Appendix A: List of Acronyms

%	percent
ABC	Activities-specific Balance and Confidence scale
ACROBAT-NRSI	Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions
AHRQ	Agency for Healthcare Research and Quality
ATL	Achilels tendon lengthening
BBS	Berg Balance Scale
BMI	Body Mass Index
CDC	Centers for Disease Control
CI	Confidence interval
DCCT	Diabetic Control and Complications Trial
DPN	Diabetic Peripheral Neuropathy
EDIC	Epidemiology of Diabetes Interventions and Complications
EPC	Evidence-based practice center
FDA	Food and Drug Administration
FES	Falls Efficacy Scale
FES-I	Falls Efficacy Scale – Internation version
FRT	Functional Reach Test
HR	Hazard Ratio
IWGDF	International Working Group on the Diabetic Foot
J-EDIT	Japanese Elderly Diabetes Intervention Trial
KQ	Key Question
NEURODIAB	Diabetic Neuropathy Study Group of the European Association for the Study of Diabetes
NMDA	N-methyl-D-aspartate
NPSI	Neuropathic Pain Symptom Inventory
NQOL	Neuropathic Quality of Life
NR	Not reported
NS	Not significant
OR	odds ratio
PENS	Percutaneous Electrical Nerve Stimulation
PICOTS	Populations, interventions, comparators, outcomes, timing, setting
QOL	Quality of Life
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation
SDIS	Stockholm Diabetes Intervention Study
SMD	Standardized Mean Difference
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors
T2DM	Type 2 diabetes mellitus
TCA	Tricyclic antidepressants
TCC	Total Contact Casting
TENS	Transcutaneous Electrical Nerve Stimulation
TOO	Task Order Officer
TUG	Timed Up and Go Test
VACSDM	Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes
VAS	Pain Visual Analogue Scale

Appendix B. Detailed Search Strategy

PubMed

A (diabetes neuropathy)	B (Interventions for KQ1 and 2)
diabetes mellitus[mh] OR diabetes [tiab] AND peripheral nervous system diseases [mh] OR “Peripheral Nerve Diseases”[tiab] OR “Peripheral Nerve Diseases”[tiab] OR neuropathy[tiab] OR Polyneuropathy[tiab] OR “Peripheral Nerve Disease”[tiab] OR neuropathies[tiab] OR Polyneuropathies[tiab] OR "PNS disease"[tiab] OR "PNS diseases"[tiab] OR “Diabetic Neuropathies” [MH] OR neuropathy[tiab] OR “diabetic polyneuropathy" [tiab] .	"hypoglycemic agents"[mh] OR Hypoglycemic[tiab] OR hypoglycaemic [tiab] OR antidiabetic[tiab] OR Antihyperglycemic[tiab] OR "insulin infusion systems"[MeSH Terms] OR insulin [tiab] OR “glycemic control”[tiab] OR “glycaemic control”[tiab] OR “metformin”[mh] or “thiazolidinediones”[mh] or “glipizide”[mh] or “glyburide”[mh] OR “Dipeptidyl-Peptidase IV Inhibitors”[mh] OR “Glucagon-Like Peptide 1”[mh] OR biguanide*[tiab] OR metformin[tiab] OR thiazolidinedione*[tiab] or pioglitazone[tiab] OR rosiglitazone[tiab] OR sulfonylurea*[tiab] or sulphonylurea*[tiab] OR glipizide[tiab] OR glyburide[tiab] OR glimepiride[tiab] OR glibenclamide[tiab] OR “insulin secretagogues”[tiab] OR sitagliptin*[tiab] OR saxagliptin*[tiab] OR dpp-4[tiab] OR(exercise [mh]) OR ((exercise[tiab] or exercises[tiab]) AND (program[tiab] OR programs[tiab] OR intervention [tiab] OR interventions [tiab] OR balance [tiab] OR coordination[tiab] OR coordinations[tiab] OR aerobic[tiab] OR isometric[tiab] OR therapy OR strength[tiab] OR endurance[tiab] OR endurances[tiab] OR running[tiab] OR walking [tiab] OR cycle[tiab] OR treadmill[tiab] OR stair[tiab]))) OR physical exertion[mh] OR ((physical [tiab]) AND (activity[tiab] OR activities[tiab] OR fitness [tiab] OR therapy[tiab] OR exercise[tiab] OR education[tiab] OR training[tiab] OR exertion[tiab] OR exertions[tiab] OR effort[tiab] OR efforts[tiab]))) OR Rehabilitation[mh] OR Rehabilitation[tiab] OR (training [tiab] AND (aerobic [tiab] OR resistance[tiab] OR strength [tiab] OR balance [tiab] OR endurance[tiab] OR endurances[tiab] OR weight[tiab])) Sports[mh] OR ((therapy[tiab] OR therapies[tiab]) AND (moving[tiab] OR sports[tiab]))) OR “Stair Navigation”[tiab] OR postural balance[mh] OR “postural stability”[tiab] OR posture[mh] or posture[tiab] OR postures[tiab] or “postural control” [tiab] OR muscle strength[mh] OR muscle strength[tiab] OR proprioception[mh] OR Proprioception[tiab] OR)) OR Weight-Bearing[mh] OR WeightBearing[tiab] OR “weight loss”[mh] OR “weight loss”[tiab] OR “Diet, Carbohydrate-Restricted”[mh] OR diet[tiab] OR “smoking cessation”[mh] OR “smoking cessation”[tiab] OR “lifestyle intervention”[tiab] OR “physical therapy”[tiab] OR” Physical Therapy Modalities”[mh] OR Rehabilitation[mh] OR Rehabilitation[tiab] OR (Acupuncture [MH])) OR ((acupuncture[tiab]) AND (injection[tiab] OR therapy [tiab] points[tiab] OR therapy[tiab]))) OR ("decompression, surgical"[mh] OR "surgical decompression"[tiab])) OR "electric stimulation therapy"[mh]) OR (((neural [tiab] OR nerve[tiab] OR therapy[tiab])) AND stimulation[tiab])) OR “TENS”[tiab]) OR (Cognitive therapy [mh] OR “Cognitive therapy” [tiab] OR “Cognitive behavioral”[tiab] or “cognition therapy”[tiab] OR “cognitive Psychotherapy”[tiab] OR “behavioral therapy”[tiab] OR “behavioral therapies”[tiab] OR “thioctic acid”[mh] OR “lipoid acid”[tiab] OR “thioctic acid”[tiab] OR acetylcarnitine[mh] OR Acetylcarnitine [tiab] OR “Acetyl-L-Carnitine”[tiab] OR carnitine[tiab]))

Appendix C. Excluded Articles

KQ1 Excluded Articles

No full report/ original data

"Effects of a combined strengthening, stretching and functional training program versus usual-care on gait biomechanics and foot function for diabetic neuropathy: a randomized controlled trial. C. D. Sartor, R. Watari, A. C. PÃ¡ssaro, A. P. Picon, R. H. Hasue and I. C. Sacco. BMC Musculoskelet Disord 2012:

Induration of the diabetic foot pad: another risk factor for recurrent neuropathic plantar ulcers. T. Brink. Biomed Tech (Berl) 1995: 205-9

Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. K. Dahl-Jorgensen, O. Brinchmann-Hansen, K. F. Hanssen, T. Ganes, P. Kierulf, E. Smeland, L. Sandvik and O. Aagenaes. Br Med J (Clin Res Ed) 1986: 1195-9

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Capsaicin 8% patch repeat treatment versus standard of care in painful diabetic peripheral neuropathy: A randomised, open-label, 52-week study. A. I. Vinik, S. Perrot, E. J. Vinik, L. Pazdera, H. Jacobs, M. Stoker, S. Long, R. Snijder, M. Van Der Stoep, E. Ortega and N. Katz. Diabetologia 2015: S514-S515

Incidence of microvascular outcomes in type 2 diabetes patients treated with vildagliptin vs sulphonylurea: A retrospective study using German electronic medical records. W. M. Kolaczynski, M. Hankins, S. H. Ong, H. Richter, A. Clemens and M. Toussi. Diabetologia 2015: S394

Pregabalin positively affects subjective pain, falls risk, and gait in persons with diabetic peripheral neuropathy. S. Morrison, H. Parson and A. I. Vinik. Diabetes 2015: A164

Incidence of microvascular outcomes among type 2 diabetes patients treated with vildagliptin vs. Sulfonylurea: A retrospective cohort study using german electronic medical records. M. Hankins, S. H. Ong, H. Richter, W. M. Kolaczynski, A. Clemens, G. Machnicki, M. Toussi and J. Vora. Diabetes 2015: A4

Effect of intensive weight reduction on neuropathy progression in patients with diabetes: A 1-year controlled clinical trial. A. Mottalib, A. Morsi, M. Shehabeldin, M. Sakr and O. Hamdy. Diabetes 2015: A51-A52

The effects of treatment modalities on outcome in diabetic foot patients and retrospective evaluation of comorbidities. E. Ozay, O. Ersen, S. Bilgic and O. Rodop. European Surgical Research 2015: 163

Incidence and impact of hypoglycemia in diabetic patients with intensified glycaemic control in clinical practice-results of DiaRegis. A. K. Gitt, P. Bramlage, S. Schneider, C. Binz, M. Krekler and D. Tschoepe. European Heart Journal 2014: 1020-1021

Regular exercise improves metabolic control and reduces chronic complications in patients with type 2 diabetes. J. Tang, X. Li, Y. Yang, L. Yuan, J. Han, C. Ju, L. Shen, Q. Lou, F. Zhao, Z. Sun and X. Guo. Diabetologia 2014: S434

Game-based guided exercise: Using an avatar with real-time feed back to improve postural stability in diabetic peripheral neuro pathy. B. Najafi, G. Grewal, J. Lee-Eng, T. K. Talal, R. A. Menzies and D. G. Armstrong. Diabetes 2014: A186

Effect of roux-en-y gastric bypass surgery on microvascular complications of type 2 diabetes mellitus. L. L. Chuah, A. D. Miras, D. Papamargaritis, A. Vusiri Kala, S. N. Jackson, N. Oliver, T. Olbers and C. W. Le Roux. Diabetes 2014: A525

Nutrition intervention for diabetic neuropathy. A. E. Bunner, J. Gonzalez, U. Agarwal, F. Valente and N. D. Barnard. Diabetes 2014: A578

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Complex neurorehabilitation programme improves quality of life of patients with diabetic polyneuropathy and diabetic foot. Y. Koleva. Annals of Physical and Rehabilitation Medicine 2013: e38-e39

Determination of the the effectiveness of home exercise program in patients with diabetic neuropathy. L. CerrahoÊ‡lu, U. KoÅŸan and E. TopcÂ¸u. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi 2013: 359

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Smart prevention device for foot infection. M. Rocklinger, P. Vacherand, F. BrÃ¶nnimann, A. Mathieu, A. StÃ©phane and Z. Pataky. BMC Proceedings 2011:

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Exploring postural compensation in diabetes-related neuropathy patients (DPN): The role of visual and somatosensory adaptation. B. Najafi, R. T. Crews, S. C. Wu and J. S. Wrobel. Diabetes 2010:

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Effects of exenatide on measures of small fiber neuropathy in patients with type 2 diabetes. M. Jaiswal, C. L. Martin and R. Pop Busui. Diabetes 2014: A149

A pilot study of intranasal insulin for the treatment of diabetic peripheral neuropathy. L. Korngut, S. Mawani, G. Francis, E. Mehina, B. Hemmelgarn, N. Jette, D. W. Zochodne, S. Wiebe and C. Toth. Journal of the Peripheral Nervous System 2013: S59

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Appendix D. Evidence Tables

Evidence Tables for KQ1a and b
KQ1A
Evidence Table 1 – KQ1a Study Design Characteristics

Author, year	**Study design** **Site(s)** **Location**	**Recruitment period (start year – end year)**	**Diabetes type**	**Key exclusions**	**Treatment duration or follow-up time** **If applicable washout period, run-In period**	**Description of intervention in each group**	**Funding support**
Knatterud, 1978[1] UGDP	RCT Multi-site U.S.	1961-65	T2DM	A prior history of ketoacidosis	12 years	Group A. Insulin variable. Goal is normal glucose - fasting blood glucose level below 110 mg/100 Group B. Control. Insulin standard. No changes.	NIH
Reichard, 1993[2] Rathsman, 2014[3] SDIS trial	Original RCT observational follow-up Sweden	1982-84 intervention end: 1992 Observational follow-up ended: 2011	T1DM	History of or ongoing ischemic foot ulcer or foot and/or leg amputation; osteoarthropathy; alcohol/drugs abuse, mental illness.	7.5 years of treatment with 28 years of follow-up in sub-group	Group A: ICT, intensified conventional treatment, multiple insulin injections daily (pre-meal + basal) Group B: ST, standard treatment (2-3 insulin injections/day)	Novo-Nordisk, Boerhinger-Mannheim
Abraira, 1997[4] VACSDM	RCT Multi-site U.S.	Start - 1991	T2DM	Serious illness , T2DM >15, CV events in last 6 mos, h/o gangrene.	7.8 +/- 4 years	Group A. intensive. Stepped plan, starting with once daily insulin ± glipizide, to multiple daily injections) designed to reach goal of HbA1c < 7.5% Group B. standard (once daily insulin)	Veterans Affairs and Roerig/ Pfizer Pharmaceuticals

Evidence Table 1 – KQ1a Study Design Characteristics (continued)

Author, year	Study design Site(s) Location	Recruitment period (start year – end year)	Diabetes type	Key exclusions	Treatment duration or follow-up time If applicable washout period, run-In period	Description of intervention in each group	Funding support
UKPDS, 1998[5]	RCT with observational followup Multisite Europe	1977-1991	T2DM	Ketonuria, serum creatinine greater than 175 µmol/L; myocardial infarction in the previous year; current angina or heart failure; more than one major vascular event.	Median follow-up 10.7 years (IQR 7.7-12.4)	Group A. Intensive. FPG < 6 mmol/L, in insulin treated patients, pre-meal glucose 4-7 mmol/L (72 -126 mg/dl) (mean A1c over 10 years 7.0%) Group B: Conventional. FPG < 15 mmol/L (<270mg/dl) and avoidance of hyperglycemia symptoms (mean A1c over 10 years 7.9%)	National Health service, Smith Kline, Glaxo Wellcome, Pfizer, Zeneca, pharmacia, Upjohn, Roche.
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	RCT, open with observation follow-up Denmark	1993-2001	T2DM	Age > 65 or < 40; malignancy; or life-threatening disease with death probable within 4 years.	Mean treatment 7.8 years, followed for mean of 5.5 more years	Group A: conventional treatment, by GP, according to the 1988 recommendations of the Danish Medical Association Group B: intensive multifactorial intervention involving strict treatment goals to be achieved through behavior modification and a stepwise introduction of pharmacologic therapy overseen by a project team (doctor, nurse, and dietitian) at the Steno Diabetes Center	Danish Health Research Council.
Dormandy, 2005[8] PROactive	RCT Multi-site Europe	2001-2022	T2DM Also evidence of extensive macrovascular disease	Taking only insulin; had planned coronary or peripheral revascularisation; heart failure, ischaemic ulcers, gangrene, or rest pain in the leg; haemodialysis; or had greater than 2·5 times the upper limit of normal concentrations of alanine aminotransferase.	Mean follow-up 34.5 months	Group A: Pioglitazone + background meds (oral pioglitazone 15 mg for the first month, 30 mg for the second month, and 45 mg thereafter to achieve the maximum tolerated dose, according to the licensed dose range for pioglitazone.) Group B: placebo + background meds	Takeda Pharmaceutical Company and Eli Lilly and Company,

