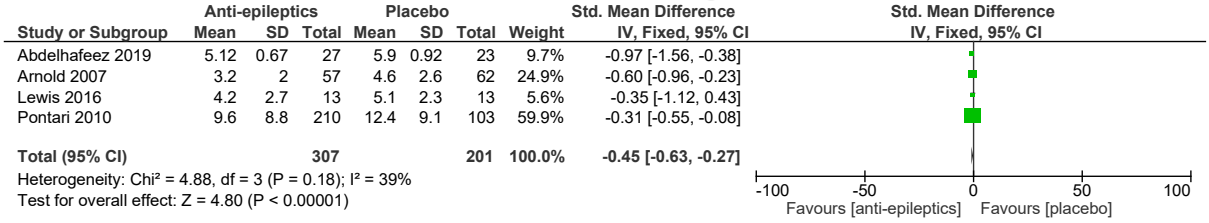



**Figure 5: Pain reduction (VAS percentage reduction, change scores, high is good outcome) at ≤3 months**

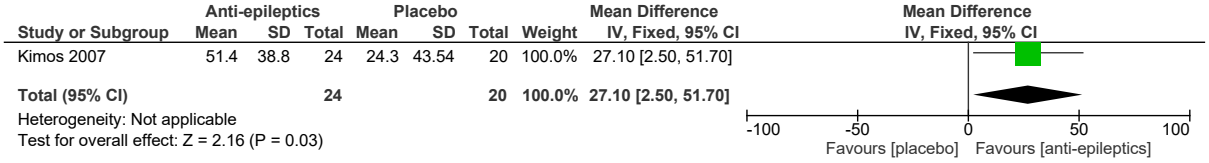
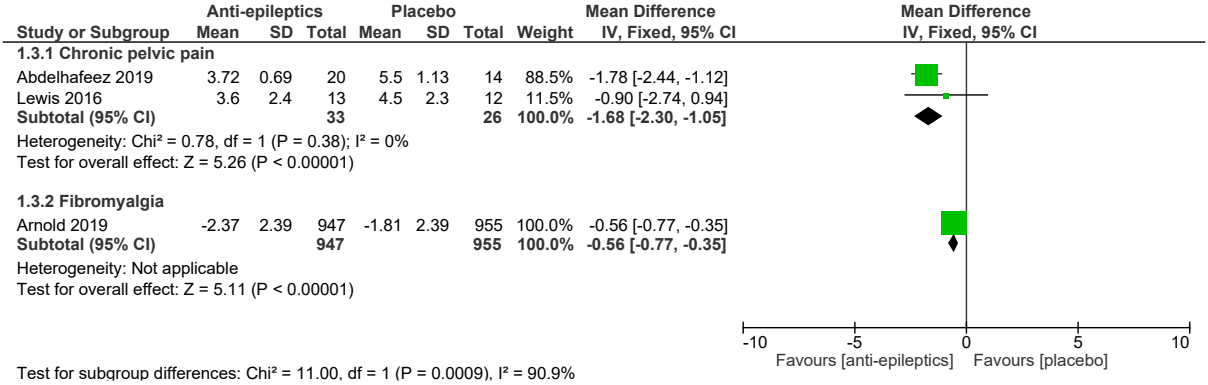



**Figure 6: Pain final values (VAS, ADPS, final values and change scores, 0-10, high is poor outcome) at >3 months**




*Heterogeneity explained by subgroup analysis (subtype of chronic primary pain). However, the sample size of the chronic pelvc pain subgroup is small and imprecise (confidence intervals cross MID) Other meta-analyses within this guideline have not shown heterogeneity between the two subgroups. Evidence for chronic pelvic pain and fibromyalgia throughout the rest of the guideline has therefore not been separated. ADPS is Average Daily Pain Score.*

**Figure 7: Quality of life (SF-12 physical component, 0-100, final values, high is good outcome) at ≤3 months**

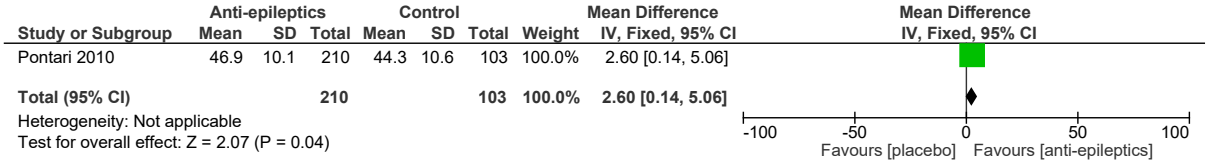



**Figure 8: Quality of life (SF-12 mental component, 0-100, final values, high is good outcome) at ≤3 months**

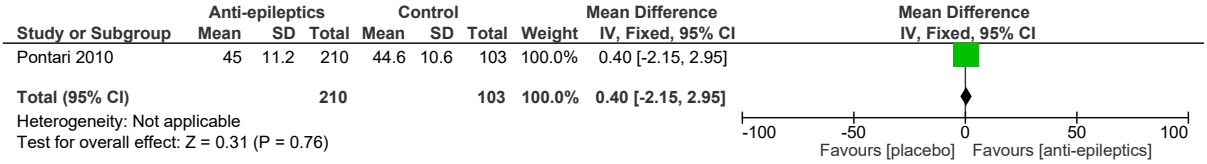



**Figure 9: Quality of life (Fibromyalgia impact questionnaire, 0-100, high is poor outcome, final values) at ≤3 months**

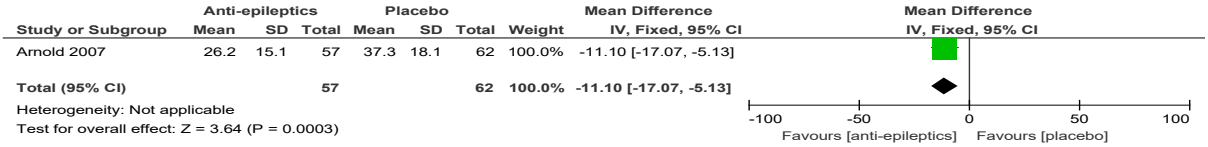



**Figure 10: Quality of life (EQ5D, 0-100, high is good outcome, change scores) at >3 months**

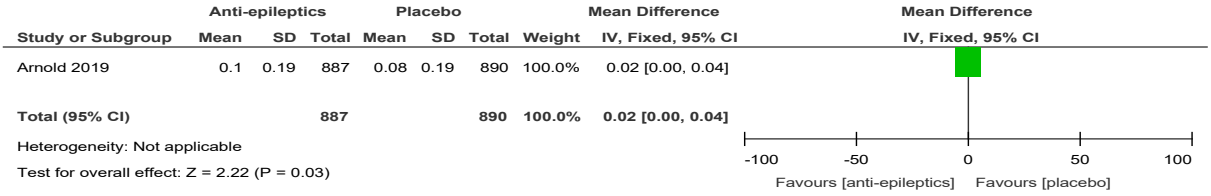



**Figure 11: Physical function final values (Pain Disability questionnaire, function subscale, 0-90, high is poor outcome, final values) at ≤3 months**

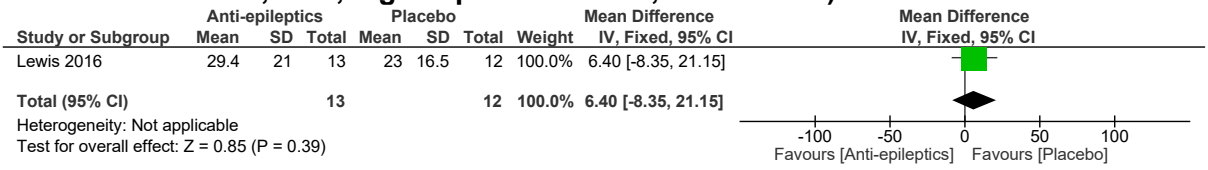


**Figure 12: Physical function final values (Pain Disability questionnaire, function subscale, 0-90, high is poor outcome, final values) at >3 months**

| Study or Subgroup | Anti-epileptics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Lewis 2016 | 23.9 | 25.3 | 13 | 20.3 | 14.8 | 12 | 100.0% | 3.60 [-12.50, 19.70] |
| **Total (95% CI)** | | | **13** | | | **12** | **100.0%** | **3.60 [-12.50, 19.70]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

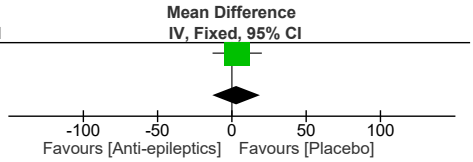



**Figure 13: Psychological distress final values (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, final values) at ≤3 months**

| Study or Subgroup | Anti-epileptics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Lewis 2016 | 8.1 | 5.4 | 12 | 8.2 | 4.2 | 13 | 100.0% | -0.10 [-3.91, 3.71] |
| **Total (95% CI)** | | | **12** | | | **13** | **100.0%** | **-0.10 [-3.91, 3.71]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

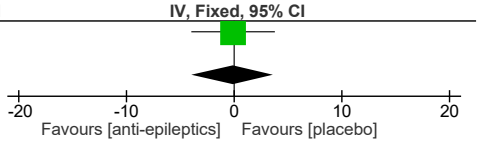



**Figure 14: Psychological distress final values (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, change scores and final values) at >3 months**

| Study or Subgroup | Anti-epileptics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Arnold 2019 | -1.03 | 3.47 | 889 | -0.84 | 3.41 | 890 | 99.5% | -0.19 [-0.51, 0.13] |
| Lewis 2016 | 7.5 | 5.7 | 13 | 9.8 | 5.3 | 12 | 0.5% | -2.30 [-6.61, 2.01] |
| **Total (95% CI)** | | | **902** | | | **902** | **100.0%** | **-0.20 [-0.52, 0.12]** |

Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.22)

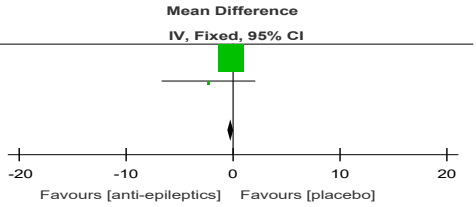



**Figure 15: Psychological distress final values (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, final values) at ≤3 months**

| Study or Subgroup | Anti-epileptics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Lewis 2016 | 5.5 | 3.9 | 13 | 4.7 | 4.5 | 13 | 100.0% | 0.80 [-2.44, 4.04] |
| **Total (95% CI)** | | | **13** | | | **13** | **100.0%** | **0.80 [-2.44, 4.04]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)

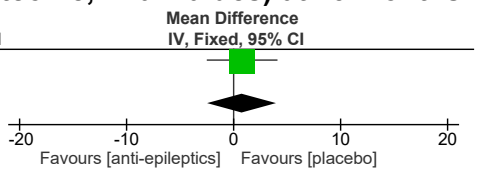
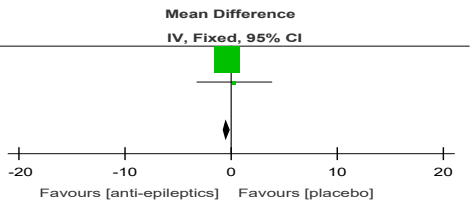


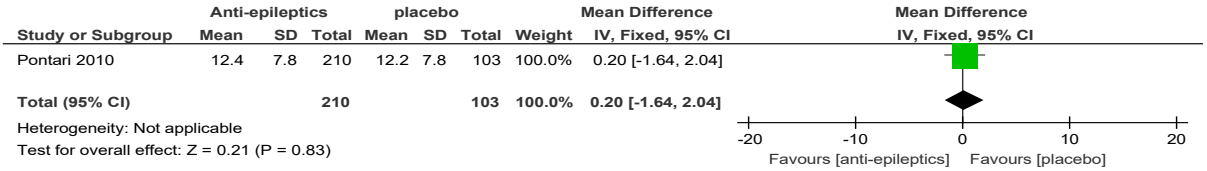

**Figure 16: Psychological distress final values (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, change scores and final values) at >3 months**

| Study or Subgroup | Anti-epileptics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Arnold 2019 | -1.23 | 3.75 | 889 | -0.8 | 3.62 | 890 | 99.0% | -0.43 [-0.77, -0.09] |
| Lewis 2016 | 5.2 | 4.9 | 13 | 4.9 | 4 | 12 | 1.0% | 0.30 [-3.20, 3.80] |
| **Total (95% CI)** | | | **902** | | | **902** | **100.0%** | **-0.42 [-0.76, -0.08]** |

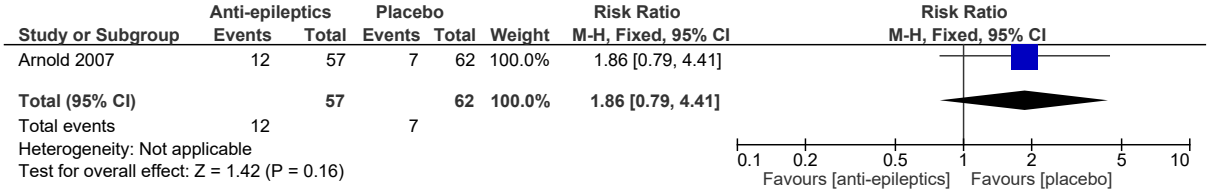
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.43 (P = 0.02)



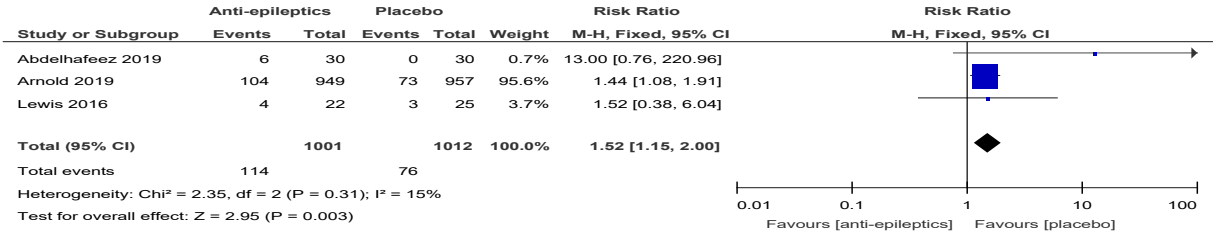
## Figure 17: Psychological distress final values (Hospital Anxiety and Depression scale (total score), 0-21, high is poor outcome, final values) at ≤3 months



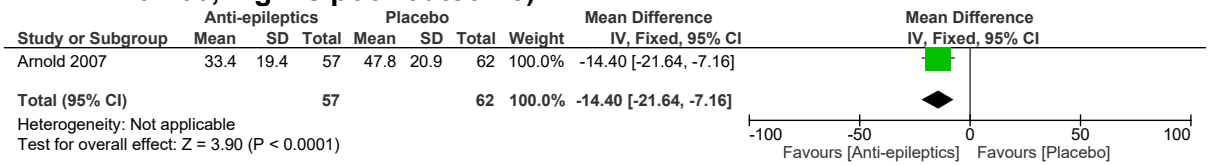

## Figure 18: Discontinuation due to adverse events (reasons not specified) at ≤3 months



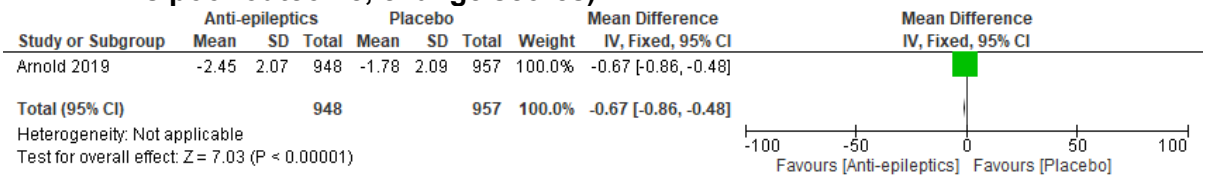

## Figure 19: Discontinuation due to adverse events at >3 months




## Figure 20: Sleep at ≤3 months (Medical Outcomes Study Sleep Problems index score, 0-100, high is poor outcome)




## Figure 21: Sleep at >3 months (Average Daily Sleep Interference score, 0-10, high is poor outcome, change scores)

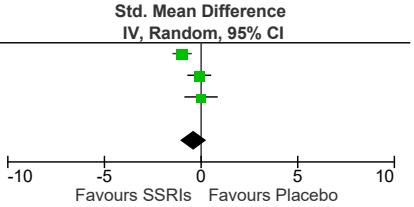


## E.1.2 SSRIs versus placebo

### Figure 22: Pain final values (VAS pain reduction, medical outcome study pain measure, high is poor outcome) at ≤3 months

| Study or Subgroup | SSRIs Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Luo 2009 | 33.08 | 18.81 | 40 | 55.3 | 25.44 | 40 | 38.0% | -0.98 [-1.45, -0.52] |
| Spinhoven 2010 | 2.2 | 1.93 | 23 | 2.38 | 1.79 | 23 | 34.6% | -0.10 [-0.67, 0.48] |
| Wolfe 1994 | 1.6 | 0.79 | 15 | 1.6 | 0.79 | 9 | 27.4% | 0.00 [-0.83, 0.83] |
| **Total (95% CI)** | | | **78** | | | **72** | **100.0%** | **-0.41 [-1.08, 0.27]** |

Heterogeneity: Tau² = 0.26; Chi² = 7.40, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 1.18 (P = 0.24)

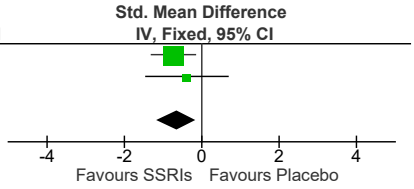



*Heterogeneity was not explained by subgroup analysis.*

### Figure 23: Pain change scores (McGill pain questionnaire and Prostatitis symptom severity scale, high is poor outcome) at >3 months

| Study or Subgroup | SSRIs Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Arnold 2002 | -10.8 | 12.3 | 25 | -1.8 | 11.9 | 26 | 77.7% | -0.73 [-1.30, -0.16] |
| Lee 2005 | -6.1 | 10.05 | 7 | -2 | 10.05 | 7 | 22.3% | -0.38 [-1.44, 0.68] |
| **Total (95% CI)** | | | **32** | | | **33** | **100.0%** | **-0.65 [-1.16, -0.15]** |

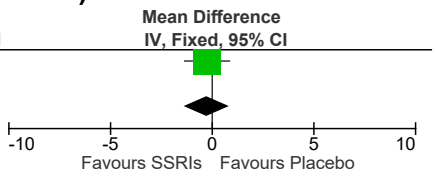
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)




### Figure 24: Pain final values (VAS, 0-10, high is poor outcome) at >3 months

| Study or Subgroup | SSRIs Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Spinhoven 2010 | 2.1 | 1.94 | 23 | 2.35 | 1.85 | 23 | 100.0% | -0.25 [-1.35, 0.85] |
| **Total (95% CI)** | | | **23** | | | **23** | **100.0%** | **-0.25 [-1.35, 0.85]** |

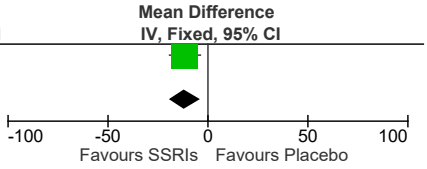
Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)




### Figure 25: Quality of life change scores (FIQ total scores, 0-100, high is poor outcome) at ≤3 months

| Study or Subgroup | SSRIs Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Arnold 2002 | -8.6 | 14.5 | 25 | 2.9 | 13.6 | 26 | 100.0% | -11.50 [-19.22, -3.78] |
| **Total (95% CI)** | | | **25** | | | **26** | **100.0%** | **-11.50 [-19.22, -3.78]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.92 (P = 0.004)




### Figure 26: Physical function final values (HAQ total scores, FIQ physical function subscale, high is poor outcome) at ≤3 months

| Study or Subgroup | SSRIs Mean | SD | Total | Placebo Mean | SD | Total | Weight | Std. Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Norregaard 1995 | 1.7 | 0.6 | 21 | 1.7 | 0.5 | 21 | 65.2% | 0.00 [-0.60, 0.60] |
| Wolfe 1994 | 0.7 | 0.43 | 15 | 0.8 | 0.76 | 9 | 34.8% | -0.17 [-1.00, 0.66] |
| **Total (95% CI)** | | | **36** | | | **30** | **100.0%** | **-0.06 [-0.55, 0.43]** |

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)

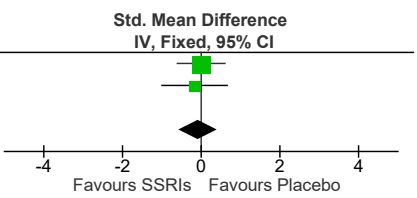


**Figure 27: Physical function change scores (Physical impairment FIQ subscale, 0-9.99, high is poor outcome) at ≤3 months**

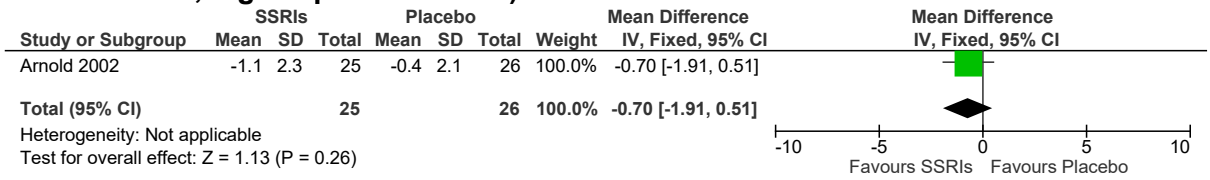



**Figure 28: Psychological distress change scores (FIQ depression subscale, HADS-D, Beck depression inventory, high is poor outcome) at ≤3 months**

