Bilaga 3

Läkemedelsbehandling av vanliga smärttillstånd hos äldre/
Pharmacological treatment of common pain conditions in the elderly,
rapport 315 (2020)

Appendix 3 Table of included studies

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Part I. Osteoarthritis (OA)/Artros

Systematic reviews/Systematiska översikter

Five systematic reviews [1-5] were included that presented data on efficacy and safety for pharmacological treatment of osteoarthritis (OA), see Table 1.

Table 1 Overview of included systematic reviews with specific interventions on pharmacological treatment of osteoarthritis.

	OA	Date search was made
Paracetamol	Leopoldini et al 2019	October 2017
Oral NSAIDs	Osani et al 2019	May 2018
Topical NSAIDs	Derry et al 2016	February 2016
Opioids except tramadol	da Costa et al 2014	August 2012
Tramadol	Toupin April et al 2019	February 2018

Table 2 Included systematic reviews on pharmacological treatment of osteoarthritis.

Author Year Reference	Study design Follow up	Population	Interventions Controls	Outcome - efficacy	Outcome - safety	Risk of bias SBU rating of risk of bias in the review
Paracetamol versus placebo						
Leopoldini et al 2019 [3]	Systematic review including 10 placebo controlled RCTs	3541 participants with clinical and imaging-based diagnosis of	**Intervention** Paracetamol, dose range 1.95 to 4 grams/day **Controls**	**Pain** Pain 0–100 VAS scale, mean difference: –3.23 (95% CI, –5.43 to –1.02) 7 RCTs 2355 participants GRADE: ⨁⨁⨁⨁	**Any adverse event:** Paracetamol: 328/1000 Placebo: 325/1000 Risk ratio: 1.01 (95% CI, 0.92 to 1.11)	Study eligibility criteria: *Low* Identification and selection of studies: *Low*

	Follow-up range 2–12 weeks	osteoarthritis in knee or hip	Placebo	**Function** Standardized WOMAC scale 0–100, mean difference: –2.92 (95% CI, –4.89 to –0.95) 7 RCTs 2354 participants GRADE: ⊕⊕⊕⊕ **Quality of life** No data	8 RCTs, 3252 participants GRADE: ⊕⊕⊕⊕ **Study withdrawal due to AE:** Paracetamol: 77/1000 Placebo: 65/1000 Risk ratio: 1.19 (95% CI 0.91 to 1.55) 7 RCTs, 3023 patients GRADE: ⊕⊕⊕ (–1 for imprecision) **Serious adverse events:** Paracetamol: 16/1000 Placebo: 11/1000 Risk ratio: 1.36 (95% CI, 0.73 to 2.53) 6 RCTs, 3209 participants GRADE: ⊕⊕⊕ (–1 for imprecision)	Data collection and study appraisal: *Low* Synthesis and findings: *Unclear* (no sensitivity analysis made) Overall risk of bias: *Low*
Oral NSAIDs versus placebo						
Osani et al 2019 [4]	Systematic review review and metanalysis including 72 randomized controlled trials Follow-up range 1–104 weeks,	Persons with knee osteoarthritis. Studies with combined knee and hip population were included if	**Intervention** NSAIDs which were categorized as: Traditional (non-selective) NSAIDs (including diclofenac, ibuprofen, indomethacin,	**Pain at 8 weeks** (7–10 weeks) This follow up period was closest to mean and median follow up periods in the included studies and therefore chosen to be extracted All NSAIDs:	**Treatment related adverse events, all NSAIDs:** Risk ratio: 1.21 (95% CI, 1.04 to 1.40), I^2=54% 24 RCTs, 9548 participants	Study eligibility criteria: *Low* Identification and selection of studies: *Unclear* (incomplete search strategy)

	mean 9 weeks, median 6 weeks	>70 had knee osteoarthritis Total group included 26424 persons	naproxen and piroxcam) Selective COX-2 inhibitors (celecoxib) Intermediate COX inhibitors (etodolac, meloxicam, nabumetone) **Controls** Placebo	SMD –0.36 (95% CI, –0.43 to –0.30), I^2=41% 13 studies, 6341 participants Traditional NSAID: SMD –0.37 (95% CI, –0.49 to –0.25), I^2=0 4 studies, 1218 participants Intermediate COX inhibitors: SMD –0.26 (95% CI, –0.49 to –0.04), I^2=0 1 study, 308 participants Celexocib: SMD –0.37 (95% CI, –0.46 to –0.28), I^2=56% 9 studies, 4970 participants **Function at 8 weeks** (7–10 weeks). This follow up period was closest to mean and median follow up periods in the included studies and therefore chosen to be extracted All NSAIDs: SMD –0.37 (95% CI, –0.45 to –0.29), I^2=0 7 studies, 2492 participants Traditional NSAID: SMD –0.40 (95% CI, –0.61 to –0.20), I^2=48% 3 studies, 911 participants	Median follow up 6 weeks. **Study withdrawal due to AE, all NSAIDs:** Risk ratio: 1.16 (95% CI, 1.02 to 1.32), I^2=22% 60 RCTs, 22993 participants Median follow up 6 weeks. **Serious adverse events, all NSAIDs:** Risk ratio: 0.90 (95% CI, 0.68 to 1.19), I^2=0 40 RCTs, 17278 participants Median follow up 12 weeks.	Data collection and study appraisal: *Low* Synthesis and findings: *Unclear* (no forest plots from meta-analysis presented) Overall risk of bias: *Low*

				Intermediate COX inhibitors (extracted at 4 weeks [3–6 weeks] due to missing data for 8 weeks): SMD –0.31 (95% CI, –0.56 to –0.07), I^2=NA 1 study, 263 participants Celexocib: SMD –0.35 (95% CI, –0.45 to –0.25), I^2=19% 4 studies, 1581 participants		
Topical NSAIDs versus carrier						
Derry et al 2016 [2]	Systematic review and meta-analysis including a total of 39 randomized controlled studies of which 23 were included in one or more meta-analysis Follow up range 2–12 weeks, mean 5 weeks, median 4 weeks	10631 adults with musculoskeletal pain of at least three months duration and at least moderate intensity Most included studies were populations with osteoarthritis with independent radiological verification at 3–6 months prior trial	**Intervention** Topical NSAIDs applied as solutions, gels, or plasters (patches) **Controls** Topical placebo was the carrier without the active NSAID Authors presents pooled results for diclofenac and ketoprofen only	**Pain** Clinical success, defined as at least 50% reduction in pain intensity. *Diclofenac:* Clinical success 60% (95% CI, 44 to 66) Control: Clinical success 50% (95% CI, 25 to 57) Clinical success RR: 1.20 (95% CI, 1.12 to 1.29) NNT 9.8 (95% CI, 7.1 to 16) 6 studies, 2343 participants. GRADE: ⊕⊕⊕ (–1 for imprecision) *Ketoprofen:* Clinical success 63% (95% CI, 41 to 89) Control: Clinical success 48% (95% CI, 28 to 78)	**Local adverse events** Diclofenac: 14% (range 0 to 51%) Control: 8% (range 0 to 43%) RR 1.8 (95% CI, 1.5 to 2.2) NNH 16 (95% CI, 12 to 23) 15 studies, 3658 participants GRADE: ⊕⊕⊕ (–1 for inconsistency) Ketoprofen: 15% (range 6 to 28%) Control: 13% (6 to 20%) RR 1.0 (95% CI, 0.85 to 1.3) NNH not calculated	Study eligibility criteria: *Low* Identification and selection of studies: *Low* Data collection and study appraisal: *Unclear (*incomplete search strategy) Synthesis and findings: *Unclear* (no sensitivity analysis made) Overall risk of bias: *Low*

				Clinical success RR: 1.10 (95% CI, 1.01 to 1.20) NNT 6.9 (95% CI, 5.4 to 9.3) 4 studies, 2573 participants. GRADE: ⊕⊕⊕ (–1 for inconsistency) **Function, Quality of life** No data	4 studies, 2621 participants GRADE: ⊕⊕⊕ (–1 for imprecision)	
da Costa et al 2014 [1]	Systematic review and meta-analyses including 22 RCT Follow up time 2–30 weeks, median follow-up time 10 weeks	Total of 8275 participants with clinically or radiologically confirmed osteoarthritis in the knee or hip	**Intervention** Any type of oral or transdermal opioid except tramadol. Dose ranges in primary studies: Buprenorphine 5–20 µg/hour, codeine 180–200 mg, fentanyl 25 µg/hour, hydromorphone 4–32 mg, morphine 30–160 mg, oxycodone dose range 10–100 mg, oxymorfon 20–100 mg, tapendatol 100–500 mg **Controls** Placebo/no intervention	**Pain** All opioids: SMD –0.28 (95% CI, –0.35 to –0.20) 22 RCTs, 8275 participants GRADE: ⊕⊕⊕⊕ *SMD –0.28 corresponds to a difference in pain scores of 7 mm (95% CI, 5 to 9 mm) on a VAS 0–100 mm between opioids and placebo.* Buprenorphine: SMD –0.19 (95% CI, –0.30 to –0.09) Codeine: SMD –0.51 (95% CI, –1.01 to –0.01) Fentanyl: SMD –0.22 (95% CI, –0.42 to –0.03) Hydromorphone: SMD 0.04 (95% CI, –0.19 to 0.28) Morphine: SMD –0.25 (95% CI, –0.42 to –0.09) Oxycodone: SMD –0.31 (95% CI, –0.47 to –0.15) Oxymorphone: SMD –0,39 (95 % CI –0.58 to –0.21)	**Any adverse event:** Opioids: 22% Placebo: 15% Risk ratio: 1.49 (95% CI, 1.35 to 1.63) 9 RCTs, 4898 participants GRADE: ⊕⊕⊕ (–1 for risk of bias) **Study withdrawal due to AE:** Opiods: 6.4% Placebo: 1.7% Risk ratio: 3.76 (95% CI, 2.93 to 4.82) 19 RCT:s, 7712 participants GRADE: ⊕⊕⊕⊕ **Serious adverse events:** Opioids: 1.3% Placebo: 0.4% Risk ratio: 3.35 (95% CI, 0.83 to 13.56)	SBU rating of risk of bias in the review: Study eligibility criteria: *Low* Identification and selection of studies: *Unclear (*incomplete search strategy) Data collection and study appraisal: *Low* Synthesis and findings: *Low* Overall risk of bias: *Low*

				Tapendatol: SMD – 0.31 (95% CI, –0.46 to –0.16) **Function** All opioids: SMD –0.26 (95% CI, –0.35 to –0.17) 12 RCTs, 3553participants GRADE: ⨁⨁⨁⨁ *SMD –0.26 corresponds to a difference in function scores of –0.6 units (95% CI, –0.8 to –0.4)* *between opioids and placebo on a standardised WOMAC disability scale ranging from 0 to 10.* Buprenorphine: SMD –0.23 (95% CI, –0.40 to –0.05) Codeine: SMD –0.42 (95% CI, –0.74 to –0.10) Fentanyl: SMD –0.28 (95% CI, –0.48 to –0.09) Morphine: SMD –0.20 (95% CI, –0.38 to –0.02) Oxycodone: SMD –0.30 (95% CI, –0.58 to –0.01) Tapendatol: SMD –0.15 (95% CI, –0.45 to 0.16) **Quality of life** No data	3 RCTs, 681 participants GRADE: ⨁⨁ (–1 for risk of bias, –1 for imprecision)	
Toupin April et al 2019 [5]	Systematic review and	Total of 6496 participants with clinically or	**Intervention** 3871 participants randomized to	**Pain** Assessed with VAS 0–100 mm	**Any adverse event** 2 039 participants, 4 RCTs	SBU rating of risk of bias in the review:

	meta-analyses including 22 RCT Follow up range 1–12 weeks. Mean follow-up time 8 weeks	radiologically confirmed osteoarthritis in any joint	tramadol alone or tramadol in combination with another analgesic. Seventeen studies evaluated tramadol alone and five evaluated tramadol plus acetaminophen. The dose of tramadol ranged from 37.5 mg to 400 mg and were pooled since the results were similar **Controls** 2625 participants randomized to placebo or active control. Thirteen studies used placebo controls and eleven studies used active controls. Two trials had both placebo and active arms	*Tramadol vs placebo* 3972 participants, 8 RCTs, mean difference: –4% absolute improvement (95% CI, –3% to –5%)* Corresponds to 4 mm better improvement with tramadol (95% CI, 3 to 5) GRADE: ⊕⊕⊕ (–1 risk of bias) **Function** Assessed with WOMAC physical funtion scale (0–1700) *Tramadol vs placebo* 2550 participants, 5 RCTs, mean difference: –4% absolute improvement (95% CI, –2% to –6%)* Corresponds to 4 units better improvement with tramadol (95% CI, 2 to 6) on a standardized WOMAC scale 0–100 GRADE: ⊕⊕⊕ (–1 for risk of bias) **Quality of life** No data *) Absolute effect on a common scale (e.g. 100 mm, 1700-point scale) calculated by multiplying the SMD by the	Tramadol: 659/1000 Placebo: 492/1000 Risk ratio: 1.34 (95% CI, 1.24 to 1.46) GRADE: ⊕⊕⊕ (–1 for risk of bias) **Study withdrawal due to AE** 4 533 participants, 9 RCTs Tramadol: 194/1000 Placebo: 73/1000 Risk ratio: 2.64 (95% CI, 2.17 to 3.20) GRADE: ⊕⊕⊕ (–1 for risk of bias) **Serious adverse events** 3612 participants, 7 RCTs Tramadol: 34/1000 Placebo: 19/1000 Risk ratio: 1.78 (95% CI, 1.11 to 2.84) GRADE: ⊕⊕ (–1 for risk of bias, –1 for imprecision)	Study eligibility criteria: *Low* Identification and selection of studies: *Unclear (*incomplete search strategy) Data collection and study appraisal: *Low* Synthesis and findings: *Low* Overall risk of bias: *Low*

				SD of the scale (in the control group at baseline) as suggested by the Cochrane Handbook for Systematic Reviews of Interventions		

AE = adverse events; **CI** = confidence interval; **COX** = cyklooxygenas; **GRADE** = The Grading of Recommendations Assessment, Development and Evaluation; **HIV** = human immunodeficiency virus; **I^2** = measure of heterogeneity; **n** = number; **NNH** = numbers needed to harm treat; **NNT** = numbers needed to treat; **NSAID** = Non steroidal anti-inflammatory drugs; **OA** = osteoarthritis; **p** = p-value; **RCT** = randomized controlled trial; **RR** = risk ratio; **SD** = standard deviation; **SMD** = standardized mean difference; **VAS** = visual analog scale; **vs** = versus; **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index

Primary studies

Primary studies were considered for relevance if they were published after search in each systematic review was performed. Two primary studies [6,7] were included.

Table 3 Included primary studies on pharmacological treatment of osteoarthritis.

Author Year Reference Country Risk of bias	Design Aim Time to follow-up	Participants Women/men Age	Intervention group Comparison group Participants Drop-out rate	Outcome - efficacy	Outcome - safety
Verkleij et al 2015 [7] Netherlands **Risk of bias** Moderate	**Design** Open label, active control, randomized, prospective study **Aim** To assess the effectiveness of diclofenac compared with paracetamol over a period of 12 weeks in patients with knee osteoarthritis. **Time to follow-up** 12 weeks	**Participants** *Inclusion*: ≥45 years of age New episode of knee OA. Pain ≥2 (0–10) *Exclusion:* Contraindication for NSAIDs and/or paracetamol use. Arthroplasty or osteotomy of the knee, use of NSAIDs or paracetamol. Surgery or major trauma of the affected joint. n=104 63% women Mean age: 64 years old (SD 9 years)	**Intervention** Diclofenac flexible dose maximum 50 mg t.i.d. *Participants* n=52 *Drop-out rate* n=4 (7.7%) Mean age: 64 years (SD 9 years) **Comparison** Paracetamol flexible dose maximum dose 1000 mg t.i.d. *Participants* n=52 *Drop-out rate* n=3 (5.8 %) Mean age: 64 years (SD 9 years)	**Primary endpoints** *Change in Knee pain from baseline over 4 weeks on NRS 0–10, ITT-analysis; mean difference in change vs paracetamol (95% CI):* Diclofenac: –0.2 (–1.0 to 0.7) *Change in Knee pain and function from baseline over 12 weeks in KOOS-score (0–100), ITT-analysis; mean difference in change vs paracetamol (95% CI):* Pain, diclofenac: –2.8 (–10.7 to 5.1) Function, diclofenac: –2.7 (–10.6 to 5.0) **Secondary endpoints** *Quality of life assessed with the EuroQol instrument EQ-5D (0–1 where 1 is full health), ITT-analysis; mean difference in change vs paracetamol (95% CI):* Diclofenac: 0.0 (–0.05 to 0.1) *Compliance after 2 weeks:* Diclofenac: 44/52 Paracetamol: 45/52	**Study withdrawal because of AE** No data **Serious adverse events** No data **Three most common AEs (paracetamol vs diclofenac)** Psychiatric: 15 (28.8%) vs 20 (38.5%) Respiratory, thoracic, and connective tissue: 8 (15.4%) vs 18 (34.6%) Gastrointestinal: 7 (13.5%) vs 19 (36.5%)

Author Year Reference Country Risk of bias	Design Aim Time to follow-up	Participants Women/men Age	Intervention group Comparison group Participants Drop-out rate	Outcome - efficacy	Outcome - safety
Serrie et al 2017 [6] Europe **Risk of bias** Moderate	**Design** Double-blind, placebo- and active-controlled, randomized trial **Aim** To assess the efficacy and safety of tapentadol prolonged release (PR) for moderate-to-severe Chronic osteoarthritis knee pain **Time to follow-up** 12 weeks	**Participants** *Inclusion*: Age ≥40 years Knee OA requiring analgesic medication ≥3 months Pain ≥5 on NRS 0–10 *Exclusion:* Clinically significant medical or psychiatric illnesses or required painful procedures during the study that might affect efficacy or safety assessments. History of substance abuse. Hepatitis B or C or HIV infection. Seizure disorder/epilepsy, traumatic brain injury, stroke, transient ischemic attack, brain neoplasm, malignancy, uncontrolled hypertension, severe renal impairment, moderate or severe hepatic impairment n=990	**Intervention** Tapentadol PR 100–250 mg b.i.d. *Participants* n=319 *Drop-out rate* n=133 (41.7%) Mean age: 62 years (SD 9 years) **Comparison** Oxycodone CR 20–50 mg b.i.d. *Participants* n=331 *Drop-out rate* n=210 (63.4%) Mean age: 62 years (SD 9 years) Placebo *Participants* n=337 *Drop-out rate* n=116 (34.4%) Mean age: 62 years (SD 9 years)	**Primary endpoints** *Change from baseline to week 12 in average pain intensity on NRS 0–10, ITT-analysis;* *LS mean difference vs placebo (95% CI):* Tapentadol: –0.3 (–0.61 to 0.09) Oxycodone: 0.2 (–0.16 to 0.54) **Secondary endpoints** *Change from baseline to week 12 in WOMAC score:* No significant differences in changes from baseline to week 12 in the WOMAC sub-scales or global scores between the two active treatments and placebo. *PGIC, percentage of patients who rated their overall helath status as "very much improved" or "much improved" at the end of treatment:* Tapentadol: 56%, p=0.015 vs placebo Oxycodone: 42.5%, N.S. vs placebo Placebo: 43.2% *Weighted EQ-5D health status index (0–1, 1=full health), difference in LS mean change vs placebo, mean (95% CI):* Tapentadol: 0.03 (–0.01 to 0.07) Oxycodone: –0.04 (0.08 to –0.00) *SF-36 health survey* No significant differences between tapentadol and placebo regarding both mental and physical component scores, but	**Study withdrawal because of AE** Placebo: 28/337 Tapentadol: 60/319 Oxycodone: 141/331 **Serious adverse events** Placebo: 4/337 Tapentadol: 2/319 Oxycodone: 13/331 **Three most common AEs (**Placebo vs tapentadol vs oxycodone) Dizziness: 29/337 vs 70/319 vs 89/331 Nausea: 21/337 vs 65/319 vs 124/331 Constipation: 31/337 vs 57/319 vs 116/331

Author Year Reference Country Risk of bias	Design Aim Time to follow-up	Participants Women/men Age	Intervention group Comparison group Participants Drop-out rate	Outcome - efficacy	Outcome - safety
		72% women Mean age: 62 years old (SD 9 years)		a significant difference in favor of placebo compared to active treatment in the mental component score.	