Evidence Table 1 – KQ1a Study Design Characteristics (continued)

Author, year	Study design Site(s) Location	Recruitment period (start year – end year)	Diabetes type	Key exclusions	Treatment duration or follow-up time If applicable washout period, run-In period	Description of intervention in each group	Funding support
Martin, 2006[9 10] (parent trial) DCCT/EDIC	RCT with observational follow-up	Recruitment 1983-1989 EDIC began in 1994, 1 yr after trial completion	T1DM	Diabetes duration < 1 years or > 15 years, no CKD or severe retinopathy	Original trial follow-up was 4-9 years, mean 6.5 years Cohort analysis is at years 8	Group A: intensive therapy (administering insulin three or more times daily by injection or by an external insulin pump) Group B: conventional therapy (one to two injections of insulin daily)	NIH
Duckworth, 2009[11] VADT	RCT Multi-site U.S.	2000-2003	T2DM	Recent CVD event, A1c <=7.5%, CHF, severe angina	Median 5.6 years	Group A: Intensive glycemic control, < 6% Group B: standard treatment	Dept. of VA Affairs, Medications provided by Pharma comps.
Griffin, 2011[12] ADDITION	RCT, cluster randomized Multi-site Europe	2001-2006	T2DM	Age <40,age >69	5·3 (SD 1·6) years	Group A: Screening + intensive treatment to goal A1c <7.0% Group B: Usual care	National Health Service Denmark, Danish Council for Strategic Research, Danish Research Foundation, Danish National Board of Health, Danish Medical Research Council, Aarhus University Research Foundation, Wellcome Trust, UK Medical Research Council, UK NIHR Health Technology Assessment Programme, UK National Health Service R&D, UK National Institute for Health Research, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, Novo Nordisk, Astra, Pfi zer, GlaxoSmithKline, Servier, HemoCue, Merck

Evidence Table 1 – KQ1a Study Design Characteristics (continued)

Author, year	Study design Site(s) Location	Recruitment period (start year – end year)	Diabetes type	Key exclusions	Treatment duration or follow-up time If applicable washout period, run-In period	Description of intervention in each group	Funding support
Araki, 2012[13] J-EDIT	RCT Multi-site Japan	2001-2002	T2DM	Age<65 or >85, A1c <8% and CVD risk factors	3 years	Group A: Intensive. The treatment goal in the intensive treatment group was HbA1c 6.9% and other CVD management goals. Group B: conventional treatment group continued their baseline treatment for diabetes, hypertension or dyslipidemia without a specific treatment goal.	Japanese Ministry of Health and Labour, and Welfare, Japan Foundation for Aging and Health.
Kostev, 2012[14]	Retrospective cohort study Germany	July 2000 and September 2007	T2DM	Patients who did not meet the continuity of follow-up criteria, received another basal insulin or premixed insulin during the observation period.	24 months	Group A: Glargine basal insulin Group B: NPH basal insulin	NR
Jaiswal, 2015[15]	RCT, open label Single site, university setting U.S.A.	2008-2014	T2DM	Neuropathy independent of diabetes, or any condition other than diabetes associated with neuropathy (e.g. hepatitis C, end stage renal disease, lupus), any lower extremity amputation or severe deformity of lower extremity, HbA1c<=7%, HbA1c > 10.	18 months	Group A: Exenatide, 5 µg twice daily for 4 weeks and then increased to 10 µg daily Group B: Insulin Glargine, 10 units daily, titrated in 2-unit increments to achieve a fasting blood glucose target level of 100 mg/dL without recurrent or severe hypoglycemia.	Amylin Pharmaceuticals, LLC, Eli Lilly and Company, Bristol-Myers Squibb Company and Astra-Zeneca

Evidence Table 2 – KQ1a Patient's Characteristics

Baseline population characteristics **Author, year**	**Group, N**	**Age** **Mean** **Median** **SD**	**Diabetes duration (years)**	**Female N (%)**	**Race N (%)**	**HbA1c** **Mean** **Median** **SD**	**BMI** **Mean** **Median** **SD**	**Neuropathic symptoms and findings at baseline**	**N of withdrawals**
Knatterud, 1978[1] UGDP	Total sample N=1027	52.7 (11.2)	NR	733 (71.4)	White (vs non-white): 53.9%	NR	NR	NR	NR
Reichard, 1993[2] SDIS	Group A: ICT, intensified conventional treatment, 48	Mean (SD): 30 (8)	18 (6)	22	NR	9.5 (1.3)	22.6 (2.1)	5 (12%)	6
	Group B: ST standard treatment with insulin, 54	Mean (SD): 32 (7)	16 (4)	26	NR	9.4 (1.4)	22.8 (2.2)	8 (17%)	7
Abraira, 1997[4] VACSDM	Group A: intensive, 75	60.4 ± 6.4	8.0 + 3.6	0 (0%)	W: 47 (62.7) B: 26 (34.7) O: 2 (2.7)	9.3 ± 1.3	30.7 ± 4.4	NR	N = 4
	Group B: standard, 78	59.9 ± 6.7	7.7 ± 4.3	0 (0%)	W: 52 (66.7) B: 22 (28.2) O: 4(5.1)	9.5 ± 1.5	31.3 ± 5.5	NR	NR

Evidence Table 2 – KQ1a Patient's Characteristics (continued)

Baseline population characteristics Author, year	Group, N	Age Mean Median SD	Diabetes duration (years)	Female N (%)	Race N (%)	HbA1c Mean Median SD	BMI Mean Median SD	Neuropathic symptoms and findings at baseline	N of withdrawals
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	Group A: conventional treatment for multiple risk factor, 80	55.2 (7.2)	Median 6 years Range 4-10	24 females (24/80)	NR	8.8 (1.7)	Men: 30.3 (5.3) Women: 28.9 (3.8)	29/80	2
	Group B: intensive, 80	54.9 (7.2)	Median 5.5 Range 20-8.8	17 females (17/80)	NR	8.4 (1.6)	Men: 29.3 (3.6) Women: 31.1 (4.5)	26/80	1
Dormandy, 2005[8] PROactive	Group A: Pioglitazone, 2605	Median (IQR) 61·9 (7·6)	Median (IQR) 8 (4–13	Male: 1735 (67%)	White 2564 (98%)	Median (IQR) 7·8 (7·0–8·9)	30·7 (4·7) 31·0 (4·8)	NR	1 lost to follow-up; 427 discontinued med; 149 withdrew consent; 43 other
	Group B: placebo, 2633	Median (IQR) 61·6 (7·8)	Median (IQR) 8 (4–14)	Male: 1728 (66%)	White 2600 (99%)	Median (IQR) 7·9 (7·1–8·9)	31·0 (4·8)	NR	1 lost to follow-up; 438 discontinued medication; 167 withdrew consent; 69 other

Evidence Table 2 – KQ1a Patient's Characteristics (continued)

Baseline population characteristics Author, year	Group, N	Age Mean Median SD	Diabetes duration (years)	Female N (%)	Race N (%)	HbA1c Mean Median SD	BMI Mean Median SD	Neuropathic symptoms and findings at baseline	N of withdrawals
Martin, 2006[9] DCCT/EDIC	Group A: (intensive), 711 at baseline Note: subgroup, 624 participated in the Neuropathy subgroup who had Neuropathy assessed at baseline, RefID 2079)	27 (7)	6 (4)	345 (49)	NR	9.1 (1.6)	23.3 (2.7)	15% (at completion of DCCT)	
	Group B: (less), 730 at baseline Subgroup, 633	27 (7)	5 (4)	335 (46)	NR	9.1 (1.6)	23.4 (2.9)	20%	
Duckworth, 2009[11] VADT	Group A: intensive , 892	60.5 (9.0	11.5 (8.0)	N = 26 (3%)	NHW: 539 Hisp: 155 (17%) Bl: 152 (17%) Other: 46	9.4 (2.0)	31.3 (3.0)	NR	120 (13.5%)
	Group B. standard treatment, 760	60.3 (9.0)	11.5 (7.0)	N = 26 (3%)	NHW: 572 Hisp: 136 (18%) Bl: 147 (19%) Other: 44	9.4 (2.0)	31.2 (4.0)	NR	139 (15.5%)
Griffin, 2011[12] ADDITION	Intensive, 1678	60.3 (6.9)	0	41.5	W: 1539 (95.8%)	Mean 7・0 (1・6)	31・6 (5・6)	NR	1678-1574 = 104

Evidence Table 2 – KQ1a Patient's Characteristics (continued)

Baseline population characteristics Author, year	Group, N	Age Mean Median SD	Diabetes duration (years)	Female N (%)	Race N (%)	HbA1c Mean Median SD	BMI Mean Median SD	Neuropathic symptoms and findings at baseline	N of withdrawals
	Routine, 1379	60.2 (6.8)	0	42.7	W: 1246 (93.4%)	Mean 7・0 (1・5)	31・6 (5・6)	NR	1379-1285 = 94
Araki, 2012[13] J-EDIT	Group A: intensive, 585	71.9 1 4.6	16.7 1 8.5	53.7	Asian: 100%	8.4 ± 0.8*	24.0 ± 3.9	Paresthesia: 22.3%	Total - 8.9% (104 cases)
	Group B: Standard, 588	71.7 1 4.7	18.0 1 9.9	53.7	Asian: 100%	8.5 ± 0.9	24.3 ± 7.3	Paresthesia: 18.5%	
Kostev, 2012[14]	Group A: Glargine, 9638	61.3 ± 15.2	6.1 ± 8.7	Male: 5326 (55%)	West Germany: 6813 (71%)	8.0 ± 1.7	29.5 ± 5.7	943 (9.8%)	NA
	Group B: (NPH), 13 757	60.2 ± 14.1	5.3 ± 7.9	Male: 7427 (54%)	West Germany: 10,467 (76%)	8.0 ± 1.7	30.7 ± 5.5	1486 (11%)	NA
Jaiswal, 2015[15]	Group A: Exenatide, 22	Mean (SD) 51 (13)	8 (5)	9 (41%)	White: 19 (86%)	8.2 ± 1.1	35 ± 3	DPN Symptoms: 21 (96%) DPN confirmed by clinical testing: 14 (67%)	3
	Group B: Insulin Glargine, 24	Mean (SD) 54 (9)	7(4)	11 (46%)	White: 21 (87%)	8.4 ± 1.4	37 ± 6	DPN symptoms: 22 (92%) DPN confirmed by clinical testing: 18 (75%)	0
Reichard, 1993[2] and Rathsman, 2014[3] SDIS	Sub-analysis 5.5 years after trial end, following iontophoresis, 35 in ICT	Mean (range) 42 (28–63)	28 (19–45)	21	NR	7.4 (5.8–9.4)	NR	N = 2	NR

Evidence Table 2 – KQ1a Patient's Characteristics (continued)

Baseline population characteristics Author, year	Group, N	Age Mean Median SD	Diabetes duration (years)	Female N (%)	Race N (%)	HbA1c Mean Median SD	BMI Mean Median SD	Neuropathic symptoms and findings at baseline	N of withdrawals
	ST, 37	Mean (range) 42 (31–63)	27 (19–39)	22	NR	8.4 (5.9–10.9)	NR	N = 8	NR
UKPDS[16]	Group A: intensive, 2729	53.2 (8.6)	Newly diagnosed	Female: 444/2729	White: 81% Indian: 10% Afro-Carib: 8% Other: 1%	Mean % (SD) 7.09 (1.54)	27.5 (5.1)	NR	N=122 122/2729= %
	Group B: conventional, 1138	Mean (SD) 53.4 (8.6)	Newly diagnosed	Female: 433/1138	White: 81% Indian: 11% Afro-Carib: 7% Other: 1%	Mean % (SD) 7.05 (1.42)	27.8 (5.5)	NR	N = 45 45/1138 = %

Evidence Table 3 – KQ1a Outcomes

Outcomes table Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
Quality of Life										
Jaiswal, 2015[15]	Group A: Exenatide, 22	Quality of life	Neuropathy specific quality of life (NeuroQOL), Global score	22	2.4 ± 1.1	18 m	19	2.3 ± 1.5	Change from baseline: 0.16 ± 1.0	NR
	Group B: Insulin Glargine, 24			24	2.9 ± 1.0	18 m	24	2.5 ± 0.9	Change from baseline: 0.40 ± 0.9	NR
Diabetic foot Ulcer										
Reichard, 1993[2] SDIS	Group A: ICT, intensified conventional treatment, 48	Diabetic foot ulcer	NR	48	NA	Median 7.5	48	0 events after 7.5 years	NA	NR
	Group B: ST standard treatment with insulin, 54		NR	54	NA	Median 7.5	54	3 events after 7.5 years	NA	NR
Abraira, 1997[4] VACSDM	Group A: intensive	Ischemic foot ulcer		75	NA	7.8 ± 4 years	75	N = 0		
	Group B: standard			78	NA		78	N = 1		
Martin, 2006[9] DCCT/EDIC	Group A	Diabetic foot ulcers		624	NA	8 years	624	Group A: 4		P = 0.01
	Group B			633	NA		633	Group B: 11		
Araki, 2012[13] J-EDIT	Group A: intensive	Ulcer or gangrene		585				N = 12 events total in 2 groups		P = 0.564 for between Group diff
	Group B: standard			588						

Evidence Table 3 – KQ1a Outcomes (continued)

Outcomes table Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
Kostev, 2012[14]	Group A: Glargine, 9638	Diabetic foot ulcer	There is no specific ICD-10 code for DFU, hence diagnosis was identified on the basis of the original handwritten diagnosis of the treating physician.	9638	NR	2 years to 6 years (mean NR)	NR	NR	NR	HR: 0.61; 95%CI: 0.38–0.98; P = 0.041 for Glargine vs. NPH
	Group B: NPH, 13 757			757	NR		NR	NR	NR	
Rathsman, 2014[3] SDIS – subrgp	Group A: ICT, 35	Diabetic foot ulcer hospitalization	ICD9 codes – discharge diagnosis	35	NA	28 years	35	3	NA	Logrank test p = 0.035 comparing Groups A and B
	Group B: ST, 37			37	NA	28 years	37	10	NA	
Amputations										
Knatterud, 1978[1] UGDP	Group A: insulin variable	Amputation of all of part of either lower limp	NR				190	3 (1.6%)		
	Group B: insulin standard						198	1 (0.5%)		
	Group C: placebo						194	3 (1.5%)		
Abraira, 1997[4] VACSDM	Group A: intensive	Amputation	NR	75	NA	7.8 ± 4 years	75	N = 1	NR	NR
	Group B: standard		NR	78	NA		78	N = 0	NR	NR

Evidence Table 3 – KQ1a Outcomes (continued)

Outcomes table Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
UKPDS, 1998[5]	Group A: intensive, 2729	Amputation of at least 1 digit	NR	2729	NA	Group B: intensive N = 80	2729	N = 27	Absolute risk per 1000 patients: 1.0	Log rank p-value for comp of ARR: 0.059 RR for intensive vs. conventional 0.81 (0.28-1.33)
	Group B: conventional, 1138		NR	1138	NA	10 years	1138	N = 18	Absolute risk per 1000 patients: 1.6	
Gaede, 2003[6] and Gaede, 2008[7] Steno-2	Group A: conventional treatment, 80	Amputations	NR	80	NA	6 years	80	N = 14	NR	NR
	Group B: intensive, 80			80	NA	6 years	80	N = 7	NR	NR
Dormandy, 2005[8] PROactive	Group A: Pioglitazone, 2605	Leg amputation above the ankle, first events	NR	2605	NA	34.5 months	2605	Group A: 26 first events Group A: 28 total events	NR	For first events - HR 1·01 (0·58–1·73)
	Group B: placebo, 2633		NR	2633	NA	34.5 months	2633	Group B: 26 Group B: 28 total events		
Martin, 2006[9] DCCT/EDIC	Group A	Lower extremity amputation		624	NA	8 years	624	Group A: 2	NA	P = 0.45
	Group B			633	NA		633	Group B: 5	NA	
Gaede, 2008[7] observational followup	Group A: conventional treatment for multiple risk factors, 80	Amputations	NR	80	Na	13.3 years	55	N = 14 patients (with 33 events)	NR	NR