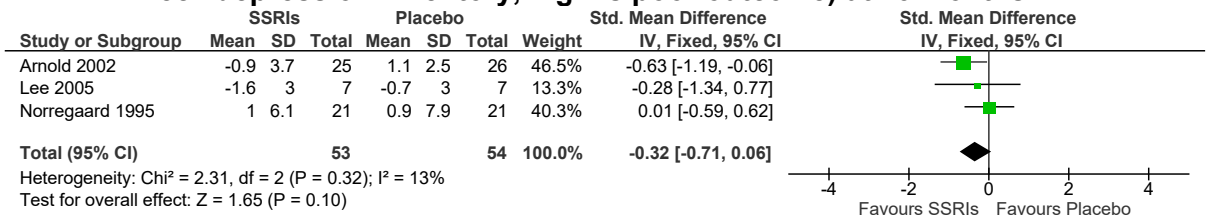



**Figure 29: Psychological distress change scores (FIQ anxiety subscale, AIMS anxiety total scores, high is poor outcome) at ≤3 months**

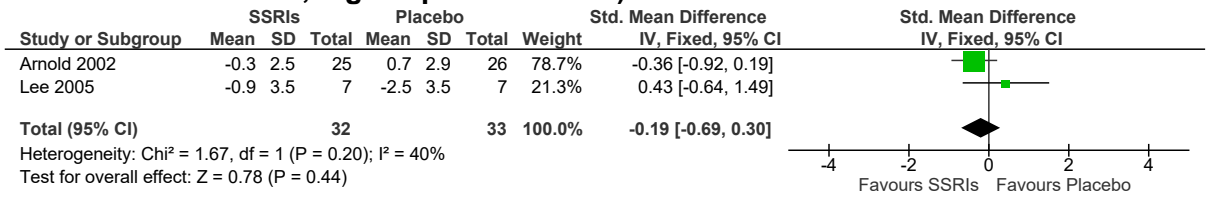



**Figure 30: Psychological distress final values (Beck depression scale, HADS:A, high is poor outcome) at ≤3 months**

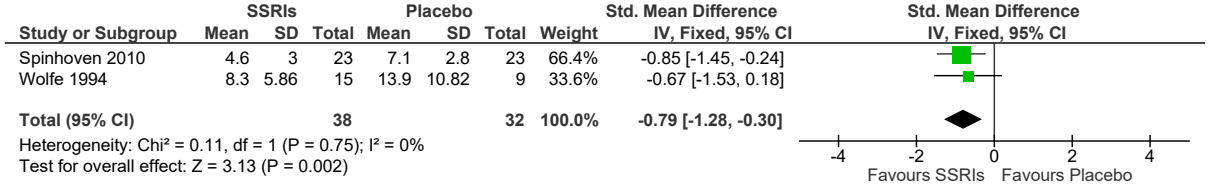



**Figure 31: Psychological distress final values (HADS-A, 0-21, high is poor outcome) at >3 months**

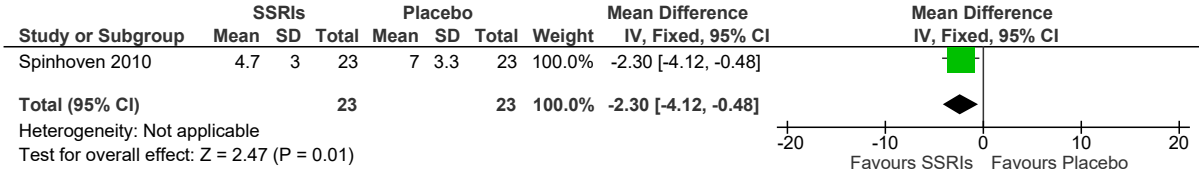


**Figure 32: Discontinuation due to adverse events at ≤3 months**

| Study or Subgroup | SSRIs Events | SSRIs Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Wolfe 1994 | 1 | 15 | 1 | 9 | 100.0% | 0.60 [0.04, 8.46] |
| **Total (95% CI)** | | **15** | | **9** | **100.0%** | **0.60 [0.04, 8.46]** |
| Total events | 1 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)

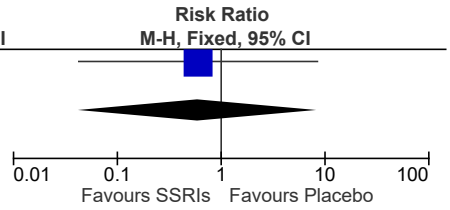



**Figure 33: Discontinuation due to adverse events (due to gastrointestinal problems) at >3 months**

| Study or Subgroup | SSRIs Events | SSRIs Total | Placebo Events | Placebo Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Lee 2005 | 0 | 7 | 1 | 7 | 100.0% | 0.14 [0.00, 6.82] |
| **Total (95% CI)** | | **7** | | **7** | **100.0%** | **0.14 [0.00, 6.82]** |
| Total events | 0 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)

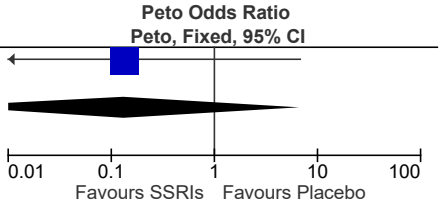
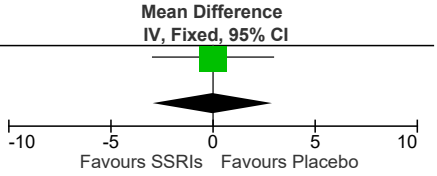



**Figure 34: Sleep final values (VAS sleep outcome, 0-15, high is poor outcome) at ≤3 months**

| Study or Subgroup | SSRIs Mean | SSRIs SD | SSRIs Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Wolfe 1994 | 7.6 | 3.1 | 15 | 7.6 | 3.83 | 9 | 100.0% | 0.00 [-2.95, 2.95] |
| **Total (95% CI)** | | | **15** | | | **9** | **100.0%** | **0.00 [-2.95, 2.95]** |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)




## E.1.3 SNRIs versus placebo

**Figure 35: Pain change scores (BPI average pain severity, VAS, high is poor outcome) at ≥3 months**

| Study or Subgroup | Favours SNRIs Mean | Favours SNRIs SD | Favours SNRIs Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Arnold 2005 | -2.4 | 2.4 | 232 | -1.16 | 2.3 | 118 | 18.0% | -1.24 [-1.76, -0.72] |
| Arnold 2010 | -2.6 | 2.7423 | 188 | -1.7 | 2.8071 | 197 | 15.6% | -0.90 [-1.45, -0.35] |
| Arnold 2012 | -2.14 | 2.4739 | 121 | -1.83 | 2.4739 | 110 | 11.8% | -0.31 [-0.95, 0.33] |
| Chappell 2008 | -1.62 | 2.5 | 158 | -1.13 | 2.5 | 167 | 16.2% | -0.49 [-1.03, 0.05] |
| Murukami 2015 | -1.6 | 2.6 | 191 | -1.22 | 2.6 | 195 | 17.8% | -0.38 [-0.90, 0.14] |
| Russell 2008 | -2.14 | 2.5 | 373 | -1.43 | 2.52 | 144 | 20.5% | -0.71 [-1.19, -0.23] |
| **Total (95% CI)** | | | **1263** | | | **931** | **100.0%** | **-0.69 [-0.91, -0.47]** |

Heterogeneity: Chi² = 8.15, df = 5 (P = 0.15); I² = 39%
Test for overall effect: Z = 6.20 (P < 0.00001)

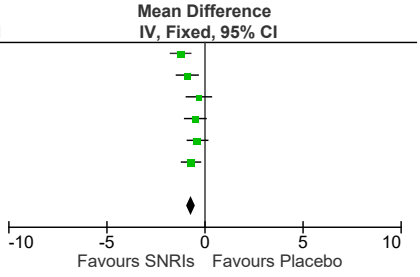
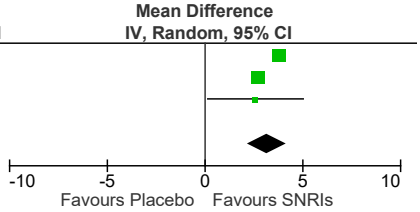


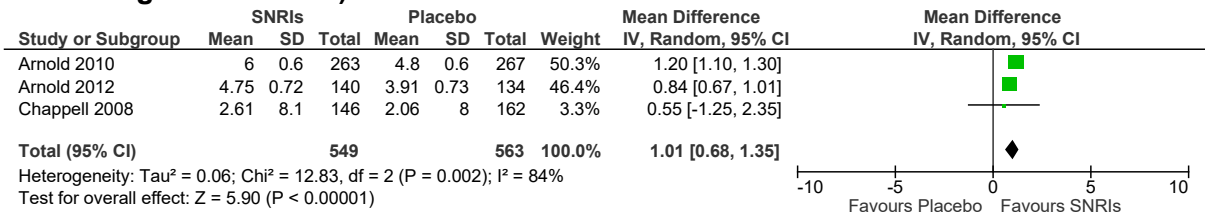

**Figure 36: Quality of life change scores (SF-36 mental component, 0-100, high is good outcome) at ≤3 months**

| Study or Subgroup | SNRIs Mean | SNRIs SD | SNRIs Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Arnold 2010 | 5.1 | 0.7 | 263 | 1.3 | 0.7 | 267 | 44.1% | 3.80 [3.68, 3.92] |
| Arnold 2012 | 5.56 | 0.85 | 140 | 2.87 | 0.87 | 134 | 43.5% | 2.69 [2.49, 2.89] |
| Chappell 2008 | 3.37 | 11 | 146 | 0.79 | 10.8 | 162 | 12.4% | 2.58 [0.14, 5.02] |
| **Total (95% CI)** | | | **549** | | | **563** | **100.0%** | **3.17 [2.15, 4.18]** |

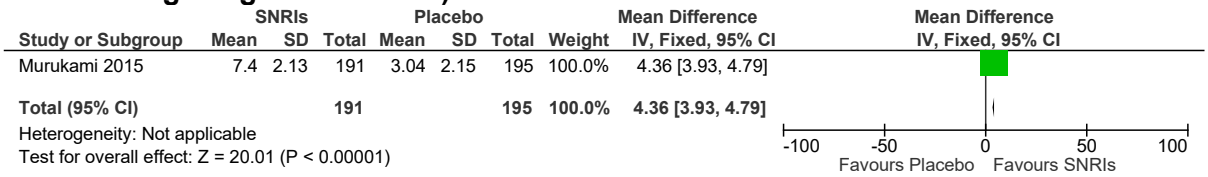
Heterogeneity: Tau² = 0.60; Chi² = 85.49, df = 2 (P < 0.00001); I² = 98%
Test for overall effect: Z = 6.13 (P < 0.00001)



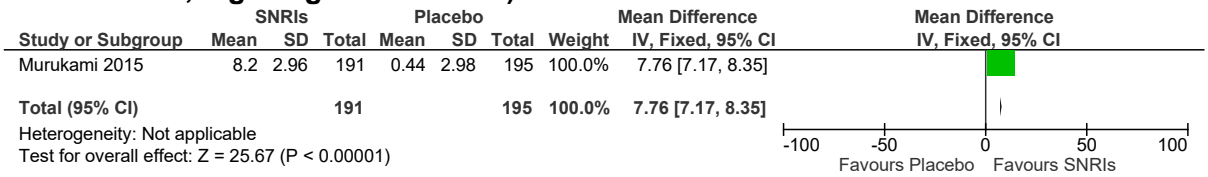
## Figure 37: Quality of life change scores (SF-36 physical component, 0-100, high is good outcome) at ≤3 months



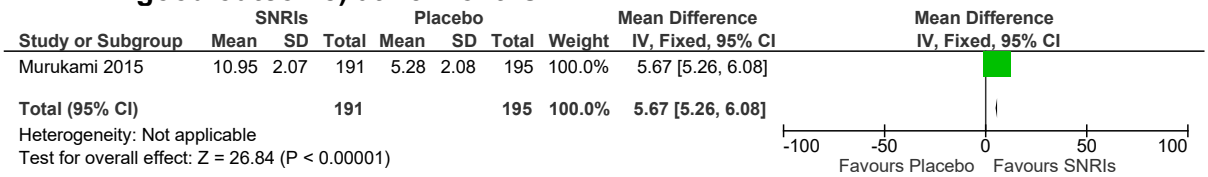

## Figure 38: Quality of life change scores (SF-36 physical functioning subscale, 0-100, high is good outcome) at >3 months



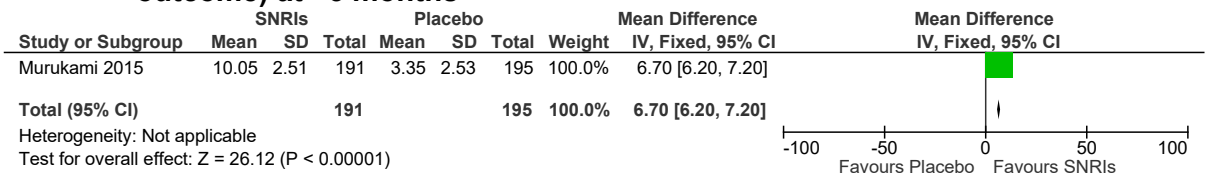

## Figure 39: Quality of life change scores (SF-36 physical role limitations subscale, 0-100, high is good outcome) at >3 months



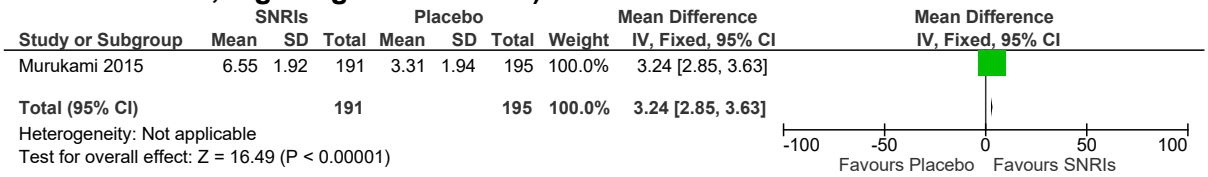

## Figure 40: Quality of life change scores (SF-36 bodily pain subscale, 0-100, high is good outcome) at >3 months



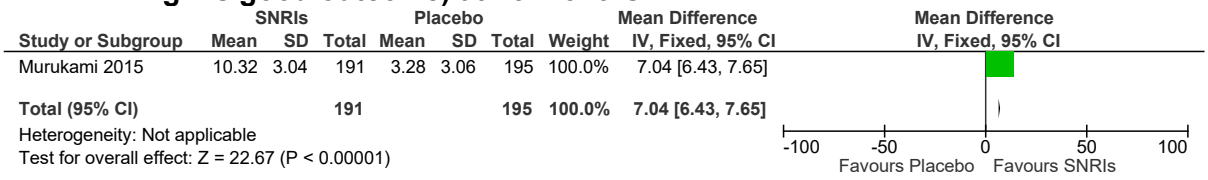

## Figure 41: Quality of life change scores (SF-36 vitality subscale, 0-100, high is good outcome) at >3 months



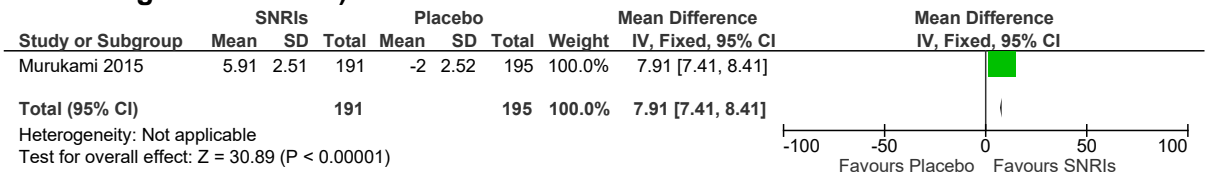
## Figure 42: Quality of life change scores (SF-36 general health perceptions subscale, 0-100, high is good outcome) at >3 months



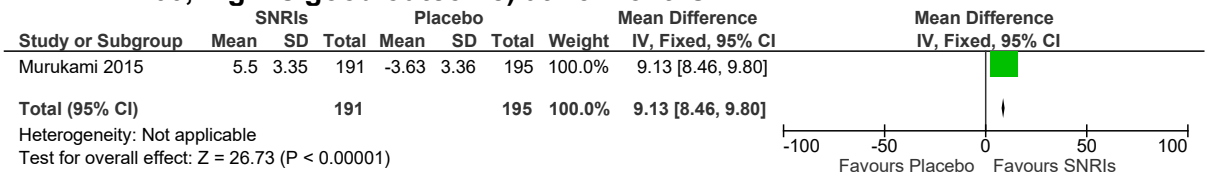

## Figure 43: Quality of life change scores (SF-36 social functioning subscale, 0-100, high is good outcome) at >3 months



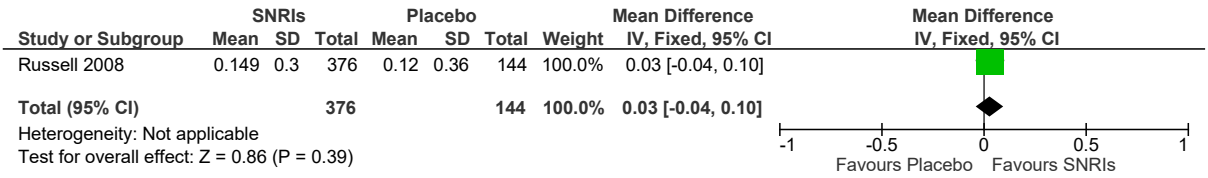

## Figure 44: Quality of life change scores (SF-36 mental health subscale, 0-100, high is good outcome) at >3 months



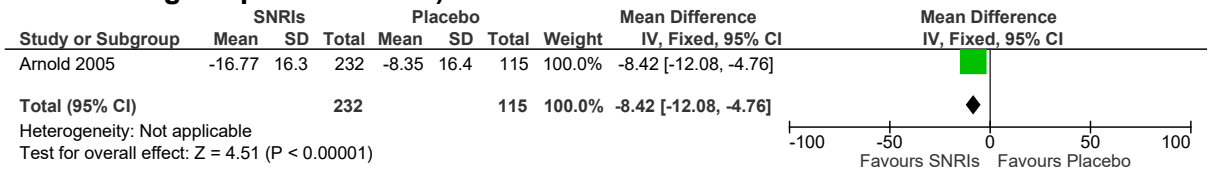

## Figure 45: Quality of life change scores (SF-36 emotional role limitations subscale, 0-100, high is good outcome) at >3 months



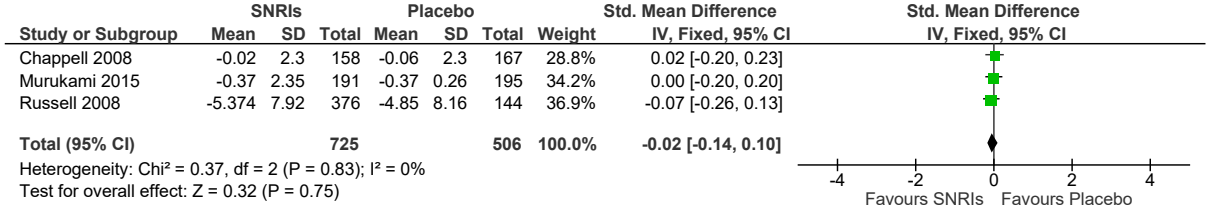

## Figure 46: Quality of life change scores (EQ-5D, 0-1, high is good outcome) at >3 months



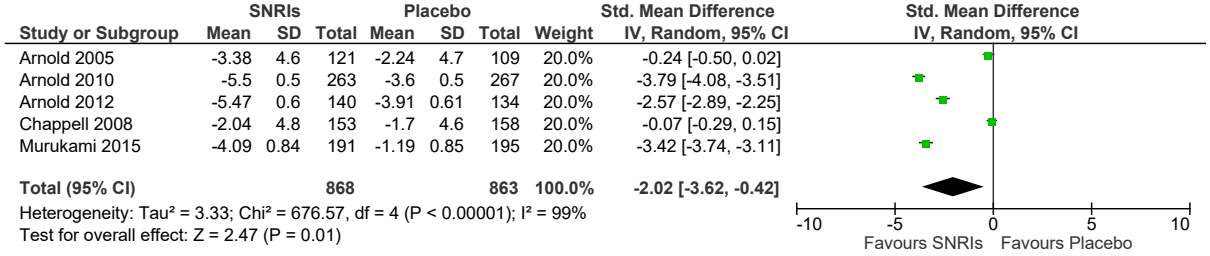
## Figure 47: Quality of life change scores (Fibromyalgia impact questionnaire, 0-100 high is poor outcome) at >3 months




## Figure 48: Physical function change scores (FIQ physical function subscale, Sheehan disability scale global functioning, high is poor outcome) at >3 months




## Figure 49: Psychological distress (Beck depression inventory, Hamilton rating scale for depression, high is poor outcome) change scores at >3 months