AE = adverse events; **b.i.d.** = bis in diē. (twice a day); **CI** = confidence interval; **CR** = controlled release; **HIV** = human immunodeficiency virus; **ITT** = Intention to treat; **KOOS** = Knee Injury and Osteoarthritis Outcome Score; **LS mean** = Least Squares Means; **n** = number; **NRS** = numerical rating scale; **NSAID** = Non steroidal anti-inflammatory drugs; **OA** = osteoarthritis; **p** = p-value; **PGIC** = Patient Global Impression of Change; **SD** = standard deviation; **SF-36** = The Short Form (36) Health Survey; **t.i.d**. = ter in die (three times a day); **vs** = versus; **WOMAC** = Western Ontario and McMaster Universities Osteoarthritis Index

Part II. Diabetic polyneuropathy

Systematic reviews

No relevant systematic reviews on pharmacological treatment of Diabetic polyneuropathy (DPN) with low risk of bias according to ROBIS were identified.

Primary studies

35 relevant primary studies [8-42] were included.

Table 4 Included primary studies on pharmacological treatment of Diabetic polyneuropathy.

Author Year Reference Country Risk of bias	Design Aim Treatment duration	Participants Women/men Age	Intervention group Comparison group Participants Drop-out rate	Outcome - efficacy	Outcome - safety
Anticonvulsants versus placebo					
Pregabalin versus placebo					
Freynhagen et al 2005 [15] Europe **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of pregabalin in patients with diabetic polyneuropathy (DPN) or post-herpetic neuralgia (PHN) **Treatment duration** 12 weeks	**Participants** *Inclusion*: ≥18 years of age DPN ≥6 months VAS or SF-MPQ ≥40/100 mm *Exclusion:* Clinically significant or unstable medical or psychiatric condition, malignancy within the past 2 years, anticipated need for surgery during the study, abnormal ECG, CrCl <60 mL/min, abused drugs or alcohol within the last 2 years, history of hepatitis or HIV infection, amputations other than toes n=338 45.9% women Mean age: 62 years (SD 11 years)	**Intervention** Pregabalin flexible dose 150–600 mg/day n=141 *Drop-out rate* n=49 (34.8%) Mean age: 62 years (SD 11 years) Pregabalin 600 mg/day n=132 *Drop-out rate* n=50 (37.9%) Mean age: 62 years (SD 11 years) **Comparison** Placebo n=65 *Drop-out rate* n=30 (46.2%) Mean age: 62 years (SD 13 years)	**Primary endpoints** *Change in the mean daily NRS (numerical rating scale)-score from baseline to the mean value over the last week compared with placebo, ITT-analysis;* *Baseline value (SD), change from baseline (SD), reproduced from figure:* Placebo: 6.6 (1.7), –2.0 (N/A) Pregabalin flexible dose: 6.7 (1.6), –3.4 (N/A), p<0.01 vs placebo Pregabalin 600: 6.7 (1.5); –3.6 (N/A), p<0.01 vs placebo *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 24.2% Pregabalin flexible dose: 48.2% (p<0.001 vs placebo) Pregabalin 600: 52.3% (p<0.001 vs placebo) **Secondary endpoints** *Patient Global Impression of Change (PGIC), proportion of patients reporting ”much” or ”very much” improved:* Placebo: 30.5% Pregabalin flexible dose: 52.0% (p<0.05 vs placebo)	**Study withdrawal because of AE** Placebo: 7.7% Pregabalin flexible dose: 17.0% Pregabalin 600: 25.0% **Serious adverse events** N/A **Three most common AEs (pregabalin 600 vs placebo)** Dizziness 28.8% vs 4.6% Weight gain 13.6% vs 3.1% Somnolence 12.9% vs 0.0%

				Pregabalin 600: 53.6% (p<0.05 vs placebo)	
Guan et al 2011 [22] China **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim**	**Participants** *Inclusion*: ≥18≤75 years of age Polyneuropathy ≥1 and ≤5 years HbA_{1c} <11% VAS or SF-MPQ ≥40/100 mm	**Intervention** Pregabalin flexible dose 150–600 mg/day n=206 *Drop-out rate* n=24 (11.7%)	**Primary endpoints** *Change in the mean daily NRS-score from baseline to follow-up, ITT-analysis; Baseline value (SD), follow-up value (SD); 95% CI:* Placebo: 6.4 (1.53), 4.3 (0.19); 4.0, 4.7 Pregabalin: 6.3 (1.58), 3.7 (0.14); 3.4, 4.0; p=0.005 vs placebo	**Study withdrawal because of AE** Placebo: 4 Pregabalin: 11 **Serious adverse events** Placebo: 2 (2.0%) Pregabalin: 3 (1.5%)

	Evaluate the efficacy and safety of pregabalin in patients with diabetic polyneuropathy (DPN) or post-herpetic neuralgia (PHN) **Treatment duration** 8 weeks	*Exclusion:* Clinically significant or unstable medical or psychiatric condition, abnormal ECG, CrCl <60 mL/min n=309 Approximately 53% women Mean age: 60 years (SD 9 years) 70% had DPN	Mean age: 60 years (SD 9 years) **Comparison** Placebo n=102 *Drop-out rate* n=17 (16.7%) Mean age: 60 years (SD 10 years)	*Endpoint LS (Least square) mean difference pregabalin – placebo (95% CI):* –0.6 (–1.1 to –0.2), p=0.05 **Secondary endpoints** *Patients who achieved ≥30% reduction in pain scores from baseline to endpoint:* Placebo: 52.0% Pregabalin: 64.0% (p=0.041 vs placebo) *Clinical Global Impression of Change (CGIC) score (0–7):* Any improvement (from ”minimally” to ”very much”): Placebo: 69.2% Pregabalin: 85.2% (p<0.05 vs placebo) Difference in LS means: –0.39, 95% CI, –0.63 to –0.16; p=0,001 *Patient Global Impression of Change (PGIC) score (0–7):* Difference in LS means: –0.33, 95% CI, –0.55 to –0.11; p=0,004	**Three most common AEs (pregabalin vs placebo)** Dizziness 11.2% vs 6.9% Lethargy 7.8% vs 2.9% Somnolence 4.9% vs 1.0%
Huffman et al 2015 [25] USA, Czech Republic, South Africa, Sweden **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, cross over study **Aim** Evaluate the efficacy and safety of pregabalin in patients with	**Participants** *Inclusion*: ≥18 years of age DPN ≥3 months. NRS pain ≥4 (out of 10) Able to walk >15 m unassisted. Pain on walking > prewalk resting pain HbA_{1c} <11% *Exclusion:*	**Intervention** Pregabalin 150 mg–300 mg/day (83% on 300 mg/day) n=198 *Drop-out rate* n=22 (11.1%) Mean age: not shown **Comparison** Placebo	**Primary endpoints** *Change in the mean daily NRS-score from baseline to the end of each treatment period, compared with placebo, ITT-analysis;* *Baseline value (SD):* Placebo → pregabalin: 6.52 (1.32) Pregabalin → placebo: 6.32 (1.36) *Endpoint, LS mean (SE):* Placebo: 4.96 (0.14), 95% CI, 4.67 to 5.24 Pregabalin: 4.73 (0.14), 95% CI, 4.46 to 5.01)	**Study withdrawal because of AE** Placebo: 2.7% Pregabalin: 6.6% **Serious adverse events** Placebo: 1.1% Pregabalin: 4.5% **Three most common treatment related AEs (pregabalin vs placebo)** Somnolence: 6.1% vs 2.2% Dizziness: 5.1% vs 2.7% Fatigue: 5.1% vs 1.1%

	diabetic polyneuropathy (DPN) who experienced pain while walking **Treatment duration** 6 weeks, 2 weeks wash-out, 6 weeks	Fluctuation >4 points on daily pain diary; failed pregabalin treatment; were intolerant to pregabalin; aid while walking; other condition that could cause pain on walking; unstable diabetes; CrCL <60 mL/min; amputation of lower extremities n=205 30–40% women Mean age: 59 years (SD 9 years)	n=186 *Drop-out rate* n=10 (5.4%) Mean age: not shown	*Endpoint LS mean difference (SE) pregabalin - placebo:* –0.22 (0.12), 95% CI, –0.46 to 0.01, p=0.0659 **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to the end of each treatment period:* Placebo period 1: 13.7%, period 2: 32.1% Pregablin period 1: 23.8%, period 2: 27.8%. OR pregabalin vs placebo 1.38 (95% CI, 0.8 to 2.38). *Patient Global Assessment (PGIC), proportion of patients reporting "much" or "very much" improved:* Placebo: 31.4% Pregabalin: 51.0% (p=0.002 vs placebo) *Nine other secondary end-points was also assessed. No significant differences was detected for those end-points.*	
Lesser et al 2004 [26] USA **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized study **Aim** Evaluate the efficacy and safety of pregabalin in patients with diabetic	**Participants** *Inclusion*: ≥18 years of age DPN ≥1 year ≤5 years Pain NRS ≥4 (0–10) VAS or SF-MPQ ≥40/100 mm HbA_{1c} <11% *Exclusion:* Clinically significant or unstable hepatic, respiratory, or hematologic illnesses.	**Intervention** Pregabalin 75 mg n=77 *Drop-out rate* n=10 (13%) Mean age: 61 years (SD 11 years) Pregabalin 300 mg n=81 *Drop-out rate* n=5 (6.2%)	**Primary endpoints** *Change in the mean daily NRS-score from baseline to the mean value over the last week compared with placebo;* *Baseline mean (SD), endpoint LS mean (SE):* Placebo: 6.6 (1.5), 5.06 (0.21) Pregabalin 75: 6.7 (1.3), 4.91 (0.24) Pregabalin 300: 6.2 (1.4), 3.80 (0.23) Pregabalin 600: 6.2 (1.5), 3.60 (0.23) *Difference vs placebo, ITT-analysis (95% CI):* Pregabalin 75: –0.15 (–0.76 to 0.46), p=0.63	**Study withdrawal because of AE** Not shown **Serious adverse events** Placebo: 3.1% Pregabalin 75: 1.3% Pregabalin 300: 0.0% Pregabalin 600: 4.9% **Three most common AEs (pregabalin 600 vs placebo)** Dizziness 39.0% vs 5.2% Somnolence 26.8% vs 4.1% Peripheral edema 13.4% vs 2.1%

	polyneuropathy (DPN) **Treatment duration** 5 weeks	Unstable cardiovascular disease. Symptomatic peripheral vascular disease. CrCL <60 mL/min Any condition that might confound pain assessment. Failure to respond to previous treatment with gabapentin at doses ≥1.200 mg/day n=338 40.1% women Mean age: 60 years (SD 10.5 years)	Mean age: 59 years (SD 9 years) Pregabalin 600 mg n=82 *Drop-out rate* n=12 (14.6%) Mean age: 62 years (SD 10 years) **Comparison** Placebo n=97 *Drop-out rate* n=8 (8.2%) Mean age: 58 years (SD 12 years)	Pregabalin 300: –1.26 (–1.86 to –0.65), p=0.0001 Pregabalin 600: –1.45 (–2.06 to –0.85), p=0.0001 *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 18% Pregabalin 75: not shown Pregabalin 300: 46% (p<0.05 vs placebo) Pregabalin 600: 48% (p<0.05 vs placebo) **Secondary endpoints** *Patient Global Impression of Change (PGIC), proportion of patients reporting "much" or "very much" improved:* Placebo: 24.2% Pregabalin 75: not shown Pregabalin 300: 55.7% (p=0.001 vs placebo) Pregabalin 600: 69.2% (p=0.001 vs placebo) *Health related quality of life, measured by SF-36* Statistically significant improvements in pregabalin 300 mg and 600 mg vs placebo, data not shown.	
Mu et al 2018 [27] China **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim**	**Participants** *Inclusion*: ≥18 years of age DPN ≥6 months ≤5 years Pain on VAS ≥40/100 *Exclusion:*	**Intervention** Pregabalin (300 mg/day n=314 *Drop-out rate* n=29 (9.2%) Mean age: 60 years (SD 10 years)	**Primary endpoints** *Change in the mean daily pain NRS-score from baseline to the mean value over the last week compared with placebo;* *Baseline mean (SD), endpoint mean (SD):* Placebo: 6.67 (1.15), 4.74 (2.05) Pregabalin: 6.65 (1.12), 4.45 (2.00)	**Study withdrawal because of AE** Placebo: 2.9% Pregabalin: 3.5% **Serious adverse events** Placebo: 1.6% Pregabalin: 2.2%

	Evaluate the efficacy and safety of pregabalin in patients with diabetic polyneuropathy (DPN) **Treatment duration** 11 weeks	Neurologic disorder, pain, or skin conditions likely to interfere with the evaluation of pain. High variability in daily pain scores Concomitant use of treatments for diabetic neuropathy. n=623 53% women Mean age: 61 years (SD 10 years)	**Comparison** Placebo n=309 *Drop-out rate* n=36 (11,7%) Mean age: 61 years (SD 10 years)	*LS mean difference vs placebo, ITT-analysis (95% CI):* Pregabalin: –0.28 (–0.58 to 0.01), p=0.0559 **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 24.1% Pregabalin: 31.1% (p=0.0384 vs placebo) *Patient Global Impression of Change (PGIC)and Clinical Global Impression of Change on a 7-point NRS, LS mean treatment difference pregabalin vs placebo (95% CI)* PGIC –0.14 (–0.28 to 0.01), p=0.0602 CGIC –0.15 (–0.29 to 0.00), p=0.0431	**Three most common AEs (pregabalin vs placebo)** Dizziness 9.6% vs 3.9% Somnolence 5.7% vs 1.9% Peripheral edema 3.2% vs 0.3%
Rosenstock et al 2004 USA [30] **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of pregabalin in patients with diabetic polyneuropathy (DPN) **Treatment duration** 8 weeks	**Participants** *Inclusion*: ≥18 years of age DPN ≥1 year ≤5 years VAS or SF-MPQ ≥40 mm HbA_{1c} <11% *Exclusion:* CrCl ≤60 ml/min Serious or unstable medical conditions. Conditions confounding evaluation of DPN. Patients who had failed to respond to treatment with gabapentin at doses ≥ 1200 mg/day for treatment of DPN	**Intervention** Pregabalin (300 mg/day n=76 *Drop-out rate* n=11 (14.5%) Mean age: 59 years (SD 12 years) **Comparison** Placebo n=70 *Drop-out rate* n=8 (11.4%) Mean age: 60 years (SD 10 years)	**Primary endpoints** *Change in the mean daily pain NRS-score from baseline to the mean value of last week of follow-up; Baseline mean (SD), endpoint LS mean (SE):* Placebo: 6.1 (N/A), 5.46 (0.28) Pregabalin: 6.5 (N/A), 3.99 (0.26) *Difference vs placebo, ITT-analysis (95% CI):* Pregabalin: –1.47 (–2.19 to –0.75), p=0.0001 *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 14.5% Pregabalin: 40.0% (p=0.001 vs placebo) **Secondary endpoints**	**Study withdrawal because of AE** Placebo: 3% Pregabalin: 11% **Serious adverse events** Not shown **Three most common AEs (pregabalin vs placebo)** Dizziness: 35.5% vs 11.4% Somnolence: 19.7% vs 2.9% Infection: 14.5% vs 5.7%

		n=146 43.8% women Mean age: 60 years (SD 10.5 years)		Any improvement (from ”minimally” to ”very much”) *on:* *Patient Global Impression of Change, PGIC:* Placebo: 39% Pregabalin: 67% (p=0.001 vs placebo) *CGIC:* Placebo: 39% Pregabalin: 59% (p=0.004 vs placebo) *Health related quality of life, measured by SF-36* Significant difference in the Bodily pain domain only, favouring pregabalin (p<0.03).	
Satoh et al 2011 [32] Japan **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of pregabalin in Japanese patients with diabetic polyneuropathy (DPN) **Treatment duration** 14 weeks	**Participants** *Inclusion*: ≥18 years of age DPN pain on VAS ≥40/100 *Exclusion:* CrCl ≤30 ml/min. Malignant tumour within the past 2 years. Pain or skin conditions that may affect the evaluation of pain. n=317 25% women Mean age: 61 years (SD 10 years)	**Intervention** Pregabalin (pre) 300 mg/day: n=134 *Drop-out rate* n=20 (14.7%) Mean age: 61 years (SD 10 years) Pregabalin (pre) 600 mg/day: n=45 *Drop-out rate* n=13 (28.9%) Mean age: 62 years (SD 10 years) **Comparison** Placebo: n=135	**Primary endpoints** *Change in the mean daily pain NRS-score from baseline to the mean value of last week of follow-up; Baseline mean (SD), endpoint LS mean change (SE) reproduced from figure:* Placebo: 6.1 (1.4), –1.2 (N/A) Pregabalin 300: 6.0 (1.4), –1.8 (N/A) Pregabalin 600: 6.1 (1.3), –1.9 (N/A) *Difference vs placebo, ITT-analysis (95% CI):* Pregabalin 300: –0.63 (–1.09 to –0.17), p=0.0075 Pregabalin 600: –0.74 (–1.39 to –0.09), p=0.0254 **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 21.5% Pregabalin 300: 29.1% (n.s. vs placebo) Pregabalin 600: 35.6% (n.s. vs placebo)	**Study withdrawal because of AE** Placebo: 5.2% Pregabalin 300: 12.7% Pregabalin 600: 28.9% **Serious adverse events** Placebo: 2.2 Pregabalin 300: 3.0% Pregabalin 600: 4.4% **Three most common AEs (pregabalin 600 vs placebo)** Somnolence 40.0% vs 8.1% Dizziness 37.8% vs 6.7% Peripheral edema 13.3% vs 4.4%