Evidence Table 3 – KQ1a Outcomes (continued)

Outcomes table Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
	Group B: Intensive, 80		NR	80	NA	13.3 years	38	N = 6 patients (with 10 events)	NR	NR
Duckworth, 2009[11] VADT	Group A: intensive, 892	Amputation	NR	892	NA	6 years	892	11	Event free rate = 0.98	HR 0.65 (95% CI 0.31-1.39)
	Group B: standard treatment, 760		NR	760	NA	6 years	760	17	Event free rate = 0.98 p-value = 0.26	

Evidence Table 3 – KQ1a Outcomes (continued)

Outcomes table Author, year	Group, N	Outcome Units	Instrument or measure	Baseline N	Baseline outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparison	Between arm comparison
Griffin, 2011[12] and Simmons RK, 2012[17] ADDITION	Intensive, 1678	Amputation	In Denmark, the national patient register was searched for deaths and for International Classification of Diseases (ICD)-10 codes for cardiovascular events and surgical procedures concerning amputations. In Cambridge and Leicester, participants were registered with the England and Wales Office of National Statistics, which provided copies of death certificates. Sensitive electronic searches of general practice records were conducted			Mean 5.3 years	1377	First event: N = 0, 2nd event: N = 0, 3 or more events: N = 1, Total events: N = 1		
	Routine, 1379	Amputation	NR				1678	First event: N = 0, 2nd event: N = 1, 3 or more events: N = 0, Total events: N = 1		

Evidence Table 4 – KQ1a Harms

Author, year	Arm	Harm	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Abraira, 1997[4] VACSDM	Group A: intensive	Hypoglycemia	75	7.8 years	5	6%
	Group B: standard		78		2	2.5%
UKPDS[5]	Arm 1: intensive glycemic control	Severe hypoglycemia	2729	10.7 years		1.2% - Chlorpropamide arm; 1.0%- Glibenclamine arm; 2.0% insulin arm
	Arm 2: conventional treatment		1138			0.7% conventional 0.6% metformin arms
Gaede, 2003[6] Steno-2	Arm 1: intensive glycemic control	Severe hypoglycemia	80	7.8 years	12	15%
	Arm 2: conventional treatment		80		5	6%
Dormandy, 2005[8] PROactive	Arm 1: Pioglitazone	Hypoglycemia	2605	34.5 months	728	28%
	Arm 2: placebo		2633		528	20%
Duckworth, 2009[11] VADT	Arm 1: intensive glycemic control	Hypoglycemia	892	6 years	76	9%
	Arm 2: standard		760		28	5%

Evidence Table 4 – KQ1a Harms (continued)

Author, year	Arm	Harm	N for analysis	Time point (s)	N of patients with outcomes	% of patients with outcomes
Jaiswal, 2015[15]	Arm 1: Exenatide	Severe hypoglycemia	22	18 months	0	1%
	Arm 2: insulin Glargine		24	18 months	1	4%
	Arm 1: Exenatide	GI problems	22	18 months	6	27%
	Arm 2: insulin Glargine,		24	18 months	4	17%

Evidence Table 5 – KQ1b Balance Study Characteristics

Author, year Country	Study design, duration of follow-up	Intervention groups, N	Total # participants	Mean age (SD)	Female, % Race, %	HbA1c mean % (SD)	BMI mean (SD)	Outcomes reported
Richardson, 2001[18] North America	RCT, 3 weeks	Control, N = 10		64.8 (9.4)	53.0 NR	NR	37.3 (8.0)	Physical activity, perceived fall risk, drop outs
		Balance training, N = 10	20	66.3 (10.6)	49.0 NR	NR	36.0 (8.2)	
Kruse, 2010[19] and LeMaster, 2008[20] North America	RCT,12 months	Control, N = 38	79	64.8 (9.4)	53 Non-white 8	NR	37.2 (8.0)	Falls, Perceived fall risk, incident/recurrent ulcer, physical activity
		Physical therapy, N = 41		66.6 (10.4)	47.0 Non-white 7	NR	35.9 (8.2)	
Song, 2011[21] Asia	RCT, 8 weeks	Control, N = 19	38	73.2	57.9 (5.4)	NR	NR	Physical activity
		Balance training, N = 19		72.9	63.2 (5.6)	NR	NR	
Lee, 2013[22] Asia	RCT, 6 weeks	Control, N = 20	60	75.8 (5.7)	50.0 NR	6.9 (1.1)	NR	Physical activity
		Whole body vibration and exercise, N = 20		76.3 (4.8)	50.0 NR	7.1 (1.2)	NR	
		Balance training, N = 20		74.05 (5.4)	55.0 NR	7.0 (1.1)	NR	
Eftekhar-Sadat, 2015[23] Asia	RCT, unclear	Control, N = 22	44	59.1 (NR)	70.6 NR	NR	26.7 (NR)	Perceived fall risk, physical activity
		Balance training, N = 22		58.8 (NR)	58.8 NR	NR	27.8 (NR)	
Grewal, 2015, North America[24] Asia	RCT, 6 weeks	Control, N = 20	39	64.9 (8.5)	50.0 NR	65.4 (29.7)	29.6 (4.2)	Perceived fall risk, quality of life, physical activity and dropouts
		Balance training, N = 19		62.6 (7.9)	57.9 NR	65.2 (19.7)	31.8 (7.5)	
Kordi, 2015[25] Asia	RCT, 6 weeks	Control, N = 20	40	57.0 (1.5)	40.0 NR	NR	28.9 (1.0)	Physical activity
		Whole body vibration, N = 20		57.0 (1.8)	40.0 NR	NR	28.5 (1.0)	

Evidence Table 6 – KQ1b Balance Intervention Characteristics

Author, year	Intervention	Description of intervention	Frequency, n per week	Time per session	Total duration of study, weeks	Total sessions, n
Richardson, 2001[18]	Control	Exercises performed in seated position- neck flexion, rotation, stretching then resistance band exercises	5 or more	NR	3 weeks	NR
	Balance training	Exercises consisted of warm up, bipedal toe raise, heel raise inversion, eversion, unipedal toe raise, heel raise, inversion, eversion, wall slides and unipedal balance	7	NR	3 weeks	NR
Kruse, 2010[19] and LeMaster, 2008[20]	Control	Participants received diabetes self-care. Participants also received telephone calls to record recent activities	NA	NA	NA	NA
	Physical therapy	First three months, intervention comprised of 8 individual sessions with PT that focused on exercises to progressively strengthen legs and promote balance with 3 additional weekly 1 hr sessions at home. Next eight months, motivational techniques to enhance exercise via regular telephone calls were implemented	NR	NR	48	8 during first 3 months
Song, 2011[21]	Control	Health education sessions	1	50 min	8 weeks	NR
	Balance training	Exercises consisted of 10 min warm up, 40 min balance exercise and 10 min cool down. Exercise consisted of 3 parts: standing on stable surface, foam and progressive balance exercises. Participants also received health education as control group	2	60 min	8 weeks	NR
Lee, 2013[22]	Control	NR	NA	NA	NA	NA
	Whole body vibration and exercise	It was conducted on an individual basis, Subjects stood upright on the platform, and were vibrated in a 110° squatting position, at frequency of 15-30 Hz and amplitude of 1-3 mm. They also underwent balance exercise described below.	WBV 3, Balance exercise 2	60 min	6 weeks	NR
	Balance training	Exercises were similar to Richardson 2001 and Song 2011. 10 min of warm-up activities, 40 min of balance training, and 10 min of cool-down activities. it consisted of 3 parts- static, dynamic and progressive balance exercises	2	60 min	6 weeks	NR
Eftekhar-Sadat, 2015[23]	Control	Physiotherapy with infrared and transcutaneous electrical nerve stimulation (TENS)	3	30 min	NR	NR
	Balance training	Biodex balance system simulates specific movement patterns or strategies by placing markers on specific locations on the screen grid; performed by a trainer. Participants also received physiotherapy similar to control group	NR	NR	NR	10
Grewal, 2015[24]	Control	standard of care	NA	NA	NA	NA
	Balance training	Included a point-to-point ankle reaching task and a virtual obstacle-crossing task with appropriate audio-visual feedback. LegSys kinematic data were processed in real-time	2	45 min	4 weeks	NR
Kordi, 2015 [25]	Control	NR	NA	NA	NA	NA
	Whole body vibration	Received applied frequency of 30 Hz, peak-peak amplitude of 2 mm	2	Increased every 2 weeks from 30 s to 45 s to 1 min	6	12

Evidence Table 7 – KQ1b Balance Incident or Recurrent Foot Ulcer Outcomes

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N Incidence rate (per person year at risk)	Within arm comparison	Between arm comparison
LeMaster, 2008[20]	Arm 1 - control	No. of lesions	N: 32, Mean: NR, SD: NR	12 months	N: 32, Rate: 0.51		Rate Ratio: 1.24 (95% CI: 0.7-2.19) p = NR
LeMaster, 2008[20]	Arm 2 - intervention	No. of lesions	N: 37, Mean: NR, SD: NR	12 months	N: 37, Rate: 0.63		Rate Ratio: 0.96 (95% CI: 0.38-2.42) p = NR

Evidence Table 8 – KQ1b Balance Falls Outcomes

Author, year	Arm	N for analysis	Outcome	Time point	Mean outcome at time point	n (%) of PATIENTS with outcomes	Between arm comparison
Kruse, 2010[19]	Arm 1 - control	38	Falls/1000 person-days of follow up	12 months	2.02		
Kruse, 2010[19]	Arm 2 - intervention	41	Falls/1000 person-days of follow up	12 months	2.06		Comparator arm: control, p: 0.95
Kruse, 2010[19]	Arm 1 - control	38	N participants with no falls in 12 month period	12 months		22 (58)	
Kruse, 2010[19]	Arm 2 - intervention	41	N participants with no falls in 12 month period	12 months		25 (61)	Difference in number of falls: comparator arm: control, p: 0.4

Evidence Table 9 – KQ1b Balance Perceived Fall Risk

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, Mean, SD	Within arm comparison	Between arm comparison
Richardson, 2000[18]	Arm 1 - control	ABC (activities-specific balance and confidence) scale	N: 7, Mean: 80, SD: 21	3 weeks	N: 7, Mean: 80, SD: 20	% change from baseline:, p: 0.64	
Richardson, 2000[18]	Arm 2 - intervention	ABC (activities-specific balance and confidence) scale	N: 9, Mean: 80, SD: 21	3 weeks	N: 9, Mean: 88, SD: 11	% change from baseline, p: 0.14	
Kruse, 2010[19]	Arm 1 - control	Falls Efficacy Scale (FES) score	N: 38, Mean: 8.3, SD: 12	12 months	N: 38, Mean: 10.9, SD: NR		
Kruse, 2010[19]	Arm 2 - intervention	Falls Efficacy Scale (FES) score	N: 41, Mean: 10.4, SD: 13.9	12 months	N: 41, Mean: 13, SD:		Mean difference from baseline, Comparator arm: control, p: 0.73
Sartor, 2014[26]	Arm 1 - control	ABC (activities-specific balance and confidence) scale	N: 29, Mean: 78, SD: 18	12 weeks	N: 29, Mean: 78, SD: 19		

Evidence Table 9 – KQ1b Balance Perceived Fall Risk (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, Mean, SD	Within arm comparison	Between arm comparison
Sartor, 2014[26]	Arm 2 - intervention	ABC (activities-specific balance and confidence) scale	N: 26, Mean: 84, SD: 16	12 weeks	N: 26, Mean: 86, SD: 8		Median difference from baseline, 0.5, Comparator arm: control, p: NS
Eftekhar, 2015[23]	Arm 1 - control	Fall risk index	N:17, Mean: 2.11, SD: NR	NR	N:17, Mean: 1.87, SD:	% change from baseline: -12.58, p: NR	
Eftekhar, 2015[23]	Arm 2 - intervention	Fall risk index	N:17, Mean: 2.77, SD: NR	NR	N: 17, Mean: 0.86, SD:	% change from baseline: -56.96, p: NR	% change from baseline, Comparator arm: control, p: <0.001
Grewal, 2015[24]	Arm 1 - control	FES-I score	N:16, Mean: 35.4, SD: 11.47	4 weeks	N:16, Mean: 32.03, SD: 12.22	Mean difference from baseline: 6.99, p: NR	
Grewal, 2015[24]	Arm 2 - intervention	FES-I score	N:19, Mean: 32.32, SD: 12.34	4 weeks	N:19, Mean: 27.5, SD: 9.17	Mean difference from baseline: 14.91, p: NR	Mean difference from baseline, Comparator arm: control, p: 0.305

Evidence Table 10 – KQ1b Balance Quality of Life

Author, year	Arm	Instrument	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 1 - control	SF-12 physical component	N: 16, Mean: 37.5, SD: 9.81	4 weeks	N: 16, Mean: 40.12, SD: 8.4	% difference from baseline: 6.99, p: NR	
Grewal, 2015[24]	Arm 2 - intervention	SF-12 physical component	N: 19, Mean: 37.62, SD: 10.36	4 weeks	N: 19, Mean: 40.36, SD: 10.37	% difference from baseline: 7.28, p: NR	Mean difference from baseline, Comparator arm: control, p: 0.643

Evidence Table 11 – KQ1b Balance Physical Activity Level

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Richardson, 2001[18]	Arm 1 - control	Functional reach	N: 7, Mean: 11.3, SD: 3.6	3 weeks	N: 7, Mean: 11.9, SD: 2.8		
Richardson, 2001[18]	Arm 2 - intervention	Functional reach	N: 9, Mean: 10.5, SD: 2.1	3 weeks	N: 9, Mean: 11.5, SD: 2.2		
LeMaster, 2008[20]	Arm 1 - control	Total daily steps	N: 32, Mean: 3350, SD: 247 (sem)	12 months	N: 35, Mean: 2921, SD: 243 (sem)	Mean difference from baseline: , SD: , p: <0.05	Mean difference from baseline: 0.16, SD: NR , p: NR
LeMaster, 2008[20]	Arm 2 - intervention	Total daily steps	N: 37, Mean: 3335, SD: 246 (sem)	12 months	N: 35, Mean: 3183, SD: 240 (sem)	Mean difference from baseline: , SD: , p: NS	
LeMaster, 2008[20]	Arm 1 - control	6 min walk	N: 32, Mean: 1103, SD: 57 (sem)	12 months	N: 35, Mean: 1012, SD: 82 (sem)	Mean difference from baseline: , SD: , p: NS	Mean difference from baseline: -0.04, SD: NR, p: NR