*NB: Heterogeneity not explained by subgroup analysis*

## Figure 50: Discontinuation due to adverse events at >3 months

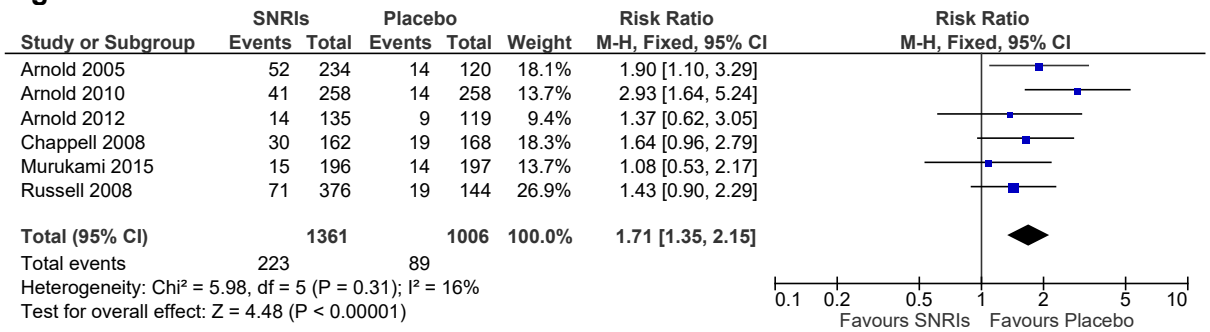
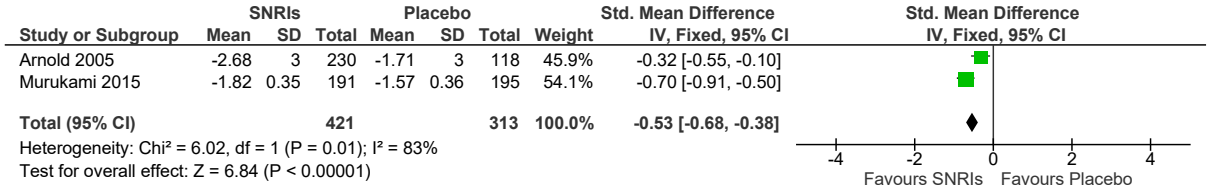
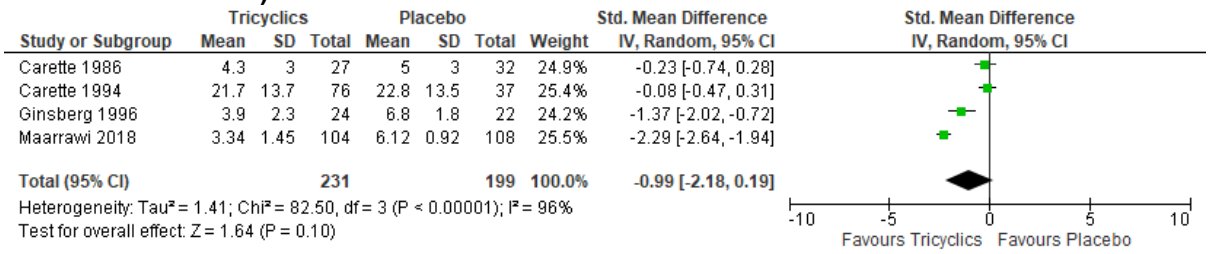


**Figure 51: Sleep (Jenkins composite score, BPI interference score sleep, high is poor outcome) at >3 months**




## E.1.4 Tricyclic antidepressants versus placebo

**Figure 52: Pain (VAS and McGill pain questionnaire final values, high is poor outcome) at ≤3 months**




*NB: Heterogeneity not explained by subgroup analysis*

**Figure 53: Pain reduction (VAS 0-10 change scores, high is poor outcome) at ≤3 months**

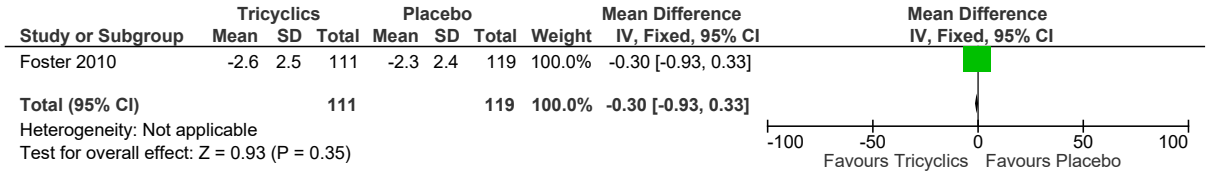



**Figure 54: Pain reduction (VAS, change scores, 0-100, high is poor outcome) at >3 months**

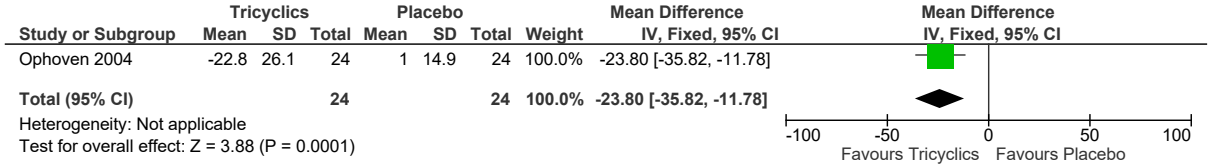
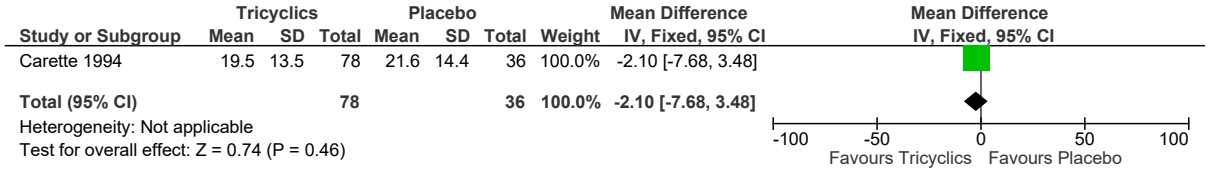


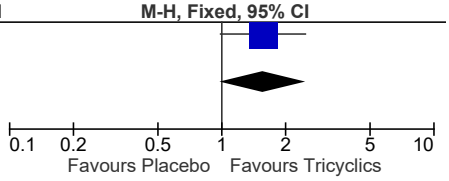

**Figure 55: Pain final values (McGill pain questionnaire, 0-78, high is poor outcome) at >3 months**



## Figure 56: Number of responders (Scale of global improvement, great or moderate improvement) at ≤3 months

| Study or Subgroup | Tricyclics Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Heymann 2001 | 45 | 73 | 13 | 33 | 100.0% | 1.56 [0.99, 2.48] |
| **Total (95% CI)** | | **73** | | **33** | **100.0%** | **1.56 [0.99, 2.48]** |
| Total events | 45 | | 13 | | | |

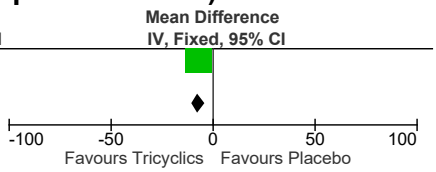
Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)




## Figure 57: Quality of life final values (FIQ, 0-100, high is poor outcome) at ≤3 months

| Study or Subgroup | Tricyclics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Heymann 2001 | 44.31 | 8.198 | 73 | 51.68 | 7.98 | 33 | 100.0% | -7.37 [-10.68, -4.06] |
| **Total (95% CI)** | | | **73** | | | **33** | **100.0%** | **-7.37 [-10.68, -4.06]** |

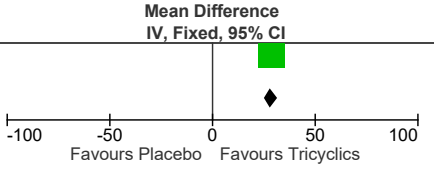
Heterogeneity: Not applicable
Test for overall effect: Z = 4.37 (P < 0.0001)




## Figure 58: Physical functioning (NPDI, % improvement) at ≤3 months

| Study or Subgroup | Tricyclics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Maarrawi 2018 | 42.22 | 15.5 | 104 | 13.69 | 9.55 | 108 | 100.0% | 28.53 [25.05, 32.01] |
| **Total (95% CI)** | | | **104** | | | **108** | **100.0%** | **28.53 [25.05, 32.01]** |

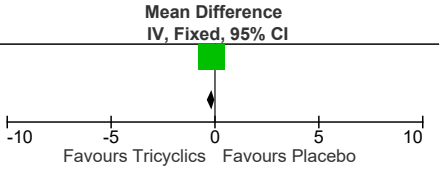
Heterogeneity: Not applicable
Test for overall effect: Z = 16.06 (P < 0.00001)




## Figure 59: Physical function final values (HAQ disability index, 0-3, high is poor outcome) at ≤3 months

| Study or Subgroup | Tricyclics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Carette 1994 | 0.6 | 0.45 | 82 | 0.77 | 0.56 | 40 | 100.0% | -0.17 [-0.37, 0.03] |
| **Total (95% CI)** | | | **82** | | | **40** | **100.0%** | **-0.17 [-0.37, 0.03]** |

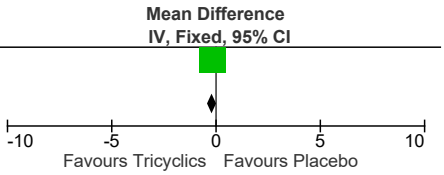
Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)




## Figure 60: Physical function final values (HAQ disability index, 0-3, high is poor outcome,) at >3 months

| Study or Subgroup | Tricyclics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Carette 1994 | 0.53 | 0.4 | 78 | 0.7 | 0.65 | 36 | 100.0% | -0.17 [-0.40, 0.06] |
| **Total (95% CI)** | | | **78** | | | **36** | **100.0%** | **-0.17 [-0.40, 0.06]** |

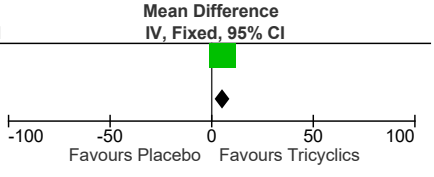
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)



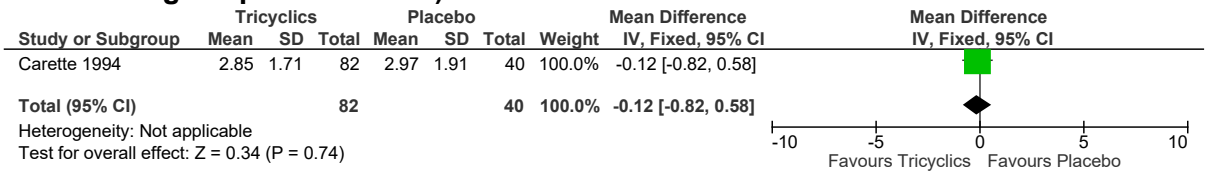

## Figure 61: Psychological distress (HAD-D, % improvement) at ≤3 months

| Study or Subgroup | Tricyclics Mean | SD | Total | Placebo Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Maarrawi 2018 | 10.36 | 14.37 | 104 | 5.04 | 11.83 | 108 | 100.0% | 5.32 [1.77, 8.87] |
| **Total (95% CI)** | | | **104** | | | **108** | **100.0%** | **5.32 [1.77, 8.87]** |

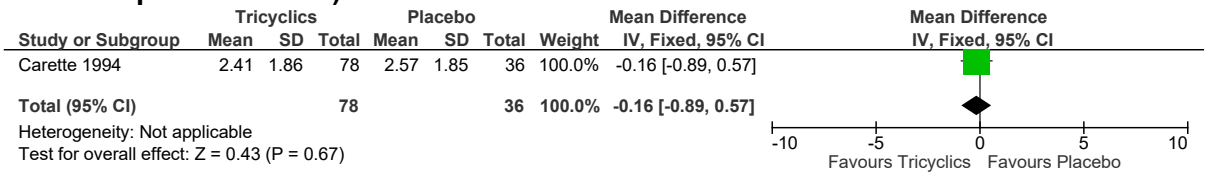
Heterogeneity: Not applicable
Test for overall effect: Z = 2.94 (P = 0.003)



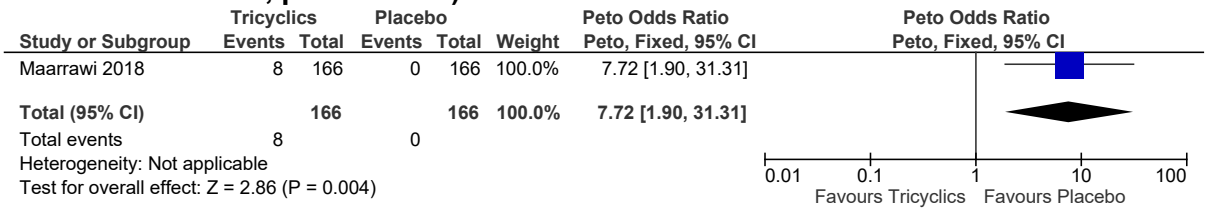
## Figure 62: Psychological distress final values (AIMS depression component, 0-10, high is poor outcome) at ≤3 months



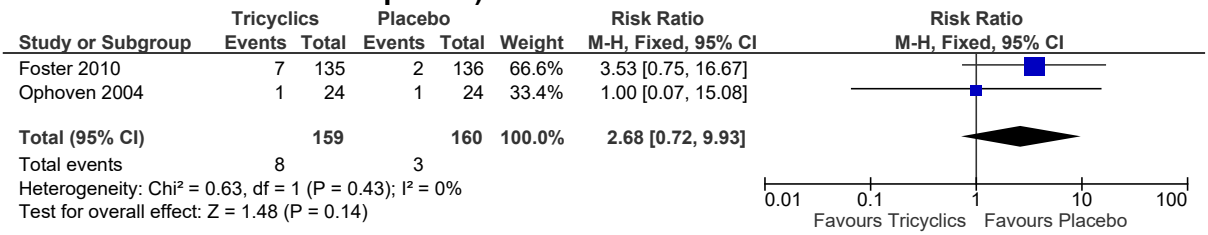

## Figure 63: Psychological distress final values (AIMS depression scale, 0-10, high is poor outcome) at >3 months



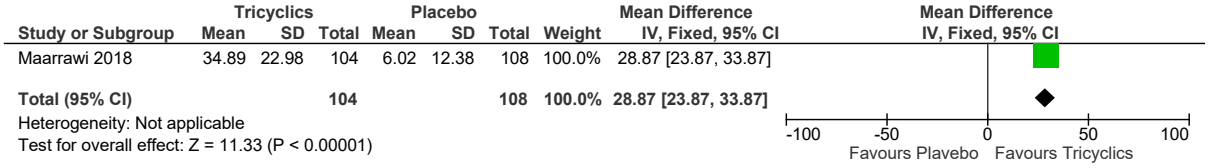

## Figure 64: Discontinuation due to adverse events (due to drowsiness, palpitations, insomnia, panic attack) at ≤3 months




## Figure 65: Discontinuation due to adverse events (reasons not specified, no serious adverse events reported) at >3 months

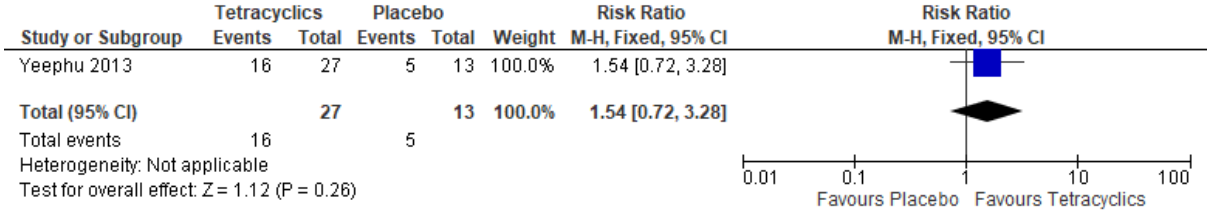



## Figure 66: Sleep disturbance (Bisprectal index scale, percentage improvement) at ≤3 months

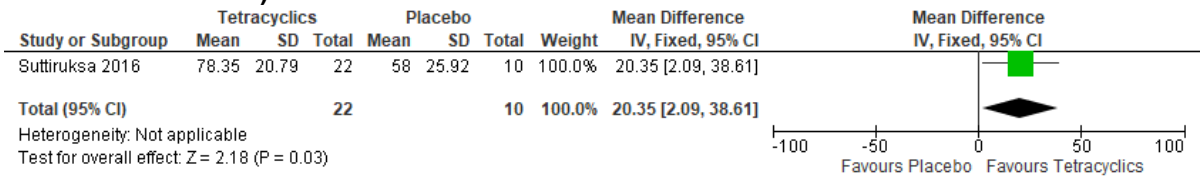


## E.1.5 Tetracyclic antidepressants versus placebo

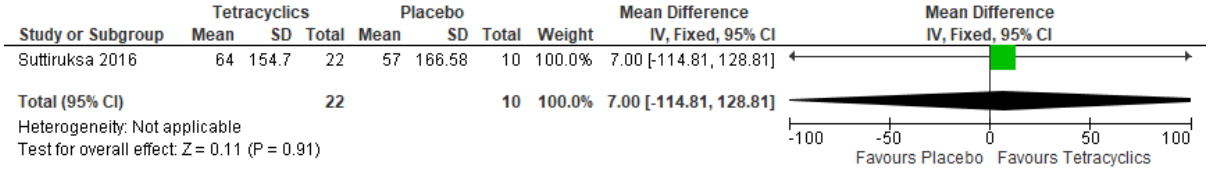
### Figure 67: Number of responders (VAS total score, VAS 24hr morning recall, 30% improvement) at >3 months



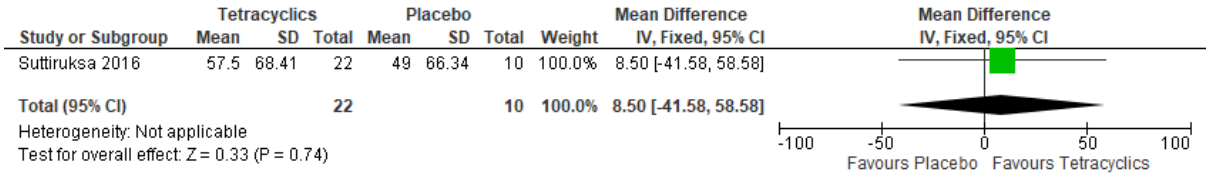

### Figure 68: Quality of life (SF-36 physical functioning subscale, 0-100, high is good outcome) at >3 months



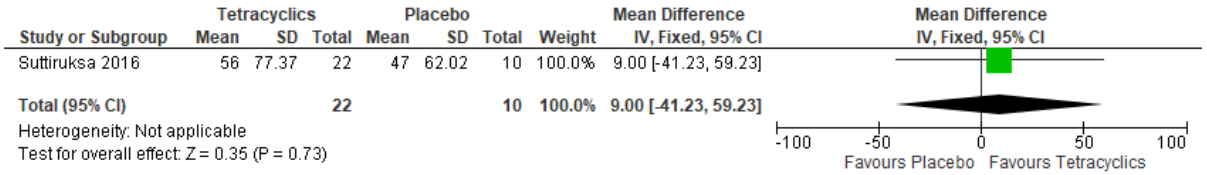

### Figure 69: Quality of life (SF-36 physical role subscale, 0-100, high is good outcome) at >3 months




### Figure 70: Quality of life (SF-36 bodily pain subscale, 0-100, high is good outcome) at >3 months




### Figure 71: Quality of life (SF-36 general health subscale, 0-100, high is good outcome) at >3 months




### Figure 72: Quality of life (SF-36 vitality subscale, 0-100, high is good outcome) at >3 months

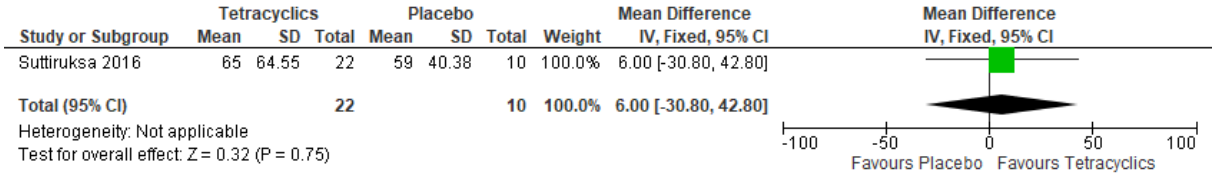


**Figure 73: Quality of life (SF-36 social functioning subscale, 0-100, high is good outcome) at >3 months**

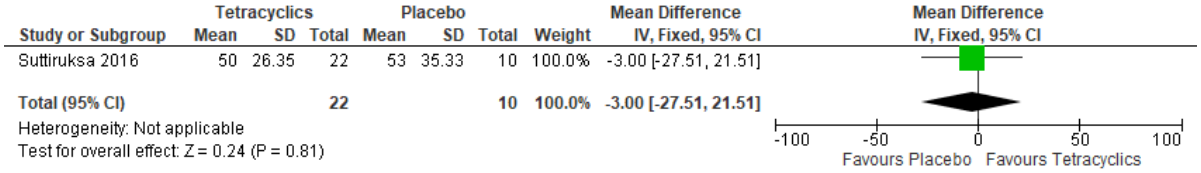



**Figure 74: Quality of life (SF-36 mental health subscale, 0-100, high is good outcome) at >3 months**

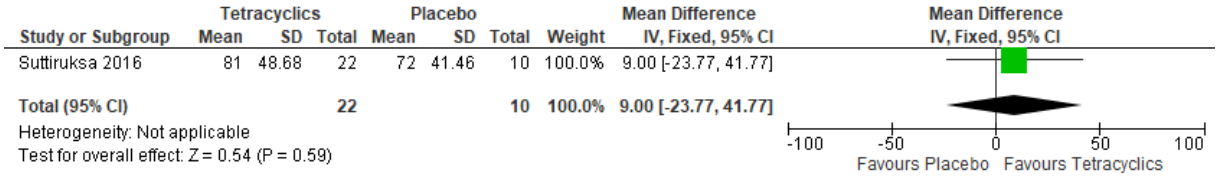



**Figure 75: Quality of life (SF-36 emotional role limitations subscale, 0-100, high is good outcome) at >3 months**

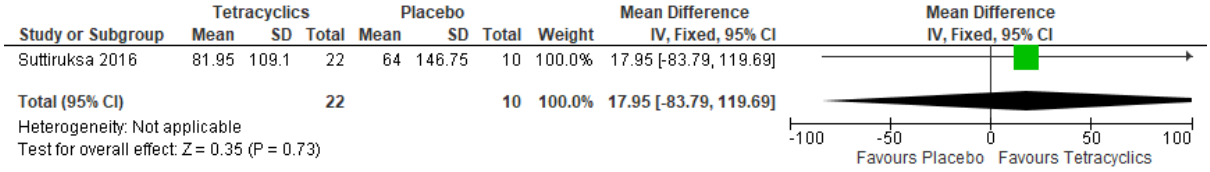
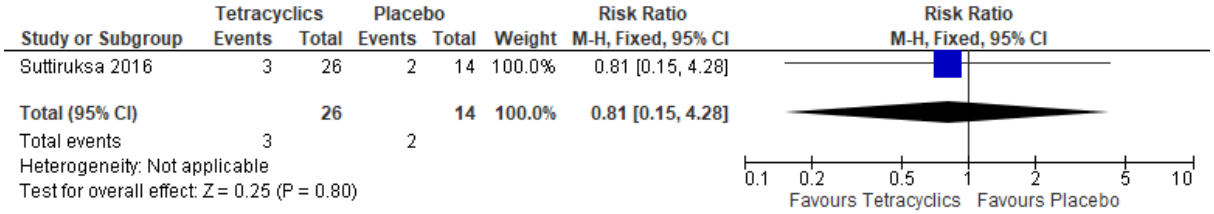