			Drop-out rate n=16 (11.8%) Mean age: 61 years (SD 10 years)	*Patient Global Impression of Change scores:* Placebo: no data shown Pregabalin 300: no data shown (n.s. vs placebo) Pregabalin 600: no data shown (p=0.0075 vs placebo, favouring pregabalin 600) *Clinical Global Impression of Change scores:* Placebo: no data shown Pregabalin 300: no data shown (p=0.0148 vs placebo, favouring pregabalin 300) Pregabalin 600: no data shown (p=0.0063 vs placebo, favouring pregabalin 600) *Health related quality of life, measured by SF-36:* Placebo: no data shown Pregabalin 300: no data shown (n.s. vs placebo) Pregabalin 600: no data shown, pregabalin 600 superior to placebo on social functioning and vitality (p<0.05)	
Tölle et al 2008 [39] Europe, Australia, South Africa **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of pregabalin in	**Participants** *Inclusion*: ≥18 years of age DPN ≥1 year VAS or SF-MPQ ≥40 mm HbA_{1c} <11%. *Exclusion:* CrCl ≤30 ml/min Clinically significant or unstable hepatic,	**Intervention** Pregabalin 150 mg: n=99 *Drop-out rate* n=17 (17.2%) Mean age: 59 years (SD 12 years) Pregabalin 300 mg: n=99	**Primary endpoints** *Change in the mean daily NRS-score from baseline to the mean value over the last week compared with placebo:* Placebo: Baseline 6.4; change –1.9 (SD N/A) Pregabalin 150: Baseline 6.2; change –2.1 (SD N/A) Pregabalin 300: Baseline 6.4; change –2.1 (SD N/A) Pregabalin 600: Baseline 6.6; change –3.0 (SD N/A)	**Study withdrawal because of AE** Placebo: 3.1% Pregabalin 150: 5.1% Pregabalin 300: 11.1% Pregabalin 600: 12.9% **Serious adverse events** Placebo: 2.1% Pregabalin 150: 4.0% Pregabalin 300: 3.0% Pregabalin 600: 5.9%

	patients with diabetic polyneuropathy (DPN) **Treatment duration** 12 weeks	respiratory, or hematologic illnesses. Unstable cardiovascular disease or symptomatic peripheral vascular disease. Severe pain or a skin condition in the area affected by neuropathy. Patients who had failed to respond to treatment with gabapentin at doses ≥1200 mg/day for treatment of DPN n=396 44,6% women Mean age: 59 years (SD 12 years)	*Drop-out rate* n= 20 (20.2%) Mean age: 57 years (SD 11 years) Pregabalin 600 mg: n=101 *Drop-out rate* n=23 (22.8%) Mean age: 60 years (SD 11 years) **Comparison** Placebo n=96 *Drop-out rate* n=17 (17.7%) Mean age: 59 years (SD 12 years)	*Difference vs placebo, ITT-analysis (95% CI):* Pregabalin 150: –0.27 (–0.87 to 0.34) Pregabalin 300: –0.10 (–0.70 to 0.50) Pregabalin 600: –0.91 (–1.51 to –0.31) *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 30.1% Pregabalin 150: 34.4% (n.s. vs placebo) Pregabalin 300: 33.3% (n.s. vs placebo) Pregabalin 600: 45.9% (p=0.036 vs placebo) **Secondary endpoints** *Patient Global Impression of Change (PGIC), proportion of patients reporting "much" or "very much" improved:* Placebo: 33.3% Pregabalin 150: 45.8% (n.s. vs placebo) Pregabalin 300: 42.5% (n.s. vs placebo) Pregabalin 600: 50.5% (p=0.021 vs placebo) *EuroQoL Health Utilities Index (EQ-5D), difference vs placebo, MITT-analysis (95% CI):* Pregabalin 150: 0.10 (0.03 to 0.16) Pregabalin 300: 0.08 (0.01 to 0.14) Pregabalin 600: 0.14 (0.07 to 0.20)	**Three most common AEs (pregabalin 600 vs placebo)** Dizziness 13.9% vs 2.1% Peripheral edema 9.9% vs 2.1% Somnolence 7.9% vs 1.0%
Oxcarbazepine versus placebo					

Beydoun et al 2006 [9] USA **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of oxcarbazepine (oxc) in patients with diabetic polyneuropathy (DPN) **Treatment duration** 16 weeks	**Participants** *Inclusion*: >18 years with DPN >6 months <5 years >50 units on a 100-unit visual analog scale (VAS) HbA_{1c} <11% Pain for >3 months *Exclusion:* Patients with other types of pain, clinically significant medical or psychiatric illnesses. n=347 44% women Mean age: 61 years ±10 years	**Intervention group** Oxc 600 mg: n=83 *Drop-out rate* n=16 (19.3%) Mean age: 61±11 Oxc 1200 mg: n=87 *Drop-out rate* n=34 (39.1%) Mean age: 60±10 Oxc 1800 mg: n=88 *Drop-out rate* n=48 (54. %) Mean age: 59±9 **Comparison group** Placebo n=89 *Drop-out rate* n=17 (19.1%) Mean age: 62±10	**Primary endpoint** *Average daily pain, VAS score, 0–100 units (SD); ITT-analysis:* Placebo: Baseline 70.8 (13.2) change – 19.1 (no SD) oxc 600 mg: Baseline 76.9 (14.2) change -25.9 (no SD) n.s. vs placebo oxc 1200 mg: Baseline 75.7 (13.8) change -29.0 (no SD) n.s. vs placebo oxc 1800 mg: Baseline 71.3 (15.6) change -26.5 (no SD) n.s. vs placebo **Secondary endpoints** *Patients Global Assessment of Therapeutic Effect (GATE)* Percentage of patients feeling ”much” or ”very much” improved compared with baseline: Placebo: 36.4% oxc 600 mg: 37.3% n.s. vs placebo oxc 1200 mg: 50.0% n.s. vs placebo oxc 1800 mg: 49.3% n.s. vs placebo *Quality of life (SF-36 Health Survey and the Profile of Mood States (POMS)* No significant differences between the oxcarbazepine groups and placebo	**Study withdrawal because of AE** oxc 1 800 mg 41.4% oxc 1 200 mg 23.5% oxc 600 mg 11% placebo 7% **Serious adverse events** oxc 1 800 mg 11.5% oxc 1 200 mg 10.6% oxc 600 mg 2.4% placebo 1.1% **Three most common AEs (oxc 1800 mg vs placebo)** Dizziness 34.5% vs 2.2% Nausea 19.5% vs 5.6% Fatigue 14.9% vs 6.7%
Dogra et al 2005 [12] USA and Canada **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim**	**Participants** *Inclusion*: >18 years with DPN >6 months <5 years VAS >50/100 units HbA_{1c} <11% *Exclusion:*	**Intervention** Oxcarbazepine (oxc) 600 mg/day, titrated up to maximum dose of 1800 mg/day (mean	**Primary endpoints** *Average daily VAS score (0–100 units) for pain severity (SD); ITT-analysis:* Placebo: Baseline 74.3 (13.7) change – 14.7 (26.4) Oxc: Baseline 71.5 (15.8) change –24.3 (27.2) p=0.0108	**Study withdrawal because of AE** Placebo 7.8% oxc 27.5% **Serious adverse events** placebo 4% oxc 10%

	Evaluate the efficacy and safety of oxcarbazepine in patients with diabetic polyneuropathy (DPN) **Treatment duration** 18 weeks	Patients with other types of pain, CrCl <30 mL/min n=146 42% women Mean age: 60 years (SD 9 years)	maintenance dose 1445 mg/day) n=69 *Drop-out rate* n=25 (36.2%) Mean age: 60 years (SD 10 years) **Comparison** Placebo n=77 *Drop-out rate* n=15 (19.5%) Mean age: 61 years (SD 8 years)	*Proportion of patients with >50% reduction from baseline in VAS score:* Placebo: 18.4% Oxc: 35.2% p=0.0156 **Secondary endpoints** *Patients Global Assessment of Therapeutic Effect (GATE)* Percentage of patients feeling ”much” or ”very much” improved compared with baseline: Placebo: 22% Oxc: 48% p=0.025 *Quality of life (SF-36 Health Survey and the Profile of Mood States (POMS)* No significant differences between the oxcarbazepine groups and placebo	**Three most common AEs (oxc vs placebo)** Dizziness 12.7% vs 1.4% Headache 9.0% vs 1.4% Somnolence 9.0% vs 0.0%
Grosskopf et al 2006 [21] USA, Germany and UK **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of oxcarbazepine in patients with diabetic	**Participants** *Inclusion*: >18 years with DPN >6 months <5 years >50 units on a 100-unit visual analog scale (VAS). VAS >40 units over 4 of the last 7 days prior to randomization. HbA_{1c} <11% *Exclusion:* Patients with other types of pain, skin	**Intervention** Oxcarbazepine (oxc) 300 mg/day, titrated to tolerability or a maximum dose of 1200 mg/day (mean maintenance dose 1091 mg/day) n=71 *Drop-out rate* n=29 (40.8%)	**Primary endpoints** *Average daily VAS score (0–100 units) for pain severity (SD); ITT-analysis:* Placebo: Baseline 70.7 (13.6) change –22.0 (SD N/A) Oxc: Baseline 72.0 (14.2) change –20.1 (SD N/A) (n.s. vs placebo) The percentage reductions in average VAS scores were 27.9% and 31.1% for the oxcarbazepine and placebo groups respectively. **Secondary endpoints** *Patients Global Assessment of Therapeutic*	**Study withdrawal because of AE** Placebo 5.9% oxc 25.4% **Serious adverse events** placebo 3% oxc 7% **Three most common AEs (oxc vs placebo)** Dizziness 8% vs 2% Nausea 6% vs 0% Headache 4% vs 1%

	polyneuropathy (DPN) **Treatment duration** 16 weeks	conditions that could affect assessment of pain, amputations (other than toes), renal insufficiency. n=141 45% women Mean age: 61 years (SD 10.5 years)	Mean age: 61 years (SD 11 years) **Comparison** Placebo n=70 *Drop-out rate* n=17 (24.3%) Mean age: 61 years (SD 11 years)	*Effect (GATE)* No significant differences between the oxcarbazepine groups and placebo *Quality of life (SF-36 Health Survey and the Profile of Mood States (POMS)* No significant differences between the oxcarbazepine groups and placebo	
Other anticonvulsants versus placebo					
Shaibani et al 2009 [34] USA **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of oral lacosamide in patients with diabetic polyneuropathy (DPN) **Treatment duration** 18 weeks	**Participants** *Inclusion*: >18 years with DPN >6 months <5 years Pain >4 on an 11-point numerical rating scale HbA_{1c} <12% *Exclusion:* Patients with other types of pain, use of certain drugs, major skin ulcers, amputations (other than toes), history of certain cardiovascular disease, CrCl <50 mL/min. n=468 43.5% women Mean age: 60 years (SD 10 years)	**Intervention** Lacosamide (Lac) 200, 400 or 600 mg/day n=403 *Drop-out rate* n=191 (47,4%) Mean age: 59–60 years (SD 10–11 years) **Comparison** Placebo n=65 *Drop-out rate* n=20 (30.7%) Mean age: 60 years (SD 8 years)	**Primary endpoints** *Change in daily NRS-score from baseline to the mean value over weeks 15–18, ITT-analysis; mean difference vs placebo ± SD (95% CI):* Lac 200: –0.33±0.31 (–0.94 to 0.27), p=0.28 Lac 400: –0.61±0.31 (–1.23 to 0.00), p=0.05 Lac 600: –0.56±0.31 (–1.17 to 0.05), p=0.07 **Secondary endpoints** *50% reduction in NRS-score:* Placebo: 27% Lac 200: 27% Lac 400: 44% Lac 600: 30% *Patient's Global Impression of Change (PGIC),* Percentage of patients feeling "better": Placebo: 71% Lac 200: 65% Lac 400: 82% p=0.05 vs placebo Lac 600: 79%	**Study withdrawal because of AE** Placebo: 13.8% Lac 200: 12.1% Lac 400: 24% Lac 600: 42.3% **Serious adverse events** Placebo: 6.2% Lac 200: 5% Lac 400: 4.8% Lac 600: 6.6% **Three most common AEs (Lac 600 mg vs placebo)** Dizziness: 28.5% vs 4.6% Nausea: 18.2% vs 6.2% Tremor: 14.6% vs 0.0%

Thienel et al 2004 [38] USA **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study. Three similar studies reported altogether. **Aim** Evaluate the efficacy and tolerability of topiramate in patients with diabetic polyneuropathy (DPN) **Treatment duration** 18–22 weeks	**Participants** *Inclusion*: 18–75 years with DPN ≥6 months. Antidiabetic regimens stable ≥3 months before study entry. HbA_{1c} ≤11% *Exclusion:* Other polyneuropathies; ulceration of extremities; amputation; significant history of unstable medical disease; history of alcohol or drug abuse; previous treatment with topiramate; patients requiring chronic use of analgesics to control pain. n=1259 43% women Mean age: 58 years (SD 10 years)	**Intervention** Topiramate (Top) 100 mg/day, 200 mg/day or 400 mg/day n=878 *Drop-out rate* n=464 (53%) Mean age: 58 years (SD 9–10 years) **Comparison** Placebo n=381 *Drop-out rate* n=156 (41%) Mean age: 59 years (SD 10 years)	**Primary endpoints** *Pain reduction based on change in 100 mm VAS scores from baseline to final visit, mean values (95% CI), ITT-analysis:* **NP 001** Top 100: Change vs placebo –9.4 (–12.1 to –0.18) Top 200: Change vs placebo –2.9 (–10.4 to 1.45) Top 400: Change vs placebo –2.0 (–7.46 to 4.40) **NP 002** Placebo: Top 200: Change vs placebo –4.3 (–10.7 to 2.76) Top 400: Change vs placebo –2.6 (–8.88 to 4.20) **NP 003** Placebo: Top 100: Change vs placebo + 1.8 (–1.88 to 11.63) Top 200: Change vs placebo + 2.9 (–1.03 to 12.46) **Secondary endpoints** *Change from baseline in Categorical Pain Score and Sleep Disruption Scale:* No significant differences between topiramate and placebo except in one comparison in one study, favoring placebo *Change from baseline in SF-36 quality-of-life:* Data not shown	**Study withdrawal because of AE** Placebo: 8% Top 100: 16% Top 200: 25% Top 400: 31% **Serious adverse events** Placebo: 8% Top (all doses): 7% **Three most common AEs (Top 400 mg vs placebo)** Fatigue 7.7% vs 2.9% Nausea 5.0% vs 1.8% Paresthesia 4.6% vs 1.3%
Antidepressants versus placebo					
Duloxetine versus placebo					

Gao et al 2010 [17] China **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Evaluate the efficacy and safety of duloxetine in Chinese patients with diabetic peripheral neuropathic pain (DPNP) **Treatment duration** 12 weeks	Participants Inclusion: ≥18 years of age DPNP ≥6 months Pain on BPI ≥4/10 Exclusion: HbA1c >12% Any condition that could compromise participation. Mania, bipolar disorder. psychosis, at risk for suicide, depression. History of hepatic dysfunction or othcr serious medical conditions n=215 53% women Mean age: 59 years (SD 10 years)	**Intervention** Duloxetine flexible dose (60 mg–120 mg per day) n=106 *Drop-out rate* n=19 (17.9%) Mean age: 59 years (SD 10 years) **Comparison** Placebo: n=109 *Drop-out rate* n=17 (15.6%) Mean age: 60 years (SD 10 years)	**Primary endpoints** *Change in BPI 24 h average pain (0–10) from baseline to endpoint; Baseline mean (SD), LS mean change (SE):* Placebo: 5.5 (1.4), –2.31 (0.18) Duloxetine: 5.5 (1.3), –2.69 (0.19) *Mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine: –0.38 (not shown), p=0.124 (n.s.) **Secondary endpoints** *Patients who achieved ≥50% reduction in BPI average pain from baseline to endpoint:* Placebo: 50.5% Duloxetine: 54.8% (p=0.584 vs placebo) *PGI-I, Patient Global Impression of Improvement (7-items, 7=very much worse"); LS mean change (SE):* Placebo: 2.64 (0.10) Duloxetine: 2.32 (0.11) *Mean difference duloxetine vs placebo, ITT-analysis:* –0.32, p=0.028 *EQ-5D (US), mean change (SE):* Placebo: 0.10 (0.02) Duloxetine: 0.12 (0.02) *Mean difference duloxetine vs placebo, ITT-analysis:* 0.02, p=0.207 (n.s.)	**Study withdrawal because of AE** Placebo: 3.7% Duloxetine: 16.7% **Serious adverse events** Not shown **Three most common AEs (duloxetine vs placebo)** Nausea 30.2% vs 11.9% Somnolence 16.0% vs 5.5% Dizziness 15.1% vs 11.0%
Gao et al 2015 [16] China **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study	**Participants** *Inclusion*: ≥18 years of age DPN pain on BPI-severity ≥4/10	**Intervention** Duloxetine 60 mg n=203 *Drop-out rate* n=30 (14.8%)	**Primary endpoints** *Change in mean weekly pain on Likert scale (0–10) from baseline to follow-up; Baseline mean (SD), LS mean change (SE):* Placebo: 5.7 (1.7), –1.97 (0.14) Duloxetine: 5.6 (1.7), –2.40 (0.14)	**Study withdrawal because of AE** Placebo: 4.0% Duloxetine: 8.4% **Serious adverse events** Placebo: 1.0%