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
LeMaster, 2008[20]	Arm 2 - intervention	6 min walk	N: 37, Mean: 1096, SD: 57 (sem)	12 months	N: 35, Mean: 996, SD: 82 (sem)	Mean difference from baseline: , SD: , p: NS	
Kruse, 2010[19]	Arm 1 - control	Berg Balance Scale	N: 38, Mean: 49.1, SD: NR	12 months	N: 38, Mean: 47.9, SD: NR		
Kruse, 2010[19]	Arm 2 - intervention	Berg Balance Scale	N: 41, Mean: 48.1, SD: NR	12 months	N: 41, Mean: 47.1, SD: NR		
Kruse, 2010[19]	Arm 1 - control	TUG	N: 38, Mean: 12.3, SD: NR	12 months	N: 38, Mean: 13.2, SD: NR		
Kruse, 2010[19]	Arm 2 - intervention	TUG	N: 41, Mean: 12.8, SD: NR	12 months	N: 41, Mean: 13.8, SD: NR		
Song, 2011[21]	Arm 1 - control	AP sway, EO (Eyes open)	N: 19, Mean: 43.5, SD: 14.7	8 weeks	N: 19, Mean: 45.4, SD: 13.7		

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Song, 2011[21]	Arm 2 - exercise	AP sway, EO (Eyes open)	N: 19, Mean: 45.9, SD: 12.3	8 weeks	N: 19, Mean: 33.3, SD: 7.9		
Song, 2011[21]	Arm 1 - control	AP sway, EC (Eyes closed)	N: 19, Mean: 59.5, SD: 20.2	8 weeks	N: 19, Mean: 59, SD: 13.5		
Song, 2011[21]	Arm 2 - exercise	AP sway, EC (Eyes closed)	N: 19, Mean: 62, SD: 19.9	8 weeks	N: 19, Mean: 49.3, SD: 13.6		
Song, 2011[21]	Arm 1 - control	ML sway, EO	N: 19, Mean: 42.4, SD: 14.3	8 weeks	N: 19, Mean: 42.3, SD: 13.5		
Song, 2011[21]	Arm 2 - exercise	ML sway, EO	N: 19, Mean: 50.4, SD: 29.3	8 weeks	N: 19, Mean: 33.2, SD: 6.9		
Song, 2011[21]	Arm 1 - control	ML sway, EC	N: 19, Mean: 59.6, SD: 26.1	8 weeks	N: 19, Mean: 61.1, SD: 22.8		

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Song, 2011[21]	Arm 2 - exercise	ML sway, EC	N: 19, Mean: 58.8, SD: 27.1	8 weeks	N: 19, Mean: 49.9, SD: 16.8		
Song, 2011[21]	Arm 1 - control	Total body sway, EO	N: 19, Mean: 68.7, SD: 21.2	8 weeks	N: 19, Mean: 66.8, SD: 19.5		
Song, 2011[21]	Arm 2 - exercise	Total body sway, EO	N: 19, Mean: 76.1, SD: 32.4	8 weeks	N: 19, Mean: 52.3, SD: 11.5		
Song, 2011[21]	Arm 1 - control	Total body sway, EC	N: 19, Mean: 94, SD: 32.7	8 weeks	N: 19, Mean: 94.2, SD: 19.3		
Song, 2011[21]	Arm 2 - exercise	Total body sway, EC	N: 19, Mean: 94.9, SD: 36.8	8 weeks	N: 19, Mean: 79.3, SD: 25.6		
Song, 2011[21]	Arm 1 - control	Berg Balance Scale	N: 19, Mean: 53.2, SD: 1.9	8 weeks	N: 19, Mean: 53.3, SD: 2.3		
Song, 2011[21]	Arm 2 - exercise	Berg Balance Scale	N: 19, Mean: 53, SD: 2.3	8 weeks	N: 19, Mean: 55.1, SD: 1.1		

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Song, 2011[21]	Arm 1 - control	FRT	N: 19, Mean: 27.3, SD: 3.2	8 weeks	N: 19, Mean: 27.4, SD: 4.4		
Song, 2011[21]	Arm 2 - exercise	FRT	N: 19, Mean: 27.1, SD: 7.4	8 weeks	N: 19, Mean: 30.9, SD: 6.1		
Song, 2011[21]	Arm 1 - control	TUG	N: 19, Mean: 11.9, SD: 2.2	8 weeks	N: 19, Mean: 11.8, SD: 2.2		
Song, 2011[21]	Arm 2 - exercise	TUG	N: 19, Mean: 11.8, SD: 2.3	8 weeks	N: 19, Mean: 10.1, SD: 2.1		
Song, 2011[21]	Arm 1 - control	10-min walk	N: 19, Mean: 9.7, SD: 1.5	8 weeks	N: 19, Mean: 9.5, SD: 1.3		

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Song, 2011[21]	Arm 2 - exercise	10-min walk	N: 19, Mean: 9.6, SD: 1.4	8 weeks	N: 19, Mean: 8.7, SD: 1.2		
Lee, 2013[22]	Arm 2 - WBV	AP sway velocity, eyes closed	N: 19, Mean: 14.09, SD: 5.27	6 weeks	N: 19, Mean: 8.35, SD: 4.48	Mean difference from baseline: -5.74, SD: 2.53, p: 0.026	
Lee, 2013[22]	Arm 3 - BE	AP sway velocity, eyes closed	N: 18, Mean: 14.34, SD: 4.86	6 weeks	N: 18, Mean: 11.54, SD: 6.59	Mean difference from baseline: -2.8, SD: 4.86, p: 0.002	
Lee, 2013[22]	Arm 1 - control	ML sway velocity, eyes closed	N: 18, Mean: 9.31, SD: 3.42	6 weeks	N: 18, Mean: 8.96, SD: 2.96	Mean difference from baseline: -0.34, SD: 3.34, p: 0.46	p: 0.000
Lee, 2013[22]	Arm 2 - WBV	ML sway velocity, eyes closed	N: 19, Mean: 9.83, SD: 3.39	6 weeks	N: 19, Mean: 6.11, SD: 2.66	Mean difference from baseline: -3.72, SD: 3.02, p: 0.026	
Lee, 2013[22]	Arm 3 - BE	ML sway velocity, eyes closed	N: 18, Mean: 9.49, SD: 4.12	6 weeks	N: 18, Mean: 7.86, SD: 3.67	Mean difference from baseline: -1.62, SD: 2.92, p: 0.001	

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Lee, 2013[22]	Arm 1 - control	Berg Balance Scale	N: 18, Mean: 50.28, SD: 2.47	6 weeks	N: 18, Mean: 50.17, SD: 2.5	Mean difference from baseline: -0.11, SD: 0.47, p: 0.331	p: 0.000
Lee, 2013[22]	Arm 2 - WBV	Berg Balance Scale	N: 19, Mean: 49.47, SD: 2.57	6 weeks	N: 19, Mean: 51.37, SD: 1.8	Mean difference from baseline: 1.89, SD: 1.52, p: 0.001	
Lee, 2013[22]	Arm 3 - BE	Berg Balance Scale	N: 18, Mean: 48.67, SD: 2.7	6 weeks	N: 18, Mean: 49.28, SD: 3.23	Mean difference from baseline: 0.61, SD: 1.2, p: 0.045	
Lee, 2013[22]	Arm 1 - control	Functional reach test (FRT)	N: 18, Mean: 27.66, SD: 4.23	6 weeks	N: 18, Mean: 26.98, SD: 2.6	Mean difference from baseline: -6.84, SD: 2.29, p: 0.336	p: 0.000
Lee, 2013[22]	Arm 2 - WBV	Functional reach test (FRT)	N: 19, Mean: 27.89, SD: 7.52	6 weeks	N: 19, Mean: 32.35, SD: 6.54	Mean difference from baseline: 4.45, SD: 3.52, p: 0.001	

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Lee, 2013[22]	Arm 3 - BE	Functional reach test (FRT)	N: 18, Mean: 27.77, SD: 4.02	6 weeks	N: 18, Mean: 29.91, SD: 4.07	Mean difference from baseline: 2.13, SD: 3.11, p: 0.01	
Lee, 2013[22]	Arm 1 - Control	TUG (Timed up and go)	N: 18, Mean: 13.43, SD: 1.85	6 weeks	N: 18, Mean: 13.45, SD: 1.51	Mean difference from baseline: 0.02, SD: 0.7, p: 0.921	p: 0.000
Lee, 2013[22]	Arm 2 - WBV	TUG (Timed up and go)	N: 19, Mean: 13.31, SD: 2.25	6 weeks	N: 19, Mean: 11.53, SD: 1.7	Mean difference from baseline: -1.79, SD: 1.09, p: 0.001	
Lee, 2013[22]	Arm 3 - BE	TUG (Timed up and go)	N: 18, Mean: 13.66, SD: 2.07	6 weeks	N: 18, Mean: 12.84, SD: 1.84	Mean difference from baseline: -0.82, SD: 1.5, p: 0.034	
Lee, 2013[22]	Arm 1 - control	FTSTS- Five time sit to stand test	N: 18, Mean: 16.42, SD: 5.01	6 weeks	N: 18, Mean: 16.91, SD: 4.92	Mean difference from baseline: 0.5, SD: 2.75, p: 0.455	p: 0.000
Lee, 2013[22]	Arm 2 - WBV	FTSTS- Five time sit to stand test	N: 19, Mean: 17.03, SD: 5.44	6 weeks	N: 19, Mean: 13.35, SD: 4.39	Mean difference from baseline: -3.68, SD: 2.4, p: 0.001	

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Lee, 2013[22]	Arm 3 - BE	FTSTS- Five time sit to stand test	N: 18, Mean: 18.03, SD: 4.61	6 weeks	N: 18, Mean: 15.92, SD: 4.66	Mean difference from baseline: -1.52, SD: 2.81, p: 0.035	
Kordi Yoosefinejad, 2015[25]	Arm 1 - control	TUG (sec)	N: 10, Mean: 9.15, SD: 0.4	6 weeks	N: 10, Mean: 9.8, SD: 0.3		p: 0.002
Kordi Yoosefinejad, 2015[25]	Arm 2 - WBV	TUG (sec)	N: 10, Mean: 9.3, SD: 0.8	6 weeks	N: 10, Mean: 8.5, SD: 0.7		
Eftekhar, 2015[23]	Arm 1 - control	TUG	N: 17, Mean: 10.8, SD: NR	Unclear	N: 17, Mean: 10.8, SD: NR	% difference from baseline: 0, SD: NR, p: NR	p: <0.001
	Arm 2 - intervention		N: 17, Mean: 11.18, SD: NR	Unclear	N: 17, Mean: 10.97, SD: NR	% difference from baseline: -2.12, SD: NR, p: NR	
Eftekhar, 2015[23]	Arm 1 - control	Berg Balance Scale	N: 17, Mean: 53, SD: NR	Unclear	N: 17, Mean: 53.05, SD: NR	% difference from baseline: 0.13, SD: NR, p: NR	p: 0.33

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

	Arm 2 - intervention		N: 17, Mean: 52.58, SD: NR	Unclear	N: 17, Mean: 53, SD: NR	% difference from baseline: 0.78, SD: NR, p: NR	
Eftekhar, 2015[23]	Arm 1 - control	API (Anterior-posterior index) sway	N: 17, Mean: 0.59, SD: NR	Unclear	N: 17, Mean: 0.54, SD: NR	% difference from baseline: -17.28, SD: NR, p: NR	p: 0.49
	Arm 2 - intervention		N: 17, Mean: 0.51, SD: NR	Unclear	N: 17, Mean: 0.24, SD: NR	% difference from baseline: -25.89, SD: NR, p: NR	
Eftekhar, 2015[23]	Arm 1 - control	MLI (Medial lateral index) sway	N: 17, Mean: 0.33, SD: NR	Unclear	N: 17, Mean: 0.44, SD: NR	% difference from baseline: 20.34, SD: NR, p: NR	p: 0.16
	Arm 2 - intervention		N: 17, Mean: 0.28, SD: NR	Unclear	N: 17, Mean: 0.14, SD: NR	% difference from baseline: -26.04, SD: NR, p: NR	
Eftekhar, 2015[23]	Arm 1 - control	OSI (Overall stability index) sway	N: 17, Mean: 0.75, SD: NR	Unclear	N: 17, Mean: 0.82, SD: NR	% difference from baseline: -2.12, SD: NR, p: NR	p: 0.2
	Arm 2 - intervention		N: 17, Mean: 0.65, SD: NR	Unclear	N: 17, Mean: 0.32, SD: NR	% difference from baseline: -26.93, SD: NR, p: NR	

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 1 - control	Center of mass (CoM) sway with eyes open	N: 16, Mean: 2.18, SD: 1.49	4 weeks	N: 16, Mean: 2.01, SD: 1.44	% difference from baseline: 7.8, SD: NR, p: NR	p: 0.009
Grewal, 2015[24]	Arm 2 - intervention	Center of mass (CoM) sway with eyes open	N: 19, Mean: 3.67, SD: 2.99	4 weeks	N: 19, Mean: 1.53, SD: 1.44	% difference from baseline: 58.31, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	CoM sway with eyes closed	N: 16, Mean: 4.91, SD: 3.97	4 weeks	N: 16, Mean: 4.26, SD: 4.12	% difference from baseline: 13.24, SD: NR, p: NR	p: 0.056
Grewal, 2015[24]	Arm 2 - intervention	CoM sway with eyes closed	N: 19, Mean: 8.12, SD: 11.23	4 weeks	N: 19, Mean: 3.03, SD: 3.09	% difference from baseline: 62.68, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	CoM AP sway with eyes open	N: 16, Mean: 1.3, SD: 0.58	4 weeks	N: 16, Mean: 1.23, SD: 0.42	% difference from baseline: 5.38, SD: NR, p: NR	p: 0.382

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 2 - intervention	CoM AP sway with eyes open	N: 19, Mean: 1.61, SD: 0.98	4 weeks	N: 19, Mean: 1.19, SD: 0.78	% difference from baseline: 26.09, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	CoM AP sway with eyes closed	N: 16, Mean: 1.91, SD: 0.93	4 weeks	N: 16, Mean: 1.89, SD: 1.06	% difference from baseline: 1.05, SD: NR, p: NR	p: 0.031
Grewal, 2015[24]	Arm 2 - intervention	CoM AP sway with eyes closed	N: 19, Mean: 2.45, SD: 1.83	4 weeks	N: 19, Mean: 1.66, SD: 1.03	% difference from baseline: 32.24, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	CoM ML sway with eyes open	N: 16, Mean: 1.54, SD: 0.49	4 weeks	N: 16, Mean: 1.51, SD: 0.6	% difference from baseline: 1.95, SD: NR, p: NR	p: 0.008
Grewal, 2015[24]	Arm 2 - intervention	CoM ML sway with eyes open	N: 19, Mean: 1.91, SD: 0.88	4 weeks	N: 19, Mean: 1.15, SD: 0.52	% difference from baseline: 39.79, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	CoM ML sway with eyes open	N: 16, Mean: 2.33, SD: 1.21	4 weeks	N: 16, Mean: 1.92, SD: 0.84	% difference from baseline: 17.6, SD: NR, p: NR	p: 0.103