**Figure 76: Discontinuation at >3 months**




## E.1.6 Benzodiazepines versus placebo

**Figure 77: Pain final values and change scores (VAS, 0-10, high is poor outcome) at ≤3 months**

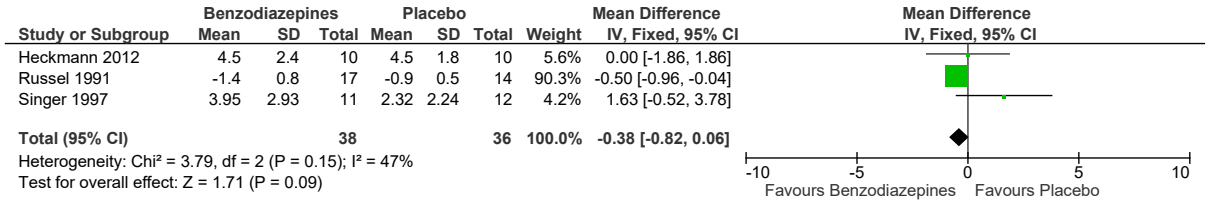
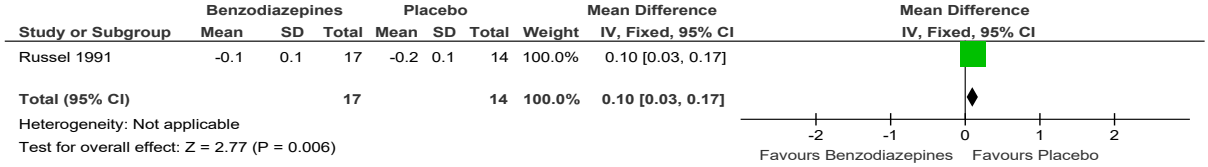
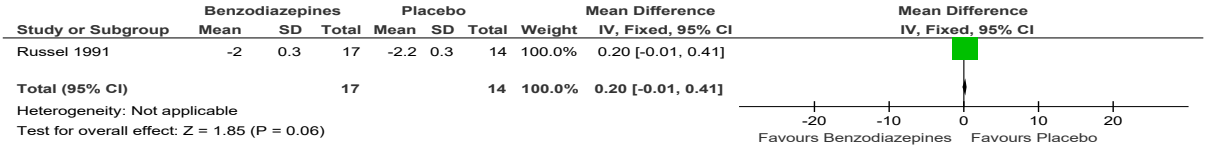


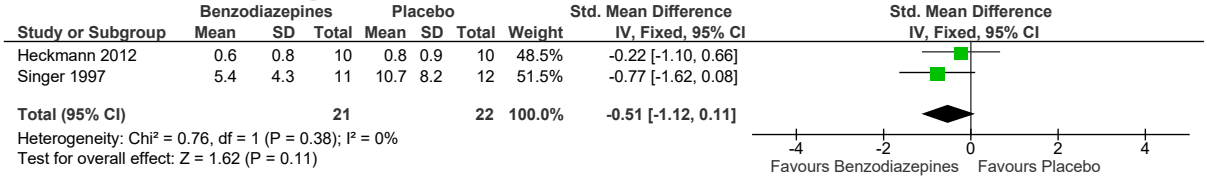

**Figure 78: Physical function (HAQ disability index, 0-3, high is poor outcome, change scores) at ≤3 months**



### Figure 79: Psychological distress (CES-D, 0-30 high is poor outcome, change scores) at ≤3 months

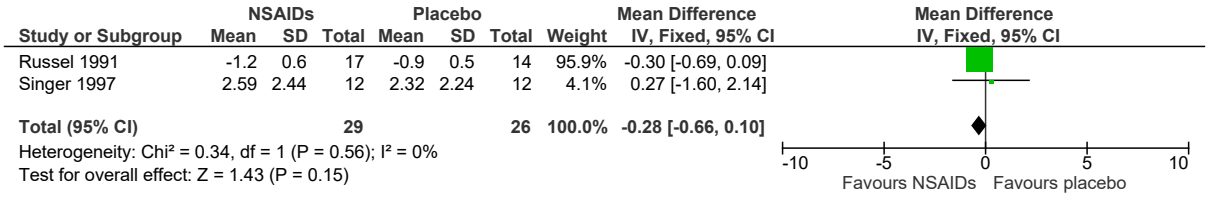



### Figure 80: Psychological distress (Beck depression inventory, depression adjective checklist, high is poor outcome, final values) at ≤3 months

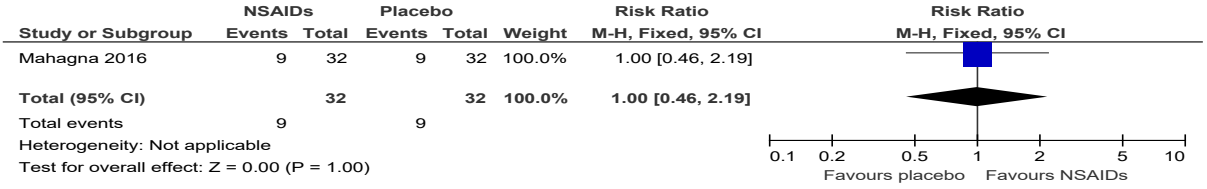



## E.1.7 Non-steroidal anti-inflammatory drugs versus placebo

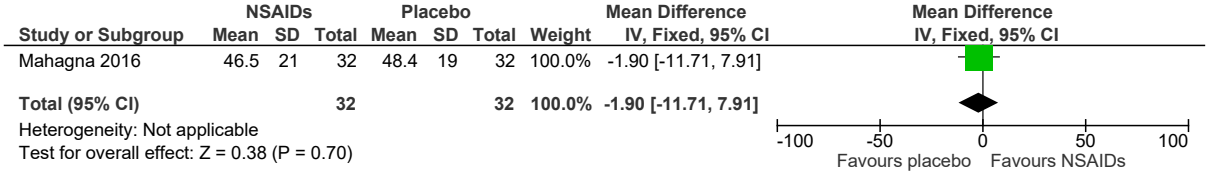
### Figure 81: Pain change scores and final values (VAS, 0-10, high is poor outcome) at ≤3 months



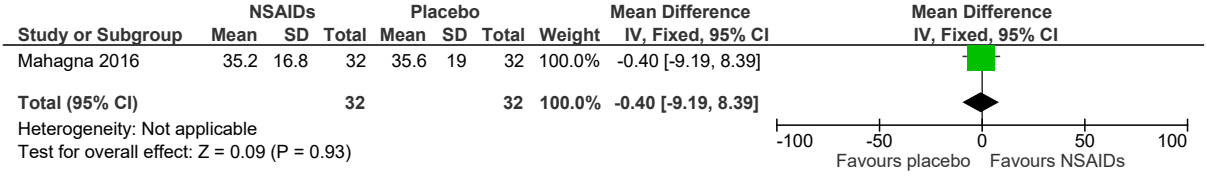

### Figure 82: Number of responders (BPI decrease of >30%) at ≤3 months



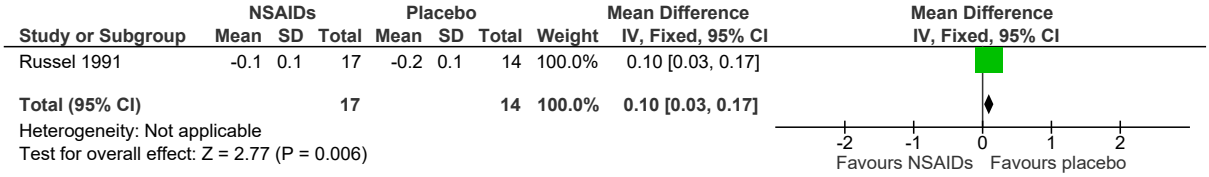

### Figure 83: Quality of life final values (SF-36 mental component, 0-100, high is good outcome) at ≤3 months



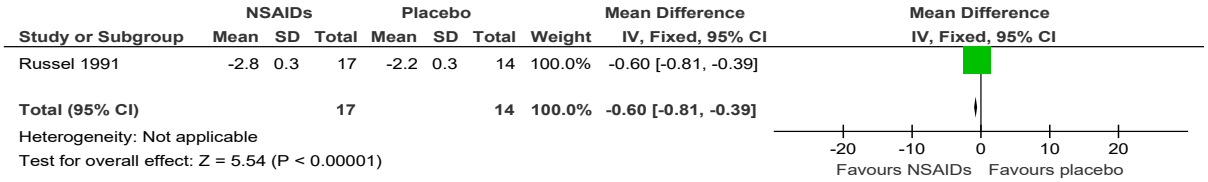

### Figure 84: Quality of life final values (SF-36 physical component, 0-100, high is good outcome) at ≤3 months



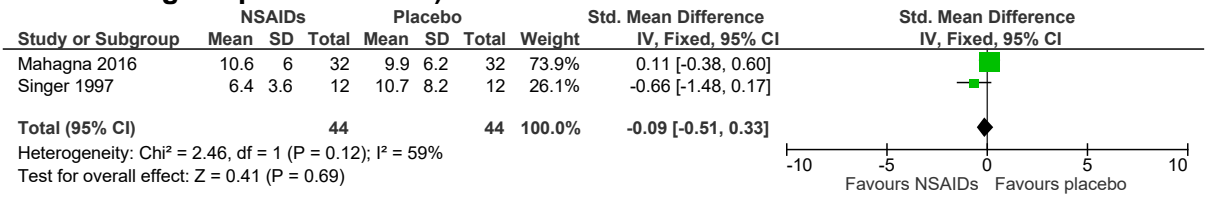
### Figure 85: Physical function change scores (HAQ disability index 0-3, high is poor outcome) at ≤3 months



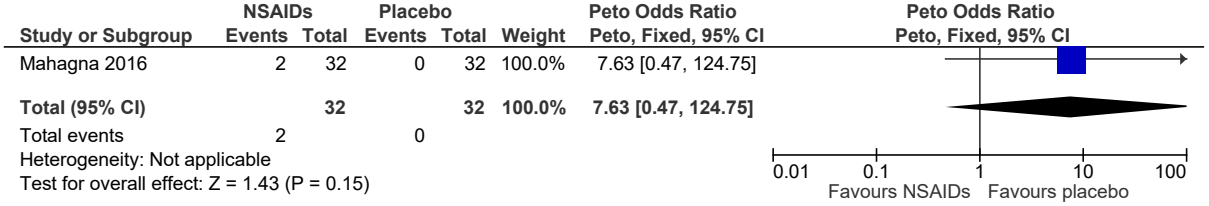

### Figure 86: Psychological distress change scores (Centre for epidemiological studies depression scale, 0-30, high is poor outcome) at ≤3 months




### Figure 87: Psychological distress final values (HAM-D, depression adjective checklist, high is poor outcome) at ≤3 months

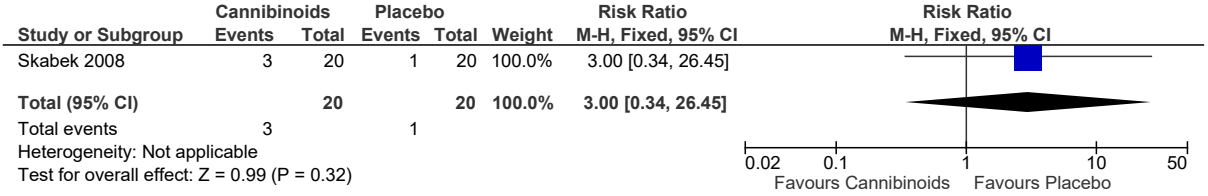



### Figure 88: Discontinuation due to adverse events (reasons not specified, no serious adverse events) at ≤3 months



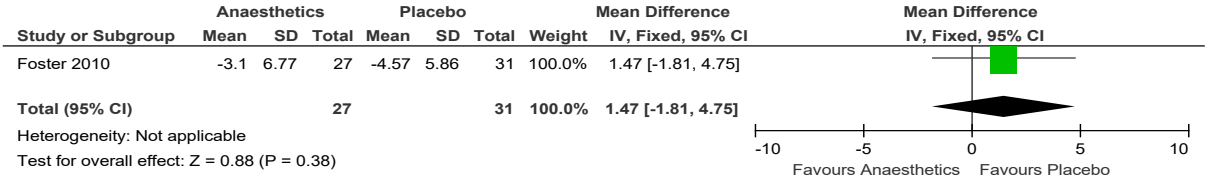

## E.1.8 Cannabinoids versus placebo

### Figure 89: Discontinuation due to adverse events (reasons not specified, no serious adverse events) at ≤3 months

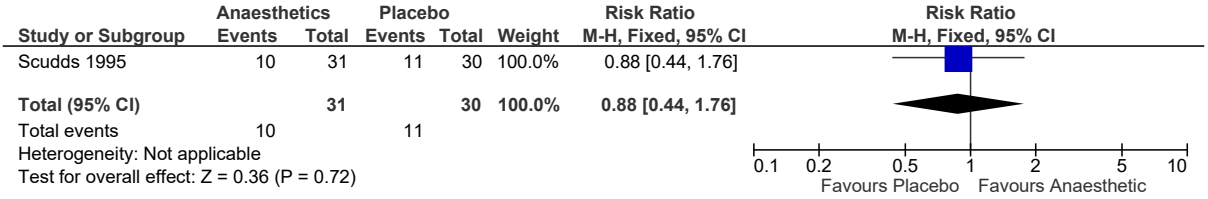


## E.1.9 Local anaesthetics (topical lidocaine) versus placebo

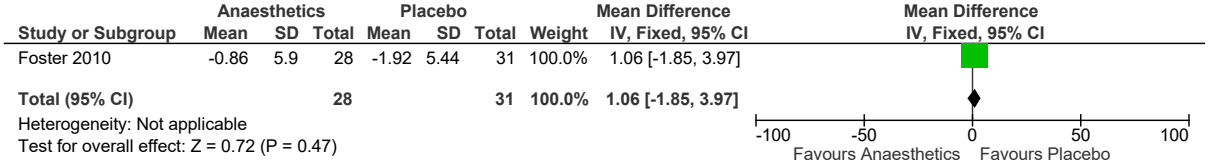
### Figure 90: Pain reduction change scores (VAS total score, 0-10, high is poor outcomes) at ≤3 months



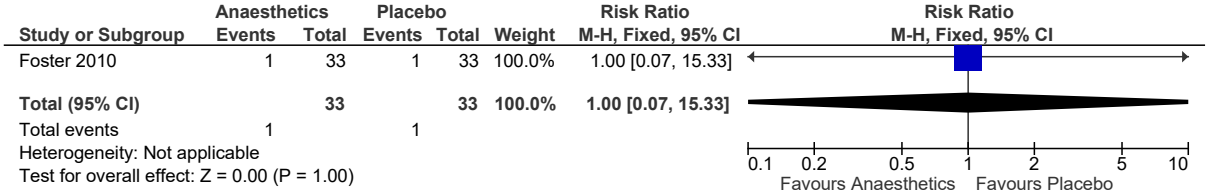

### Figure 91: Number of responders (VAS score, 30% reduction) at ≤3 months




### Figure 92: Psychological distress change scores (Beck depression inventory, 0-63, high is poor outcome) at ≤3 months

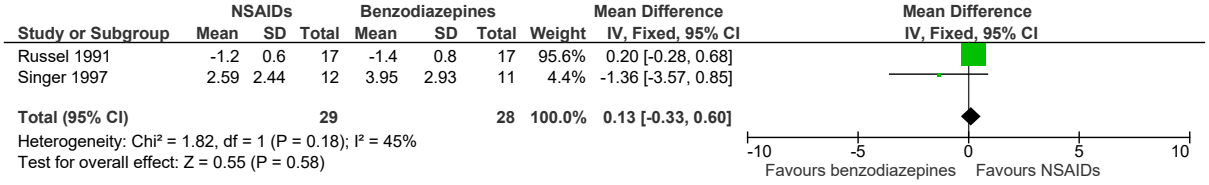



### Figure 93: Discontinuation due to adverse events (reasons not stated) at ≤3 months




## E.1.10 NSAIDs versus benzodiazepines

### Figure 94: Pain change scores and final values (VAS, 0-10, high is poor outcome) at ≤3 months




### Figure 95: Physical function changes scores (HAQ disability index , 0-3, high is poor outcome) at ≤3 months

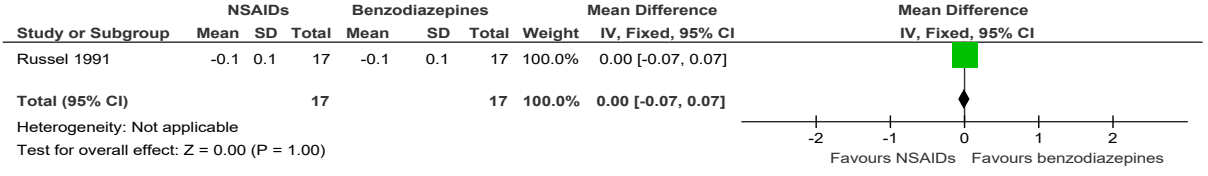


**Figure 96: Psychological distress change scores (Centre for epidemiological studies depression scale, 0-30, high is poor outcome) at ≤3 months**

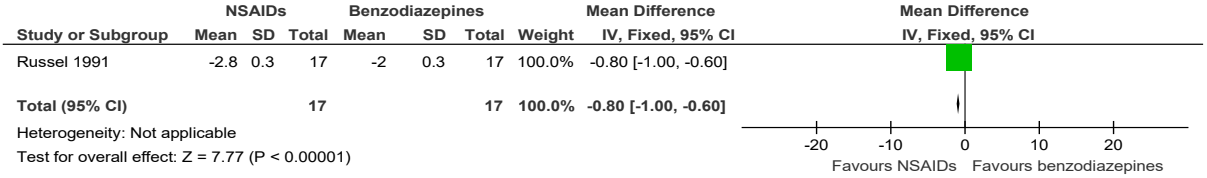
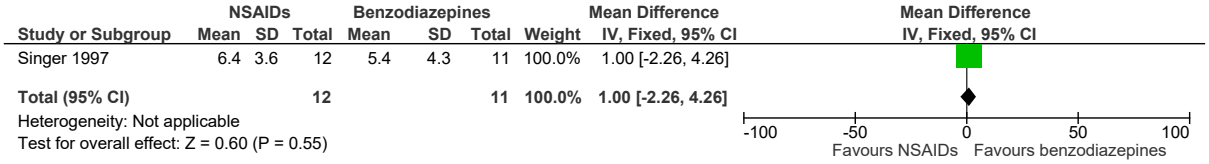