	Aim Evaluate the efficacy and safety of duloxetine in Chinese patients with diabetic polyneuropathy (DPN) **Treatment duration** 12 weeks	*Exclusion:* HbA_{1c} >12% Major depressive disorder, mania, bipolar disorder, dysthymia, anxiety disorders, alcohol or eating disorders, psychosis, risk for suicide. Serious or unstable cardiovascular, hepatic, renal, respiratory, or haematological illness, symptomatic peripheral vascular disease, or the presence of other serious medical conditions. n=405 55% women Mean age: 61 years (SD 10 years)	Mean age: 62 years (SD 10 years) **Comparison** Placebo: n=202 *Drop-out rate* n=26 (12.9%) Mean age: 61 years (SD 9 years)	*LS mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine: –0.43 (–0.82 to –0.04), p=0.030 **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 28.8% Duloxetine: 42.0% (p=0.006 vs placebo) *Patients experiencing "much better" improvement on PGI, Patient Global Impression of Improvement:* Placebo: 33.9% Duloxetine: 47.2% Difference vs placebo –0,21 (–0.4, –0.02) (p=0.034) *BPI-interference, average of 7 items ranging 0–10 (worst interference); Baseline mean (SD), LS mean change (SE):* Placebo: 4.1 (2.3), –1.82 (0.14) Duloxetine: 4.4 (2.3), –2.42 (0.13) *LS mean difference duloxetine vs placebo, ITT-analysis (95% CI)*: –0.60 (–0.96 to –0.24), p=0.001 *Sheehan Disability Scale (SDS) measuring function, 5 items ranging 0–10 (extremely impaired; Baseline mean total score (SD), LS mean change (SE):* Placebo: 11.2 (7.6), –5.09 (0.42) Duloxetine: 10.5 (7.3), –6.36 (0.40) *LS mean difference duloxetine vs placebo, ITT-analysis (95% CI):* –1.26 (–2.33 to –0.2), p=0.02	Duloxetine: 1.5% **Three most common AEs (duloxetine vs placebo)** Nausea 10.4% vs 3.5% Somnolence 8.4% vs 0.5% Dizziness 8.4% vs 4.5%

Goldstein et al 2005 [20] USA **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Describe the efficacy and safety of duloxetine in reducing pain in patients with diabetic peripheral neuropathic pain (DPNP) **Treatment duration** 12 weeks	**Participants** *Inclusion*: ≥18 years of age DPNP ≥6 months Pain on 24 h average pain score ≥4/10 (Likert scale) *Exclusion:* Depression, dysthymic disorder, generalized anxiety disorder, alcohol or eating disorders, mania, bipolar disorder, pain that could interfere with the assessment of DPNP, history of substance abuse n=457 39% women Mean age: 60 years (SD 11 years)	**Intervention** Duloxetine (dul) 20 mg n=115 *Drop-out rate* n=24 (20.9%) Mean age: 60 years (SD 11 years) Duloxetine 60 mg n=114 *Drop-out rate* n=28 (24.6%) Mean age: 59 years (SD 12 years) Duloxetine 120 mg n=113 *Drop-out rate* n=33 (29.2%) Mean age: 61 years (SD 11 years) **Comparison** Placebo: n=115 *Drop-out rate* n=28 (24.3%) Mean age: 60 years (SD 11 years)	*Primary endpoints* *Change in mean weekly pain on Likert scale (0–10) from baseline to follow-up; Baseline mean (SD), LS mean change (SE):* Placebo: 5.8 (1.5), –1.91 (0.22) Duloxetine 20: 5.9 (1.6), –2.36 (0.21) Duloxetine 60: 6.0 (1.7), –2.89 (0.22) Duloxetine 120: 5.9 (1.4), –3.24 (0.23) *LS mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine 60: –1.17 (–1.84 to –0.50) Duloxetine 120: –1.45 (–2.13 to –0.78) *Secondary endpoints* *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 26% Duloxetine 20: 41%, p<0.05 vs placebo Duloxetine 60: 49%, p<0,05 vs placebo Duloxetine 120: 52%, p<0,05 vs placebo *Patient Global Impression of Improvement; Mean change (SE):* Placebo: 2.91 (0.12) Duloxetine 20: 2.68 (0.12), n.s vs placebo Duloxetine 60: 2.21 (0.12), p≤0.001 vs placebo Duloxetine 120: 2.24 (0.12), p≤0.01 vs placebo *Euro Quality of Life, EQ-5D; Mean change (SE):* Placebo: 0.08 (0.02) Duloxetine 20: 0.1 (0.02) Duloxetine 60: 0.13 (0.02) p<0.05 vs placeo	**Study withdrawal because of AE** Placebo: 6/115 Duloxetine 20: 5/115 Duloxetine 60: 15/114 Duloxetine 120: 22/113 **Serious adverse events** Not shown **Three most common AEs (duloxetine 120 mg vs placebo)** Nausea: 27.4% vs 9.6% Somnolence: 28.3% vs 7.8% Dizziness: 23% vs 7%

				Duloxetine 120: 0.13 (0.02) p<0.05 vs placebo *CGI-severity; Mean change (SE):* Placebo: –0.83 (0.12) Duloxetine 20: –1.28 (0.11), p≤0.05 vs placebo Duloxetine 60: –1.42 (0.12), p≤0.001 vs placebo Duloxetine 120: 1.70 (0.12), p≤0.01 vs placebo	
Raskin et al 2005 [28] USA and Canada **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Assess the efficacy and safety of duloxetine in patients with diabetic peripheral neuropathic pain (DPNP) **Treatment duration** 12 weeks	**Participants** *Inclusion*: ≥18 years of age DPNP ≥6 months Pain on 24 h average pain score ≥4/10 (Likert scale) *Exclusion:* Prior renal transplant or current renal dialysis, serious or unstable illness, or other condition that might compromise participation in the study. Current major depressive disorder, dysthymia, generalized anxiety disorder, alcohol or eating disorders. Previous diagnosis of mania, bipolar disorder, or psychosis.	**Intervention** Duloxetine 60 mg n=116 *Drop-out rate* n=15 (13%) Mean age: 58 years (SD 11 years) Duloxetine 120 mg n=116 *Drop-out rate* n=21 (18%) Mean age: 59 years (SD 10 years) **Comparison** Placebo: n=116 *Drop-out rate* n=16 (14%) Mean age: 59 years (SD 10 years)	**Primary endpoints** *Change in mean weekly pain on Likert scale (0–10) from baseline to follow-up; Baseline mean (SD), Mean change (SE):* Placebo: 5.5 (1.3), –1.6 (0.18) Duloxetine 60: 5.5 (1.1), –2.5 (0.18), p<0,001 vs placebo Duloxetine 120: 5.7 (1.3), –2.47 (0.18), p<0,001 vs placebo *Mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine 60: –0.9 (–1.39 to –0.42) Duloxetine 120: –0.87 (–1.36 to –0.39) *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 30% Duloxetine 60: 50% Duloxetine 120: 39% **Secondary endpoints** *BPI-interference, average of 7 items ranging 0–10 (worst interference); Mean change (SE):* Placebo: –1.56 (0.18)	**Study withdrawal because of AE** Placebo: 2.6% Duloxetine 60: 4.3% Duloxetine 120: 12.1% **Serious adverse events** Placebo: 3.4% Duloxetine 60: 3.4% Duloxetine 120: 1.7% **Three most common AEs (duloxetine 120 mg vs placebo)** Not shown

		n=348 53% women Mean age: 59 years (SD 10 years)		Duloxetine 60: –2.43 (0.18), p<0,001 vs placebo Duloxetine 120: –2.54 (0.18), p<0,001 vs placebo *Mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine 60: –0.88 (–1.38 to –0.38) Duloxetine 120: –0.98 (–1.49 to –0.47) *Patient Global Impression of Improvement (7-items, 7=very much worse"), Mean change (SE):* Placebo: 3.04 (0.10) Duloxetine 60: 2.5 (0.10), p<0.001 vs placebo Duloxetine 120: 2.54 (0.10), p<0,001 vs placebo *LS mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine 60: –0.53 (–0.81 to –0.26) Duloxetine 120: –0.49 (–0.77 to –0.21)	
Wernicke et al 2006 [40] USA and Canada **Risk of bias** Moderate	**Design** Double-blind, randomized, study **Aim** To assess the efficacy of duloxetine on the reduction of pain severity, as well as secondary outcome measures in patients with	**Participants** *Inclusion*: ≥18 years of age DPNP ≥6 months Pain ≥4 (0–10) HbA1c ≤12% *Exclusion:* Pregnancy, breast feeding, renal transplant, renal dialysis. Serious or unstable cardiovascular, hepatic, renal, respiratory or hematologic illness.	**Intervention** Duloxetine 60 mg n=114 *Drop-out rate* n=29 (25.4%) Mean age: 60 years (SD 11 years) Duloxetine 120 mg n=112 *Drop-out rate* n=34 (30.4%) Mean age: 62 years (SD 10 years)	**Primary endpoint** *Change in weekly mean pain on Likert scale (0–10) from baseline to follow-up; Baseline mean (SD), Mean change (SE):* Placebo: 5.9 (1.4), –1.39 (0.23) Duloxetine 60: 6.1 (1.6), –2.72 (0.22), p<0,001 vs placebo Duloxetine 120: 6.2 (1.5), –2.84 (0.23), p<0,001 vs placebo *Mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine 60: –1.32 (–1.95 to –0.69) Duloxetine 120: –1.44 (–2.08 to –0.81) **Secondary end-points**	**Study withdrawal because of AE** Placebo: 8/108 Duloxetine 60: 17/114 Duloxetine 120: 20/112 **Serious adverse events** Placebo: 5/108 Duloxetine 60: 5/114 Duloxetine 120: 2/112 **Three most common AEs** (Placebo vs duloxetine 60 vs duloxetine 120): Nausea: 6.5% vs 28.1% vs 32.1% Dizziness: 5.6% vs 15.8% vs 10.7% Headache: 6.5% vs 10.5% vs 13.4%

	diabetic peripheral neuropathic pain (DPNP). **Treatment duration** 12 weeks	Symptomatic peripheral vascular disease, or other conditions that might compromise participa- tion in the study. Dysthymia, generalized anxiety disorder, alcohol, or eating disorders. Mania, bipolar disorder or psychosis. n=334 39% women Mean age: 61 years (SD 11 years)	**Comparison** Placebo: n=108 *Drop-out rate* n=23 (21.3%) Mean age: 61 years (SD 11 years)	*Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 27% Duloxetine 60: 43% Duloxetine 120: 53% *Euro Quality of Life, EQ-5D; Mean change (SE):* Placebo: 0.08 (0.02) Duloxetine 60: 0.15 (0.02) Duloxetine 120: 0.15 (0.02) *SF 36, physical functioning; Mean change (SE):* Placebo: 3.64 (1.90) Duloxetine 60: 11.96 (1.81) Duloxetine 120: 11.20 (1.86) *BPI-interference, average of 7 items ranging 0–10 (worst interference), LS mean change (SE):* Placebo: –1.72 (0.19) Duloxetine 60: –2.36 (0.19) Duloxetine 120: –2.79 (0.19)	

Yasuda et al 2011 [42] Japan **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** Describe the efficacy and safety of duloxetine in reducing pain in Japanese patients with diabetic neuropathic pain (DNP) **Treatment duration** 12 weeks	**Participants** *Inclusion*: 20–80 years of age DNP ≥6 months Pain on 24 h average pain score ≥ 4/10 on NRS scale HbA_{1c} ≤9.4% *Exclusion:* Current or past mania, bipolar disorder, depression, anxiety disorders or eating disorders. A complication that might affect assessment of DNP. n=339 24% women Mean age: 61 years (SD 10 years)	**Intervention** Duloxetine (dul) 40 mg: n=85 *Drop-out rate* n=13 (15.1%) Mean age: 62 years (SD 9 years) Duloxetine 60 mg: n=86 *Drop-out rate* n=16 (18.6%) Mean age: 60 years (SD 12 years) **Comparison** Placebo: n=167 *Drop-out rate* n=17 (10.2%) Mean age: 61 years (SD 9 years)	**Primary endpoints** *Change in mean weekly pain on NRS (0–10) from baseline to follow-up; Baseline mean (SD), mean change (SE):* Placebo: 5.78 (1.17), –1.61 (0.18) Duloxetine 40: 5.79 (1.23), –2.41 (0.21) Duloxetine 60: 5.76 (1.17), –2.53 (0.21) *Mean difference vs placebo, ITT-analysis (95% CI):* Duloxetine 40: –0.8 (–1.18 to –0.43) Duloxetine 60: –0.92 (–1.30 to –0.56) **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 33/167 (19.8%) Duloxetine 40: 32/85 (37.6%) Duloxetine 60: 35/86 (40.7%) *Patient Global Impression of Improvement (7-items, 7=very much worse"); mean change (SE):* Placebo: 3.18 (0.12) Duloxetine 40: 2.53 (0.14) Duloxetine 60: 2.52 (0.14) *BPI-interference, average of 7 items ranging 0–10 (worst interference); Baseline mean (SD), mean change (SE):* Placebo: 3.75 (2.15), –1.56 (0.20) Duloxetine 40: 3.88 (2.25), –2.00 (0.24) Duloxetine 60: 4.09 (2.13), –2.08 (0.24)	**Study withdrawal because of AE** Placebo: 9/167 (5.4%) Duloxetine 40: 9/85 (10.6%) Duloxetine 60: 12/86 (14.0%) **Serious adverse events** Placebo: 0/167 Duloxetine 40: 3/85 Duloxetine 60: 2/86 **Three most common AEs (duloxetine 60 mg vs placebo)** Somnolence 24.4% vs 8.4% Nausea 16.3% vs 1.8% Nasopharyngitis 16.3% vs 14.4%
Other antidepressants versus placebo					
Rowbotham et al 2004 [31]	**Design** Double-blind, placebo	**Participants** *Inclusion*: ≥18 years of age	**Intervention** Venlafaxine 75 mg:	**Primary endpoints**	**Study withdrawal because of AE** Placebo: 3/81 Ven 75: 6/81

USA **Risk of bias** Moderate	controlled, randomized, study **Aim** To evaluate the efficacy, safety, and tolerability of various doses of venlafaxine ER in alleviating the pain associated with diabetic neuropathy. **Treatment duration** 6 weeks	Metabolically stable diabetes Pain on 24 h average pain score ≥40/100 on VAS pain intensity (VAS-PI) scale *Exclusion:* Clinically significant psychiatric disorders, cardiovascular, renal, or hepatic disease. History of recent drug or alcohol abuse. History of seizure disorders. Clinically significant abnormalities in physical examination results. n=244 41% women Mean age: 59 years (SD 10 years)	n=82 *Drop-out rate* n=13 (15.8%) Mean age: 59 years (SD 9 years) Venlafaxine 150–225 mg: n=82 *Drop-out rate* n=18 (22%) Mean age: 58 years (SD 12 years) **Comparison** Placebo: n=81 *Drop-out rate* n=12 (15%) Mean age: 60 years (SD 10 years)	*Change in mean weekly VAS-PI (0–100) from baseline to follow-up; Baseline mean (SD), mean change (SE):* Placebo: 68.8 (n/a), –18.7 (n/a) Ven 75: 69.9 (n/a), –22.4 (n/a) Ven 150–225: 67.3 (n/a), –33.8 (n/a) *Mean difference vs placebo, ITT-analysis (95% CI):* Ven 75: –3.7 (not shown) n.s vs placebo Ven 150–225: –15.1 (not shown) p<0.001 vs placebo **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint, LOCF:* Placebo: 34% Ven 75: 39%, n.s vs placebo Ven 150-225: 56%, p<0.001 vs placebo *CGI-S, CGI-I, Patient global pain relief not extracted due to lack of description of scales and/or lack of baseline values.*	Ven 150-225: 8/82 **Serious adverse events** Placebo: 10% Ven 75: 9% Ven 150-225: 12% **Three most common AEs (venlafaxine 150-225 mg vs placebo)** Somnolence 15/82 vs 1/81 Nausea 10/82 vs 5/81 Dyspepsia 10/82 vs 1/81
Opioids versus placebo					
Oxycodone versus placebo					
Gimbel et al 2003 [19] USA **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim**	**Participants** *Inclusion*: DPN pain >5/10 on NRS HbA_{1c} ≤11%. *Exclusion:* Unstable diabetes. Chronic pain unrelated to DPN. History of	**Intervention** Oxycodone ER, maximum 60 mg bid. Mean average daily dose 42 mg. n=82 *Drop-out rate* n=19 (23%)	**Primary endpoints** *Change in daily pain NRS-score; Baseline mean scores (SD):* Placebo: 6.8 (1.3) Oxycodone: 6.9 (1.4) LS mean change from baseline (SE), *ITT-analysis:* Placebo: –1.0 (0.23)	**Study withdrawal because of AE** Placebo: 4/77 Oxycodone: 7/82 **Serious adverse events** Data not shown **Three most common AEs (placebo vs oxycodone)**