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 2 - intervention	CoM ML sway with eyes open	N: 19, Mean: 2.54, SD: 1.31	4 weeks	N: 19, Mean: 1.54, SD: 0.92	% difference from baseline: 39.37, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	Daily physical activity during 48 h, % time spent sitting	N: 16, Mean: 45.91, SD: 20.22	4weeks	N: 16, Mean: 48.93, SD: 17.88	% difference from baseline: -0.04, SD: NR, p: NR	p: 0.621
Grewal, 2015[24]	Arm 2 - intervention	Daily physical activity during 48 h, % time spent sitting	N: 19, Mean: 49.87, SD: 15.35	4 weeks	N: 19, Mean: 49.85, SD: 16.31	% difference from baseline: 6.58, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	Daily physical activity during 48 h, % time spent standing	N: 16, Mean: 14.73, SD: 6.57	4weeks	N: 16, Mean: 14.66, SD: 7.05	% difference from baseline: -0.48, SD: NR, p: NR	p: 0.359
Grewal, 2015[24]	Arm 2 - intervention	Daily physical activity during 48 h, % time spent standing	N: 19, Mean: 13.74, SD: 4.98	4weeks	N: 19, Mean: 15.96, SD: 5.1	% difference from baseline: 16.16, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	Daily physical activity during 48 h, % time spent walking	N: 16, Mean: 7.53, SD: 5.62	4weeks	N: 16, Mean: 7.25, SD: 5.4	% difference from baseline: -3.72, SD: NR, p: NR	p: 0.076

Evidence Table 11 – KQ1b Balance Physical Activity Level (continued)

Author, year	Arm	Outcome	Baseline N, mean, SD	Time point(s)	At time point(s), N, mean, SD	Within arm comparison	Between arm comparison
Grewal, 2015[24]	Arm 2 - intervention	Daily physical activity during 48 h, % time spent walking	N: 19, Mean: 6.75, SD: 3.4	4weeks	N: 19, Mean: 8.59, SD: 3.98	% difference from baseline: 27.26, SD: NR, p: NR	
Grewal, 2015[24]	Arm 1 - control	Total steps taken	N: 16, Mean: 9785, SD: 8081	4weeks	N: 16, Mean: 9264, SD: 7670	% difference from baseline: -5.32, SD: NR, p: NR	p: 0.064
Grewal, 2015[24]	Arm 2 - intervention	Total steps taken	N: 19, Mean: 8656, SD: 4589	4weeks	N: 19, Mean: 11052, SD: 5365	% difference from baseline: 27.68, SD: NR, p: NR	

Evidence Table 12 – KQ1b Balance Drop Outs

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %
Richardson, 2001[18]	Arm 1 - control	0	0
Richardson, 2001[18]	Arm 2 - intervention	1	
Grewal, 2015[24]	Arm 1 - control	0	0
Grewal, 2015[24]	Arm 2 - intervention	0	0

Evidence Table 13 – KQ1b Exercise Study Characteristics

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
LeMaster 2003[27]	Prospective cohort Single center: North America	Government	NR	No	
Dixit, 2013[28]	Parallel randomized controlled trial Single center: Asia	NR	2009-2012	No	
Taveggia, 2013[29]	Parallel randomized controlled trial Single center: Europe	No funding	2009-2009	No	
Sartor, 2014[26]	Parallel randomized controlled trial Single center: South America	NR	2010-2012	No	Initially started out as randomized cross over but due to adherence issues, was only assessed as a parallel RCT

Evidence Table 14 – KQ1b Exercise Interventions Characteristics

Author, year	Arm	Time per session Total number of sessions	Comments
LeMaster 2003[27]	Arm 1 - CONTROL-least active		Fewer than 4.5 active hours per day
LeMaster 2003[27]	Arm 2 - moderately active		4.6- 7.4 active hours per day
LeMaster 2003[27]	Arm 3-most active		More than 7.5 active hours per day
Dixit, 2013[28]	Arm 1 - CONTROL-control		Standard medical care, education for foot care and diet
Dixit, 2013[28]	Arm 2 - intervention	5-6/week 150-360 minutes/ week	Moderate intensity supervised exercise training (target heart rate 40-60% of heart rate reserve) using treadmill
Taveggia, 2013[29]	Arm 1-CONTROL-standard care	5 per week 60 minutes/ session	Activities targeted to improve the endurance, manual exercises of lower limb muscle strengthening, and stretching exercises, in substitution of the robotic treadmill and dynamometer (ie, sitting to standing, walking up and down a slope, and stair climbing). feedback focused, isokinetic dynamometric muscle strengthening, and balance retraining on dynamic balance platform or a standard care intervention for activities targeted to improve endurance, manual exercises of muscle strengthening, stretching exercises, gait, and balance exercises.

Evidence Table 14 – KQ1b Exercise Interventions Characteristics

Author, year	Arm	Time per session Total number of sessions	Comments
Taveggia, 2013[29]	Arm 2 - experimental		Multimodal, 20 mins of analyzing treadmill with feedback focused on symmetry and length of stride, 20 mins of isokinetic dynamometric muscle strengthening of flexor and extensor muscles of tibio tarsal and 20 mins of balance retraining on dynamic balance platform

Evidence Table 15 – KQ1b Exercise Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN Unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
LeMaster 2003[27]	Arm 1 – CONTROL - least active	2 years	(13)	mean: 64, SD: 10	NR	NR	NR	NR	NR
LeMaster 2003[27]	Arm 2 - moderately active	2 years	(24)	mean: 63, SD: 10	NR	NR	NR	NR	NR
LeMaster 2003[27]	Arm 3 - most active	2 years	(31)	mean: 60, SD: 9	NR	NR	NR	NR	NR
Dixit, 2013[28]	Arm 1 – CONTROL - control	8 weeks	17(35.4)	mean: 59.45, SD: 1.16	NR	mean: 25.95, SD: 5.68	NR	NR	10
Dixit, 2013[28]	Arm 2 - intervention	8 weeks	17(43.6)	mean: 54.4, SD: 1.24	NR	mean: 26.38, SD: 3.77	NR	NR	11
Taveggia, 2013[29]	Arm 1-CONTROL-standard care	4 weeks	9(64.3)	mean: 71, SD: 7	mean: 8.5, SD: 1.5	mean: 35.3, SD: 6.7	NR	NR	NR
Taveggia, 2013[29]	Arm 2-experimental	4 weeks	8(61.5)	mean: 73, SD: 10	mean: 8.8, SD: 1.9	mean: 29.6, SD: 5.9	NR	NR	NR

Evidence Table 16 – KQ1b Exercise Physical Activity Level

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean SD:	Within arm comparison	Between arm comparison
Taveggia, 2013[29]	Arm 1 - standard care	6 minute walk	N:13, Mean: 313.8, SD:102.9	4 weeks	N:13, Mean: 5.4, SD:1.7	Mean difference from baseline: 59.8, p: 0.049	Mean difference from baseline: -44.1, p: NR
Taveggia, 2013[29]	Arm 2 - experimental	6 minute walk	N:14, Mean: 330.1, SD:151.1	4 weeks	N:14, Mean: 6.2, SD:1.9	Median difference from baseline: 35.2, p: 0.009	

Evidence Table 17 – KQ1b Exercise Incidence or Reoccurrence of Ulcers

Author, year	Arm	Outcome	Time point	N for analysis	Incidence rate, per person year at risk	Between arm comparison
LeMaster, 2003[27]	Arm 1 - least active	Re-ulceration in feet	2 years	133	16.5 (95% CI: 10.4-25%)	p: NS
LeMaster, 2003[27]	Arm 2 - moderately active	Re-ulceration in feet	2 years	134	13.4 (95% CI: 7.9-21.2)	p: NS
LeMaster, 2003[27]	Arm 3 - most active	Re-ulceration in feet	2 years	123	13 (95% CI: 7.4-21.1)	p: NS

Evidence Table 18 – KQ1b Exercise Quality of Life

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison
Dixit, 2013[28]	Arm 1 - control	Neuro - QOL score	N:47, Mean: 33.55, SD:1.37	8 weeks	N:37, Mean: 34.16, SD:1.37	% difference from baseline: -4.12, p: <0.001
Dixit, 2013[28]	Arm 2 - intervention	Neuro - QOL score	N:40, Mean: 32.85, SD:1.32	8 weeks	N:29, Mean: 24.41, SD:1.12	% difference from baseline: 24.28, p: NR

Evidence Table 19 – KQ1b Exercise Adverse Events

Author, year	Select arm	Adverse events	N for analysis	Patients with adverse events, N (%)
Dixit, 2013[28]	Arm 1 - control	Hypoglycemia (severe and total)	47	11 (23.4)
Dixit, 2013[28]	Arm 2 - intervention	Hypoglycemia (severe and total)	40	2 (5.0)

Evidence Table 20 – KQ1b Physical Therapy Study Characteristics

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Mueller, 2013[30]	Parallel randomized controlled trial Single center: North America	Government	2009-2011	No
Chatchawan, 2015[31]	Parallel randomized controlled trial Single center: Asia	University	NR	No

Evidence Table 21 – KQ1b Physical Therapy Interventions Characteristics

Author, year	Arm	Time per session Total number of sessions	Session with physical therapist	Comments
Mueller, 2013[30]	Arm 1 - CONTROL-non weight bearing	12 weeks 14 min/36 sessions	Yes	All exercises were conducted in sitting or lying position. elastic resistance bands with increasing stiffness for load resistance used, stationary upright or recumbent cycle ergometer for aerobic exercise
Mueller, 2013[30]	Arm 2 - weight bearing	12 weeks 15 min/36 sessions	Yes	Participants were instructed to increase center-based step count every 2 weeks by 24%. they conducted most of exercises in standing position, used body weight for resistance exercises and treadmill or walking around circular hallways for aerobic exercise
Chatchawan, 2015[31]	Arm 1 – CONTROL - control	2 weeks 30 min/6 sessions	No	Health education on foot self-care and active foot exercises at home
Chatchawan, 2015[31]	Arm 2 - Thai foot massage	2 weeks 30 min/6 sessions	No	Modified foot massage performed by traditional Thai massage therapist

Evidence Table 22 – KQ1b Physical Therapy Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Mueller, 2013[30]	Arm 1 – CONTROL - non weight bearing	12 weeks	7(50)	mean: 63.9, SD: 12.5	NR	mean: 33.1, SD: 7.3	NR	NR	NR
Mueller, 2013[30]	Arm 2 - weight bearing	12 weeks	5(33.3)	mean: 65.2, SD: 12.8	NR	mean: 36.8, SD: 6.3	NR	NR	NR
Chatchawan, 2015[31]	Arm 1 – CONTROL - control	2 weeks	20(66.7)	mean: 57.6, SD: 6.5	NR	mean: 25.9, SD: 3.7	NR	NR	0
Chatchawan, 2015[31]	Arm 2 - Thai foot massage	2 weeks	20(66.7)	mean: 57.8, SD: 6.5	NR	mean: 25.3, SD: 2.7	NR	NR	0

Evidence Table 23 – KQ1b Physical Therapy Physical Activity Level

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean SD:	Within arm comparison	Between arm comparison
Mueller, 2013[30]	Arm 1 - NWB	Average daily steps	N: 14, Mean: 6571, SD: 2186	12 weeks	N: 14, Mean: 6078, SD: 2023	Mean difference from baseline:-493 (95% CI:-1232 to 246), p: NR	Mean difference from baseline:1178 (95% CI:150 to 2205), p: 0.026
Mueller, 2013[30]	Arm 2 - WB	Average daily steps	N: 15, Mean: 4909, SD: 1398	12 weeks	N: 15, Mean: 5593, SD: 1449	Mean difference from baseline:685 (95% CI:-29 to 1399), p: NR	
Mueller, 2013[30]	Arm 1 - NWB	6 min walk	N: 14, Mean: 418, SD: 106	12 weeks	N: 14, Mean: 417, SD: 112	Mean difference from baseline:-2 (95% CI:-18 to 14), p: NR	Mean difference from baseline:29 (95% CI:6 to 51), p: 0.014
Mueller, 2013[30]	Arm 2 - WB	6 min walk	N: 15, Mean: 378, SD: 72	12 weeks	N: 15, Mean: 404, SD: 78	Mean difference from baseline:27 (95% CI:11 to 42), p: NR	
Chatchawan, 2015[31]	Arm 1 - control	TUG	N: 30, Mean: 8.8, SD: 1.91	2 weeks	N: 30, Mean: 8.56, SD: 1.67	P: <0.05	p: <0.05

Evidence Table 23 – KQ1b Physical Therapy Physical Activity Level

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean SD:	Within arm comparison	Between arm comparison
Chatchawan, 2015[31]	Arm 2 - Thai foot massage	TUG	N: 30, Mean: 8.31, SD: 1.42	2 weeks	N: 30, Mean: 7.06, SD: 1.14	P: <0.05	

Evidence Table 24 – KQ1b Physical Therapy Incidence or Reoccurrence of Ulcers

Author, year	Arm	Outcome	Time point	N for analysis	Incidence, N	Between arm comparison
Mueller, 2013[30]	Arm 1 - NWB	Number of lesions- superficial injury	12 weeks	14	6	P: NR
Mueller, 2013[30]	Arm 2 - WB	Number of lesions- superficial injury	12 weeks	15	7	P: NR
Mueller, 2013[30]	Arm 1 - NWB	Number of ulcers- full thickness skin wound	12 weeks	14	3	P: NR
Mueller, 2013[30]	Arm 2 - WB	Number of ulcers- full thickness skin wound	12 weeks	15	1	P: NR

Evidence Table 25 – KQ1b Lifestyle Intervention Study Design Characteristics

Author, year	Study design Site(s) Location	Recruitment period (Start year –End year)	Diabetes type	Key inclusions and exclusions	Treatment duration Washout period Run-in period If applicable	Groups (dose)	Funding support	Comments
Bunner, 2015[32]	RCT Single site U.S. (Washington DC)	November 2012 to January 2013 and October 2013 to January 2014.	Type 2	+ Symptoms of painful diabetic neuropathy for 6 months Exclude B12 deficiency, current vegan diet	20-weeks	Group A: intervention group – received vitamin B12 supplement (1000 mcg daily) instructed to follow the low-fat vegetarian diet and attend weekly nutrition classes offering education and social support for 20 weeks. Group B: Control group: Vitamin B12 supplement (1000 mcg daily)	Physicians Committee for Responsible Medicine	Note on dietary adherence Two-day diet records conducted at midpoint and 20 weeks showed that 13 of 17 intervention-group participants avoided all animal products at the midpoint and endpoint assessments. Of those 13, 8 reported consuming a low-fat (25% kcal or less from fat) diet at both time points. An additional three of those thirteen reported consuming a low-fat diet at one of the two time points. An additional 2 of the 17 intervention-group participants were fully compliant with the low-fat guidelines at both assessments, but reported consuming at least modest amounts of animal products in one diet record, and two participants were noncompliant with the low-fat guidelines and the plant-based guidelines. No data on vitamin B12 supplement adherence were collected.