**Figure 97: Psychological distress final values (HAM-D, 0-21, high is poor outcome) at ≤3 months**




## E.1.11 SNRIs versus anti-epileptics

**Figure 98: Pain reduction at <3 months (Widespread Pain Index, 0-19, final values, high is poor outcome)**

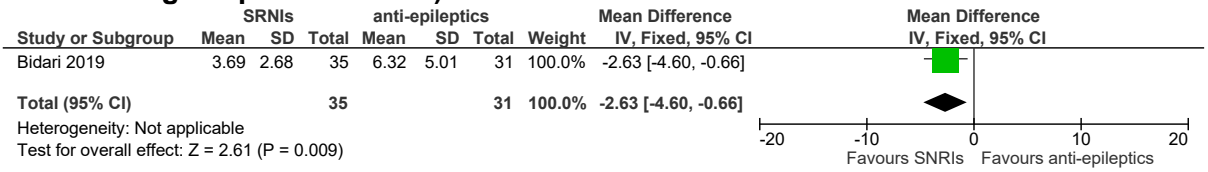



**Figure 99: Quality of life at <3 months (SF-12 Physical component, 0-100, final values, high is good outcome)**

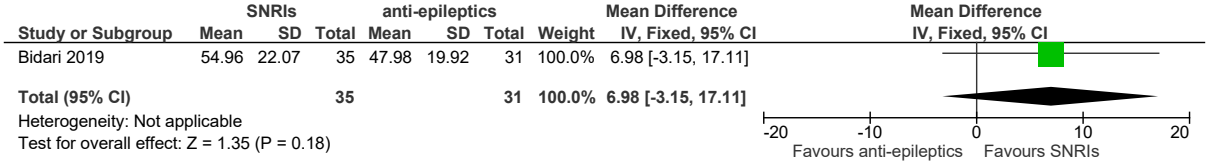
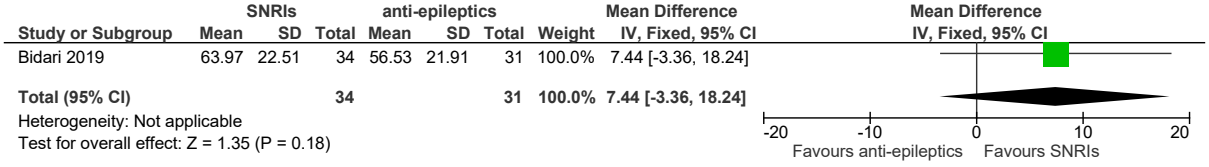



**Figure 100: Quality of life at <3 months (SF-12 Mental component, 0-100, final values, high is good outcome)**




*Note: Significant difference in outcome at baseline may affect final values. Baselines, mean (SD): SNRI group 56.69 (24.33), anti-epileptics group 45.77 (27.31)*

**Figure 101: Psychological distress at <3 months (Beck Depression Inventory-II, 0-63, final values, high is poor outcome)**

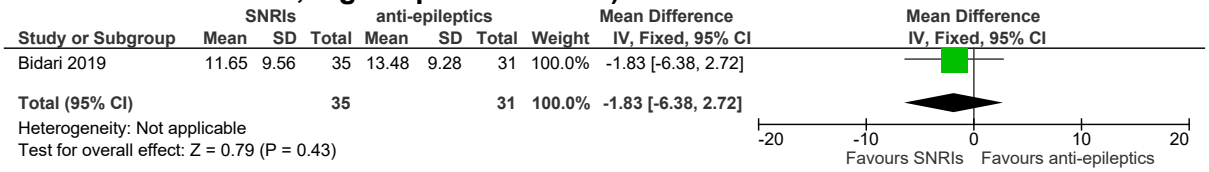
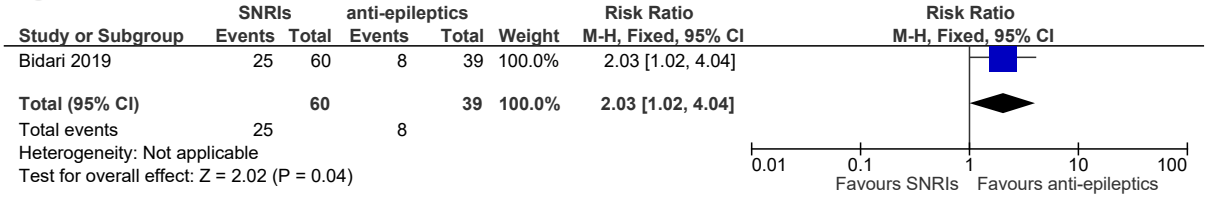



**Figure 102: Discontinuation due to adverse events at <3 months**




# E.2 Opioid safety

None

# E.3 Gabapentinoid safety

None

# Appendix F: GRADE tables

## F.1 Pharmacological management

**Table 21: Clinical evidence profile: Anti-epileptics versus placebo**

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Anti-epileptics versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Pain reduction at ≤3 months (VAS, Brief Pain Inventory average pain severity score, range, McGill pain questionnaire, high is poor outcome, final values)** | | | | | | | | | | | | |
| 4 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 307 | 201 | - | SMD 0.45 lower (0.63 to 0.27 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Pain reduction at ≤3 months (VAS percentage reduction, change scores)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 24 | 20 | - | MD 27.1 higher (2.5 to 51.7 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Pain reduction at >3 months (VAS, 0-10, high is poor outcome, final values, change scores); chronic pelvic pain subgroup** | | | | | | | | | | | | |
| 2 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 33 | 26 | - | MD 1.68 lower (2.3 lower to 1.05 lower) | ⊕⊕OO LOW | CRITICAL |
| **Pain reduction at >3 months (Average daily pain score, 0-10, change scores, high is poor outcome, final values); fibromyalgia subgroup** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 947 | 955 | - | MD 0.56 lower (0.77 lower to 0.35 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Quality of life at ≤3 months (SF-12 physical component, high is good outcome, 0-100, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 210 | 103 | - | MD 2.6 higher (0.14 to 5.06 lower) | ⊕⊕⊕O MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quality of life ≤3 months (SF-12 mental component, high is good outcome, 0-100, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 210 | 103 | - | MD 0.4 higher (2.15 lower to 2.95 higher) | HIGH | CRITICAL |
| **Quality of life at ≤3 months (Fibromyalgia impact questionnaire, 0-100, high is poor outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 57 | 62 | - | MD 11.1 lower (17.07 to 5.13 lower) | LOW | CRITICAL |
| **Quality of life at >3 months (EQ5D, 0-100, high is good outcome, change scores)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 887 | 890 | - | MD 0.02 higher (0 to 0.04 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Physical function at ≤3 months (Pain Disability Questionnaire function subscale, 0-90, high is poor outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[1] | none | 13 | 12 | - | MD 6.4 higher (8.35 lower to 21.15 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Physical function at >3 months (Pain Disability Questionnaire function subscale, 0-90 high is poor outcome)** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 13 | 12 | - | MD 3.6 higher (12.5 lower to 19.7 higher) | ⊕⊕OO LOW | CRITICAL |
| **Psychological distress at ≤3 months (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 12 | 13 | - | MD 0.1 lower (3.91 lower to 3.71 higher) | ⊕⊕OO VERY LOW | CRITICAL |
| **Psychological distress at >3 months (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, final values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 902 | 902 | - | MD 0.2 lower (0.52 lower to 0.12 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Psychological distress at ≤3 months (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious risk of bias | no serious inconsistency | no serious indirectness | very serious[1] | none | 13 | 13 | - | MD 0.8 higher (2.44 lower to 4.04 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological distress at >3 months (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, final values)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 902 | 902 | - | MD 0.42 higher (0.76 to 0.08 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Psychological distress at ≤3 months (Hospital Anxiety and Depression scale, 0-21, high is poor outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 210 | 103 | - | MD 0.2 higher (1.64 lower to 2.04 higher) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Discontinuation due to adverse events at ≤3 months (reasons not specified)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | very serious[1] | none | 12/57 (21.1%) | 7/62 (11.3%) | RR 1.86 (0.79 to 4.41) | 97 more per 1000 (from 24 fewer to 385 more) | ⊕⊕OO LOW | CRITICAL |
| **Discontinuation due to adverse events at >3 months (reasons not specified)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 114/1001 (11.4%) | 46/1012 (7.5%) | RR 1.52 (1.15 to 2) | 39 more per 1000 (from 11 more to 75 more) | ⊕⊕OO LOW | CRITICAL |
| **Sleep at ≤3 months (Medical Outcomes Study Sleep Problems index score, 0-100, high is poor outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | serious[1] | none | 57 | 62 | - | MD 14.4 lower (21.64 to 7.16 lower) | ⊕⊕OO LOW | IMPORTANT |
| **Sleep at >3 months (Average Daily Sleep Interference score, 0-10, high is poor outcome, change values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[2] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 948 | 957 | - | MD 0.67 lower (0.86 to 0.48 lower) | ⊕⊕⊕O MODERATE | IMPORTANT |

1 Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

2 Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias

## Table 22: Clinical evidence profile: SSRIs versus placebo

| | | | | |
|---|---|---|---|---|

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SSRIs versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Pain reduction final values (VAS , medical outcomes study pain measure, high is poor outcome) ≤3 months** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[1] | serious[3] | no serious indirectness | serious[2] | none | 78 | 72 | - | SMD 0.41 lower (1.08 lower to 0.27 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Pain reduction change scores (McGill pain questionnaire, Prostatitis symptom severity scale, high is poor outcome) at >3 months** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 32 | 33 | - | SMD 0.65 lower (1.16 to 0.15 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Pain reduction (VAS final values, 0-10, high is poor outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 23 | 23 | - | MD 0.25 lower (1.35 lower to 0.85 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life at ≤3 months (FIQ total scores, 0-100, high is poor outcome, change scores)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 25 | 26 | - | MD 11.5 lower (19.22 to 3.78 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Physical function (HAQ total scores, FIQ physical function subscale, high is poor outcome, final values) at ≤3 months** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 36 | 30 | - | SMD 0.06 lower (0.55 lower to 0.43 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Physical function (physical impairment on Fibromyalgia impact questionnaire, 0-9.99, high is poor outcome, change scores) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 25 | 26 | - | MD 0.7 lower (1.91 to 0.51 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological distress (FIQ depression subscale, HADS-D, beck depression inventory, high is poor outcome) change scores ≤3 months** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 53 | 54 | - | SMD 0.32 lower (0.71 to lower 0.06 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological distress (FIQ anxiety subscale, AIMS anxiety, high is poor outcome) change scores at ≤3 months** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 32 | 33 | - | SMD 0.19 lower (0.69 lower to 0.3 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological distress (Beck depression scale, HADS:A, high is poor outcome) final values at ≤3 months** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[2] | no serious inconsistency | no serious indirectness | serious[2] | none | 36 | 34 | - | SMD 0.79 lower (1.28 to 0.3 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological distress (HADS:A, 0-21, high is poor outcome, final values) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 24 | 22 | - | MD 2.3 lower (4.12 lower to 0.48 higher) | ⊕OOO VERY LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Discontinuation due to adverse events at ≤3 months (due to gastrointestinal problems)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 1/15 (6.7%) | 1/9 (11.1%) | RR 0.6 (0.04 to 8.46) | 44 fewer per 1000 (from 107 fewer to 829 more) | ⊕OOO VERY LOW | CRITICAL |
| **Discontinuation due to adverse events at >3 months (reasons not stated due to no events in intervention arm; placebo discontinuation due to feeling 'spaced out')** | | | | | | | | | | | | |
| 2 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 1/29 (3.4%) | 14.3% | OR 0.14 (0.00 to 6.82) | 100 fewer per 1000 (from 136 fewer to 107 more) | ⊕OOO VERY LOW | CRITICAL |
| **Sleep (VAS sleep outcome, 0-15, high is poor outcome) final values at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 15 | 9 | - | MD 0 higher (2.95 lower to 2.95 higher) | ⊕OOO VERY LOW | IMPORTANT |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

[3] Downgraded due to heterogeneity, unexplained by subgroup analysis

## Table 23: Clinical evidence profile: SNRIs versus placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **SNRIs versus placebo** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Pain reduction (Brief Pain Inventory average pain severity, VAS, high is poor outcome) change scores at ≥3 months** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 1263 | 931 | - | MD 0.69 lower (0.91 to 0.47 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Quality of life (SF-36 mental component, low is poor outcome) change scores at <3 months** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[3] | serious[2] | no serious indirectness | serious[1] | none | 549 | 563 | - | MD 3.17 higher (2.15 to 4.18 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life (SF-36 physical component, low is poor outcome) change scores at <3 months (7-12 weeks)** | | | | | | | | | | | | |
| 3 | randomised trials | serious[3] | serious[2] | no serious indirectness | serious[1] | none | 549 | 563 | - | MD 1.01 higher (0.68 to 1.35 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 physical functioning subscale, 0-100, changes scores, high is good outcome) at ≥3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 4.36 higher (3.93 to 4.79 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 physical role limitations subscale, 0-100, changes scores, high is good outcome) at ≥3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 7.76 higher (7.17 to 8.35 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 bodily pain subscale, 0-100, changes scores, high is good outcome) at ≥3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 5.67 higher (5.26 to 6.08 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 vitality subscale, 0-100, high is good outcome) at ≥3 months** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 6.7 higher (6.2 to 7.2 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 general health perceptions subscale, 0-100, changes scores, high is good outcome) at ≥3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 3.24 higher (2.86 to 3.63 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 social functioning subscale, 0-100, changes scores, high is good outcome) at ≥3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 7.04 higher (6.43 to 7.65 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 mental health subscale, 0-100, changes scores, high is good outcome) at ≥3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 7.91 higher (7.41 to 8.41 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 emotional role limitations subscale, 0-100, changes scores, high is good outcome) at ≥3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 191 | 195 | - | MD 9.13 higher (8.46 to 9.8 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (EQ-5D, low is poor outcome) change scores at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | serious[1] | none | 376 | 144 | - | MD 0.03 higher (0.04 lower to 0.1 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life (Fibromyalgia impact questionnaire, low is poor outcome) change scores at >3 months** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | serious[1] | none | 232 | 115 | - | MD 8.42 lower (12.08 to 4.76 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Physical function (FIQ PF subscale, high is poor outcome, 0-10) change scores at >3 months** | | | | | | | | | | | | |
| 3 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 725 | 506 | - | SMD 0.02 lower (0.14 lower to 0.1 higher) | ⊕⊕OO LOW | CRITICAL |
| **Psychological distress (Beck depression inventory, Hamilton rating scale for depression, high is poor outcome) change scores at >3 months** | | | | | | | | | | | | |
| 5 | randomised trials | very serious[3] | serious[2] | no serious indirectness | serious[1] | none | 868 | 863 | - | SMD 2.02 lower (3.62 to 0.42 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Discontinuation due to adverse events at >3 months** | | | | | | | | | | | | |
| 8 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 229/1414 (16.2%) | 93/1033 (9%) | RR 1. 71 (1.35 to 2.09) | 60 more per 1000 (from 42 more to 92 more) | ⊕⊕OO LOW | CRITICAL |
| **Sleep (Jenkins composite score, MOS-Sleep Index I, BPI interference score sleep, change scores, high is poor outcome) at >3 months** | | | | | | | | | | | | |
| 2 | randomised trials | very serious[3] | no serious inconsistency | no serious indirectness | serious[1] | none | 421 | 313 | - | SMD 0.53 lower (0.68 to 0.38 lower) | ⊕OOO VERY LOW | IMPORTANT |

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by heterogeneity, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias

## Table 24: Clinical evidence profile: Tricyclic antidepressants versus placebo

| | | | | |
|---|---|---|---|---|

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Tricyclics versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Pain reduction (VAS and McGill pain questionnaire, final values, high is poor outcome) at ≤3 months** | | | | | | | | | | | | |
| 4 | randomised trials | serious[1] | very serious[3] | no serious indirectness | serious[2] | none | 231 | 199 | - | SMD 0.99lower (2.18 lower to 0.19 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Pain reduction (VAS 0-10, high is poor outcome, change scores) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 111 | 119 | - | MD 0.3 lower (-0.93 to 0.33 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Pain reduction change scores (VAS 0-100, high is poor outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 24 | 24 | - | MD 23.8 lower (35.82 to 11.78 lower) | ⊕⊕OO LOW | CRITICAL |
| **Pain final values (McGill pain questionnaire, 0-78, high is poor outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[2] | no serious inconsistency | no serious indirectness | serious[2] | none | 78 | 36 | - | MD 2.1 lower (7.68 lower to 3.48 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Number of responders (Scale of global improvement, great or moderate improvement) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | - | - | RR 1.56 (0.99 to 2.48) | 220 more per 1000 (from 4 fewer to 583 more) | ⊕⊕⊕O MODERATE | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quality of life final values (FIQ, 0-100, high is poor outcome, final values) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 73 | 33 | - | MD 7.37 lower (10.68 to 4.06 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Physical functioning (NPDI, % improvement) at <3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 104 | 108 | - | MD 28.53 higher (25.05 to 32.01 higher) | ⊕⊕⊕⊕ HIGH | CRITICAL |
| **Physical function final values (HAQ disability index, 0-3, high is poor outcome) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 82 | 40 | - | MD 0.17 lower (0.37 lower to 0.03 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Physical function (HAQ diability index, 0-3, high is poor outcome, final values) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 78 | 36 | - | MD 0.17 lower (0.4 lower to 0.06 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological distress (HAD-D, % improvement) at <3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 104 | 108 | - | MD 5.32 higher (1.77 to 8.87 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Psychological distress final values (Arthritis Impact Measurement Scale [AIMS] depression component, 0-10, final values, high is poor outcome) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 82 | 40 | - | MD 0.12 lower (0.82 lower to 0.58 higher) | ⊕⊕OO LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Psychological distress final values (Arthritis Impact Measurement Scale [AIMS] depression component, 0-10, final values, high is poor outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 78 | 36 | - | MD 0.16 lower (0.89 lower to 0.57 higher) | ⊕⊕OO LOW | CRITICAL |
| **Discontinuation due to adverse events at ≤3 months (due to drowsiness, palpitations, insomnia, panic attack)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 8/166 (4.8%) | 0/166 (0%) | OR 7.72 (1.9 to 31.31) | 50 more per 1000 (from 10 more to 80 more)[3] | ⊕⊕⊕O MODERATE | CRITICAL |
| **Discontinuation due to adverse events at ≥3 months (reasons not specified, no serious adverse events reported)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 8/159 (5%) | 2.8% | RR 2.68 (0.72 to 9.93) | 47 more per 1000 (from 8 fewer to 250 more) | ⊕⊕OO LOW | CRITICAL |
| **Sleep disturbance (Bisprectal index scale, % improvement) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | no serious imprecision | none | 104 | 108 | - | MD 28.87 higher (23.87 to 33.87 higher) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

[3] Downgraded by 1 increment for heterogeneity, unexplained by subgroup analysis

## Table 25: Clinical evidence profile: Tetracyclic antidepressants versus placebo

| Quality assessment | | | | | | | No of patients | | Effect | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|

| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Tetracyclic antidepressant versus placebo | Control | Relative (95% CI) | Absolute | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Number of responders (VAS total score, VAS 24h morning recall, 30% improvement) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 16/27 (59.3%) | 38.5% | RR 1.54 (0.72 to 3.28) | 208 more per 1000 (from 108 fewer to 878 more) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life (SF-36 physical functioning subscale, 0-100, final values, high is good outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | serious[2] | none | 22 | 10 | - | MD 20.35 higher (2.09 to 38.61 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Quality of life (SF-36 physical role limitations subscale, 0-100, final values, high is good outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22 | 10 | - | MD 7 higher (114.81 lower to 128.81 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 bodily pain subscale, 0-100, final values, high is good outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22 | 10 | - | MD 8.5 higher (41.58 lower to 58.58 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 general health perceptions subscale, 0-100, final values, high is good outcome) at >3 months** | | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22 | 10 | - | MD 9 higher (41.23 lower to 59.23 higher) | ⊕⊕OO LOW | CRITICAL |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quality of life (SF-36 vitality subscale, 0-100, final values, high is good outcome) at >3 months** | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22 | 10 | - | MD 6 higher (30.8 lower to 42.8 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 social functioning subscale, final values, 0-100, high is good outcome) at >3 months** | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22 | 10 | - | MD 3 lower (27.51 lower to 21.51 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 mental health subscale, 0-100, final values, high is good outcome) at >3 months** | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22 | 10 | - | MD 9 higher (23.77 lower to 41.77 higher) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life (SF-36 emotional role limitations subscale, 0-100, final values, high is good outcome) at >3 months** | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 22 | 10 | - | MD 17.95 higher (83.79 lower to 119.69 higher) | ⊕⊕OO LOW | CRITICAL |
| **Discontinuation due to adverse events at >3 months** | | | | | | | | | | | |
| 1 | randomised trials | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious[2] | none | 3/26 | 2/14 | RR 0.81 (0.15 to 4.28) | 28 fewer per 1000 (from 116 fewer to 485 more) | ⊕⊕OO LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

## Table 26: Clinical evidence profile: Benzodiazepines versus placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Benzodiazepines versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Pain reduction final values and change scores (VAS, 0-10, high is poor outcome) at ≤3 months** | | | | | | | | | | | | |
| 3 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 38 | 36 | - | MD 0.38 lower (0.82 lower to 0.06 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Physical function (HAQ disability index, 0-3 high is poor outcome, change scores) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 17 | 14 | - | MD 0.1 higher (0.03 to 0.17 higher) | ⊕⊕OO LOW | CRITICAL |
| **Psychological distress (Centre for epidemiological studies depression scale, 0-30, high is poor outcome, change scores) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 17 | 14 | - | MD 0.2 higher (0.01 lower to 0.41 higher) | ⊕⊕OO LOW | CRITICAL |
| **Psychological distress (BDI, depression adjective checklist, high is poor outcome, final values) at ≤3 months** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 21 | 22 | - | MD 0.51 lower (1.12 lower to 0.11 higher) | ⊕⊕OO LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

## Table 27: Clinical evidence profile: NSAIDs versus placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | NSAIDs versus placebo | Control | Relative (95% CI) | Absolute | | |
| **Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, change scores and final values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 29 | 26 | - | MD 0.28 lower (0.66 lower to 0.1 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Number of responders (Brief pain inventory, decrease of >30%) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 9/32 (28.1%) | 9/32 (28.1%) | RR 1 (0.46 to 2.19) | 0 fewer per 1000 (from 220 fewer to 220 more) | ⊕⊕OO LOW | CRITICAL |
| **Quality of life at ≤3 months (SF-36 mental component, 0-100, high is good outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 32 | 32 | - | MD 1.9 lower (11.71 lower to 7.91 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life at ≤3 months (SF-36 physical component, 0-100, high is good outcome, final values)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 32 | 32 | - | MD 0.4 lower (9.19 lower to 8.39 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Physical function at ≤3 months (HAQ disability index, 0-3 high is poor outcome, change scores)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17 | 14 | - | MD 0.1 higher (0.03 to 0.17 higher) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Psychological distress at ≤3 months (Centre for epidemiological studies depression scale, 0-30, high is poor outcome, change scores)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 17 | 14 | - | MD 0.6 lower (0.81 to 0.39 lower) | ⊕⊕⊕O MODERATE | CRITICAL |
| **Psychological distress at ≤3 months (HAM-D, depression adjective checklist, high is poor outcome, final values)** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 44 | 44 | - | SMD 0.09 lower (0.51 lower to 0.33 higher) | ⊕⊕OO LOW | CRITICAL |
| | | | | | | | | | | | | |
| **Discontinuation due to adverse events (reasons not specified, no serious adverse events)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 2/32 (6.3%) | 0/32 (0%) | OR 7.63 (0.47 to 124.75) | 6 more per 1000 (from 4 fewer to 16 more)[3] | ⊕⊕OO LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

## Table 28: Clinical evidence profile: Cannabinoids versus placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Cannibinoids versus placebo** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Discontinuation due to adverse events at ≤3 months (dizziness, disorientation, nausea, poor coordination, headache, drowsiness and fatigue)** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[3] | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 20 | 20 | RR 3 (0.34 to 26.45) | 100 more per 1000 (from 33 fewer to 1000 more) | ⊕OOO VERY LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

[3] Study also reported quality of life and pain reduction outcomes but these were reported in insufficient detail for quality assessment or inclusion in the analysis. See clinical evidence tables for further details.