	Evaluate the efficacy and safety of controlled-release oxycodone in subjects with moderate to severe pain due to diabetic neuropathy (DPN) **Treatment duration** 6 weeks	substance or alcohol abuse. Serum creatinine ≥2.5 mg/dL. Hepatic dysfunction. History of active cancer. Rapidly escalating pain. Recent neurologic deficit. Autonomic neuropathy or gastrointestinal dys-function. Need for surgery during the study period. n=159 48% women Mean age: 59 years (SD 11 years)	Mean age: 59 years (SD 10 years) **Comparison** Placebo n=77 *Drop-out rate* n=25 (32%) Mean age: 59 years (SD 12 years)	Oxycodone: –2.0 (0.23), p<0.001 vs placebo **Secondary endpoints** *Physical functioning (Sickness Impact Profile)* No data shown (No significant differences were observed) *General health status (SF-36 Health Survey)* No data shown (No significant differences were observed)	Constipation: 11/77 (14%) vs 35/82 (42%) Somnolence: 1/77 (1%) vs 33/82 (40%) Nausea: 6/77 (8%) vs 30/82 (36%)
Hanna et al 2008 [23] Europe and Australia **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** To assess the potential benefit of adding oxycodone to gabapentin in painful diabetic neuropathy (PDNP) patients **Treatment duration** 12 weeks	**Participants** *Inclusion*: PDNP ≥3 months Stable dose of gabapentin ≥1 month but still had pain ≥5/10 on NRS HbA_{1c} ≤11% *Exclusion:* Non stated n=338 36% women Mean age: 60 years (SD 10 years)	**Intervention** Gabapentin plus oxycodone ER max 80 mg bid. n=169 *Drop-out rate* n=42 (26%) Mean age: 60 years (SD 11 years) **Comparison** Gabapentin plus placebo bid. n=169 *Drop-out rate* n=37 (22%) Mean age: 61 years (SD 10 years)	**Primary endpoints** *Change in mean BS-11 pain score (0–10); Baseline mean (SD), mean change (SD):* Placebo: 6.5 (1.71), –1.5 (2.38) Oxycodone: 6.4 (1.76), –2.1 (2.61) *Difference vs placebo (95%CI), ITT-analysis:* Oxycodone: –0.55 (0.15, 0.95), p=0.007 vs placebo **Secondary endpoints** *Global assessment of pain relief; patients rating their overall treatment as "good" or "very good":* Placebo: 51/169 (40%) Oxycodone: 72/169 (60%)	**Study withdrawal because of AE** Placebo: 9/169 Oxycodone: 27/169 **Serious adverse events** Data not shown **Three most common AEs (placebo vs oxycodone)** Constipation: 10/167 (6%) vs 45/168 (27%) Nausea: 18/167 (11%) vs 43/168 (26%) Somnolence: 9/167 (5%) vs 37/168 (22%)

Tramadol versus placebo					
Harati et al 1998 [24] USA **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim** To evaluate the efficacy and safety of tramadol in treating the pain of diabetic neuropathy (DNP) **Treatment duration** 6 weeks	**Participants** *Inclusion*: Age ≥18 years Moderate DNP pain on likert pain rating scale HbA_{1c} <14% *Exclusion:* Neuropathy other than diabetic**,** pain more severe than the neuropathic pain, severe depression, CrCl <30 mL/min, clinically significant medical conditions, profound autonomic dysfunction, brittle diabetes, history of narcotic or alcohol abuse, amputations (including toes), open ulcers, or Charcot joint. n=131 41% women Mean age: 59 years (SD not shown)	**Intervention** Tramadol 100–400 mg/day. Mean dose 210 mg (SD 113 mg) n=65 *Drop-out rate* n=22 (34%) Mean age: 59 years (SD not shown) **Comparison** Placebo n=66 *Drop-out rate* n=27 (41%) Mean age: 59 years (SD not shown)	**Primary endpoints** *Change in daily pain intensity score on a 5 point Likert scale (0–4, 4= extreme pain) from baseline to day 42;* *Baseline mean (SD), end-point mean (SD):* Placebo: 2.6 (0.1), 2.2 (0.1) Tramadol: 2.5 (0.1), 1.4 (0.1), p<0.001 vs placebo *Mean difference vs placebo (SD):* Tramadol: –0.7 (not shown) *Mean change not shown* **Secondary endpoints** *Physical functioning (1 out of 6 items in Health and daily activities evaluation), mean score at end-point (SD):* Placebo: 55.1 (4.0) Tramadol: 64.3 (3.8), p=0.02 vs placebo	**Study withdrawal because of AE** Placebo: 1/66 Tramadol: 9/65 **Serious adverse events** Data not shown **Three most common AEs (placebo vs tramadol)** Nausea: 2/66 (3%) vs 15/65 (23%) Constipation: 2/66 (3%) vs 14/65 (22%) Headache: 3/66 (4%) vs 11/65 (17%)
Buprenorphine versus placebo					
Simpson et al 2016 [36] Australia **Risk of bias** Moderate	**Design** Double-blind, placebo controlled, randomized, study **Aim**	**Participants** *Inclusion*: DPN pain ≥6 months DPN pain ≥4/10 on NRS *Exclusion:* Eczema, cutaneous atrophy, dermatological	**Intervention** Flexible dose transdermal buprenorphine 5–40 µg/h n=93 *Drop-out rate*	**Primary endpoints** *Proportion of patients with ≥30% reduction in average pain intensity (NRS 0–10) from baseline to week 12, ITT-analysis*: Placebo: 38/92 (41.3%) Buprenorphine: 46/89 (51.7%), N.S. vs placebo	**Study withdrawal because of AE** Placebo: 6/93 Buprenorphine: 28/93 **Seroius adverse events** Placebo: 4/93 Buprenorphine: 7/93

	To evaluate the efficacy and safety of transdermal buprenorphine in patients with diabetic peripheral neuropathic pain (DPNP) **Treatment duration** 12 weeks	disorder that may preclude correct use of the patch. Hypersensitivity to opioids or patch adhesives. Need for treatment with external heat sources. n=186 33% women Mean age: 63 years (SD 10 years)	n=37 (39.8%) Mean age: 63 years (SD 10 years) **Comparison** Placebo n=93 *Drop-out rate* n=24 (25.8%) Mean age: 63 years (SD 9 years)	**Secondary endpoints** *Proportion of patients with ≥ 50% reduction in average pain intensity (NRS 0–10) from baseline to week 12, ITT-analysis*: Placebo: 19/92 (20.7%) Buprenorphine: 31/89 (34.8%), p<0.05 vs placebo *Change from baseline in HRQOL (SF-36), ITT-analysis:* Non-significant changes vs placebo in all items, with exception of "Bodily pain" which favored buprenorphine (p<0.05) *Change from baseline to week 12, ITT-analysis* PGIC: Buprenorphine better than placebo, p<0.05. CGIC: Buprenorphine vs placebo N.S.	**Three most common AEs** Data not shown
Capsaicin comparisons					
Capsaicin versus vehicle					
Donofrio et al 1991 [13] USA **Risk of bias** Moderate	**Design** Double blind, vehicle controlled, randomized study **Aim** Establish the effects of topically applied capsaicin on daily activities in patients with painful diabetic neuropathy.	**Participants** *Inclusion*: >18<85 years Pain of moderate to severe intensity daily interfering with daily activities or sleep. *Exclusion:* Other skin condition in the area affected by the neuropathy. HbA_{1c} >11%. Other organic disease or disorder not under long-term concrol.	**Intervention** 0.075% capsaicin cream q.i.d n=138 *Drop-out rate* n=38 (28%) Mean age: 60 years (SD not shown) **Comparison** Vehicle cream q.i.d n=139 *Drop-out rate* n=20 (14%)	**Endpoints** *Change in pain, VAS (0–100) from baseline to follow-up; Baseline mean (SD), mean reduction (SD):* Vehicle: 76 (n/a), –21.1 (n/a) Capsaicin: 76 (n/a) –30.5 (n/a), p=0.014 vs vehicle. *Mean difference capsaicin vs vehicle (95% CI):* –9.4 (n/a) *Physicians global evauation (PGE), change in pain status during the study, on a scale -2 – +3 (+3= pain completely gone), % of patients improved:* Vehicle: 53.4%	**Study withdrawal because of AE** Vehicle: 5/139 Capsaicin: 18/138 **Serious adverse events** Not shown **Three most common AEs (Vehicle vs capsaicin)** Burning: 23/139 vs 87/138 Coughing/sneezing:2/139 vs 16/138 Rash/erythema: 4/139 vs 10/138

	Treatment duration 8 weeks	n=277 50% women Mean age: 60 years (SD not shown)	Mean age: 60 years (SD not shown)	Capsaicin: 69.5%, p=0.012. No baseline data shown. *Data from Dailey 1992 et al* [43] *(double publication of data): Functional capacity scale. Interference of pain for 6 items on a scale 1–4 (4=severe interference).* No data extracted due to no average of interference data was shown	
Capsaicin versus placebo					
Simpson et al 2017 [35] USA **Risk of bias** Moderate	**Design** Double blind, placebo controlled, randomized study **Aim** To evaluate the efficacy and safety of capsaicin 8% patch versus placebo patch in painful diabetic peripheral neuropathy (PDPN) of the feet. **Treatment duration** 8 weeks	**Participants** *Inclusion*: Age>18 years HbA_{1c} ≤11% <1% difference in HbA_{1c} between screening and prescreening Pain on NRS ≥4/10 *Exclusion:* DPN pain in the ankles or above. Conditions that might interfere with, the assessment of DPN. Current or previous foot ulcer. Clinically significant cardiovascular disease within 6 months before screening. Significant peripheral vascular disease. Clinically significant foot deformities. Any amputation of lower extremity. Body mass index ≥40.	**Intervention** 8% capsaicin patch n=186 *Drop-out rate* n=9 (5%) Mean age: 64 years (SD 11 years) **Comparison** Placebo patch n=183 *Drop-out rate* n=8 (4%) Mean age: 62 years (SD 11 years)	**Primary endpoint** *Change in mean 24 h pain on NRS (0–10) from baseline to follow-up; Baseline mean (SD), end-point mean (SD), mean change from baseline:* Placebo: 6.4 (1.5), 5.0 (2.2), –1.34 Capsaicin: 6.6 (1.4), 4.9 (2.2), –1.81 *Mean difference vs placebo, re-calculated from percentage values, ITT-analysis (95% CI):* Capsaicin: –0.47 (–0.88 to –0.26), p=0.025 vs placebo **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Placebo: 18.0% Capsaicin: 21.0%, n.s vs placebo *Patient Global Impression of change, percentage of patients reporting ”much” or ”very much” improved:* Placebo: 30.2% Capsaicin: 39.4%, n.s vs placebo *Euro Quality of Life, EQ-5D*	**Study withdrawal because of AE** Not shown **Serious adverse events** Capsaicin: 2 (1.1%) Placebo: 7 (3.8%) **Most common AEs (Placebo vs capsaicin)** Application site TEAE: 8.2% vs 33.9%

		n=369 42% women Mean age: 63 years (SD 11 years)		No notable differences observed at any time point for the change from baseline in EQ-5D total score	
Capsaicin versus standard of care					
Vinik et al 2016 [41] Europe **Risk of bias** Moderate	**Design** Open label, controlled, randomized study **Aim** To evaluate the long-term safety	**Participants** *Inclusion*: Age >18 years HbA_{1c} ≤9 % Stable glycaemic control for ≥6 months prior to screening visit Pain on NRS ≥4/10	**Interventions** 8% capsaicin patch 30 min + SOC n=156 *Drop-out rate* n=24 (15%) Mean age: 61 years (SD 11 years)	**Primary endpoint** *Percentage change from baseline to end of study in the Norfolk QOL-DN total score, mean percentage difference vs SOC, ITT-analysis (95% CI):* Capsaicin 30: –20.9 (–31.7 to –10.1) Capsaicin 60: –26.1 (–36.8 to –15.4) **Secondary endpoints**	**Study withdrawal because of AE** SOC: 3/155 Capsaicin 30: 7/156 Capsaicin 60: 8/157 **Severe adverse events** SOC: 6.5% Capsaicin 30: 12.2% Capsaicin 60: 7.6%

	and tolerability of capsaicin 8% patch versus standard of care (SOC) in painful diabetic peripheral neuropathy (PDPN) **Treatment duration** 52 weeks	*Exclusion:* DPN pain in the ankles or above. Significant pain due to an aetiology other than PDPN. Any amputation of lower extremity. Clinically significant cardiovascular disease. Active signs of skin inflammation around onychomycosis sites. BMI ≥40 kg/m^2. Conditions that might interfere with the assessment of PDPN. CrCl <30 mL/min. Significant peripheral vascular disease. n=468 53% women Mean age: 61 years (SD 10 years)	8% capsaicin patch 60 min + SOC n=157 *Drop-out rate* n=29 (18%) Mean age: 61 years (SD 10 years) **Comparison** SOC alone n=155 *Drop-out rate* n=27 (17%) Mean age: 59 years (SD 10 years)	*Utah Early Neuropathy Scale (UENS). A 4 point reduction represent a clinical significant improvement. Mean difference vs SOC, ITT-analysis (95% CI):* Capsaicin 30: –0.9 (–1.8 to 0.1) Capsaicin 60: –1.7 (–2.7 to –0.8) *Pain score, pain severity index, pain interference index measured on NRS 0–10:* Data not shown *Patient Global Impression of change, percentage of patients reporting "much" or "very much" improved:* Data not shown	**Most common AEs (Capsaicin 30 vs Capsaicin 60)** *SOC frequencies not shown*: Application site pain: 28.2% vs 29.3% Burning sensation: 9.0% vs 9.6% Application site erythema: 7.7% vs 8.9%
Head to head comparisons					
Antidepressants versus anticonvulsants					
Boyle et al 2012 [11] UK **Risk of bias** Moderate	**Design** Double-blind, active treatment controlled, randomized, study **Aim**	**Participants** *Inclusion*: ≥18 years of age and DPN with LANS score >12. *Exclusion:* Cognitive impairment, end-stage disease of a	**Intervention/comparison groups:** Pregabalin 300–600 mg/day n=27 *Drop-out rate* n=8 (30%)	**Primary endpoint** *Subjective pain assessed by the Brief Pain Inventory (BPI*), *ITT-analysis, mean value baseline (SE), mean value after 2 weeks (SE*): *mean value after 4 weeks (SE)*: Pregabalin: 3.1 (0.4), 2.3 (0.4), 2.4 (0.4) Duloxetine: 3.4 (0.5), 2.5 (0.4), 2.2 (0.4) Amitryptiline: 3.5 (0.4), 2.7 (0.4), 2.6 (0.4)	**Study withdrawal because of AE** Pregabalin: 6 (22%) Duloxetine: 3 (11%) Amitryptiline: 1 (4%) **Serious adverse events** Data not shown

	To compare the analgesic efficacy of pregabalin, amitriptyline, and duloxetine, and their effect on polysomnographic sleep, daytime functioning, and quality of life in patients with diabetic polyneuropathy (DPN). **Treatment duration** 4 weeks. Two weeks of low dose followed by two weeks of high dose.	major system, evidence of a recurrent and/or severe hypoglycemic event in the last 3 years, recent cardiac or cerebral ischemic event. n=83 31% women Mean age: 65 years (SD 9 years) Total drop out in all three arms n=18 (22%)	Mean age: 66 years (SD 8 years) Duloxetine 60–120 mg/day n=28 *Drop-out rate* n=5 (18%) Mean age: 65 years (SD 10 years) Amitryptiline 25–50 mg/day n=28 *Drop-out rate* n=5 (18%) Mean age: 65 years (SD 9 years)	**Secondary endpoints** *Quality of life using SF-36, ITT-analysis, mean value baseline (SD), mean value after 4 weeks (SD):* *SF-36 mental component summary:* Pregabalin: 52.8 (9.3), 52.4 (10.0) Duloxetine: 50.2 (9.0), 51.0 (8.8) Amitryptiline 50: 51.1 (7.3), 51.7 (8.0) *SF-36 physical component summary:* Pregabalin: 34.2 (8.2), 31.1 (10.9) Duloxetine: 37.8 (10.0), 36.6 (9.4) Amitryptiline: 39.5 (9.3), 38.5 (8.8) *No statistically significant differences between treatment arms in any outcome.*	**Three most common treatment emergent AEs with pregabalin** Fatigue *no frequency data* Dizziness *no frequency data* Somnolence *no frequency data*
Gilron et al 2009 [18] Canada **Risk of bias** Moderate	**Design** Double-blind, active treatment controlled, randomized, cross-over trial **Aim** To assess the efficacy and tolerability of combined nortriptyline and	**Participants** *Inclusion*: ≥18 years of age and Pain ≥ 4/10 on NRS for ≥6 months ASAT/ALAT ≤120% of upper limit (UL) CrCL ≤150% of UL HbA_{1c} ≤13% *Exclusion:* Patient history of	**Intervention/comparison groups:** Gabapentin. Mean MTD 2433 mg/day (first cycle) n=19 *Drop-out rate* n=4 (21%) Mean age: not shown	**Primary endpoint** *Daily pain intensity (NRS 0–10) per treatment cycle; mean value baseline (95% CI), all groups:* 5.4 (5.0 to 5.8). *For patients with diabetic polyneuropathy, mean value at MTD period in each cycle (95% CI)*: Gabapentin: 3.1 (2.4 to 3.7) Nortriptyline: 2.9 (2.3 to 3.6) Combination: 2.2 (1.5 to 2.8) **Secondary endpoints**	**Study withdrawal because of AE (treatment in first cycle)** Gabapentin: 0/19 Nortriptyline: 2/18 Combination: 3/19 **Serious adverse events** No serious adverse events were recorded for any patients during the trial. **Three most common AEs at MTD**