Evidence Table 26 – KQ1b Lifestyle Intervention Population Characteristics

Author, year	Group, N (dose)	Age mean, median, SD	Female N (%)	Race N (%)	HbA1c mean, median SD	BMI mean, median SD	Pain on visual analog scale (cm)	N of withdrawals
Bunner, 2015[32]	Group A, N = 17	Mean 57 (SD 6)	11 (65%)	Black: 11 (65%) Hispanic: 4 (25%):	8.0 (1.7)	36 (6)	5.3 (2.7)	0
	Group B, N = 17 (n = 18 randomized)	Mean 58 (SD 6)	8 (47%)	Black: 5 (29%) Hispanic: 1 (6%)	7.8 (1.6)	36 (7)	5.8 (2.4)	2 (n = 1 not included in Table 1 b/c withdrew)

Evidence Table 27 – KQ1b Lifestyle Intervention Outcomes

Author, year	Group, N (dose)	Outcome Units	Baseline N	Baseline Outcome	Time point(s)	N at time point(s)	Outcome at time point(s)	Within arm comparisons	Between arm comparisons
Bunner, 2015[32]	Group A, N=17	Quality of life (total score)- Norfolk Quality of Life Questionnaire	17	27.9 (14.3)	20 weeks	17	19.6 (17.9)	− 8.4 (13.6)‡	− 4.0 (−15.1 to 7.1) 0.43
	Group B, N=17 (n=18 randomized)		17	29.6 (15.7) −	20 weeks	17	24.6 (17.5)	-5.1 (10.5)a	

Foot care intervention:

The evidence tables from the Netten et. al review are available at: http://www.iwgdf.org/files/2015/PreventionSR.pdf
The data from the newly identified tables are describe in the following tables:

Evidence Table 28 – KQ1b Foot care Study Characteristics

Author, year	Study design	Study site Study location	Funding	Recruitment Start YEAR - End YEAR	Incident or recurrent foot ulcer	Amputation	Adverse effect
Skafjeld, 2015[33]	Parallel randomized controlled trial	Single center: Europe; Norway	Non-profit.	NR	x		x
Shah, 2015[34]	Retrospective cohort study	Multi-center: North America; Canada; Ontario	Non-profit and government.	2006-2012	x	x	x
Monami, 2015[35]	Parallel randomized controlled trial	Single center: Europe; Italy	Not Reported	NR	x	x	
Gibson, 2014[36]	Retrospective cohort study	Multiple center: MarketScan database	Non-profit	2005-2009		x	
Chin, 2014[37]	Retrospective cohort study	Multiple center: Asia; Two hospitals in Taiwan	Non-profit	2010-2011	x		

Evidence Table 29 – KQ1b Foot care Patient Characteristics

Author, year	Arm ,N at enrollment (i.e., at randomization or at beginning of exposure period)	Length of follow-up	Female, n, % Age (years), mean, SD Race, n, %	HbA1c BMI	Patients with type 1/2/1&2 diabetes, n %	Number of withdrawals and/or losses to provide follow-up: N	Comments
Skafjeld, 2015[33]	Control, 20	mean: 1 year	Female: n: NR, %: 25 Age: mean: 59.4, SD:13 Race: 100% Caucasian	HbA1c Mean: 7.9% BMI Mean: 31.1	Type 1:%: 30, Type 2:%: 70,	0	% with Urinary albumin/creatinin ratio > 3: 20% in control, 65% in intervention (p<0.01)
Skafjeld, 2015[33]	Intervention, 21	mean: 1 year	Female: n: NR, %: 14 Age: mean: 57.1, SD:10.2 Race: 100% Caucasian	HbA1c Mean: 8.3% BMI Mean: 31.4	Type 1: %:29 Type 2:%: 71,	3	
Shah, 2015[34]	Non-attendee ,8260	median: 5.3year	Female: n: 4334, %: 52.5 Age: mean: 73.1, SD: 5.4	NR	Type 2:%: 100,	0	Two groups differed in all aspects of baseline characteristics after propensity score matching
Shah, 2015[34]	Attendee ,8260	median: 5.3year	Female: n: 4334, %: 52.5 Age: mean: 73.1, SD: 5.4	NR	Type 2:%: 100,	0	
Monami, 2015[35]	Standard Care ,61	mean: 6 month	Female: n: 28, %: 46.7 Age: mean: 69.4 ± 11.3, SD: 11.3	HbA1c 7.3 ± 1.4 BMI 30.0 ± 5.6	Type 2:%: 100	0	Total N = 121; Only reported N = 120 (completers)
Monami, 2015[35]	Educational Program ,60	mean: 6 month	Female: n: 20, %: 33.3 Age: mean: 72.0 ± 8.9, SD: 8.9	HbA1c 7.4 ± 1.3 BMI 29.4 ± 4.7	Type 2:%: 100,	1	
Gibson, 2014[36]	Arm 1 - CONTROL: Commercial, Podiatrist visit, n = 7597	23.22 (SD 15.04)	Female: %: 44·7 Age: mean: 55·0, SD: 6.8	NR	NR	0	
Gibson, 2014[36]	Arm 2: Commercial, No Podiatrist visit, n = 12611	21.85 (SD: 14.93)	Female: n:, %: 38·1 Age: mean: 53·7, SD: 7.6	NR	NR	0	

Evidence Table 29 – KQ1b Foot care Patient Characteristics (continued)

Author, year	Arm ,N at enrollment (i.e., at randomization or at beginning of exposure period)	Length of follow-up	Female, n, % Age (years), mean, SD Race, n, %	HbA1c BMI	Patients with type 1/2/1&2 diabetes, n %	Number of withdrawals and/or losses to provide follow-up: N	Comments
Gibson, 2014[36]	Arm 3: Medicare, Podiatrist visit, n = 13692	23.26 (SD: 15.50) months	Female: %: 48·5 Age: mean: 77·6, SD: 6.9	NR	NR	0	
Gibson, 2014[36]	Arm 4:Medicare, no podiatrist visit, n = 13853	21.24 (SD: 15.24)	Female: %: 44·4 Age: mean: 76·7, SD: 6.9	NR	NR	0	
Chin, 2014[37]	Overall :295; only report baseline characteristics & results for n = 290 not lost to follow-up	mean: 1 year	Female: n: 141, %: 50.7 Age: mean: 66.97, SD:11.01 Race Asian, n: 295, %: 100	HbA1c Mean: 8.53 SD: 1.77	Type 2: n: 295, %: 100,	5- unclear which arm	

Evidence Table 30 – KQ1b Foot care Interventions Characteristics

Author, year	Arm	Foot care intervention : DESCRIPTION	Duration (weeks)	Time/session	Total number of sessions	Adherence to the intervention (please describe briefly)
Skafjeld, 2015[33]	Arm 1 - control	Advised to always wear their customized footwear.	52 weeks	The percentage of days with a check indicating foot inspection was recorded in the daily log in the course of the study.	NR	70 % (14/20) recorded foot observations ≥80 % of the time.
Skafjeld, 2015[33]	Arm 2 - intervention	Trained to use a digital infrared thermometer to monitor foot temperature. Instructed to record daily physical activity using a step-counter during the first week of the study.	52 weeks	Adherence to skin temperature monitoring was recorded as the percentage of days with foot temperature measurements recorded in the daily log in the course of the study.	NR	67 % (14/21) recorded foot observations and skin temperatures ≥80 % of the time.
Shah, 2015[34]	Arm 1 - non-Attendee-di not attend self-management program	NA	5 years	NA	NA	NA
Shah, 2015[34]	Arm 2 - Attendee -attended group or in-person self-management program	By linking with the registry of self-management education program visits, those individuals who attended a program in 2006 were identified.	5 years	Attended self-management program	One or more	NA
Monami, 2015[35]	Arm 1 - standard care	Provided brief leaflet with some recommendations for ulcer prevention	Once	NR	One	NR

Evidence Table 31 – KQ1b Foot care Interventions Characteristics (continued)

Author, year	Arm	Foot care intervention : DESCRIPTION	Duration (weeks)	Time/session	Total number of sessions
Monami, 2015[35]	Arm 2 - educational program	Two-hour program provided to groups of 5–7 patients (mean: n = 6), including a 30-minute face-to-face lesson on risk factors for foot ulcers, and a 90- minute interactive session with practical exercises on behaviors for reducing risk. The intervention involved a physician (for 15 minutes) and a nurse (for the remaining 105 minutes).	Once	2 hours	1
Gibson, 2014[36]	Podiatry care	if the patient received care from a podiatrist during the year prior to the index diabetic foot ulcer diagnosis	NA	The primary analyses compared patients without any visits to a podiatrist during the year prior to the index date (comparison) with those having one or more visits (case).	The primary analyses compared patients without any visits to a podiatrist during the year prior to the index date (comparison) with those having one or more visits (case).
Gibson, 2014[36]	No podiatry care)	N/A	NA	NA	NA
Chin, 2014[37]	Arm 1 – CONTROL	Less self-reported care	NA	NA	NA
Chin, 2014[37]	Arm 2 - self-reported Diabetes Foot Self-Care	Self-reported Diabetes Foot Self-Care Behavior Scale (inspecting the bottom of the foot and between toes, washing and drying between toes, applying moisturizing lotion, inspecting inside of the shoes, and breaking in the shoes)	NA	NA	NA

Evidence Table 32 – KQ1b Footcare Incidence or Recurrent – Ulcer

Author, year	Arm	Outcome	Baseline N, mean: SD	Time point(s)	At time point(s), N, mean:	Between arm comparison -
Skafjeld, 2015[33]	Arm 1 - control	Incident diabetic foot ulcer assessed with clinical examination by nurse-	N: 20	1 year	N = 10/20(50%)	Comparator arm: control, p:0.532
Skafjeld, 2015[33]	Arm 2 - intervention		N: 21	1 year	N = 7/21 (39%)	
Shah, 2015[34]	Arm 1 - non attendee	Hospital discharge diagnosis -rate per 1000 person-year	N: 8260	5 years	Incidence rate mean: 8.92per 1000 person year	Comparator arm: not attendee, relative hazard:1.16, 95% CI: 0.95-1.41, p:0.055
Shah, 2015[34]	Arm 2 - attendee		N: 8260	5 years	Incidence rate mean: 10.04 per 1000 person year	
Monami, 2015[35]	Arm 1 - standard care	Clinical diagnosis-n, % foot ulcer	N: 60	6 month	N = 6 (10%)	Comparator arm: standard care, p:0.012
Monami, 2015[35]	Arm 2 - educational program		N: 61	6 month	N = 0 (0%)	
Chin, 2014[37]	Arm 1 - no self-care	Diabetic foot ulcer	N =	1 year	NR	Reference group
Chin, 2014[37]	Arm 2 – self-care, examine bottom of feet		N =	1 year	NR	Comparator arm: no self-care, relative hazard:1.1, 95% CI:0.97-1.25, p:0.132
Chin, 2014[37]	Arm 3 - examine between toes		N =	1 year	NR	Comparator arm: no self-care, relative hazard:1.05, 95% CI:0.93-1.19, p:0.446
Chin, 2014[37]	Arm 4 - lotion application		N =	1 year	NR	Comparator arm: no self-care, relative hazard:1.19, 95% CI:1.04-1.36, p:0.012

Evidence Table 33 – KQ1b Footcare Lower Extremity Amputation

Author, year	Arm, N for analysis	Outcome	Time point	n of PATIENTS with outcomes	Between arm
Shah, 2015[34]	Arm 1 - not attendee, 8260	Hospital discharge diagnosis of lower extremity amputation - rate per 1000 person-year	5 years	0.76 per 1000 person year	Comparator arm: non-attendee, Relative hazard: 1.41, 95%CI: 99% CI: 0.40-5.04, p: 0.484
Shah, 2015[34]	Arm 2 - attendee, 8260	Hospital discharge diagnosis -rate per 1000 person-year	5 years	0.60 per 1000 person year	
Monami, 2015[35]	Arm 1 - control, 60	-	6 month	N = 0	NA
Monami, 2015[35]	Arm 2 - education, 59	-	6 month	N = 0	
Gibson, 2014[36]	Arm 1 - Commercial, No pre-period podiatrist visit, 7597	Lower extremity amputation using procedure codes on the claims-incidence amputation	5 years study; 40% of enrollees could be followed over 24months	1682	Comparator arm: Arm 1, Relative hazard: 0·748, 95%CI: 0·686–0·816, p: <0.001
Gibson, 2014[36]	Arm 2 - Commercial, 1+ pre-period podiatrist visit, 12 611	Lower extremity amputation using procedure codes on the claims-incidence amputation		811	
Gibson, 2014[36]	Arm 3 - Medicare, No pre-period podiatrist visit, 13 692	Lower extremity amputation using procedure codes on the claims-incidence amputation		1240	Comparator arm: Arm 3, Relative hazard: 0·796, 95%CI: 0·730–0·867, p: <0.001
Gibson, 2014[36]	Arm 4 - Medicare, 1+ pre-period podiatrist visit, 13 853	Lower extremity amputation using procedure codes on the claims-incidence amputation		1042	

Evidence Table 33 – KQ1b Footcare Lower Extremity Amputation (continued)

Author, year	Arm, N for analysis	Outcome	Time point	n of PATIENTS with outcomes	Between arm
Gibson, 2014[36]	Arm 1 - Commercial, No pre-period podiatrist visit, 7597	Major amputation- knee or higher.		380	Comparator arm: Arm1, Relative hazard: 0·691, 95%CI: 0·578–0·825, p: <0.001
Gibson, 2014[36]	Arm 2 - Commercial, 1+ pre-period podiatrist visit, 12 611	Major amputation- knee or higher.		179	
Gibson, 2014[36]	Arm 3 - Medicare, No pre-period podiatrist visit, 13 692	Major amputation- knee or higher.		407	Comparator arm:Arm3, Relative hazard: 0·652, 95%CI: 0·555–0·766, p: <0.001
Gibson, 2014[36]	Arm 4 - Medicare, 1+ pre-period podiatrist visit, 13 853	Major amputation- knee or higher.		280	

Evidence Table 34 – KQ1b Footcare Adverse Effects

Author, year	Arm, N for analysis	Adverse effects	EVENTS with outcomes, n, %	Between arm
Skafjeld, 2015[33]	Arm 1 - control, 20	Dropouts	0	NR
	Arm 2 - intervention, 21		3 withdraws: 1 dropout; 2 illness	NR
Shah, 2015[34]	Arm 1 - non attendee, 8260	Glycaemia-related ED visit)	n: 44, %: 0.60%	Comparator arm: Non attendee, Relative hazard:1.02, 99% CI: 0.58-1.77, p: 0.938
	Arm 2 - attendee, 8260		n: 43, %: 0.50	
Shah, 2015[34]	Arm 1 - non attendee, 8260	Coronary artery disease	15.14 per 1000 person year	Comparator arm: non attendee, Relative hazard:1.13, 99% CI: 0.97 - 1.31, p: 0.036
	Arm 2 - attendee, 8260		16.66 per 1000 person year	

Evidence Table 35 – Surgery Patient characteristics

Author, year	Arm ,N at enrollment (i.e., at randomization or at beginning of exposure period)	Length of follow-up	Female, n, % Age (years), mean, SD Race, n, %	HbA1c BMI	Patients with type 1/2/1&2 diabetes, n %	Number of withdrawals and/or losses to follow-up: N	Comments
Mueller, 2004[38]	Control, TCC Only, n = 14	mean: 8 months	Female: n: 4, %: NR Age: mean: 54.8, SD: 9.5 Race: NR	HbA1c Mean: 8.9% BMI Mean: 31.8	Type 1:n: 5, Type 2:n: 9,	0	Original trial included Subjects with ATL followed by TCC (ATL group; n 31) or TCC alone (TCC group; n 3).the analyses described in this study include only those subjects who completed testing on all three test occasions
Mueller, 2004[38]	Intervention, TCC plus ATL, n = 14	mean: 8 months	Female: n: 3, %:NR Age: mean: 54.3, SD: 9.9 Race: NR	HbA1c Mean: 8.7% BMI Mean: 33.6	Type 1: n: 3 Type 2:n: 11	0	

Evidence Table 36 – KQ1b Surgery Interventions characteristics

Author, year	Arm	Foot care intervention : DESCRIPTION	Duration (weeks)	Time/session	Total number of sessions	Adherence to the intervention (please describe briefly)
Mueller, 2004[38]	Arm 1 - TCC	Total contact casting (TCC)	NA	NA	Once	NA
Mueller, 2004[38]	Arm 2 - ATL	TCC plus ATL: Achilles tendon–lengthening: After wound debridement, subjects assigned to the ATL group underwent a percutaneous ATL procedure before application of a TCC using a modified Hoke triple hemisection technique.	NA	NA	Once	NA