## Table 29: Clinical evidence profile: Local anaesthetics versus placebo

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **Local anaesthetics versus placebo** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Pain reduction change scores (VAS score 0-10, high is poor outcomes) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 27 | 31 | - | MD 1.47 higher (1.81 lower to 4.74 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Number of responders (100mm VAS score, 30% reduction) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 10/31 (32.3%) | 11/30 (36.7%) | RR 0.88 (0.44 to 1.76) | 44 fewer per 1000 (from 205 fewer to 279 more) | ⊕OOO VERY LOW | CRITICAL |
| **Psychological distress (Beck depression inventory 0-63, change score; high is poor outcome) at ≤3 months** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 28 | 31 | - | MD 1.06 higher (1.85 lower to 3.97 higher) | ⊕⊕OO LOW | CRITICAL |
| **Discontinuation due to adverse events at ≤3 months (reasons not stated)** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 33 | 33 | RR 1 (0.07 to 15.33) | 0 more per 1000 (from 8 fewer to 8 more) | ⊕⊕OO LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

## Table 30: Clinical evidence profile: NSAIDs versus benzodiazepines

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **NSAIDs versus benzodiazepines** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Pain reduction (VAS, 0-10, high is poor outcome, change scores and final values) at ≤3 months** | | | | | | | | | | | | |
| 2 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 29 | 28 | - | MD 0.13 higher (0.33 lower to 0.6 higher) | ⊕⊕OO LOW | CRITICAL |
| **Physical function changes scores (HAQ disability index, 0-3, high is poor outcome) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 17 | 17 | - | MD 0 higher (0.0.7 to 0.07 higher) | ⊕⊕OO LOW | CRITICAL |
| **Psychological distress change scores (Centre for epidemiological studies depression scale, 0-30, high is poor outcome) at ≤3 months** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | randomised trials | serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 17 | 17 | - | MD 0.8 lower (1 to 0.6 lower) | ⊕⊕OO LOW | CRITICAL |
| **Psychological distress final values (HAM-D, 0-21, high is poor outcome) at ≤3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | very serious[2] | none | 12 | 11 | - | MD 1 higher (2.26 lower to 4.26 higher) | ⊕OOO VERY LOW | CRITICAL |

[0] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

## Table 31: Clinical evidence profile: SNRIs versus anti-epileptics

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **SNRIs versus anti-epileptics** | **Control** | **Relative (95% CI)** | **Absolute** | | |
| **Pain reduction at <3 months (Widespread Pain Index, 0-19, final values, high is poor oucome)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 35 | 31 | - | MD 2.63 lower (4.60 to 0.66 lower) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life at <3 months (SF-12 Physical component, 0-100, final values, high is good oucome)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 35 | 31 | - | MD 6.98 higher (3.15 lower to 17.11 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Quality of life at <3 months (SF-12 Mental component, 0-100, final values, high is good oucome)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | no serious indirectness | serious[2] | none | 34 | 31 | - | MD 7.44 higher (3.36 lower to 18.24 higher) | ⊕OOO VERY LOW | CRITICAL |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Psychological distress at <3 months (Beck Depression Inventory-II, 0-63, final values, high is poor outcome)** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[2] | no serious inconsistency | no serious indirectness | serious[2] | none | 35 | 31 | - | MD 1.83 lower (6.38 lower to 2.72 higher) | ⊕OOO VERY LOW | CRITICAL |
| **Discontinuation due to adverse events at <3 months** | | | | | | | | | | | | |
| 1 | randomised trials | very serious[1] | no serious inconsistency | serious[3] | serious[2] | none | 25/60 (41.7%) | 8/39 (20.5%) | RR 2.03 (1.02 to 4.04) | 212 more per 1000 (from 14 more to 440 more) | ⊕OOO VERY LOW | CRITICAL |

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and 2 increments if the majority of evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[3] Downgraded for outcome indirectness

## F.2 Opioid safety

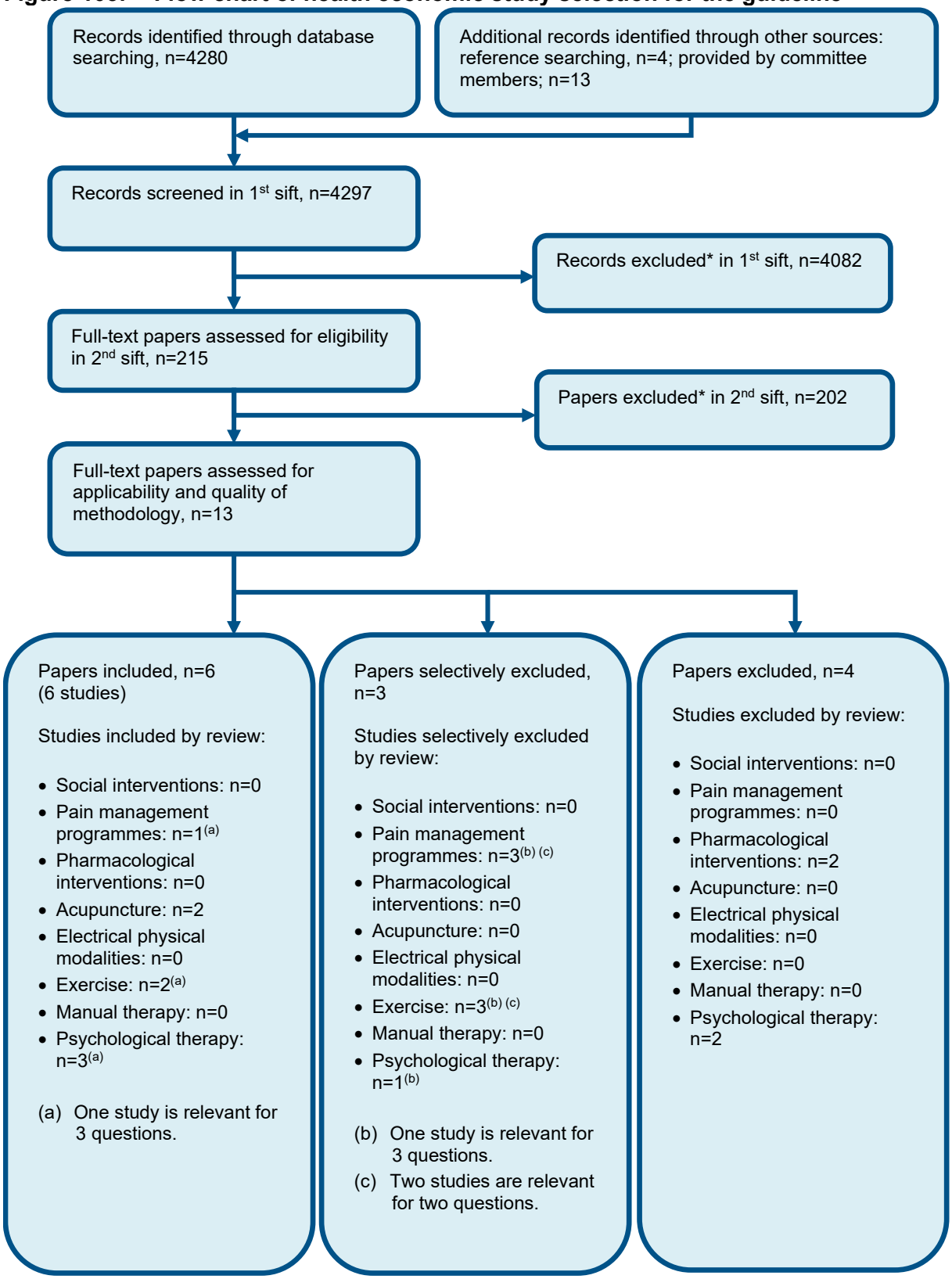
None

## F.3 Gabapentinoid safety

None

# Appendix G: Health economic evidence selection

**Figure 103: Flow chart of health economic study selection for the guideline**




* Non-relevant population, intervention, comparison, design or setting; non-English language

# Appendix H: Health economic evidence tables

None

# Appendix I: Excluded studies

## I.1 Excluded clinical studies

### I.1.1 Pharmacological management

**Table 32: Studies excluded from the clinical review**

| Study | Exclusion reason |
|---|---|
| Aboumarzouk 2012[3] | Cochrane review with different outcomes |
| Achariyapota 2008[4] | No useable outcomes |
| Acuna 2008[5] | Literature review |
| Ahmed 2016[9] | Systematic review: study designs inappropriate. Crossover study |
| Aiyer 2018[11] | Systematic review with different PICO |
| Albazaz 2008[12] | Literature review |
| Albertoni giraldes 2016[13] | Inappropriate comparison |
| Allan 2001[15] | Systematic review: study designs inappropriate. Crossover study. Not review population |
| Anderberg 2000[18] | No useable outcomes |
| Andreae 2012[19] | Not review population |
| Andrews 2011[20] | Systematic review with different PICO |
| Anon 2015[600] | Protocol |
| Anonymous 2006[26] | Retrospective study |
| Anonymous 2006[23] | Abstract |
| Anonymous 2009[22] | Incorrect study design |
| Anothaisintawee 2011[27] | Systematic review with different PICO |
| Arai 2015[29] | Pre-randomisation crossover for half the patients, but not for the other half, due to run-up period of fentanyl treatment of all patients. The washout period was unreported. Not review population |
| Argoff 2015[30] | Wrong study design |
| Arnold 2004[42] | Not review population. Incorrect study design (placebo run in) |
| Arnold 2007[33] | Both studies already on database. Incorrect design |
| Arnold 2007[44] | Systematic review is not relevant to review question or unclear PICO. This is a pooled report of two studies that have already been included for extraction. |
| Arnold 2008[46] | Placebo run-in phase |
| Arnold 2009[38] | Inappropriate comparison |
| Arnold 2009[41] | Wrong study design |
| Arnold 2010[32] | Both studies on database. Incorrect design |
| Arnold 2010[43] | Incorrect interventions |
| Arnold 2014[35] | Responders only. Not guideline condition |
| Arnold 2015[47] | Crossover study |
| Arnold 2016[48] | Not review population |
| Arnold 2017[34] | Crossover study |
| Arnold 2018[36] | Systematic review with different PICO |
| Ataoglu 1997[51] | Not review population |
| Aviram 2017[53] | Wrong population |

| Study | Exclusion reason |
|---|---|
| Azari 2012[54] | Inappropriate comparison. Pooled analysis. References checked |
| Bateman 2013[60] | Wrong population |
| Beaulieu 2007[61] | Crossover study |
| Bennett 2003[63] | Incorrect interventions. Drug combination |
| Bennett 2005[64] | Incorrect interventions |
| Benyamin 2009[65] | Not review population |
| Berger 2011[68] | Abstract |
| Berry 1982[69] | Not review population |
| Bhadra 2010[70] | No useable outcomes |
| Biasi 1998[72] | Duration too short |
| Binsfeld 2010[74] | Not review population |
| Birse 2012[77] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Bogetto 1997[79] | Abstract |
| Bohme 2004[80] | Not review population |
| Bradley 2010[84] | No useable outcomes |
| Branco 2010[85] | Incorrect interventions |
| Breuer 2014[86] | Incorrect interventions |
| Broglio 2017[87] | Incorrect study design |
| Brown 2008[90] | Inappropriate comparison |
| Brown 2009[91] | Inappropriate comparison |
| Brown 2017[88] | Abstract |
| Brown 2018[89] | Crossover study. Inappropriate outcomes |
| Brutcher 2019[94] | Pain not chronic primary. Not guideline condition |
| Burgstaller 2014[96] | Not review population |
| Busse 2018[98] | Systematic review with different PICO |
| Buynak 2015[99] | Not review population |
| Campbell 2001[103] | Systematic review with different PICO |
| Campbell 2017[107] | Not review population |
| Cantini 1995[109] | Not in English |
| Capaci 2002[110] | No SD reported for outcomes. Not guideline condition |
| Cappelleri 2009[111] | Post hoc analysis |
| Caruso 1987[117] | Incorrect interventions |
| Castagnera 1994[118] | Inappropriate comparison |
| Choi 2012[127] | article not in English |
| Chou 2003[130] | Systematic review with different PICO |
| Chou 2013[128] | Not review population |
| Choy 2011[133] | Systematic review with different PICO |
| Chu 2018[135] | Inappropriate comparison |
| Clair 2016[139] | Pooled analysis, not all trials included |
| Clauw 2008[140] | Not review population |
| Clauw 2013[141] | Not review population. Incorrect study design (responders only) |
| Cohen 2012[142] | Systematic review, references checked |
| Cooper 2017[147] | Cochrane review with different PICO |
| Cooper 2017[146] | Not review population. Cochrane review |
| Cording 2015[149] | Cochrane review, drug not available in the UK |

| Study | Exclusion reason |
|---|---|
| Cossins 2013[152] | Systematic review, references checked |
| Crofford 2005[155] | Not review population. Excluded known non-responders |
| Crofford 2008[154] | Not review population. Only responders |
| De moraes 2012[159] | Systematic review with different PICO |
| De vries 2016 [161] | Crossover study. Incorrect interventions |
| De vries 2017[162] | Not review population (secondary visceral pain). Incorrect interventions |
| Deer 2019[163] | Systematic review with different PICO |
| Derry 2016[166] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Derry 2016[167] | Cochrane review with different outcomes (some overlap), minimum trial duration requirement of 8 weeks |
| Derry 2016[168] | Cochrane review with incorrect population (neuropathic pain) |
| Derry 2017[169] | Cochrane review with different outcomes (some overlap) |
| Derry 2017[170] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Desai 2013[172] | Literature review |
| Distler 2010[176] | Incorrect interventions |
| Domzal 1985[177] | Abstract |
| Doraiswamy 2006[178] | Placebo run in phase |
| Drewes 1993[179] | No useable outcomes |
| Driessens 1994[180] | Crossover study |
| Duehmke 2017[183] | Not review population. Cochrane review |
| Dwight 1998[186] | Inappropriate comparison |
| Eckmann 2011[187] | Crossover study |
| Edelbroek 1986[188] | Not review population |
| Els 2017[196] | Cochrane review with different outcomes (some overlap) |
| Els 2017[194] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Engel 1998[197] | Crossover study |
| Erhan 2000[198] | Not in English |
| Eroglu 2013[199] | Nottingham Health Profile is only scale |
| Esteve 2013[200] | Not review population |
| Eyigor 2010[205] | Not review population. Inappropriate comparison |
| Finch 2009[208] | Crossover study |
| Fleuret 2014[210] | Incorrect study design |
| Forssell 2004[213] | Crossover study |
| Franco 2002[218] | Inappropriate comparison |
| Franco 2017[217] | Protocol |
| Freynhagen 2006[219] | Not review population |
| Frost 1986[220] | Duration too short |
| Furlan 2006[222] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Gaskell 2014[227] | Cochrane review. Not review population |
| Gaskell 2016[228] | Cochrane review, references checked |
| Geisser 2011[231] | Pooled analysis |

| Study | Exclusion reason |
|---|---|
| Gill 2011[232] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Giordano 1999[234] | No useable outcomes |
| Goldenberg 1986[239] | No useable outcomes |
| Goldenberg 1996[237] | Crossover study |
| González 2007[242] | Cochrane review protocol |
| Gourlay 1986[244] | Crossover study |
| Grosset 2005[249] | Crossover study |
| Guerriero 2015[255] | Not review population |
| Gulec 2007[256] | Not in English |
| Haggman-henrikson 2017[258] | Systematic review with different PICO |
| Hale 1999[259] | Crossover study |
| Hale 2015[263] | Incorrect study design |
| Hale 2016[260] | Not review population |
| Hale 2017[262] | Not review population |
| Haroutounian 2012[264] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Harris 2013[265] | Crossover study |
| Hauser 2013[269] | Systematic review with incorrect PICO |
| Häuser 2013[270] | Cochrane review with incorrect study design (minimum trial duration 4 weeks, including incorrect interventions) |
| Hauser 2015[271] | Duplicate of Walitt 2016 (excluded) |
| Hauser 2015[266] | Cochrane review with different outcomes |
| Hauser 2018[267] | Systematic review with different PICO |
| Hearn 2012[273] | Not review population |
| Hearn 2013[274] | Protocol |
| Hedayati 2005[276] | Not review population |
| Hofmann 2016[282] | Not review population |
| Hsu 2012[284] | Not review population |
| Imanaka 2013[288] | Not review population |
| Jafarinia 2016[289] | Not review population |
| Jamison 1998[291] | Not review population |
| Johansson 1979[295] | Not review population |
| Juel 2015[297] | Not review population |
| Kalita 2006[299] | Not review population |
| Kalita 2014[298] | Not review population |
| Kang 2018[300] | <3 month pain present in population |
| Kapil 2015[301] | Incorrect interventions |
| Kater 1968[303] | Not review population |
| Kiefer 2008[308] | Incorrect study design |
| Kim 2013[309] | Cross-over design. |
| Kim 2018 [310] | Incorrect population (neuropathic pain, <50% had complex regional pain syndrome) |
| Kisely 2016[312] | Systematic review with different PICO |
| Kleinstäuber 2014[314] | Not review population |
| Korting 1999[315] | Incorrect interventions. <3 month pain present in population |

| Study | Exclusion reason |
|---|---|
| Kurian 2019[320] | Systematic review with different PICO |
| Landau 2007[321] | Not review population |
| Lawson 2016[327] | Systematic review with different PICO |
| Le marshall 2011[328] | Literature review |
| Learman 2005[329] | Literature review |
| Lee 2006[330] | Incorrect interventions |
| Lee 2012[333] | Incorrect study design |
| Lee 2016[334] | Systematic review with different PICO |
| Leo 2013[335] | Systematic review with different PICO |
| Lin 2012[338] | Not review population |
| Lipkovich 2014[340] | Meta-analysis |
| List 2003[341] | Systematic review with different PICO |
| Liu 2018[342] | Systematic review with different PICO |
| Loldrup 1989[344] | Not review population |
| Loldrup 1991[343] | Cancelled, unavailable |
| Lopez-d'alessandro 2011[345] | No relevant outcomes |
| Lunn 2014[346] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Lynch 2011[348] | Systematic review with different PICO |
| Lynch 2015[349] | Systematic review with different PICO |
| Macfarlane 2017[352] | EULAR report on review of systematic reviews |
| Magistro 2016[353] | Systematic review with different PICO |
| Maina 2002[356] | Incorrect study design |
| Malik 2017[358] | No extractable outcomes. Incorrect interventions (Dronabinol not licensed in the UK) |
| Manchikanti 2011[359] | Systematic review with different PICO |
| Marangell 2011[361] | Meta-analysis |
| Martin-sanchez 2009[363] | Systematic review. Chronic pain mixed population |
| Matthey 2013[364] | Incorrect interventions |
| Mcintyre 2013[366] | Abstract |
| Mcintyre 2014[365] | Not guideline condition. Not review population |
| Mcmillan 1997[367] | Inappropriate comparison |
| Mcmillan 2016[368] | Cochrane review with different outcomes |
| Mcnaughton 2001[369] | Cochrane review with incorrect interventions |
| Mcnicol 2013[371] | Cochrane review, incorrect population |
| Mcnicol 2017[370] | Cochrane review, incorrect population |
| Mcquay 1992[372] | Not review population |
| Mease 2008[377] | Incorrect study design (placebo run in) |
| Mease 2010[373] | Incorrect study design (placebo run in) |
| Mease 2009[374] | Incorrect interventions |
| Mease 2010[378] | Inappropriate comparison |
| Mease 2011[379] | Meta-analysis |
| Mease 2014[376] | Meta-analysis |
| Mease 2014[375] | Incorrect study design |
| Menzies 2017[382] | Incorrect study design |
| Meske 2018[384] | Systematic review with different PICO |