	gabapentin compared with each drug given alone in patients with diabetic polyneuropathy (DPN, 70%) or postherpetic neuralgia. **Treatment duration** 18 weeks, 6 weeks per treatment cycle. Evaluation of effect at maximum tolerated dose (MTD) period (day 25–31 in each cycle).	neuropathy attributable to other causes. Any major organ system disease. Cardiovascular autonomic neuropathy. Postural hypotension of more than 20 mm Hg. Sedation or ataxia. Symptoms attributable to benign prostatic hypertrophy. Psychiatric or substance abuse disorder. Coexisting disorder causing pain as severe as the neuropathic pain. n=56 38% women Mean age: 65 years (SD 8 years)	Nortriptyline. Mean MTD 60 mg/day (first cycle) n=18 *Drop-out rate* n=3 (17%) Mean age: not shown Gabapentin plus nortriptyline. Mean MTD 2180 and 50 mg/day, respectively (first cycle) n=19 *Drop-out rate* n=4 (21%) Mean age: not shown	*SF-36 Total score (0–100, 100= good health)* *per treatment cycle; mean value baseline (SD), all groups:* 56.8 (2.1) *All grous, mean value at MTD period in each cycle (SD)*: Gabapentin: 65.4 (1.8) Nortriptyline: 63.1 (1.8) Combination: 66.3 (1.8) No statistically significant differences between groups in SF-36 total scores.	*Gabapentin, nortriptyline and combination, respectively:* Dry mouth: 8/46 (17%), 29/46 (58%), 30/50 (60%) Fatigue: 2/46 (4%), 6/46 (12%), 4/50 (8%) Dizziness: 4/46 (9%), 2/46 (4%), 4/50 (8%)
Tanenberg et al 2011 [37] Canada, Germany, USA, Puerto Rico **Risk of bias** Moderate	**Design** Open label, active treatment controlled, randomized, study **Aim** To determine whether duloxetine is noninferior to Pregabalin in the treatment of	**Participants** *Inclusion*: ≥18 years of age and Treated with stable gabapentin dose ≥900 mg/day and DPN pain ≥4/10 on NRS HbA_{1c} ≤12% *Exclusion:* Past or current diagnosis of mania, bipolar disorder, obsessive-compulsive disorder, or	**Intervention/comparison groups:** Duloxetin 60 mg/day n=138 *Drop-out rate* n=51 (37%) Mean age: 61 years (SD 10 years) Pregabalin 300 mg/day n=134	**Primary endpoint** *Change on BPI (0–10) from baseline to week 12 in weekly mean of 24-hour pain, ITT-analysis, mean value baseline (SD), mean change at week 12 (SD)*: Duloxetine: 5.7 (1.7), –2.4 (0.2) Pregabalin: 5.6 (1.9), –1.8 (0.2) *Mean difference vs pregabalin (95% CI), ITT-analysis:* Duloxetine: –0.49 (n.s.) **Secondary endpoints** *Patients who achieved ≥50% reduction in pain scores from baseline to endpoint:* Duloxetine: 50/120 (41.7%)	**Study withdrawal because of AE** Duloxetine: 19.6% Pregabalin: 10.4%, p=0.04 vs duloxetine **Serious adverse events** Duloxetine: 3/138 (2.2%), Pregabalin: 6/134(4.5%) Combination: 5/135 (3.7%) *No significant differences* **Three most common treatment emergent AEs (duloxetine vs pregabalin)**

	pain associated with diabetic peripheral neuropathy (DPN). **Treatment duration** 12 weeks.	posttraumatic stress disorder or were judged to beat risk of suicide. Historical exposure to drugs known to cause neuropathy. n=407 41% women Mean age: 62 years (SD 11 years)	*Drop-out rate* n=38 (28%) Mean age: 62 years (SD 11 years) Combination n=135 *Drop-out rate* n=36 (27%) Mean age: 62 years (SD 11 years)	Pregabalin: 48/127 (37.8%), n.s. vs duloxetine *ClinicalGlobal Impression of Severity* No significant differences *Sheehan Disability Scale* No significant diffeernces	*Nausea:* 19 (13.8%) vs 2 (1.5%), p<0.001 *Fatigue:* 16 (11.6%) vs 7 (5.2%), n.s *Peripheral edema*: 2 (1.4%) vs 18 (13.4%), p<0.001
Shahid et al 2019 [33] Pakistan **Risk of bias** Moderate	**Design** Open label, active treatment controlled, randomized study **Aim** To compare the efficacy of duloxetine with pregabalin in patients with painful diabetic neuropathy in a tertiary care hospital **Treatment duration** 12 weeks.	**Participants** *Inclusion*: Diagnosis of diabetes. History of pain and numbness in hands and Feet. Biothesiometer score of 16 volts or above. *Exclusion:* Diabetes-related foot injuries, ulcers, and/or any other painful wound/lesion. n=173 42% women Mean age: 63 years (SD 7 years)	**Intervention/comparison groups:** Duloxetin 60 mg/day n=87 *Drop-out rate* n=5 (37%) Mean age: not shown Pregabalin 300 mg/day n=86 *Drop-out rate* n=7 (28%) Mean age: not shown	**Primary endpoint** *Change on VAS (0–10) from baseline to week 12. Mean value baseline (SD), mean value at week 12 (SD)*: Duloxetine: 6.8 (0.9), 4.0 (1.1) Pregabalin: 7.0 (1.1), 4.9 (0.8) *Mean difference vs pregabalin (95% CI), ITT-analysis:* Duloxetine: –0.72 (no CI shown), p=0.90	**Study withdrawal because of AE** Duloxetine: 0/87 Pregabalin: 2/86 **Serious adverse events** Data not recorded/shown **Three most common treatment emergent AEs (pregabalin vs duloxetine)** *Somnolence:* 7 (8.1%) vs 1 (1.1%) *Peripheral edema:* 3 (3.4%) vs 0 *Constipation*: 3 (3.4%) vs 6 (6.9%)
Enomoto et al 2018 [14] Japan	**Design** Double blind, active treatment controlled,	**Participants** *Inclusion*:	**Intervention/comparison groups:** Duloxetin 20–60 mg/day. Average	**Primary endpoint** *Change on NRS (0–10) from baseline to week 12. Mean value baseline (SD), mean value at week 12 (SD)*:	**Study withdrawal because of AE** Duloxetine: 10/152 Pregabalin: 12/151

Risk of bias Moderate	randomized study **Aim** To assess the noninferiority of duloxetine compared with pregabalin after 12 weeks of treatment in adult patients with DPNP in Japan **Treatment duration** 12 weeks.	≥20 and <80 years with diabetic polyneuropathy. Duloxetine and Pregabalin naive. score of ≥4 on NRS 0–10. HbA1c ≤9.4% *Exclusion:* Poor glycemic control last 70 days. Psychiatric diseases including MDD. Complications of diseases that could affect the assessment of DPNP. Neuropathic pain suspected to be caused by alcohol. n=303 27% women Mean age: 59 years (SD 9 years)	dose approx. 60 mg/day. n=152 *Drop-out rate* n=15 (10%) Mean age: 59 years (SD 8 years) Pregabalin 150–600 mg/day. Average dose approx. 300 mg/day. n=151 *Drop-out rate* n=21 (14%) Mean age: 60 years (SD 10 years)	Duloxetine: 5.38 (1.079), 3.09 (not shown) Pregabalin: 5.35 (1.129), 2.99 (not shown) *LS mean change (SE) at week 12:* Duloxetine: –2.286 (0.133) Pregabalin: –2.358 (0.133) *Mean difference vs pregabalin (95% CI), ITT-analysis:* Duloxetine: 0.072 (–0.295 to 0.439) **Secondary endpoints** *Euro Quality of Life, EQ-5D* *LS mean change (SE) at week 12:* Duloxetine: 0.1144 (0.0112) Pregabalin: 0.1004 (0.0112) *Mean difference vs pregabalin (95% CI), ITT-analysis:* Duloxetine: 0.0140 (–0.0161 to 0.0441)	**Serious adverse events** Duloxetine: 1/152 Pregabalin: 6/151 **Three most common treatment emergent AEs (pregabalin vs duloxetine)** *Somnolence:* Duloxetine: 18/152 Pregabalin: 22/151 *Dizziness:* Duloxetine: 6/152 Pregabalin: 16/151 *Nausea*: Duloxetine: 11/152 Pregabalin: 5/151
Other head to head comparisons					
Baron et al 2009 [8] Europe **Risk of bias** Moderate	**Design** Randomized study **Aim** To compare efficacy and safety of 5% lidocaine medicated plaster with pregabalin in patients with post-herpetic	**Participants** *Inclusion*: >18 years pain intensity of >4 on NRS HbA_{1c} <11%. Pain for >3 months. *Exclusion:* Venous insufficiency, post-thrombotic syndrome, ulcers on lower extremities, CrCl of <30 mL/min,	**Intervention** 5% lidocaine medicated plaster *DPN participants* n=105 *Drop-out rate* n=6 (5.7%) Mean age: 61 years (SD 10 years) **Comparison** Pregabalin 150 mg/day week 1,	**Primary endpoint** *Response rate* (at least 2 points change or a value of 4 or less on NRS-3 scale) *Response rates in DPN patients; Full analysis set:* Lidocaine patch 68%, pregabalin, 68.3% (n.s.) **Secondary endpoints** *NRS-3 changes in DPN patients from baseline (SD):* Lidocaine patch baseline 6.6 (1.32), change –2,4 (2,07)	**Study withdrawal because of AE** Lidocaine patch 5.8% pregabalin 25.5% **Serious adverse events** Lidocaine patch 1.8% pregabalin 0.7% **Three most common AEs (Lidocaine vs pregabalin)** Dizziness 11.8% vs 0.0% Fatigue 8.5% vs 0.0% Vertigo 7.8% vs 0.0%

	neuralgia (PHN) or DPN **Treatment duration** 4 weeks	concomitant use of adjuvant drugs for neuropathic pain. n=311 48% women Mean age: 62 years (SD 10 years)	300 mg/day week 2. If NRS-3 ≥4, titration to 600 mg/day. *DPN participants* n=105 *Drop-out rate* n=11 (10.4%) Mean age: 61 years (SD 9 years)	Pregabalin baseline 6.7 (1.26), change –2.0 (2.24) *Proportion of patients with 50% reductions from baseline in NRS-3 score* Lidocaine patch n=59 (59.6%) Pregabalin n=53 (56.4%) **EQ-5D estimated health in DPN patients** Lidocaine patch baseline 0.49 (0.29), change 0.13 (0.245) Pregabalin baseline 0.56 (0.249), change 0.06 (0.211)	
Bisbroeck et al 1995 [10] USA and Canada **Risk of bias** Low	**Design** Double blind, double dummy, active treatment controlled randomized study **Aim** To compare the safety and effectiveness of topical capsaicin with oral amitriptyline in diabetic patients with pain associated with sensory polyneuropathies involving the feet.	**Participants** *Inclusion*: ≥21≤ 85 years Painful DPN in feet ≥4 months *Exclusion:* Non stated n=235 44% women Mean age: 60 years (SD not shown)	**Intervention** 0.075% capsaicin cream qid + placebo capsules n=118 *Drop-out rate* n=14 (13%) Mean age: 60 years (SD not shown) **Comparison** Amitriptyline 25-125 mg/day + vehicle cream qid n=117 *Drop-out rate* n= 9 (8%) Mean age: 60 years (SD not shown)	**Primary endpoint** *Physicians global evaluation (PGE) of change in pain severity from –2 (much worse) to +3 (completely gone), patients reporting at least "better".* Capsaicin: 73% Amitriptyline: 73% **Secondary endpoints** *Patient reported change in pain, VAS (0–100) from baseline to follow-up; Baseline mean (SD), mean change (SD):* Capsaicin: 62.1 (n/a), –26.1 (2.9) Amitriptyline: 66.4 (n/a), –29.1 (3.0) *No significant between treatment difference was noted* *QoL, pain interference with daily activities:* No significant between treatment differences were noted.	**Study withdrawal because of AE** Not shown **Serious adverse events** Not shown **Three most common AEs (Capsaicin vs amitriptyline):** Burning: 44% vs 0% Somnolence: 0% vs 46% Dry mouth: 0% vs 33%

	Treatment duration 8 weeks				
Raskin et al 2006 [29] Australia, Canada, South America and Taiwan **Risk of bias** Moderate	**Design** Open label, randomized, study **Aim** Assess the safety and tolerability of duloxetine in patients with diabetic peripheral neuropathic pain (DPNP). Evaluation of efficacy was a secondary objective. **Treatment duration** 28 weeks	**Participants** *Inclusion*: ≥18 years of age DPNP ≥6 months HbA_{1c} ≤12%. *Exclusion:* Previous or current diagnosis of mania, bipolar disorder, psychosis, substance abuse or dependence. Judged to be at risk for suicide. Serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness. Symptomatic peripheral vascular disease or other conditions that would compromise study participation. Elevated ALT, AST or serum creatinine. Renal transplants or renal dialysis. n=449 48% women Mean age: 60 years (SD 11 years)	**Intervention** Duloxetine 60 mg twice daily n=334 *Drop-out rate* n=121 (36.2%) Mean age: 60 years (SD 10 years) **Comparison** Duloxetine 120 mg once daily n=115 *Drop-out rate* n=43 (37.4%) Mean age: 60 years (SD 11 years)	**Primary endpoint** *Percentage of patients who discontinued the study prematurely:* Duloxetine 60 x 2: 36.2% Duloxetine 120 x 1: 37.4% (p=0.823 n.s) *≥1 Treatment-emergent adverse events:* Duloxetine 60 x 2: 96.1% Duloxetine 120 x 1: 92.2% (p=0.129 n.s) **Secondary endpoints** (data reproduced from figure): *BPI-severity (0–10); Mean change from baseline (SD):* Duloxetine 60: –2.8 (2.7) Duloxetine 120: –2.8 (2.7) *Mean difference (95% CI):* Duloxetine 120: 0.0 (not shown) *BPI-interference w function, ranging 0–10 (worst interference); Mean change (SD):* Duloxetine 60: –2.9 (2.7) Duloxetine 120: –3.0 (3.1) *Mean difference (95% CI):* Duloxetine 120: 0.1 (not shown)	**Study withdrawal because of AE** Duloxetine 60 x 2: 20.1% Duloxetine 120 x 1: 27.0% **Serious adverse events** Duloxetine 60 x 2: 7.5% Duloxetine 120 x 1: 8.7% **Three most common AEs** **(**Duloxetine 60 x 2 vs Duloxetine 120): Nausea: 40.4% vs 42.6% Somnolence: 33.5% vs 36.5% Dizziness: 19.5% vs 16.5%

AE = adverse events; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **BPI** = Brief Pain Inventory; **CI** = confidence interval; **CGIC** = Clinical Global Impression of Change controlled release; **CGI-S** = Clinical Global Impression – Severity; **CGI-I** = Clinical Global Impression – Improvement scale; **DNP** = diabetic

neuropathic pain; **DPNP** = diabetic peripheral neuropathic pain; **ECG** = electrocardiogram; **HbA1c** = Hemoglobin A1c; **HIV** = human immunodeficiency virus; **HRQOL** = Health related quality of life; **ITT** = Intention to treat; **LOCF** = Last observation carried forward; **LS mean** = Least Squares Means; **MITT** = modified intention-to-treat; **n** = number; **N/A** = not applicable; **NRS** = numerical rating scale; **p** = p-value; **PGIC** = Patient Global Impression of Change; **q.i.d**. = Quater in die (four times each day); **QOL-DN** = Quality of Life Questionnaire - Diabetic Neuropathy; **SD** = standard deviation; **SF-36** = The Short Form (36) Health Survey; **SF-MPQ** = Short-form McGill Pain Questionnaire; **vs** = versus; **VAS** = visual analog scale; **VAS-PI** = visual analog scale - pain intensity;

Part III. Pain associated with spinal compression fractures

Systematic reviews

One systematic review was found [44]. This review found no studies that studied the effect or safety of the drugs in our PICO.

Primary studies

We performed a search of primary studies from January 2014 (date when Rzewuska et al performed their search) and onwards but found no relevant studies.

Part IV. NSAIDs and the risk of acute renal failure

Systematic reviews

One systematic review was found [45] that studied the correlation of the treatment with NSAIDs and the risk of acute renal failure in adult patients. Of the studies included in the review, three were considered relevant to our PICO [46-48].

Primary studies

We performed a search of primary studies from 2016 (when Zhang et al performed their search) and found one additional relevant study with low risk of bias [49].

Table 5 Included primary studies on NSAIDs and the risk of acute renal failure.

Author Year Reference Country Risk of bias	Design Aim Time to follow-up	Participants Women/men Age	Intervention group Participants Age	Comparison group Participants Age	Outcome
Henry et al 1997 [47] Australia **Risk of bias** Moderate	**Design** Matched case-control study **Aim** Assess the relationship between recent use of NSAIDs and the presence of functional renal impairment present at the time of hospitalisation with a range of clinical problems **Time to follow-up** Point prevalence of functional renal impairment at time of hospitalisation.	**Participants** *Cases* Consecutive patients admitted acutely to the study hospitals who had serum creatinine levels greater than or equal to 0.15 mmol/L. *Controls* Two controls to each case. Controls were subjects of the same sex and age (to within 5 years) as the cases, admitted to the same hospital, who had normal serum creatinine levels (<0.12 mmol/L) throughout their hospital stay. n=299 45% women Mean age: 76 years old (SD 7 years)	**Intervention group** Cases *Participants* n=110 Mean age: 77 years (SD 7 years) Cases more likely than controls to have a past history of malignancy, hypertension, heart disease, renal/urinary tract disease and gout/hyperuricemia ACE-I use 33.6% in cases and 20.1% in controls. High-ceiling diuretics use 34.6% in cases and 8.5% in controls	**Comparison group** Controls *Participants* n=189 Mean age: 75 years (SD 7 years)	*Consumption of NSAID use (excluding prophylactic aspirin) prior to hospitalisation and elevated serum creatinin level* *Use in the past month:* Cases 43/110 (39.1%), controls 45/189 (23.8%) OR (95% CI) 2.1 (1.3 to 3.7) Adjusted OR (95% CI) 1.8 (0.97 to 3.4) *Use in the past week:* Cases: 38/110 (34.6%) Controls: 40/189 (21.2%) OR (95% CI): 2.0 (1.2 to 3.5) Adjusted OR (95% CI) 1.5 (0.80 to 2.9) *The relationship between the odds of functional renal impairment and the half life of the NSAIDs* Half -life of NSAID — Adjusted OR (95 % CI) No NSAID — 1 ≤4 h — 1.1 (0.5 to 2.5) 4–12 h — 2.1 (0.77 to 5.9) ≥12 h — 2.9 (0.72 to 11.6) OR adjusted for age, a history of gout, a heart disease and renal disease OR not adjusted for differences in use of ACE-I or diuretics.