Evidence Table 37 – KQ1b Surgery Incidence or Recurrent – Ulcer

Author, year	Arm	Outcome	Baseline N, mean: SD	Time point(s)	At time point(s), N, %	Between arm comparison -
Mueller, 2004[38]	Arm 1 –TCC	Foot ulcer recurrence assessed with clinical examination	N: 14	8 months	38%	NA
Mueller, 2004[38]	Arm 2 - ATL		N: 14	8 months	21%	NA

Evidence Table 38 – KQ1b Surgery Quality of Life

Author, year	Arm, N for analysis	Outcome	Baseline score mean; SD	Time point	Follow-up score Mean; SD	Between arm
Mueller, 2004[38]	Arm 1 - TCC, n = 14	SF-36 Physical Summary	33.9; 7.5	8 months	39.4; 10.9	Comparator arm: TCC, P = 0.035
Mueller, 2004[38]	Arm 2 - ATL, n = 14	SF-36 Physical Summary	35.5; 6.9	8 months	31.0; 6.2	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	SF-36 mental summary	49.9; 11.3	8 months	51.8; 11.5	Comparator arm: TCC, P = 0.56
Mueller, 2004[38]	Arm 2 - ATL, n = 14	SF-36 mental summary	51.2; 12.3	8 months	51.6; 13	

Evidence Table 39 – KQ1b Surgery Physical Activity

Author, year	Arm, N for analysis	Outcome	Baseline score mean; SD	Time point	Follow-up score mean; SD	Between arm
Mueller, 2004[38]	Arm 1 - TCC, n = 14	Simulated dressing	2.9; 0.7	8 months	2.7; 1.1	Comparator arm: TCC, P = 1.0
Mueller, 2004[38]	Arm 2 - ATL, n = 14	Simulated dressing	2.6 ; 0.9	8 months	2.4; 1.1	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	50-foot walking test	15.9; 4.8	8 months	15.1; 4	Comparator arm: TCC, P = 0.1
Mueller, 2004[38]	Arm 2 - ATL, n = 14	50-foot walking test	15.2; 2.8	8 months	15.5; 3.4	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	Climb one flight	2.3 ; 1	8 months	2.4; 1.2	Comparator arm: TCC, P = 0.54
Mueller, 2004[38]	Arm 2 - ATL, n = 14	Climb one flight	2.3; 0.9	8 months	2.1; 1.1	
Mueller, 2004[38]	Arm 1 - TCC, n = 14	Walking velocity	63.2; 21.2	8 months	64.8; 17.9	Comparator arm: TCC, P = 0.97
Mueller, 2004[38]	Arm 2 - ATL, n = 14	Walking velocity	61.8; 10.4	8 months	61.9; 15.9	

KQ1A Risk of Bias – RCTs

RefID	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Bunner, 2015[32]	Low	Low	Low	Low	High	Low	Low	High
Jaiswal, 2015[15]	Unclear	Unclear	High	Unclear	Low	Low	Low	Unclear
Reichard P, 1993[2] and Rathsman, 2014[3]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Dormandy, 2005[8]	Low	Low	Low	Low	Low	Low	Low	Low
Gaede, 2008[7] and Gaede, 2003[6]	Low	Low	Low	Low	Low	Low	Low	Low
UKPDS, 1998[16]	Low	Low	Low	Low	Low	Low	Low	Low
Martin, 2006[9] and 1998[10]	Low	Low	Low	Low	Low	Low	Low	Low
Duckworth, 2009[11]	Low	Low	Low	Low	Low	Low	Low	Low
Abraira, 1997[4]	Unclear	Low	Low	Low	Low	Low	Low	Unclear
Knatterud, 1978[1]	Low	Low	Low	Low	Low	Low	Low	Low

KQ1B Risk of Bias – RCTs

RefID	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding outcome: outcome assessor blinded by critical outcomes (xxx)	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Balance									
Song, 2011[21]	Unclear	Unclear	NA	Unclear		Low	Low	Low	Unclear
Kordi Yoosefinejad, 2015[25]	Low	Unclear	NA	Unclear		Unclear	Low	Unclear	Unclear
Lemaster, 2008[20] and Kruse, 2010[19]	Low	Low	NA	Low		Low	Low	Low	Low
Grewal, 2015[24]	Low	Unclear	NA	Low		Low	Low	Low	Low
Lee, 2013[22]	Low	Low	NA	Unclear		Low	Low	Low	Low
Eftekhar-Sadat, 2015[23]	Low	Unclear	NA	Low		Low	Low	Low	Low
Richardson, 2001[18]	High	High	NA	Unclear		High	Low	Low	High
Physical Therapy									
Chatchawan, 2015[31]	Low	Low	NA	Unclear		Low	Low	Low	Low
Mueller, 2013[30]	Low	Low	NA	Low		Low	Low	Low	Low

KQ1B Risk of Bias – RCTs (continued)

RefID	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding outcome: outcome assessor blinded by critical outcomes (xxx)	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Exercise									
Dixit, 2014[28]	Low	Low	NA	Low		Unclear	Low	Low	Low
Taveggia, 2014[29]	Low	Low	NA	Low		Low	Low	Low	Low
Lemaster, 2008[20] and Kruse, 2010[19]	Low	Low	NA	Low		Low	Low	Low	Low
Sartor, 2014[26]	Low	Unclear	NA	Low		Low	Low	Unclear	Low
Footcare									
Skafjeld, 2015[33]	Low	Low	High	High	Unclear	Low	Low	Low	Unclear
Monami, 2015[35]	Low	Low	High	High	High	Low	Unclear	Low	High

KQ1B Risk of Bias – Cohorts

Author, year	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias
Exercise								
Lemaster, 2003[27]	Moderate	Moderate	Low	Moderate	Moderate	Low	Unclear	Moderate
Footcare								
Shah, 2015[34]	low	low	low	low	low	low	low	Low
Gibson, 2014[36]	low	low	low	low	low	low	low	Low
Chin, 2014[37]	moderate	low	low	moderate	low	low	moderate	Moderate

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Evidence Tables for KQ2a and b

The evidence tables from the Griebeler et. al review are available at: http://www.ncbi.nlm.nih.gov/pubmed/23198755

The data from the newly identified tables are describe in the following tables:

Evidence Table 1 – KQ2a -Study Design Characteristics

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Allen, 2014[1]	Parallel randomized controlled trial Multiple center: North America	Industry	2006-2009	No	
Arezzo, 2008[2]	Parallel randomized controlled trial Multiple center: North America	Industry	NR	Yes	
Atli, 2005[3]	Parallel randomized controlled trial Single center: NR	Academic Industry	NR	Yes	
Campbell, 2012[4]	Parallel randomized controlled trial Multiple center: North America	Industry	NR	No	
Chad, 1990[5]	Parallel randomized controlled trial Multiple center: North America	NR	NR	No	

Evidence Table 1 – KQ2a -Study Design Characteristics (continued)

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Freeman, 2007[6]	Parallel randomized controlled trial Multiple center: North America	Industry	NR	No	
Gao, 2015[7]	Parallel randomized controlled trial Multiple center: Asia	Industry	NR	No	
Ghasemi, 2014[8]	Parallel randomized controlled trial Multiple center: Asia	Academic	2011-2012	No	
Hanna, 2008[9]	Parallel randomized controlled trial Multiple center: Europe, Australia	Industry	2003-2005	Yes	
Harati, 1998[10]	Parallel randomized controlled trial Multiple center: NR	Industry	NR	Yes	Assume North America; run-in period 7-21 days (some drugs stopped for 7 and some 21 days)
Jiang, 2011[11]	Parallel randomized controlled trial Single center:NR	Industry	2006-2008	No	
Karmakar, 2014[12]	Crossover randomized controlled trial Single center: North America	Industry	2011-2013	Yes	

Evidence Table 1 – KQ2a -Study Design Characteristics (continued)

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Kulkantrakorn, 2013[13]	Crossover randomized controlled trial Single center: Asia	Academic	2009-2011	No	
Max, 1987[14]	Crossover randomized controlled trial Single center: North America	NR	NR	Yes	
Niesters, 2014[15]	Parallel randomized controlled trial Single center: Europe	Academic	2012-2012	No	Study intervention listed as analgesic agent
Raskin, 2006[16]	Parallel randomized controlled trial Multiple center: North America	Industry	NR	No	
Raskin, 2014[17]	Parallel randomized controlled trial Multiple center: North America, Africa	Industry	2010-2012	Yes	
Rauck, 2013[18]	Parallel randomized controlled trial Multiple center: North America	Industry	2008-2009	No	
Rowbotham, 2012[19]	Parallel randomized controlled trial Multiple center: NR	Industry	2007-2008	Yes	
Sandercock, 2012[20]	Parallel randomized controlled trial Multiple center: North America	Industry	2006	Yes	

Evidence Table 1 – KQ2a -Study Design Characteristics (continued)

Author, year	Study design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Schwartz, 2015[21]	Parallel randomized controlled trial Multiple center: NR	Industry	NR	Yes	Note that this is a 2ry analysis of other studies that are included -therefore characteristics should not be reported separately. Open label run in period - all patients received tapentadol 50mg bid x 3 days, then 100mg bid then in 50mg increments up to 250mg bid as tolerated
Shaibani, 2012[22]	Parallel randomized controlled trial Multiple center: NR	Industry	NR	Yes	
Tesfaye, 2013[23]	Parallel randomized controlled trial Multiple center: Europe, Asia, North America, Australia	Industry	2010-2011	No	Head to head and dose; combination comparison; several authors are Lilly employees
Toth, 2012[24]	Parallel randomized controlled trial Single center: North America	Industry	2006-2011	Yes	
Wernicke, 2007[25]	Parallel randomized controlled trial Multiple center: Europe, North America,	NR	NR	Np	
Vinik, 2014[26]	Parallel randomized controlled trial Multiple center: North America	Industry	2009-2011	Yes	Analgesic intervention. All participants started out in a titration period. After randomization, placebo group was down-titrated before start of placebo to avoid withdrawal symptoms.
Yuan, 2009[27]	Crossover randomized controlled trial	Industry	NR	No	

	Single center: Asia				
Ziegler, 2015[28]	Parallel randomized controlled trial Multiple center: NR	Industry	2011-2011	Yes	

Evidence Table 2 – KQ2a -Interventions Characteristics

Author, year	Arm	Administration route Dosage	Comments
Allen, 2014[1]	Arm 1 - placebo	Oral	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Oral 50 mg/day	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Oral 100 mg/day	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Oral 200 mg/day	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Oral 400 mg/day	
Allen, 2014[1]	Arm 6 - Open label extension phase	Oral 100mg/day up to 400mg/day per patient	
Arezzo, 2008[2]	Arm 1 - placebo	Oral Placebo given same time as intervention	
Arezzo, 2008[2]	Arm 2 - Pregabalin	Oral Daily dosage escalated for 1 week from 150mg to 300mg BID, which was continued for 12 weeks.	
Atli, 2005[3]	Arm 1 - placebo	Oral Placebo given same time as intervention, contains small amount of lactulose	
Atli, 2005[3]	Arm 2 - Zonisamide	Oral Administered 100-600mg per day, with minimum target dosage of 300mg per day	

Evidence Table 2 – KQ2a -Interventions Characteristics (continued)

Author, year	Arm	Administration route Dosage	Comments
Campbell, 2012[4]	Arm 1 - placebo	Topical Placebo	
Campbell, 2012[4]	Arm 2 - Clonindine	Topical 3.9mg per day (both feet) 0.65mg clonidine per dose, 3x per day per feet (topical application)	
Chad, 1990[5]	Arm 1 – Control - Vehicle	Topical Vehicle	
Chad, 1990[5]	Arm 2 - Capsaicin	Topical 0.075% capsaicin, 4 times a day for 4 weeks	
Freeman, 2007[6]	Arm 1 - placebo	Oral Placebo given same time as intervention	
Freeman, 2007[6]	Arm 2 - Topiramate	Oral 200	Median average daily dose was 156.2 mg/day
Gao, 2015[7]	Arm 1 - placebo	Oral 60	
Gao, 2015[7]	Arm 2 - Duloxetine	Oral 60	

Evidence Table 2 – KQ2a -Interventions Characteristics (continued)

Author, year	Arm	Administration route Dosage	Comments
Ghasemi, 2014[8]	Arm 1 - placebo	Intradermal 100 units	
Ghasemi, 2014[8]	Arm 2 - intervention	Intradermal 100 units	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Oral Placebo pill taken 12 hourly. Gabapentin dose determined by investigator	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Oral Oxycodon pill taken 12 hourly. Gabapentin dose determined by investigator	
Harati, 1998, 306	Arm 1 - placebo	Oral Titrated from 50mg/day up to max of 400mg/day per patient. Must be minimum of 100mg/day by day 14. Average tramadol dose 210 +/- 113 mg/day	
Harati, 1998, 306	Arm 2 - Tramadol	Oral Titrated from 50mg/day up to max of 400mg/day per patient. Must be minimum of 100mg/day by day 14. Average tramadol dose 210 +/- 113 mg/day	

Evidence Table 2 – KQ2a -Interventions Characteristics (continued)

Author, year	Arm	Administration route Dosage	Comments
Jiang, 2011[11]	Arm 1 - Control-Placebo	Oral Placebo	Mean dose 535.7mg (SD: 140.6, Range 150-600)
Jiang, 2011[11]	Arm 2 - Pregabalin	Oral 75mg BID, titrated up to 150mg BID in 7 days, then 300mg BID for 2 weeks	Mean dose 460mg (SD:165, Range 150-600)
Karmakar, 2014, 2024	Overall - all study subjects	Oral 150mg x 7 days, 300mg x 7 days then 600mg	Pregabalin first mean dose 205.8mg, Placebo first mean dose 188.1mg
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	Topical Placebo	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	Topical 0.025%, 2 inches of gel around feet three to four times daily	
Max, 1987[14]	Arm 1 - Control-Placebo	Oral 1mg Benztropine + Placebo	
Max, 1987[14]	Arm 2 - Amitriptyline	Oral 1-6 25mg Amitriptyline capsules per day	
Niesters, 2014[15]	Arm 1 - Control-Placebo	Oral Placebo	
Niesters, 2014[15]	Arm 2 - Tapentadol	Oral 100mg BID in week1, 200 mg BID in week2, 250mg BID in week3 and week4	
Rauck, 2013[18]	Arm 1 - Control-Placebo	Oral Placebo tablets presented same frequency as intervention arms	

Evidence Table 2 – KQ2a -Interventions Characteristics (continued)

Author, year	Arm	Administration route Dosage	Comments
Raskin, 2006[16]	Arm 1 - Routine Care	Oral	
Raskin, 2006[16]	Arm 2 – Duloxetine	Oral Began at 60mg QD for 3 days, then 60mg BID up to 1 week prior week 52, then reduced to 60 mg QD for remainder.	
Raskin, 2014[17]	Arm 1 - Placebo	Oral Single-blind stage: 150-300mg/d pregabalin Double-blind stage: Placebo	Withdrawal trial. Data was reported from baseline of single-blind stage, not from start of randomization in double-blind stage.
Raskin, 2014[17]	Arm 2 – Pregabalin	Oral Single-blind stage: 150-300mg/d Double-blind stage: 150-300mg/d	
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	Oral 1200mg per day, in 600mg tablets	
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	Oral 2400mg per day, in 600mg tablets	
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	Oral 3600mg per day, in 600mg tablets	
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	Oral 300mg per day, in 50 and 100mg tablets	
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	Oral Placebo	
Rowbotham, 2012[19]	Arm 2 – Duloxetine	Oral 60mg per day	