| Study | Exclusion reason |
|---|---|
| Michelet 2018[385] | Systematic review with different PICO |
| Miki 2016[386] | Placebo run in phase |
| Miller 2002[387] | Narrative literature review |
| Minguez serra 2007[389] | Literature review |
| Mohs 2012[390] | No relevant outcomes |
| Moore 2005[393] | Systematic review. Not review population |
| Moore 2009[394] | Cochrane review with different outcomes |
| Moore 2011[395] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Moore 2014[391] | Meta-analysis |
| Moore 2015[392] | Cochrane review with incorrect population |
| Muller 2004[400] | Inappropriate comparison |
| Muller 2005[401] | Inappropriate comparison |
| Murakami 2017[402] | Crossover study |
| Murray 2005[404] | Conference abstract |
| Nalamachu 2011[407] | Not review population |
| Nalamachu 2012[406] | Meta-analysis. Not review population |
| Nasser 2014[409] | Dose comparison |
| Natelson 2015[410] | Incorrect interventions |
| Nct 2010[412] | Citation only |
| Nguyen 2012[413] | Systematic review |
| Nickel 2000[415] | Narrative literature review |
| Nickel 2003[418] | Incorrect interventions |
| Nickel 2008[416] | Incorrect study design |
| Nickel 2012[417] | Incorrect interventions |
| Niimi 2012[419] | Citation only |
| Nishishinya 2006[421] | Protocol |
| Nishishinya 2008[420] | Systematic review with different PICO |
| Nitecka-Buchta 2019 [422] | Incorrect intervention. Unclear population (duration of pain not specified) |
| Noble 2008[424] | Not review population. Systematic review |
| Noble 2010[423] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Nuesch 2013[427] | Systematic review with different PICO |
| Nugent 2017[428] | Not review population. Systematic review |
| O'connell 2013[429] | Cochrane review with incorrect interventions and different outcomes |
| Offiah 2013[433] | Systematic review |
| Ohta 2012[437] | Incorrect study design (placebo run in) |
| Ohta 2013[436] | Incorrect study design |
| O'malley 1999[431] | Systematic review with different PICO |
| O'malley 2000[430] | Systematic review with different PICO |
| Onghena 1992[438] | Systematic review with different PICO |
| Ottman 2018[440] | Systematic review with different PICO |
| Ozerbil 2006[441] | No relevant outcomes |
| Padilla 2000[443] | Not review population |

| Study | Exclusion reason |
|---|---|
| Pae 2009[445] | Secondary analysis of an excluded study |
| Pae 2009[444] | No relevant outcomes |
| Papadopoulou 2016[447] | Systematic review with different PICO |
| Papandreou 2009[448] | Systematic review with different PICO |
| Papazisis 2010[449] | Systematic review with different PICO |
| Parsons 2015[451] | Meta-analysis |
| Parsons 2016[450] | Meta-analysis of excluded studies |
| Patkar 2005[456] | Conference abstract |
| Patkar 2007[455] | Incorrect study design (placebo run in) |
| Patton 2007[457] | Systematic review with different PICO |
| Pauer 2011[458] | Incorrect study design (placebo run in) |
| Pazin 2016[460] | Systematic review with different PICO |
| Perez 2001[462] | Systematic review with different PICO |
| Pergolizzi 2013[465] | Systematic review with different PICO |
| Perrot 2014[466] | Systematic review with different PICO |
| Petzke 2013[467] | Incorrect interventions |
| Pickering 2018[468] | Incorrect interventions. Milnacipran not licensed in UK |
| Pilowsky 1990[469] | Not review population. Non-responders to all other treatments |
| Polackwich 2016[470] | Literature review |
| Pontari 2009[472] | Abstract |
| Posner 1994[474] | Inappropriate comparison |
| Potvin 2012[475] | Incorrect interventions. Quetiapine as add-on treatment and no detail on other treatments being used in each group |
| Purcell 2004[477] | Conference abstract |
| Quijada 1994[479] | Not in English |
| Quijada-carrera 1996[478] | Incorrect interventions |
| Radbruch 2003[481] | Not review population |
| Rasmussen 1970[482] | single blind design |
| Rauck 2013[483] | Not review population |
| Reichenbach 2015[485] | No relevant outcomes |
| Reinecke 2015[486] | Not review population. Systematic review |
| Ren 2016[487] | Not in English |
| Riediger 2017[491] | Systematic review with different PICO |
| Riera 2015[492] | Abstract |
| Rizzatti-barbosa 2003[493] | No extractable outcomes |
| Rodriguez de rivera campillo 2010[495] | Not review population |
| Rodriguez de rivera-campillo 2011[494] | Not in English |
| Roldan 1990[496] | Not in English |
| Roskell 2011[497] | Systematic review with different PICO |
| Rossi 1983[498] | Incorrect interventions |
| Roth 2012[500] | Crossover study |
| Roth 2016[499] | Crossover study |
| Russell 2000[506] | Not review population |
| Russell 2009[504] | Secondary analysis of an excluded study |

| Study | Exclusion reason |
|---|---|
| Salerno 2002[510] | Not review population. Systematic review |
| Samborski 2004[511] | Non-randomised trial |
| Santos 2015[512] | Cochrane review with incorrect population (includes pain other than chronic primary pain), different outcomes |
| Santos 2018[513] | Systematic review with different PICO |
| Sarzi-puttini 2008[514] | Systematic review with different PICO |
| Sator-katzenschlager 2005[515] | Not review population |
| Schaeffer 2013[517] | Abstract |
| Schilder 2013[521] | Secondary analysis |
| Schoevers 2016[523] | Systematic review with different PICO |
| Schwartzman 2009[524] | Not review population |
| Scrivani 1999[525] | Incorrect study design |
| Seidel 2013[527] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Sencan 2004[528] | Inappropriate comparison |
| Senye 2012[529] | Systematic review with different PICO |
| Sigtermans 2009[534] | No useable outcomes |
| Siler 2011[535] | Systematic review with different PICO |
| Silverman 2017[536] | Crossover study |
| Smith 2011[541] | Systematic review with different PICO |
| Smith 2016[542] | Literature review |
| Smith 2019[543] | Inappropriate comparison |
| Sorensen 1995[546] | Crossover study |
| Sorge 2004[547] | Not review population |
| Spaeth 2006[548] | Summary and comment |
| Spoelstra 2013[550] | Systematic review with different PICO |
| Stannard 2016[552] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Staud 2014[554] | No extractable outcomes |
| Staud 2015[553] | Incorrect interventions |
| Sternbach 1977[555] | Incorrect study design |
| Stockings 2018[556] | Systematic review with different PICO |
| Straube 2010[558] | Meta-analysis of excluded studies |
| Straube 2011[559] | Meta-analysis of excluded studies |
| Strauss 2015[560] | Crossover study |
| Sultan 2008[562] | Systematic review with different PICO |
| Ta 2004[564] | Not review population |
| Tammiala-salonen 1999[566] | Incorrect interventions |
| Tanum 1994[568] | Abstract |
| Taskaynatan 2004[569] | Incorrect interventions |
| Theoharides 2008[573] | Systematic review with different PICO |
| Todorov 2005[575] | Not review population. Inappropriate comparison |
| Trugman 2014[576] | Incorrect study design (placebo run in) |
| Tsang 2016[577] | Systematic review with different PICO |
| Tschopp 1996[578] | No useable outcomes |
| Turkington 2002[579] | No useable outcomes |

| Study | Exclusion reason |
|---|---|
| Tyrer 1996[583] | Conference abstract |
| Tzellos 2010[585] | Systematic review with different PICO |
| Uceyler 2008[586] | Systematic review with different PICO |
| Üçeyler 2017[587] | Withdrawn systematic review |
| Usha 1995[588] | No relevant outcomes |
| Vaisman 1996[589] | Not in English |
| Van de Donk 2019 [590] | Crossover study. Incorrect interventions |
| Van de vusse 2004[591] | Crossover study |
| Van houdenhove 1992[592] | Crossover study. Incorrect interventions |
| Vanderweide 2015[594] | Systematic review with different PICO |
| Varia 2000[595] | Incorrect study design (placebo run in) |
| Venâncio rde 2008[598] | Not review population |
| Vitton 2004[601] | Incorrect interventions |
| Walitt 2015[608] | Cochrane review that included crossover studies, minimum trial duration of 4 weeks, different outcomes |
| Walitt 2016[606] | Cochrane review that included crossover studies, minimum trial duration of 4 weeks, different outcomes |
| Walitt 2016[607] | Cochrane review that included crossover studies, minimum trial duration of 4 weeks, different outcomes |
| Wallace 2000[609] | Incorrect study design. No relevant outcomes |
| Wang 2003[613] | Not in English |
| Wang 2011[611] | Meta-analysis |
| Wang 2012[612] | Systematic review with different PICO |
| Wang 2017[610] | Systematic review with different PICO |
| Ware 2010[614] | Crossover study |
| Wen 2013[620] | Not review population |
| Wertli 2014[622] | Systematic review with different PICO |
| Wieckiewicz 2015[623] | Literature review |
| Wiffen 2005[624] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2011[629] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2013[627] | Systematic review with different PICO |
| Wiffen 2013[625] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2013[626] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2014[628] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Wiffen 2016[631] | Cochrane review with incorrect population (includes pain other than chronic primary pain) |
| Wu 2008[637] | Not in English |
| Xu 2006[638] | Not in English |
| Xu 2016[639] | Systematic review with different PICO |
| Yang 2014[640] | Secondary analysis. No relevant outcomes |
| Yunus 1989[645] | No useable outcomes |
| Zakrzewska 2003[647] | Systematic review with different PICO |

| Study | Exclusion reason |
|---|---|
| Zakrzewska 2005[646] | Cochrane review with different outcomes and incorrect interventions |
| Zhao 2009[650] | Placebo run in phase |
| Zhao 2018[648] | Systematic review with different PICO |
| Ziegler 2010[651] | No useable outcomes |
| Zitman 1990[652] | Unclear population |
| Zoppi 1990[653] | Conference abstract |

### I.1.2 Opioid safety

**Table 33: Studies excluded from the clinical review**

| Reference | Reason for exclusion |
|---|---|
| Abdel Shaheed 2016[1] | Systematic review with different PICO |
| Adams 2006[6] | Unclear duration of intervention |
| Afilalo 2013[7] | Intervention received for <6 months |
| Ahmedani 2014[10] | No relevant outcomes (poisoning/overdose per whole population) |
| Aiyer 2018[11] | <1000 people received the intervention for >6 months |
| Alford 2013[14] | Incorrect study design (review article) |
| Allegri 2019 [16] | Systematic review with different PICO |
| Altman 2010[17] | Incorrect study design (literature review) |
| Annemans 2011[21] | Incorrect study design (narrative review) |
| Anonymous 1996[25] | Incorrect study design (summary article) |
| Anonymous 2017[24] | Systematic review with different PICO |
| Apolone 2009[28] | Intervention received for <6 months |
| Arner 1988[31] | <1000 people received the intervention |
| Atli 2010[52] | <1000 people received the intervention |
| Baillargeon 2019 [55] | Unclear duration of intervention (at least 90 days over 12 months) |
| Baldini 2012[56] | Systematic review with different PICO |
| Banta-Green 2010[57] | <5000 people received the intervention and non-comparative data only |
| Bartoli 2015[58] | <1000 people received the intervention |
| Barutell 2008[59] | Intervention received for <6 months; no relevant outcomes |
| Bialas 2020 [71] | <5000 people received the intervention and non-comparative data only |
| Birke 2018 [75] | Incorrect study design (cross-sectional) |
| Birke 2019 [76] | Unclear duration of intervention (former use within previous 2 years) |
| Birthi 2015[78] | Systematic review with different PICO |
| Bohnert 2011[82] | Incorrect study design; no relevant outcomes |
| Bohnert 2016[81] | Incorrect study design; no relevant outcomes |
| Boland 2014[83] | Systematic review with different PICO |
| Brown 1996[92] | Incorrect study design (literature review) |
| Bruera 2003[93] | Citation |
| Burgess 2001[95] | Incorrect study design (review article) |

| Reference | Reason for exclusion |
|---|---|
| Buynak 2009[100] | Abstract only |
| Buynak 2009[101] | Abstract only |
| Buynak 2015[99] | <5000 people received the intervention and non-comparative data only |
| Campbell 2015[105] | <5000 people received the intervention and non-comparative data only |
| Campbell 2015[106] | <5000 people received the intervention and non-comparative data only |
| Campbell 2016[104] | <5000 people received the intervention and non-comparative data only |
| Campbell 2017 [102] | No relevant outcomes |
| Candiotti 2010[108] | Incorrect study design (narrative review) |
| Carman 2011[114] | Unclear duration of intervention (participants whose dispensing reached 180 days of cumulative exposure over 3 years were eligible for inclusion; dosage within the preceding 90 days was considered in the analysis) |
| Carmona-Bayonas 2017[115] | Incorrect study design (narrative review) |
| Carson 2011[116] | Systematic review with different PICO |
| Chamberlin 2007[120] | Incorrect study design (literature review) |
| Chan 2011[121] | Incorrect study design (narrative review) |
| Chaparro 2013[122] | Systematic review with different PICO |
| Chen 2015[124] | Incorrect study design (literature review) |
| Chenaf 2016[125] | No relevant outcomes (shopping behaviour) |
| Chenaf 2016[126] | No relevant outcomes (shopping behaviour) |
| Chou 2009[129] | Systematic review with different PICO |
| Chou 2014[132] | Systematic review with different PICO |
| Chou 2015[131] | Systematic review with different PICO |
| Chung 2019 [136] | Unclear duration of intervention |
| Cichowski 2018 [137] | Unclear duration of intervention |
| Citron 1998[138] | <1000 people received the intervention and intervention received for <6 months |
| Collett 2001[143] | Incorrect study design (literature review) |
| Colson 2011[144] | Systematic review with different PICO |
| Coluzzi 2018 [145] | Systematic review with different PICO |
| Cooper 2017[147] | Systematic review with different PICO |
| Coplan 2017[148] | Duration of intervention not reported |
| Corli 2014[150] | Incorrect study design (literature review) |
| Coutinho 2018 [153] | No relevant outcomes |
| Currow 2015[156] | Intervention received for <6 months |
| Da 2014[157] | Systematic review with different PICO |
| Dauri 2014[158] | Incorrect intervention (opioid combined with pregabalin); no relevant outcomes (side effects e.g. Nausea, constipation) |
| Degenhardt 2015[164] | <5000 people received the intervention and non-comparative data only |
| Degenhardt 2015[165] | No relevant outcomes (cannabis use) |
| Derry 2016[168] | Systematic review with different PICO |

| Reference | Reason for exclusion |
|---|---|
| Dersh 2008[171] | Incorrect population (opioid use not an inclusion criteria); incorrect comparison (opioid dependents vs. Non opioid dependents) |
| Desai 2019 [173] | No relevant outcomes |
| De Vries 2019 [160] | Systematic review with different PICO |
| Deyo 2013[174] | Incorrect population (back pain at any visit; mix of acute, subacute and chronic and unclear how many were chronic) |
| Diasso 2020 [175] | Systematic review with different PICO |
| Dublin 2015[181] | Unclear duration of intervention |
| Dublin 2019 [182] | Unclear duration of intervention (at least 70 out of 90 days); unclear population (does not specifiy chronic pain) |
| Duehmke 2017[183] | Systematic review with different PICO |
| Dunn 2010[184] | No relevant outcomes (overdose) |
| Dupoiron 2017[185] | <1000 people received the intervention |
| Edlund 2007[191] | <1000 people received the intervention; intervention received for <6 months |
| Ekholm 2014[192] | <1000 people received the intervention for >6 months |
| Elrashidi 2018 [193] | No relevant outcomes |
| Els 2017[194] | Overview of Cochrane reviews with different PICO |
| Els 2017[196] | Overview of Cochrane reviews with different PICO |
| Els 2017 [195] | Overview of Cochrane reviews with different PICO |
| Etropolski 2009[202] | Conference abstract |
| Etropolski 2009[203] | Abstract only |
| Etropolski 2009[204] | Abstract only |
| Etropolski 2014[201] | <1000 people received the intervention for >6 months; no relevant outcomes |
| Feingold 2018 [206] | <1000 people received the intervention |
| Felden 2011[207] | Incorrect interventions (ordered in error) |
| Foley 2003[211] | Editorial |
| Fonda 2020 [212] | No relevant outcomes; unclear duration of intervention ( ≥1 refill within 3 months of opioid prescription) |
| Furlan 2014[221] | Review protocol |
| Gabrielle Page 2016[223] | Incorrect population (opioid use not an inclusion criterion); no relevant outcomes (opioid abuse risk) |
| Gallagher 2009[224] | Incorrect comparison (opioid vs. Opioid); no relevant outcomes (constipation, nausea, dizziness) |
| Garg 2017[225] | Incorrect comparison (opioid dosage); no relevant outcomes (opioid overdose death) |
| Gaskell 2014[227] | Systematic review with different PICO |
| Gatti 2011[229] | <5000 people received the intervention and non-comparative data only |
| Gehling 2011[230] | Intervention received for <6 months |
| Gisev 2019 [235] | Unclear duration of intervention |
| Goesling 2015[236] | Duration of intervention not reported |
| Goldenberg 2016[238] | Incorrect study design (literature review) |
| Gomes 2011[241] | Incorrect study design (case control where cases were opioid related deaths and controls were opioid users without opioid related deaths) |

| Reference | Reason for exclusion |
|---|---|
| Gomes 2011[240] | Unclear duration of intervention |
| Gordon 2006[243] | Incorrect study design (literature review) |
| GrAÐ'Â¬nenthal 2010[250] | Citation |
| Graham 2008[245] | Unclear population and duration of intervention; no relevant outcomes (rate of opioid related deaths per whole population) |
| Green 2011[246] | Incorrect population (people being assessed for substance abuse treatment) |
| Griessinger 2005[247] | Intervention received for <6 months |
| Grond 1999[248] | Intervention received for <6 months |
| Guay 2007[253] | Incorrect study design (literature review) |
| Guay 2009[251] | Incorrect study design (literature review) |
| Guay 2010[252] | Incorrect study design (literature review) |
| Gudin 2019 [254] | <1000 people received the intervention |
| Hadley 2013[257] | Systematic review with different PICO |
| Hale 1997[261] | <1000 people received the intervention and duration <6 months |
| Haroutounian 2012[264] | Systematic review with different PICO |
| Hauser 2017[267] | No relevant outcomes (mental and/or behavioural disorders/ intoxication admissions, prescriptions for antidepressants/antipsychotics, opioid prescriptions by >3 physicians) |
| Hauser 2018 [268] | Incorrect study design (cross-sectional) |
| Hayes 2020 [272] | Unclear duration of intervention (≥90 days within 2 180 day periods) |
| Higgins 2018 [279] | Systematic review with different PICO |
| Higgins 2019 [278] | Systematic review with different PICO |
| Hitzeman 2010[280] | Incorrect study design (interpretation of a Cochrane review) |
| Hoffman 2017[281] | Incorrect comparison (<90 days vs. >90 days); <1000 people received the intervention for >6 months |
| Howe 2012[283] | <5000 people received the intervention and non-comparative data only |
| Huang 2017[285] | Systematic review with different PICO |
| Ilgen 2016[286] | Incorrect study design (case-cohort); unclear duration of intervention |
| Im 2015[287] | Intervention received for <6 months |
| James 2019 [290] | Unclear duration of intervention (chronic defined as ≥3 months) |
| Janssen Pharmaceutical 2009 [292] | Citation |
| Jassal 2019 [293] | Systematic review with different PICO |
| Jayawardhana 2019 [294] | Unclear duration of intervention (included any duration) |
| Kaplovitch 2015[302] | No relevant outcomes (opioid related death) |
| Katz 2009[304] | Incorrect study design (literature review) |
| Kay 2019 [305] | Unclear duration of intervention at least 90 days per year, not necessarily consecutive) |
| Khodneva 2016[306] | Duration of intervention not reported |
| Khodneva 2019 [307] | Duration of intervention not reported |
| Kissin 2013[313] | Incorrect study design (literature review) |
| Krebs 2011[316] | Unclear duration of intervention |