	Retrospective drug use assessment by structured interview.				
Griffin et al 2000 [46] USA **Risk of bias** Moderate	**Design** Nested case-control study **Aim** Evaluate the risk of important deterioration of renal function due to NSAID use **Time to follow-up** Four years of data collection. Retrospective drug use assessment, by data base prescription fillment, prior to hospitalisation with acute renal failure.	**Participants** Tennessee Medicaid enrollees aged ≥65 years who had been enrolled for at least 1 year *Cases* Hospital admissions for acute renal failure with admission creatinine level of >180 µmol/L (2 mg/dl) and either a >20% increase in creatinine from a baseline value or a >20% decline in creatinine during hospitalization. Exclusion: Patients with end-stage renal disease or hospital-acquired acute renal failure. *Controls* Randomly selected from Tennessee Medicaid database. n=11698 76% women Mean age: not shown	**Intervention group** Cases *Participants* n=1799 Mean age: not shown Cases were older, more often nursing home residents, had greater prevalence of recent hospitalization and greater use of diuretics and ACE-I, compared with controls	**Comparison group** Controls *Participants* n=9899 Mean age: not shown	**Endpoints** *Association between current use of NSAID and hospitalisation due to acute renal failure:* *Current NSAID use:* Cases: 326/1799 (18.1%) Controls: 1119/9899 (11.3%) Adjusted OR (95% CI) 1.58 (1.34 to 1.86) Current use was defined as the individuals NSAID supply included the index date. Nonuse of NSAIDs in the past year was the reference category. OR adjusted for age, gender, ethnicity, nursing home resident, recent hospitalisation, use of loop-diuretics, thiazides, ACE-inhibitors, antibiotics and six other drugs within the past 30 days
Schneider et al 2006 [48] Canada **Risk of bias** Moderate	**Design** Nested case-control study **Aim** To assess the association	**Participants** New NSAID users older than 65 years from the administrative health care databases of Quebec, Canada Exclusion: Kidney transplantation.	**Intervention group** Cases *Participants* n=4228	**Comparison group** Controls *Participants* n=84540	**Endpoints** *Association between use of NSAID and hospitalisation due to acute renal failure:* Current and recent use of NSAID (use in the past month AND the two preceeding months):

	between exposure to NSAIDs and hospitalization for acute renal failure. **Time to follow-up** Four years of data collection. Retrospective drug use assessment, by data base prescription fillment, prior to hospitalisation with acute renal failure	*Cases* Hospital admissions for acute renal failure. *Controls* Up to 20 randomly selected individulas per case from the database, matched to cases on year and month of cohort entry as well as age at cohort entry (±1 year) n=88768.	Mean age: 78 years, SD 6 years. Women: 54% Cases were more likely to be male and to have hypertension, diabetes, and preexisting renal diseases, including previous episodes of acute renal failure. In the year before the index date, cases used more health care services and required a higher number of drugs. Exposure to nephrotoxic drugs and contrast media was also more frequent in cases.	Mean age: 78 years, SD 6 years. Women: 68%	Cases: 149/4228 (3.5%) Controls: 2205/84540 (2.6%) Unadjusted RR (95% CI): 1.83 (1.47 to 2.26) Adjusted RR (95% CI): 1.62 (1.29 to 2.04) Rate ratios (RR) adjusted for age, gender, comorbidity, chronic disease score, charlson index, number of drugs, use of anticoagulants, corticosteroids, psychotropics, thyroid drugs, aspirin, nephrotoxic drugs, exposure to contrast media, health care utilisation. The risk of acute renal failure for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted RR 2.05 (1.61, 2.60) and receded thereafter. The association with acute renal failure within 30 days of therapy initiation was comparable for different NSAIDs with regards to COX-selectivity.
Nash et al 2019 [49] Canada **Risk of bias** Moderate	**Design** Retrospective chort study **Aim** Quantify the 30-day risk of acute kidney injury (AKI) and hyperkalemia in older adults	**Participants** New NSAID users older than 65 years from the administrative health care databases of Ontario, Canada. Exclusion: NSAID prescription in the prior 6 months. Discharge from hospital in the 2 days prior to the index date. eGFR >150mL/min/1.73 m2. End-stage kidney disease.	**Intervention group** Cases after matching *Participants* n=46107 Mean age: 74 years, SD 7 years. Women: 58%	**Comparison group** Controls after matching *Participants* n=46107 Mean age: 74 years, SD 7 years. Women: 58%	**Endpoints** *Association between use of NSAID and 30-day risk of acute kidney injury:* Current and recent use of NSAID (use in the past month AND the two preceeding months): Cases: 380/46107 (0.82%) Controls: 272/ 46107 (0.59%) OR (95% CI): 1.41 (1.20 to 1.65)

	after NSAID initiation **Time to follow-up** Eight years of data collection. Retrospective drug use assessment, by data base prescription fillment, prior to hospital visit with acute kidney injury.	*Cases* Acute kidney injury defined as serum creatinine increase ≥50% or an absolute increase of at least 26.5 mmol/L. *Controls* Matched with cases with similar baseline health n=92214			We calculated a propensity score for the probability of receiving an NSAID prescription using a multivariable logistic regression model that incorporated >150 baseline characteristics (including indications for NSAID use and risk factors for AKI.

ACE-1 = Angiotensin-converting enzyme; **AKI** = Acute kidney injury; **CI** = confidence interval; **COX** = cyklooxygenas; **eGRF** = Estimated glomerular filtration rate; **n** = number; **NSAID** = Non steroidal anti-inflammatory drugs; **OR** = odds ratio; **RR** = relative risk; **SD** = standard deviation

Part V. NSAIDs and the risk of gastrointestinal perforations, bleeds or ulcerations

Systematic reviews

One systematic review, CNT Collaboration 2013 [50], with analysis of individual patient data in 274 RCTs was included. CNT Collaboration 2013 studied the correlation of treatment with NSAIDs and the risk of gastrointestinal perforations, bleeds or ulcerations (PUBs) in adult patients with sub-group analysis of patients younger than 60 years and patients 60 years and older.

Table 6 Table of the included systematic review on treatment with NSAIDs and the risk of PUBs.

Author Year Reference	Study design Follow up	Population	Interventions and controls	Outcome - safety	Risk of bias SBU rating of risk of bias in the review
Coxib and traditional NSAID Trialists' (CNT) Collaboration 2013 [50]	Systematic review and meta-analysis of individual patient data of cardiovascular events and symptomatic upper GI events in 280 trials of NSAIDs versus placebo (124513 participants, 68342 person-years) and 474 trials of one NSAID versus another NSAID (229296 participants, 165456 person-years). This results in a mean follow up period on an	Mean age at randomisation was 61 years, about two thirds were female, and 79% were white. 7% of the patients had a history of upper gastrointestinal peptic ulcer. Overall, the indication for treatment with an NSAID was rheumatoid arthritis or osteoarthritis in around four fifths of participants	Four comparisons was extracted: **Coxibs vs placebo** **tNSAIDs* vs placebo** **Coxibs vs tNSAIDs (naproxen excluded)** **Coxibs vs naproxen** *) traditional NSAIDs eg ibuprofen, diclofenac, naproxen. The predominant daily doses in the includes studies were diclofenac 150 mg, ibuprofen 2400	Rate ratios (RR) for symptomatic upper GI event (perforation, ulcer, obstruction, or bleed) **Coxibs vs placebo** *<60 years* 0.43% vs 0.12% (44/10233 vs 8/6667) RR 2.74 (95% CI, 1.22 to 6.12) *≥60 years* 0.74% vs 0.37% (116/15676 vs 49/13243) RR 1.77 (95% CI, 1.14 to 2.74) RR in <60 years vs ≥60 years χ^2=2.9, p=0.23 **tNSAIDs vs placebo** *<60 years* 0.80% vs 0.12% (154/19250 vs 8/6667) Adj RR 5.03 (95% CI, 2.30 to 10.97)	Study eligibility criteria: *Low* Identification and selection of studies: *Low* Data collection and study appraisal: *Unclear (no formal risk of bias assessment)* Synthesis and findings: *Low* Overall risk of bias: *Low*

	individual level of 7.9 months. Search was performed in january 2009		mg, naproxen 1000 mg, celecoxib 200–400 mg	≥*60 years* 1.24% vs 0.37% (370/29839 vs 49/13243) RR 3.12 (95% CI, 1.98 to 4.91) RR in <60 years vs ≥60 years χ^2=1.9, p=0.17 **Coxibs vs tNSAID (naproxen excluded)** *<60 years* 0.46% vs 0.80% (94/20435 vs 154/19250) RR 0.51 (95% CI, 0.36 to 0.72) ≥*60 years* 0.78% vs 1.24% (245/31410 vs 370/29839) RR 0.58 (95% CI, 0.47 to 0.72) RR in <60 years vs ≥60 years χ^2=1.3, p=0.53 **Coxibs vs naproxen** *<60 years* 1.04% vs 2.20% (77/7404 vs 126/5727) RR 0.51 (95% CI, 0.35 to 0.74) ≥*60 years* 1.35% vs 3.54% (121/8963 vs 276/7797) RR 0.4 (95% CI, 0.3 to 0.52) RR in <60 years vs ≥60 years χ^2=2.1, p=0.36	

CI = confidence interval; **CNT** = Coxib and traditional NSAID; **NSAID** = Non steroidal anti-inflammatory drugs; **tNSAID** = traditional Non steroidal anti-inflammatory drugs; **vs** = versus;

Primary studies

We performed a search of primary studies from 2009 (when CNT Collaboration 2013 performed their search) and onwards. We included three [51-53] additional primary studies.

Table 7 Included primary studies on treatment with NSAIDs and the risk of PUBs.

Author Year Reference Country Risk of bias	Design Aim Time to follow-up	Participants Women/men Age	Intervention group n Age	Comparison group n Age	Outcome
Non-randomized studies					
Bakhriansyah et al 2017 [51] Netherlands **Risk of bias** Moderate	**Design** Register based case-control study **Aim** Assess the risk of gastrointestinal perforation, ulcers, or bleeding (PUB) associated with the use of NSAIDs and selective COX-2 inhibitors, with or without PPIs. **Follow-up time** Study period 1998–2012.	**Participants** *Cases* Patients aged ≥18 years at first hospital admission (index date) with diagnosis of PUB in the GI tract. *Controls* Patients without any diagnoses of GI toxicity. For each case, up to four controls were matched on year of birth and sex. *Exposure to study drugs* Patients were classified as current users when the theoretical end date of the last prescription ended after the index date.	**Intervention group** Subgroup analysis of patients ≥75 years relevant to this review: Cases NSAID users=988 COX-2 users=142 Mean age in subgroup ≥75 years: not shown	**Comparison group** Subgroup analysis of patients ≥75 years relevant to this review: Controls NSAID users=1831 COX-2 users=353 Mean age in subgroup ≥75 years: not shown	**Risk of hospital admission due to a PUB in individuals ≥75 years. Adjusted OR (95% CI).** *NSAID users with PPI vs NSAID users without PPI:* Adj OR: 0.69 (0.47 to 1.03) *COX-2 users without PPI vs NSAID users without PPI:* Adj OR: 0.88 (0.64 to 1.22) *NSAID users without PPI vs COX-2 users with PPI:* Adj OR: 0.71 (0.53 to 0.97) NSAID users with PPI: *Individuals aged ≥75 years vs individuals <75 years:* Adj interaction OR: 0.79 (0.64 to 0.99) COX-2 users without PPI:

	Individual retrospective follow up from index date to date of last prescription for study drugs.	n=2634 cases and 5074 controls were users of NSAIDs or COX-2 inhibitors (with or without PPIs) at the index date 60% women Mean age: 69 years old (SD 15 years)			*Individuals aged ≥75 years vs individuals <75 years:* Adj interaction OR: 1.22 (1.01 to 1.47) COX-2 users with PPI: *Individuals aged ≥75 years vs individuals <75 years:* Adj interaction OR: 0.84 (0.7 to 1.00) *Adjusted OR for sex, concomitant drugs (acid-lowering drugs, vitamin K antagonists, platelet aggregation inhibitors, glucocorticoids, and selective serotonin receptor inhibitors), and a history of drug use (conventional NSAID, selective COX-2 inhibitors, and acid-lowering drugs).*
Chang et al 2011 [52] Taiwan **Risk of bias** Moderate	**Design** Case cross-over study **Aim** Evaluate the risks of upper (GI) adverse events of coxibs and nonselective NSAIDs in the general population of Taiwan **Follow-up time** Study period 2006.	**Participants** *Cases* Patients aged ≥20 years who were hospitalized for upper GI adverse events (peptic ulcer, bleeding, gastritis or duodenitis) *Exposure to study drugs* Outpatient pharmacy prescription database was searched for individual NSAID use during the case and control periods. n=40635 patients hospitalized for upper GI adverse events were included. 37% women	**Intervention group** Subgroup analysis of patients ≥65 years relevant to this review: The case period was defined as 1–30 days before the date of hospitalization Neither number of patients, nor the characteristics of these, were shown for this subgroup.	**Comparison group** Subgroup analysis of patients ≥65 years relevant to this review: The control period was defined as 31–60 days before the date of hospitalization Neither number of patients, nor the characteristics of these, were shown for this subgroup.	**Risk of hospital admission due to upper GI events** (peptic ulcer, bleeding, gastritis or duodenitis) **in individuals ≥65 years. Adjusted OR (95% CI).** Celecoxib users: *Case period vs control period* Adj OR 65–79 years: 1.97 (1.53 to 2.54) Adj OR ≥80 years: 1.63 (1.18 to 2.24) Oral nonselective NSAIDs *Case period vs control period* Adj OR 65–79 years: 3.42 (3.14 to 3.72) Adj OR ≥80 years: 4.35 (3.85 to 4.93) Adjusted OR for important potential time-varying confounding variables including selective serotonin reuptake inhibitors, other antidepressants, calcium channel blockers, nitrates, systemic corticosteroids, low-dose

	For each patient, the case period was defined as 1–30 days and the control period as 31–60 days before the date of hospitalization	Mean age: 61 years old (SD 18 years)			aspirin, proton pump inhibitors, histamine 2 receptor blockers, and sucralfate.
Randomized studies					
Dahlberg et al 2009 [53] Scandinavia **Risk of bias** Moderate	**Design** Double-blind, active and placebo controlled, randomized, prospective study **Aim** To compare the adverse event-related discontinuation rate with celecoxib vs. diclofenac associated with knee or hip osteoarthritis in elderly patients **Time to follow-up** 52 weeks	**Participants** *Inclusion*: ≥60 years of age OA in hip or knee Functional capacity classification of I–III according to ACR criteria *Exclusion:* History of NSAID-induced peptic ulcer, two or more episodes of peptic ulceration or GI bleeding, active GI disease or any type of malignancy, diagnos of an oesophageal, gastric, or duodenal ulcer within 30 days of randomization, history of renal or hepatic disease, clinically significant congestive heart failure, anticipated need for digoxin/digitoxin, requirement of corticosteroid or hyaluronic	**Intervention** Celecoxib 200 mg q.d. *Participants* n=458 *Drop-out rate* n=181 (39.5%) Mean age: 71 years (SD 7 years)	**Comparison** Diclofenac 50 mg b.i.d. *Participants* n=458 *Drop-out rate* n=185 (40.3%) Mean age: 71 years (SD 7 years)	**Primary endpoints** Incidence of discontinuation of study drug due to AEs: Celecoxib: 124/458 (27.1%) Diclofenac:142/458 (31.0%) *Celecoxib vs diclofenac (9 % CI):* –3.9% (–9.8 to 1.9), p=0.22 **Secondary endpoints** Time to discontinuation of study medication, log rank test Kaplan-Meier survival: p=0.23 Hazard ratio (95% CI) diclofenac vs celecoxib: 1.16 (0.91 to 1.47)

		acid within 30 days of randomization n=925 68.5% women Mean age: 71 years old (SD 7 years)			

AE = adverse events; **ACR** = American College of Radiology; **b.i.d.** = bis in diē. (twice a day); **CI** = confidence interval; **COX** = cyklooxygenas; **GI** = Gastrointestinal; **n** = number; **NSAID** = Non steroidal anti-inflammatory drugs; **OR** = odds ratio; **p** = p-value; **PPI** = proton pump inhibitor; **PUB** = peptic ulcer bleeding; **q.d** = quaque die (once a day); **SD** = standard deviation

Part VI. Opioids and the risk of falls

Systematic reviews

One systematic review, Seppala 2018 [54], was included. Seppala et al included 30 studies that investigated the correlation of treatment with opioids and the risk of falls. Eight of them were suitable for meta-analysis.

Table 8 Included systematic review on treatment with opioids and the risk of falls.

Author Year Reference	Study design Follow up	Population	Interventions and controls	Outcome – safety	Risk of bias SBU rating of risk of bias in the review
Seppala et al 2018 [54]	Systematic review and meta-analysis of 281 studies (randomized and non-randomized studies) that investigated nonpsychotropic and noncardiovascul	All settings (population-based, community dwellers, hospital wards, long-term care institutions, and outpatient clinics). Participants needed to be at least 60 years old, or the mean age of the participants had to	Use, as compared with non-use, of index drug.	The risk of falling with opioid use vs non-use in 8 non-randomized studies (total 366036 participants) with individuals 65 years or older that presented adjusted odd ratios: *Opioid use vs non-use (95% CI):* Adjusted OR 1.6 (1.35 to 1.91)	Study eligibility criteria: *Low* Identification and selection of studies: *Low* Data collection and study appraisal: *Low* Synthesis and findings: *Unclear (no information on sensitivity analysis or robustness of findings)*

	ar medications as risk factors for falls. Meta-analysis was performed using the generic inverse variance method, pooling unadjusted and adjusted odds ratio (OR) estimates separately.	be 70 years or more, or the results of the older age group needed to be reported separately.			Overall risk of bias: *Low*

CI = confidence interval; **OR** = odds ratio

Primary studies

We performed a search of primary studies from 2016 (when Seppala et al performed their search) and onwards. We included five [55-59] additional primary studies.

Table 9 Included primary studies on treatment with opioids and the risk of falls.