| Reference | Reason for exclusion |
|---|---|
| Krebs 2020 [317] | No relevant outcomes |
| Kuo 2019 [318] | Unclear intervention (unclear if opioids were prescribed for chronic pain) |
| Kuperwasser 2009[319] | Abstract only |
| Landsman-Blumberg 2017[323] | Incorrect comparison (types of opioid); no relevant outcomes (health care utilisation) |
| Landsman-Blumberg 2017 [322] | Unclear duration of intervention |
| Lange 2015[324] | No relevant outcomes (potential opioid misuse) |
| Lange 2018 [325] | Intervention received for <6 months |
| Lanier 2019 [326] | <1000 people received the intervention |
| Lee 2016[331] | Intervention received for <6 months; no relevant outcomes |
| Li 2013[337] | Unclear duration of intervention |
| Lintzeris 2016[339] | No relevant outcomes (sleep) |
| MacFarlane 2020 [351] | Unclear duration of intervention ('regular use' not defined) |
| Mailis-Gagnon 2012[355] | Systematic review with different PICO |
| Makris 2015[357] | Duration of intervention not reported |
| Manchikanti 2011[360] | Incorrect study design (narrative review) |
| Marschall 2016[362] | No relevant outcomes (mental and/or behavioural disorders/ intoxication admissions, prescriptions for antidepressants/antipsychotics, opioid prescriptions by >3 physicians) |
| McNicol 2013[371] | Systematic review with different PICO |
| McNicol 2017[370] | Systematic review with different PICO |
| Mejjad 2011[380] | Intervention received for <6 months; no relevant outcomes |
| Meng 2017[381] | Systematic review with different PICO |
| Merchant 2013[383] | Intervention received for <6 months |
| Miller 2015[388] | Unclear duration of intervention; no relevant outcomes (unintentional overdose) |
| Morgan 2019 [396] | No relevant outcomes |
| Mosher 2014[397] | Incorrect population (hospitalised people); no relevant outcomes (in-hospital and 30-day mortality) |
| Moulin 2010[398] | <1000 people received the intervention and intervention received for <6 months |
| Mubashir 2020 [399] | Systematic review with different PICO |
| Mystakidou 2004[405] | <5000 people received the intervention and non-comparative data only |
| Nalamachu 2012[406] | Intervention received for <6 months |
| Narayana 2015[408] | Incorrect comparison (breakthrough pain vs. No breakthrough pain vs. No pain) |
| Nicholson 2007[414] | Systematic review with different PICO |
| Niimi 2012[419] | Citation |
| Noble 2010[423] | Systematic review with different PICO |
| Novick 2019 [426] | Unclear duration of intervention (first opioid prescription) |
| Oh 2019 [434] | Unclear duration of intervention (chronic defined as at least 90 days) |
| O'Neil 2012[432] | Systematic review with different PICO |
| Ortman 2020 [439] | Systematic review with different PICO |

| Reference | Reason for exclusion |
|---|---|
| Pace 2007[442] | <1000 people received the intervention and intervention received for <6 months |
| Pampati 2016[446] | Duration of intervention not reported |
| Pascual 2007[452] | <5000 people received the intervention and non-comparative data only |
| Pask 2020 [453] | Systematic review with different PICO |
| Passik 2011[454] | No relevant outcomes (aberrant behaviour) |
| Paulus 2019 [459] | <1000 people received the intervention |
| Peacock 2016[461] | No relevant outcomes (non-adherence) |
| Pergolizzi 2017[464] | Systematic review with different PICO |
| Pergolizzi 2019 [463] | Systematic review with different PICO |
| Porucznik 2011[473] | Intervention received for <6 months |
| Przeklasa-Muszynska 2011[476] | Intervention received for <6 months |
| Radbruch 2001[480] | Intervention received for <6 months |
| Rentsch 2019 [488] | Unclear duration of intervention (new users with ≥7 consecutive days) |
| Reps 2020 [489] | Unclear duration of intervention (new users) |
| Richardson 2018 [490] | Unclear duration of intervention |
| Roxburgh 2011[501] | Unclear population and duration of intervention |
| Ruan 2007[502] | Incorrect study design (literature review) |
| Rubinstein 2017[503] | Unclear duration of intervention |
| Salas 2017[509] | <5000 people received the intervention and non-comparative data only |
| Salas 2018[508] | Unclear duration of intervention |
| Santos 2015[512] | Systematic review with different PICO |
| Saunders 2010[516] | Incorrect comparison (opioids vs. Previous opioid use) |
| Scherrer 2014[520] | <5000 people received the intervention and non-comparative data only |
| Scherrer 2016[519] | <1000 people received the intervention for >6 months |
| Scherrer 2016[518] | Unclear population and duration of intervention |
| Schmidt-Hansen 2017[522] | Systematic review with different PICO |
| Setnik 2016[530] | <1000 people received the intervention for >6 months; no relevant outcomes |
| Setnik 2017[531] | No relevant outcomes (opioid misuse) |
| Shen 2018 [532] | Unclear duration of intervention |
| Shipton 2017[533] | Duration of intervention not reported |
| Sjogren 2010[538] | Unclear duration of intervention and unclear how many people received the intervention |
| Skurtveit 2011[540] | Unclear whether >1000 received the intervention for >6 months |
| Solomon 2010[544] | Unclear duration of intervention (outcomes are reported 180 days after the start of opioid exposure, but inclusion criterion was at least 1 opioid prescription and median supply of opioids was for between 2 and 6 weeks) |
| Solomon 2010[545] | Unclear duration of intervention |
| Stannard 2016[552] | Systematic review with different PICO |
| Stollenwerk 2018 [557] | Incorrect study design (integrated descriptive analysis of post-marketing safety data); unclear duration of intervention |

| Reference | Reason for exclusion |
|---|---|
| Sullivan 2018[561] | Incorrect study design (literature review) |
| Tagarro 2005[565] | Intervention received for <6 months |
| Tang 2019 [567] | Systematic review with different PICO |
| Taylor 2013[570] | Systematic review with different PICO |
| Thakral 2018 [571] | Unclear duration of intervention (at least 70 day supply in 90 days) |
| Thakur 2015[572] | Systematic review with different PICO |
| Tkacz 2013[574] | No relevant outcomes (problematic opioid use) |
| Turner 2015[580] | No relevant outcomes (overdose) |
| Turner 2016[581] | Unclear duration of intervention in those with reported outcomes |
| Turner 2016[582] | Unclear duration of intervention in those with reported outcomes |
| Varma 2018[596] | Incorrect study design (literature review) |
| Veiga 2018 [597] | No relevant outcomes |
| Ventafridda 1986[599] | <1000 people received the intervention and intervention received for <6 months |
| Von Korff 2017[602] | <5000 people received the intervention and non-comparative data only |
| Voon 2017[603] | Review of systematic reviews with different PICO |
| Vosburg 2018[604] | Duration of intervention not reported |
| Vowles 2015[605] | Systematic review with different PICO |
| Wang 2017[610] | <1000 people received the intervention |
| Warfield 1998[615] | Incorrect study design (narrative review) |
| Weber 2009[616] | Conference abstract |
| Weber 2010[617] | Conference abstract |
| Wei 2020 [618] | Unclear duration of intervention (new users) |
| Welsch 2020 [619] | Systematic review with different PICO |
| Wen 2013[620] | No relevant outcomes (application site adverse events e.g. Skin irritation) |
| Wersocki 2017[621] | Systematic review with different PICO |
| Wiffen 2015[630] | Systematic review with different PICO |
| Wiffen 2016[631] | Systematic review with different PICO |
| Wild 2010[632] | <5000 people received the intervention and non-comparative data only |
| Wolff 2012[634] | Systematic review with different PICO |
| Won 2006[635] | <1000 people received the intervention |
| Worley 2017[636] | <1000 people received the intervention |
| Yarborough 2019 [641] | <1000 people received the intervention |
| Yee 1992[642] | Incorrect study design (literature review) |
| Yue 2020 [644] | Systematic review with different PICO |
| Zhao 2017[649] | Systematic review with different PICO |
| Zorba Paster 2010[654] | Incorrect study design (literature review) |

### I.1.3 Gabapentinoid safety

**Table 34: Studies excluded from the clinical review**

| Study | Exclusion reason |
|---|---|
| Aboumarzouk 2012 [3] | No relevant outcomes, less than minimum sample size |
| Bell 2009 [62] | No relevant outcomes |
| Agarwal 2017 [8] | No relevant outcomes |
| Berger 2003 [66] | Incorrect population (postherpetic neuralgia), less than minimum sample size |
| Berger 2009 [67] | Less than minimum sample size, no relevant outcomes |
| Burkill 2017 [97] | Abstract |
| Fleet 2018 [209] | Incorrect population (multiple morbidities including cardiovascular disease) |
| Fragoso 2000 [216] | Less than minimum sample size |
| Gatti 2011 [229] | Incorrect interventions (combination of drugs, different classes) |
| Moore 2009 [394] | Less than minimum sample size, no relevant outcomes |
| Moore 2011 [395] | Less than minimum sample size, no relevant outcomes |
| Ohta 2012 [435] | Abstract |
| Ray 2016[484] | Incorrect interventions (combination of drugs, different classes) |
| Stacey 2008 [551] | Less than minimum sample size |
| Tzellos 2009 [584] | Abstract |

## I.2 Excluded health economic studies

### I.2.1 Pharmacological management

**Table 35: Studies excluded from the health economic review**

| Reference | Reason for exclusion |
|---|---|
| Lewis et al 2016 [336] | This study was assessed as directly applicable with very serious limitations. It was considered to have methodological flaws such as: it was a within trial analysis based on a small study, with a 6 month follow up. It did not include the cost of adverse events associated with treatment or the effects on other healthcare resource use other than GP consultations. |
| Choy 2010 [134] | This study was assessed as partially applicable with very serious limitations. It was considered to have methodological flaws such as: Most studies informing treatment effects are excluded from the clinical review. |

### I.2.2 Opioid safety

None

### I.2.3 Gabapentinoid safety

None

# Appendix J: Research recommendations

## J.1 Pharmacological interventions

**Research question: What is the clinical and cost effectiveness of gabapentinoids or local anaesthetics for managing complex regional pain syndrome in people aged 16 years and over?**

**Why this is important:**

Complex Regional Pain Syndrome (CRPS) is a condition that often has a significant impact on those who have it. It results in dysfunction within multiple body-systems. For this reason, the committee recognised that CRPS does not always fit easily within the categorisation of a chronic primary pain condition. Current Royal College of Physicians CRPS guidelines (Complex Regional Pain Syndrome in Adults – UK Guidelines for Diagnosis, Management & Referral in Primary & Secondary Care) recommend that pharmacological management of this condition should involve the use of neuropathic pain medication.

In their review of the evidence for pharmacological interventions in the management of chronic primary pain, the committee found limited evidence for some treatments, often in a limited range of pain conditions. The committee's clinical experience suggested that, although there was limited evidence discovered to support their use, local anaesthetic (injections or transdermal plasters) and gabapentinoids have been noted to provide relief to people with CRPS.

While the evidence was insufficient to support a recommendation for their general use for chronic pain, the committee concluded that, with a very limited range of treatment options, it was important to establish whether the continued use of these treatments in the management of CRPS was clinically justifiable and cost-effective.

**Criteria for selecting high-priority research recommendations:**

| | |
|---|---|
| **PICO question** | Population: People, aged 16 and over, with complex regional pan syndrome<br>Intervention(s):<br>• Local anaesthetic by injection or transdermal route<br>• Gabapentinoids.<br>Comparison: Placebo<br>(Note: A stepped approach can be taken for within-class comparisons. If the evidence suggests superiority of a particular class after the class-comparison, within class comparison of that class will be explored.)<br>Outcome(s):<br>Critical:<br>• Pain reduction<br>• Health related quality of life (including meaningful activity)<br>• Physical function<br>• Psychological distress (depression/ anxiety)<br>• Discontinuation due to adverse events<br>Important:<br>• Use of healthcare services<br>• Sleep |
| **Importance to patients or the population** | CRPS is often severely painful and associated with significant distress and disability with no known cure and few treatment options. Understanding the efficacy of commonly used neuropathic pain treatments applied to CRPS has great significance. |

| | |
|---|---|
| | Early, targeted treatment of people who have pain which might become CRPS might reduce the severity of the condition, limiting the impact. The committee's experience suggests these treatments may be helpful, but little research evidence was available to substantiate this. This gap in evidence is important to fill. |
| **Relevance to NICE guidance** | No recommendations for treating CRPS pain were made in this guideline. High quality studies investigating whether to recommend these commonly used neuropathic pain treatments for CRPS would allow evidence-based recommendations to be made in future guideline updates. |
| **Relevance to the NHS** | Limiting the course of pain after injury with successful treatment for people who seem to be developing CRPS would reduce the need for further treatment and future healthcare utilisation. Conversely, understanding whether gabapentinoids, which can lead to significant harms, are effective in treating CRPS might avoid the potential for harm to people with CRPS. |
| **National priorities** | None |
| **Current evidence base** | There was no evidence specific to people with CRPS identified in the guideline review of this evidence. |
| **Equality** | No effect on protected characteristics as defined in the Equality Act. |
| **Study design** | Appropriately powered randomised controlled studies in adults with CRPS recognising the different phases observed in the condition (acute versus chronic or 'cold' CRPS).<br>Measurement of change in pain intensity, function (including area affected by CRPS), and global functioning, quality of life; distress and well-being. |
| **Feasibility** | This research would require multi-centre design to recruit sufficient numbers.<br>The trial is feasible and should be straightforward to carry out. Partnership working with patient groups would be essential to ensure recruitment of sufficient participants. Recruitment should be carried out by those experienced in using the Budapest diagnostic criteria. |
| **Other comments** | CRPS has few treatment options; it is thought intuitive that early treatment with neuropathic medication is the ideal, however a clear understanding of the efficacy of gabapentinoids and local anaesthetic treatments is currently lacking. |
| **Importance** | High: the research is essential to inform future updates of key recommendations in the guideline. |

# Appendices

# Appendix K: MIDs for continuous outcomes

**Table 36: MIDs for continuous outcomes (0.5 x SD): Anti-epileptics versus placebo**

| Outcomes | MID |
|---|---|
| Pain reduction at ≤3 months (VAS, Brief Pain Inventory average pain severity score, range, McGill pain questionnaire, high is poor outcome, final values) | 0.5 (SMD) |
| Pain reduction at ≤3 months (VAS percentage reduction, change scores) | 21.77 |
| Pain reduction at >3 months (VAS, 0-10, high is poor outcome, final values); chronic pelvic pain subgroup | 0.86 |
| Pain reduction at >3 months (Average daily pain score, 0-10, high is poor outcome, change scores); fibromyalgia subgroup | 1.2 |
| Quality of life at ≤3 months (SF-12 physical component, high is good outcome, 0-100, final values) | 5.3 |
| Quality of life ≤3 months (SF-12 mental component, high is good outcome, 0-100, final values) | 5.3 |
| Quality of life at ≤3 months (Fibromyalgia impact questionnaire, 0-100, high is poor outcome, final values) | 9.05 |
| Physical function at ≤3 months (Pain Disability Questionnaire function subscale, 0-90, high is poor outcome, final values) | 8.25 |
| Physical function at >3 months (Pain Disability Questionnaire function subscale, 0-90 high is poor outcome) | 7.4 |
| Psychological distress at ≤3 months (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, final values) | 2.1 |
| Psychological distress at >3 months (Hospital Anxiety and Depression scale anxiety subscale, 0-21, high is poor outcome, final values) | 2.18 |
| Psychological distress at ≤3 months (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, final values) | 2.25 |
| Psychological distress at >3 months (Hospital Anxiety and Depression scale depression subscale, 0-21, high is poor outcome, final values) | 1.91 |
| Psychological distress at ≤3 months (Hospital Anxiety and Depression scale, 0-21, high is poor outcome, final values) | 3.9 |
| Sleep at ≤3 months (Medical Outcomes Study Sleep Problems index score, 0-100, high is poor outcome, final values) | 10.45 |
| Sleep at >3 months (Average Daily Sleep Interference score, 0-10, high is poor outcome, change) | 1.05 |

**Table 37: MIDs for continuous outcomes (0.5 x SD): SSRIs versus placebo**

| Outcomes | MID |
|---|---|
| Pain reduction final values (VAS , medical outcomes study pain measure, high is poor outcome) ≤3 months | 0.5 (SMD) |
| Pain reduction change scores (McGill pain questionnaire, Prostatitis symptom severity scale, high is poor outcome) at >3 months | 0.5 (SMD) |
| Pain reduction (VAS final values, 0-10, high is poor outcome) at >3 months | 0.93 |
| Quality of life at ≤3 months (FIQ total scores, 0-100, high is poor outcome, change scores) | 6.8 |
| Physical function (HAQ total scores, FIQ physical function subscale, high is poor outcome, final values) at ≤3 months | 0.5 (SMD) |
| Physical function (physical impairment on Fibromyalgia impact questionnaire, 0-9.99, high is poor outcome, change scores) at ≤3 months | 1.05 |
| Psychological distress (FIQ depression subscale, HADS-D, beck depression inventory, high is poor outcome) change scores ≤3 months | 0.5 (SMD) |
| Psychological distress (FIQ anxiety subscale, AIMS anxiety, high is poor outcome) change scores at ≤3 months | 0.5 (SMD) |
| Psychological distress (Beck depression scale, HADS:A, high is poor outcome) final values at ≤3 months | 0.5 (SMD) |
| Psychological distress (HADS:A, 0-21, high is poor outcome, final values) at >3 months | 1.65 |
| Sleep (VAS sleep outcome, 0-15, high is poor outcome) final values at ≤3 months | 1.92 |

**Table 38: MIDs for continuous outcomes (0.5 x SD): SNRIs versus placebo**

| Outcomes | MID |
|---|---|
| Pain reduction (Brief Pain Inventory average pain severity, VAS, high is poor outcome) change scores at ≥3 months | 1.26 |
| Quality of life (Fibromyalgia impact questionnaire, 0-100, high is poor outcome) change scores at >3 months | 8.2 |
| Physical function (FIQ physical function subscale, Sheehan disability scale global functioning, high is poor outcome) change scores at >3 months | 0.5 (SMD) |
| Psychological distress (Beck depression inventory, Hamilton rating scale for depression, high is poor outcome) change scores at >3 months | 0.5 (SMD) |
| Sleep (Jenkins composite score, MOS-Sleep Index I, Brief pain inventory interference score for sleep, high is poor outcome, change scores) at ≥3 months | 0.5 (SMD) |

**Table 39: MIDs for continuous outcomes (0.5 x SD): Tricyclic antidepressants versus placebo**

| Outcomes | MID |
|---|---|
| Pain reduction (VAS and McGill pain questionnaire, final values, high is poor outcome) at ≤3 months | 0.5 (SMD) |
| Pain reduction (VAS 0-10, high is poor outcome) change scores at ≤3 months | 1.20 |
| Pain reduction change scores (VAS 0-100, high is poor outcome) at >3 months | 7.45 |
| Pain final values (McGill pain questionnaire, 0-78, high is poor outcome) at >3 months | 7.20 |
| Quality of life final values (FIQ, 0-100, high is poor outcome) at ≤3 months | 3.99 |
| Physical functioning (NPDI, % improvement) at ≤3 months | 4.78 |
| Physical function final values (HAQ disability index, 0-3, high is poor outcome) at ≤3 months | 0.28 |
| Physical function final values (HAQ disability index, 0-3, high is poor outcome,) at >3 months | 0.33 |
| Psychological distress (HAD-D, % improvement) at ≤3 months | 5.92 |
| Psychological distress final values (Arthritis Impact Measurement Scale depression component, high is poor outcome) at ≤3 months | 0.96 |
| Psychological distress final values (Arthritis Impact Measurement Scale depression component, 0-10, high is poor outcome) at >3 months | 0.93 |
| Sleep disturbance (Bisprectal index scale, % improvement) at ≤3 months | 6.19 |

**Table 40: MIDs for continuous outcomes (0.5 x SD): Benzodiazepines versus placebo**

| Outcomes | MID |
|---|---|
| Pain reduction final values and change scores (VAS, 0-10, high is poor outcome) at ≤3 months | 0.9 |
| Physical function (HAQ disability index, 0-3 high is poor outcome, change scores) at ≤3 months | 0.05 |
| Psychological distress (Centre for epidemiological studies depression scale, 0-30, high is poor outcome, change scores) at ≤3 months | 0.15 |
| Psychological distress (BDI, depression adjective checklist, high is poor outcome, final values) at ≤3 months | 0.5 (SMD) |

**Table 41: MIDs for continuous outcomes (0.5 x SD): NSAIDs versus placebo**

| Outcomes | MID |
|---|---|
| Pain reduction at ≤3 months (VAS, 0-10, high is poor outcome, change scores and final values) | 0.69 |
| Physical function at ≤3 months (HAQ disability index, 0-3 high is poor outcome, change scores) | 0.05 |
| Psychological distress at ≤3 months (Centre for epidemiological studies depression scale, 0-30, high is poor outcome, change scores) | 0.15 |
| Psychological distress at ≤3 months (HAM-D, depression adjective checklist, high is poor outcome, final values) | 0.5 (SMD) |

**Table 42: MIDs for continuous outcomes (0.5 x SD): Local anaesthetics versus placebo**

| Outcomes | MID |
|---|---|
| Pain reduction change scores (VAS score 0-10, high is poor outcomes) at ≤3 months | 2.93 |
| Psychological distress (Beck depression inventory 0-63, change score; high is poor outcome) at ≤3 months | 2.72 |

**Table 43: MIDs for continuous outcomes (0.5 x SD): NSAIDs versus benzodiazepines**

| Outcomes | MID |
|---|---|
| Pain reduction (VAS, 0-10, high is poor outcome, change scores and final values) at ≤3 months | 0.93 |
| Physical function change scores (HAQ disability index, 0-3, high is poor outcome) at ≤3 months | 0.05 |
| Psychological distress change scores (Centre for epidemiological studies depression scale, 0-30, high is poor outcome) at ≤3 months | 0.15 |
| Psychological distress final values (HAM-D, 0-21, high is poor outcome) at ≤3 months | 2.15 |

**Table 44: MIDs for continuous outcomes (0.5 x SD): SNRIs versus anti-epileptics**

| Outcomes | MID |
|---|---|
| Pain reduction at <3 months (Widespread Pain Index, 0-19, final value, high is poor outcome) | 2.51 |
| Quality of life at <3 months (SF-12 Physical component, 0-100, final value, high is good outcome) | 9.96 |

| Outcomes | MID |
|---|---|
| Quality of life at <3 months (SF-12 Mental component, 0-100, final value, high is good outcome) | 10.96 |
| Psychological distress at <3 months (Beck Depression Inventory-II, 0-63, final value, high is poor outcome) | 4.64 |