Author Year Reference Country Risk of bias	Design Aim Time to follow-up	Participants Women/men Age	Intervention group Participants Age	Comparison group Participants Age	Outcome
Daoust et al 2018 [55] Canada **Risk of bias** Moderate	**Design** Retrospective cohort study **Aim** To examine the association between recent opioid use and the risk, as well	**Participants** Patients aged ≥65 years who were admitted for injury in any adult trauma centres in the province of Quebec. Information on medical consultations and medications were extracted from two governmental population databases.	**Cohort** Patients who were admitted for injury sustained from a fall n=3041 78.1% women Mean age: not shown	**Control** Patients who were admitted for injury sustained from another mechanism n=85 % women: not shown	**Risk of falling with opioid use** Opioid users were 2.4 times (95% CI, 1.9 to 3.0) more likely to have suffered a fall rather than an injury via another mechanism

	as the clinical outcomes, of fall-related injuries in a large trauma population of older adults **Follow-up time** Study period 2004–2014. Individual retrospective follow up 2 weeks preceding the trauma in patients who sustained a fall	Patients with no recorded mechanism of their injury were excluded. n=67929 69% women Mean age: 81 years old (SD 8 years)		Mean age: not shown	
Grewal et al 2018 [56] Canada **Risk of bias** Moderate	**Design** Retrospective cohort study **Aim** To examine the risk of fractures in discharged Emergency Deparment (ED) patients with peripheral vertigo who were being prescribed opioids during the same time period	**Participants** Patients aged ≥65 years with index diagnos in an administrative database that contains abstracted data on all ED patient visits in the province of Ontario. Drug use was examined in the Ontario drug benefit database. Patients were excluded if they were admitted to the hospital from the ED, were from a long-term care facility/nursing home, died in the ED, or were seen in an ED that was not open 24 hours a day 68% women	**Cohort** Patients who were discharged from ED with diagnosis of peripheral vertigo 1676 (12,9%) had access to a filled opioid prescription n=13012 62% women Mean age: 76 years old (SD 7 years)	**Control group** Patients who were discharged from ED with diagnosis of urinary tract infection (UTI) 18969 (24.7%) had access to a filled opioid prescription n=76885 69% women Mean age: 78 years old (SD 8 years)	**Risk of fractures with opioid use** *Vertigo patients, adjusted hazard ratios (95% CI):* Opioid users vs non opioid users, 3.59 (1.97 to 6.13). *UTI patients, adjusted hazard ratios (95% CI):* Opioid users vs non opioid users, 1.68 (1.43 to 1.97).

	Follow-up time Study period 2006–2011. Individual retrospective opioid use 90 days preceding the ED visit/ Hospitalization for a fracture	Mean age: 78 years old (SD 8 years)			
Hunnicut et al 2018 [57] USA **Risk of bias** Moderate	**Design** Retrospective cohort study **Aim** To estimate the comparative safety of initiating commonly used opioids among older, long-stay United States nursing home residents with fracture hospitalizations **Follow-up time** Study period 2011–2013. Incident opioid users were followed for 180 days.	**Participants** Medicare beneficiaries aged ≥65 who were long-stay nursing home residents (≥120 consecutive days in facility) and who initiated short-acting oral formulations of hydrocodone, oxycodone, or tramadol. Initiation was defined as being prescribed a study drug with no prior prescriptions of any opioid in the 120 days before the initiating fill date. *Exclusion criteria:* Recently hospitalized or received skilled nursing facility care. Treatment episodes were the resident was comatose, had cancer, received hospice care, or had missing data on potential confounders. Those initiating unusually high opioid doses.	**Cohorts** *Oxycodone:* 14373 treatment episodes 72% women Mean age: 84 years (SD 9 years) *Hydrocodone:* 69182 treatment episodes 75% women Mean age: 84 years (SD 9 years) *Tramadol:* 50877 treatment episodes 79% women Mean age: 86 years (SD 8 years)		**Risk of fractures with different opioids** *Incidence of fracture hospitalizations per 100 person-years (95% CI):* Oxycodone: 9.4 (7.5 to 11.7) Hydrocodone: 7.9 (7.1 to 8.8) Tramadol: 5.0 (4.3 to 5.7) *Adjusted hazard ratio (95% CI):* Oxycodone vs hydrocodone: 1.08 (0.79 to 1.48)

		n=110862 residents contributed to 134432 treatment episodes. 76% women Mean age: 85 years (SD 9 years)			
Krebs et al 2016 [58] USA **Risk of bias** Moderate	**Design** Prospective cohort study **Aim** To examine longitudinal relationships between opioid use and falls, clinical fractures, and changes in physical performance **Follow-up time** Participants completed baseline visits from 2000 to 2002 and were followed for 9.1 (SD 4.0) years.	**Participants** Community dwelling men ≥65 years of age included in the Osteoporotic Fractures in Men Study (MrOS), a large prospective longitudinal cohort study. MrOS enrolled 5994. The present study included 2902 participants with back, hip, or knee pain most or all of the time at baseline. Medication exposure and covariate data were collected from participants at baseline and two follow-up visits. Opioid use was defined as participant-reported daily or near-daily use of any opioid analgesic. 0% women Mean age: 74 years old (SD 6 years)	**Cohort** Patients with opioid use n=129 0% women Mean age: 75 years old (SD 6 years)	**Control group** Patients without opioid use n=2603 0% women Mean age: 74 years old (SD 6 years)	**Risk of falls and fractures with opioid use** *Adjusted relative risk of falls (95% CI):* Opioid users vs non opioid users: 1.10 (0.99 to 1.24) *Adjusted hazard ratio of any clinical fracture (95% CI):* Opioid users vs non opioid users: 1.13 (0.94 to 1.36) *Adjusted hazard ratio of hip fracture (95% CI):* Opioid users vs non opioid users: 1.64 (0.97 to 2.79)
Taipale et al 2018 [59] Finland	**Design** Matched cohort study **Aim**	**Participants** All community dwelling persons who were diagnosed with AD between 2005 and	**Cohort** Incident opioid users n=4750	**Matched cohort** Opioid non-users n=4750	**Risk of hip fracture** *Adjusted HR (95% CI), Incident opioid use vs non-use*:

Risk of bias Moderate	To investigate whether incident opioid use is associated with an increased risk of hip fractures among community-dwelling persons with Alzheimer disease (AD) and to assess the association in terms of duration of use and opioid strength. **Study period** Between 2005 and 2011	2011 in Finland. Incident opioid users were matched with opioid nonusers. Matching was based on age, sex, and time since AD diagnosis at opioid initiation. Data on drug use and hip fractures were retrieved from nationwide registers. Incident opioid users were identified with a 1-year washout. n=9500 67% women Mean age: 83 years old (SD 7 years)	67% women Mean age: 83 years old (SD 7 years)	67% women Mean age: 83 years old (SD 7 years)	According to duration of use: All follow-up: 1.96 (1.27 to 3.02) 1–60 days: 2.37 (1.04 to 5.41) 61–180 days: 1.79 (0.82 to 3.89) 181–365 days: 1.43 (0.61 to 3.37) >365 days: 2.59 (0.92 to 7.28) According to opioid strength: Weak opioid: 1.75 (0.91 to 3.35) Buprenorphine: 2.10 (1.41 to 3.13) Strong opioid: 2.89 (1.32 to 6.32)

CI = confidence interval; **HR** = hazard ratio; **n** = number; **SD** = standard deviation; vs = versus

Part VII – Experiences of encounters between elderly with pain and health care staff

Primary studies

We included 20 relevant primary studies [60-79].

Table 10 Included primary studies on experiences of encounters between elderly with pain and health care staff.

Author Year Ref Country	Aim	Theory or approach Competence of researchers	Setting, recruitment	Participants	Data collection	Data analysis
Baumann et al 2007 [60] France	Explore expectations of the patient-physician relationship to improve the health care provision for persons with OA	No specific theory or approach Two teams of senior academic sociologists and rheumatologists	10 pharmacies in 10 towns in 10 regions, randomly selected. The first 10 customers that purchased medication for OA were approached	n=96 elderly (81% women) Mean age: 65 years (42–89) Duration of disease: 18 years	10 focus groups with 10 participants each. Moderated by 2 teams with 2 interviewers each. Two hours duration	Not described
Berglund et al 2015 [61] Sweden	Describe HCP:s experiences of providing health care to older adults with long-term musculoskeletal pain at home to gain a deep understanding	Reflective lifeworld research (RLR), based on phenomenology Three researchers, speciality not stated	Integrated social services and medical care at home in three communities in the western region of Sweden Nomination by the heads of the health care units	n=10 registered HCP (5 nurses, 3 physiotherapists, 2 occupational therapists) (8 women) Mean age: 52 years (range 35 to 56 years) Experience of working with elderly with pain: mean 19 years (range 5 to 34 years)	Interviews grounded in the RLR approach	Grounded in the RLR approach and directed towards discovering patterns and nuances of qualitative meanings.

Blomqvist et al 2002 [63] Sweden	Explore sense of self, sense of pain, daily living with pain, sense of others and ways of handling pain	Construction of a typology One junior and one senior registered nurse	People receiving care from nursing auxiliaries in their homes or in sheltered accommodation. Invitation letters to individuals above 75 years and with persistent pain who were able to be interviewed were identified by staff	n=90 (73% women) Mean age: 85 years (SD 6.0) Duration of pain: 8 years (3–20 years)	Interviews with open and structured questions, lasting 45–90 minutes. Performed in the respondents' homes	Development of a typology based on the literature Manifest content analysis for ways of handling the pain
Blomquist 2003 [62] Sweden	Explore nursing and paramedical staff perceptions of elderly with persistent pain and the day-to-day management of pain	Not reported One senior researcher and one co-investigator	Nursing auxiliaries (NA) in their homes or in sheltered accommodation in a municipality of southern Sweden All RNs and P/OTs were included	n=52 (33 NA, 10 RN, P/OT) (46 women) Mean age: 46 years >10 years' experience of care of elderly with persistent pain: n=47	Interviews with at strategy to obtain concrete descriptions of management of all elderly whom the staff had met the previous week (n=150). The interviews lasted between 20 and 45 minutes	Manifest content analysis and construction of typology for types of elderly in pain
Bower et al 2006 [64] Canada	Explore factors that influence patients to choose coxibs	Grounded theory Four researchers in family medicine	Community, two urban areas Random selection from a sample that had completed a quantitative survey	n=16	Interviews in the homes of the participants, conducted by the principal investigator. Data collection continued until perceived saturation	Consistent with grounded theory

Carmona-Terés et al 2017 [65] Spain	Explore patient related factors that can affect the implementation of an intervention for knee OA Explore perceptions and experiences of living with knee OA	Lazarus stress model Eight researchers in primary care research, rheumatology and psychology; one specialised in interviewing	Primary care Recruitment by GPs at each of 4 PHCCs Theoretical sampling based on a priori defined patient characteristics	n=10 (70% women) with mild – moderate knee OA. Age: 60–85 years Duration of knee OA: 1–20 years	Semi-structured interviews conducted by the first author at the PHCCs and lasting 30–60 minutes. Observational field notes	Content thematic analysis
Clarke 2014 [66] UK	Explore experiences of interacting with health professionals	No specific theory or approach Seven university researchers, specialised in nursing, medicine, occupational therapy and one GP	Community Purposive sampling through media advertising	n=23 (70% women) with self-reported chronic musculoskeletal pain Median age: 73 years (66–89 years)	Two in-depth interviews with each participant: n=14 One group interview: n=7 One individual interview: n=2 Interviews lasted for one hour	Framework analysis
Davis et al 2002 [67] USA	Explore barriers to pain management	Grounded theory Three registered nurses: one professor, one doctoral student and one practitioner	Community, respondents with arthritis that lived in own homes or in retirement settings and were functioning independently Recruitment via ads and flyers	n=57 (79% women) Mean age: 79 years (SD 6.88) Arthritis: OA (63.2%), osteoporosis (33.3%), RA (29.8%), tendinitis or bursitis (19.3%)	8 focus groups (group size 5 to 9).	Open coding of data followed by axial and selective coding
Erwin et al 2018 [68] UK	Explore expectations on community-based HP to improve	Partly phenomenology	Community Recruitment through	n=25 (64% women) Age: 28 to 84 years	Four focus groups, between 4 and 8 participants. Duration: 1 hour	Deductive thematic analysis

	care of people with arthritis	Seven researchers, senior and junior with various backgrounds	advertisements and flyers to local support groups, GP surgeries and local newspapers	Arthritis: IA or OA	The approach was phenomenological	
Gudmansdottir et al 2009 [69] Iceland	Explore the lived experiences of elderly with chronic pain	Interpretive phenomenology according to the Vancouver school One professor and one junior researcher in nursing research	Nursing homes Purposeful sampling. Recruitment via head nurses	n=12 (42% women) Mean age: 86 years (74–97 years)	Open interviews, two per participant, lasting for 10–44 minutes (mean 46 minutes for both interviews)	According to the Vancouver School
Higgins 2005 [70] Australia	Explore the lived experience of being old with chronic pain	Phenomenology according to Merleau-Ponty One senior researcher in nursing sciences	Three nursing homes Recruitment via the nursing unit manager	n=13 (77% women) Age: 78–97 years Pain mostly was related to arthritis and ageing pathology like OA and vascular disease	In-depth interviews and observational field notes. Interviews lasted <1 hour and most participants were interviewed several times	Phenomenologic reduction
Hill et al 2010 [71] UK	Explore experiences of the treatment and management of hand OA	No specific theory or approach Three researchers from the Arthritis Research UK National Primary Care Centre	Primary and secondary care Purposive sampling from a longitudinal study	n=17 (82% women) Mean age: 64.9 years (51–84 years) Duration of hand OA: 1–30 years	Two focus groups in primary care and two in secondary care	Inductive thematic analysis with the constant comparison method
Kaasalainen 2010 [72] Canada	Explore barriers to pain management with qualitative and quantitative methods (only qualitative reported here)	Not reported Twelve researchers with broad expertise	Two LTC homes in the Ontario area Purposive sampling, recruited by the advance	n=53; 70% of HCP women Mean age: 49 years	Focus groups: one at each site with RNs, one with RPNs; one at each site with UCPs; and one with physicians from both sites	Content analysis for the interviews Analysis according to Duggleby [80] and Stevens [81] for the focus groups

			practice nurse at each site		Individual interviews (30 minutes) with 2 pharmacists, 2 PTs, 2 administrators, 2 directors and 2 residents	
McHugh et al 2006 [73] UK	Explore patients' experiences of management and care in order to improve care	No specific theory or approach Three senior researchers in nursing or rheumatic disease epidemiology	Primary care, persons with end-stage lower limb OA, waiting for JR Purposeful sampling from 105 randomly selected patients who were part of a longitudinal study	n=21 (80% women) Mean age: 65 years (48–86 years) Duration of OA: 7 months to 38 years	Semi-structured individual interviews in the homes of the respondents. Duration on average 45 minutes	Framework analysis
Park et al 2015 [74] South Korea	Explore barriers influencing chronic pain management of nurses providing home-visiting care for low-income elderly	No specific theory or approach Three senior researchers in nursing	Home-visiting care from four PHC in one area	n=23 Median age: 46 years (range 32–53 years) Experience: median 8 (range 1–23 years) for RN median 5.7 years (range 3–13 years) for community nurses	4 focus groups with 5–6 participants per group which lasted around 1.5 hours.	Inductive thematic analysis
Paskins et al 2015 [75] UK	Increase understanding of the consultation in order to improve the care and management of OA	No specific theory or approach The team included competencies in qualitative research, rheumatology, sociology and	Seven GP surgeries Invitation to members of local research networks. Consecutive patients >45 years	n_1=17 patients (68% women) Median age: 69 years (49 to 84 years)	Video-recorded real-life consultations and interviews after the consultation. Interviews were conducted by one investigator	Constant comparison

		epidemiology and primary care. Both senior and junior researchers	where the GP used OA or arthritis diagnostically or findings supported the diagnosis	n_2=13 GPs (3 women) Experience as GP: median 17 years (range 3 to 29)		
Rosemann et al 2006 [76] Germany	Identify health care needs of patients with OA and barriers to improvements in primary care management of OA	No specific theory or approach Six senior researchers with expertise in primary care and implementation science; two had experience from qualitative research	Unclear number of GP surgeries Unclear method for selecting GPs and nurses. Random selection of patients from the GPs computer files	n_1=20 patients (12 women) Mean age: 56 years (40–78 years) n_2=20 GPs (4 women) Mean age: 43, 5 (33–57) Years working experience: mean 11 (8–19 years) n_3=20 practice nurses (20 women) Mean age: 41 (29–56) Years working experience: 22 (13-–35)	Individual, semi-structured interviews	Unclear method, but data was analysed with Atlas.ti software and all steps in the analysis was conducted independently by four researchers followed by consensus.
Spitaels et al 2016 [77] Belgium	Explore perceived barriers and facilitators in current care of knee OA in order to improve guideline adherence	Framework for implementation by Grol and Wensing The team included one expert in qualitative research	GP practices in a region and advertisement in the national federation for patients with rheumatic diseases	n=11 (64% women) Mean age: 66.2 years (40–90 years)	Face-to-face interviews in the participants' homes, guided by the Belgian set of quality indicators	Directed content analysis

					Median duration: 52 minutes (28–88 minutes)	
Svensson et al 2016 [78] Sweden	Explore the experience of women living with VCF	Phenomenological hermeneutic approach Five researchers	One outpatient clinic in Gothenburg Purposeful selection of women one or several osteoporotic VCFs.	n=10 Mean age: 80 years	Face-toface interviews in the participants' homes, lasting between 50 and 75 minutes. Memos and field notes were taken to capture body language and emotions	Based on the theoretical approach where the interpretation was based on a dialectic dialogue between the naïve understanding and the structural analysis. Conducted by two researchers
Yates et al 1995 [79] Australia	Provide an in-depth account of the beliefs, attitudes and perceptions to pain of elderly.	No specific theory or approach Three senior researchers in nursing	Five residential care settings in Brisbane Residents able to participate were identified by the directors of nursing	n=42 (35 women) Age: 65 years or older	10 focus group interviews (4-9 participants per group), lasting around 1 hour	According to Marshall and Rossman 1989; independent coding followed by meetings to agree upon codes and categories

GP = general practitioner; **HCP** = Health care professionals; **HP** = Health Practitioners; **IA** = Inflammatory arthritis; **JR** = joint replacement; **LTC** = long-term care; **n** = number; **OA** = osteoarthritis; **PHC** = primary health care; **PHCC** = primary health care centre; **P/OT** = physiotherapists and occupational therapists; **RA** = rheumatoid arthritis; **RN** = Registered Nurses; **RPN** = Registered Practical Nurses; **SD** = standars deviation; **UCP** = Unlicensed Care Providers; **VCF** = Vertebral compression fractures

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