Evidence Table 2 – KQ2a -Interventions Characteristics (continued)

Author, year	Arm	Administration route Dosage	Comments
Sandercock, 2012[20]	Arm 1 - Control-Placebo	Oral Placebo tablets	
Sandercock, 2012[20]	Arm 2 - Gabapentin single dose, 3000mg	Oral 3000mg per day, given in one dose tablets	
Sandercock, 2012[20]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Oral 3000mg per day, given 1800mg in the evening and 1200mg in morning tablets	
Schwartz, 2015[21]	Arm 1 - placebo	Oral Titrated from 50mg bid up to max of 250mg bid. Median of 300mg/day during open label phase and 400mg during double blind phase	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	Oral Titrated from 50mg bid up to max of 250mg bid. Median of 300mg/day during open label phase and 400mg during double blind phase	
Shaibani, 2012[22]	Arm 1 - placebo	Oral Placebo	
Shaibani, 2012[22]	Arm 2 – Dextromethorphan/Quinidine (45/30)	Oral 45mg of Dextromethorphan and 30mg Quinidine per tablet. 1 tablet per day in run-in, 2 tablets per day in rest of trial	Note that quinidine is administered to maintain bioavailability of dextromethorphan and is a very subtherapeutic dose
Shaibani, 2012[22]	Arm 3 - Dextromethorphan/Quinidine (30/30)	Oral 30mg of Dextromethorphan and 30mg Quinidine per tablet. 1 tablet per day in run-in, 2 tablets per day in rest of trial	

Evidence Table 2 – KQ2a -Interventions Characteristics (continued)

Author, year	Arm	Administration route Dosage	Comments
Tesfaye, 2013[23]	Arm 1 – control - Duloxetine 60mg, then Duloxetine 120mg	Oral 60mg per day duloxetine for 7 weeks, increased to 120mg per day duloxetine for 7 weeks.	
Tesfaye, 2013[23]	Arm 2 - Duloxetine 60mg, then combination therapy	Oral 60mg per day duloxetine for 7 weeks, then was switched to 300mg per day pregablin + 60mg per day duloxetine for 7 weeks	
Tesfaye, 2013[23]	Arm 3 - Pregablin 300mg, then combination therapy	Oral 300mg per day pregablin for 7 weeks, then was switched to 300mg per day pregablin + 60mg per day duloxetine for 7 weeks	
Tesfaye, 2013[23]	Arm 4 - Pregablin 300mg, then Pregablin 600mg	Oral 300mg per day pregablin for 7 weeks, increased to 600mg per day pregablin for 7 weeks.	
Toth, 2012[24]	Arm 1 - placebo	Oral Placebo	
Toth, 2012[24]	Arm 2 - Nabilone	Oral Starting dose of 1.0mg per day and titrated as high as 4.0mg per day as tolerated over 3 weeks. This was continued in the double blind phase	
Wernicke, 2007[25]	Arm 1 - Routine Care	NR Routine care provided by physician	
Wernicke, 2007[25]	Arm 2 – Duloxetine	NR Given duloxetine 60mg BID over 52-weeks	
Vinik, 2014[26]	Arm 1 - placebo	Oral Placebo given same time as intervention"	After randomization, placebo group was down-titrated for 3 days before start of placebo to avoid withdrawal symptoms.
Vinik, 2014[26]	Arm 2 - Tapentadol ER	Oral 200 - 500	Variable dose based on response in open-label initial phase. 100 - 250 mg BID

Evidence Table 2 – KQ2a -Interventions Characteristics (continued)

Author, year	Arm	Administration route Dosage	Comments
Yuan, 2009[27]	Arm 1 - placebo	Intradermal Injection 0.9% Saline	
Yuan, 2009[27]	Arm 2 – Botulinum toxin	Intradermal Injection 50 units BoNT/A in 1.2 0.9% saline	
Ziegler, 2015[28]	Arm 1 - placebo	Oral 2 placebo capsules twice daily	
Ziegler, 2015[28]	Arm 2 - Pregabalin	Oral 150mg x 7 days then 300mg	

Evidence Table 3 – KQ2a -Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Allen, 2014[1]	Arm 1 - placebo	13 weeks	25 (28)	mean: 59, SD: 8.5	NR	NR	42.1 years	NR	25
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	13 weeks	16 (25)	mean: 61.6, SD: 8.6	NR	NR	41.8 years	NR	12
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	13 weeks	20 (23)	mean: 60.7, SD: 9.2	NR	NR	45.3 years	NR	18
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	13 weeks	30 (30)	mean: 59.8, SD: 9.4	NR	NR	40.6 years	NR	31
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	13 weeks	17 (25)	mean: 61.1, SD: 10	NR	NR	40.4 years	NR	27
Arezzo, 2008[2]	Arm 1 - placebo	13 weeks	40 (47.1)	mean: 58.3, SD: 10.9	NR	mean: 35.8, SD: 8.4	NR	4.4 years	24
Arezzo, 2008[2]	Arm 2 - Pregabalin	13 weeks	24 (29.3)	mean: 58.2, SD: 9.6	NR	mean: 36.6, SD: 8.3	NR	4.9 years	28
Atli, 2005[3]	Arm 1 - placebo	14 weeks	NR	mean: 61.5, SD: 10.2	NR	mean: 31.7, SD: NR	NR	NR	1
Atli, 2005[3]	Arm 2 - Zonisamide	14 weeks	NR	mean: 55.9, SD: 9.5	NR	mean: 36.8, SD: NR	NR	NR	8
Campbell, 2012[4]	Arm 1 - placebo	16 weeks	48 (53)	mean: 57.6, SD: 9.5	NR	NR	2.9 years	NR	NR
Campbell, 2012[4]	Arm 2 - Clonindine	16 weeks	45 (51)	mean: 59.4, SD: 9.9	NR	NR	3 years	NR	NR

Evidence Table 3 – KQ2a Pain Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Chad, 1990[5]	Arm 1 – Control - Vehicle	4 weeks	NR	NR	NR	NR	NR	NR	NR
Chad, 1990[5]	Arm 2 - Capsaicin	4 weeks	NR	NR	NR	NR	NR	NR	NR
Freeman, 2007[6]	Arm 1 - placebo	18 weeks	10 (31)	mean: 57.8, SD: 11.53	NR	mean: 31.2, SD: 4.7	NR	NR	4
Freeman, 2007[6]	Arm 2 - Topiramate	18 weeks	13 (39)	mean: 58.5, SD: 8.51	NR	mean: 33.9, SD: 5.3	NR	NR	9
Gao, 2015[7]	Arm 1 - placebo	12 weeks	111 (55)	mean: 61.2, SD: 9.4	NR	mean: 24.5, SD: 3.2	NR	3.1 years	26
Gao, 2015[7]	Arm 2 - Duloxetine	12 weeks	112 (55.2)	mean: 61.6, SD: 9.7	NR	mean: 24.6, SD: 3.6	NR	3.5 years	30
Gao, 2015[7]	Overall - total	12 weeks	223 (55.1)	mean: 61.4, SD: 9.5	NR	mean: 24.6, SD: 3.4	NR	3.3 years	56
Ghasemi, 2014[8]	Arm 1 - placebo	3 weeks	11 (NR)	mean: 59.3, SD: 9.6	NR	NR	NR	NR	0
Ghasemi, 2014[8]	Arm 2 - intervention	3 weeks	7 (NR)	mean: 62.7, SD: 9.9	NR	NR	NR	NR	0
Hanna, 2008[9]	Overall - total	12 weeks	118 (36)	mean: 60.1, SD: 10.24	NR	NR	NR	NR	89
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	12 weeks	55 (33)	mean: 60.7, SD: 9.93	NR	NR	NR	NR	41
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	12 weeks	63 (39)	mean: 59.6, SD: 10.54	NR	NR	NR	NR	48

Evidence Table 3 – KQ2a -Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Harati, 1998[10]	Arm 1 – control – placebo	42 days	27 (41)	mean: 59, SD: NR	mean: 10.6, SD: NR	NR	NR	NR	22
Harati, 1998[10]	Arm 2 - Tramadol	42 days	26 (40)	mean: 59, SD: NR	mean: 10.8, SD: NR	NR	NR	NR	22
Kulkantrakorn, 2013[13]	Overall - total	8 weeks	17 (51.5)	mean: 58.0, SD: NR	NR	NR	4.7	NR	25
Jiang, 2011[11]	Arm 1 - Control-Placebo	4 weeks	6 (30)	mean: 59.7, SD: 12.5	7.96, SD: 1.98	mean: 32.3, SD: 8.7	4.66 years	NR	6
Jiang, 2011[11]	Arm 2 - Pregabalin	4 weeks	9 (45)	mean: 55.1, SD: 14.4	8.33, SD: 2.9	mean: 31, SD: 8.1	10.1 years	NR	5
Karmakar, 2014[12]	Overall - all study subjects	15 weeks	11 (39)	mean: 64.6, SD: 10.4	NR	NR	NR	5.7 years	4
Max, 1987[14]	Arm 1 - Control-Placebo	6 weeks	12	Median: 57	NR	NR	2	NR	NR
Niesters, 2014[15]	Arm 1 - placebo	4 weeks	5 (NR)	median: 64, SD: NR	NR	NR	NR	6.5 years	0

Evidence Table 3 – KQ2a Pain Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Niesters, 2014[15]	Arm 2 - Tapentadol	4 weeks	5 (NR)	median: 63, SD: NR	NR	NR	NR	6	0
Raskin, 2006[16]	Arm 1 - Routine Care	65 weeks	30 (39.5)	mean: 60.6, SD: 10.3	NR	NR	NR	3.1	13
Raskin, 2006[16]	Arm 2 – Duloxetine	65 weeks	62 (38.5)	mean: 59.7, SD: 10.7	NR	NR	NR	3.9	45
Raskin, 2014[17]	Overall – single blind phase	6 weeks	302 (45.4)	mean: 58.4, SD: 10.1	NR	NR	5.5	4.9	371
Raskin, 2014[17]	Arm 1 - Control-Placebo	13 weeks	67 (45.6)	mean: 58.3, SD: 10.5	NR	NR	5.8	5.2	34
Raskin, 2014[17]	Arm 2 – Pregabalin	13 weeks	72 (49.0)	mean: 58.8, SD: 9.2	NR	NR	5.4	5.0	22

Evidence Table 3 – KQ2a Pain Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Rauck, 2013[18]	Arm 1 – placebo	16 weeks	47 (39)	mean: 60.1, SD: 10.63	NR	NR	NR	NR	NR
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	16 weeks	28 (45)	mean: 57.5, SD: 10.32	NR	NR	NR	NR	NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	16 weeks	19 (34)	mean: 60.8, SD: 8.97	NR	NR	NR	NR	NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	16 weeks	45 (39)	mean: 57.5, SD: 9.87	NR	NR	NR	NR	NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	16 weeks	32 (48)	mean: 57.7, SD: 10.59	NR	NR	NR	NR	NR
Rauck, 2013[18]	Overall	16 weeks	171 (41)	mean: 58.7, SD: 10.2	NR	NR	NR	NR	NR
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	8 weeks	23 (45.1)	mean: 59.6, SD: 7.0	NR	NR	4.4	NR	7
Rowbotham, 2012[19]	Arm 2 – Duloxetine	8 weeks	25 (43.9)	mean: 60.1, SD: 7.8	NR	NR	4.8	NR	13

Evidence Table 3 – KQ2a -Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Sandercock, 2012[20]	Arm 1 - Control-Placebo	5 weeks	19 (33)	mean: 58, SD: 9.1	mean: 7.1, SD: 1.4	mean: 33.4, SD: 8.2	NR	NR	5
Sandercock, 2012[20]	Arm 2 - Gabapentin single dose, 3000mg	5 weeks	29 (63)	mean: 58, SD: 8.0	mean: 7.6, SD: 1.4	mean: 34.2, SD: 6.7	NR	NR	4
Sandercock, 2012[20]	Arm 3 – Gabapentin asymmetric dose, 3000mg	5 weeks	18 (36)	mean: 60, SD: 7.5	mean: 7.0, SD: 1.5	mean: 34.3, SD: 7.2	NR	NR	7
Schwartz, 2015[21]	Arm 1 - placebo	Median: 84 NR days	141 (41.1)	mean: 59.9, SD: 9.94	NR	NR	NR	6.1 years	103
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	Median: 84 NR days	142 (39.4)	mean: 59.1, SD: 10.62	NR	NR	NR	5.3 years	104
Shaibani, 2012[22]	Arm 1 - placebo	13 weeks	55 (44.7)	mean: 62.0, SD: 9.8	mean: 7.4, SD: 1.7	NR	3.2	3.8	34
Shaibani, 2012[22]	Arm 2 – Dextromethorphan /Quinidine (45/30)	13 weeks	50 (38.2)	mean: 61.0, SD: 10.4	mean: 7.3, SD: 1.4	NR	3.8	4.0	52
Shaibani, 2012[22]	Arm 3 - Dextromethorphan /Quinidine (30/30)	13 weeks	40 (32.0)	mean: 59.8, SD: 10.1	mean: 7.2, SD: 1.3	NR	3.0	3.6	51

Evidence Table 3 – KQ2a –Pain Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Tesfaye, 2013[23]	Arm 1 – control - Duloxetine 60mg, then Duloxetine 120mg	18 weeks	NR	mean: 61.5, SD: 10.62	mean: 8, SD: 1.7	mean: 30.7, SD: 6.18	2 years	2 years	124
Tesfaye, 2013[23]	Arm 2 - Duloxetine 60mg, then combination therapy	18 weeks	NR	mean: 61.5, SD: 10.62	mean: 8, SD: 1.7	mean: 30.7, SD: 6.18	2 years	2 years	129
Tesfaye, 2013[23]	Arm 3 - Pregablin 300mg, then combination therapy	18 weeks	NR	mean: 61.9, SD: 10.95	mean: 7.9, SD: 1.57	mean: 30.9, SD: 5.94	2 years	2 years	107
Tesfaye, 2013[23]	Arm 4 - Pregablin 300mg, then Pregablin 600mg	18 weeks	NR	mean: 61.9, SD: 10.95	mean: 7.9, SD: 1.57	mean: 30.9, SD: 5.94	2 years	2 years	105
Toth, 2012[24]	Arm 1 - placebo	5 weeks	4 (31)	mean: 61.6, SD: 14.6	mean: 7.2, SD: 1.6	NR	NR	7.1 years	0
Toth, 2012[24]	Arm 2 - Nabilone	5 weeks	8 (62)	mean: 60.8, SD: 15.3	mean: 7.1, SD: 1.8	NR	NR	7.2 years	1
Wernicke, 2007[25]	Arm 1 - Routine Care	65 weeks	49 (51)	mean: 58.5, SD: 9.3	NR	NR	NR	4	10
Wernicke, 2007[25]	Arm 2 – Duloxetine	65 weeks	109 (55.3)	mean: 58.1, SD: 10.5	NR	NR	NR	4.4	8

Evidence Table 3 – KQ2a –Pain Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Vinik, 2014[26]	Arm 1 – placebo	12 weeks	64 (42.1)	mean: 59, SD: 9	NR	mean: 34.5, SD: 7.84	NR	NR	45
Vinik, 2014[26]	Arm 2 - Tapentadol ER	12 weeks	67 (40.4)	mean: 58.5, SD: 10.63	NR	mean: 35.1, SD: 11.47	NR	NR	46
Yuan, 2009[27]	Overall	12 weeks	12	mean: 65.6, SD: 9.2	NR	NR	NR	NR	2
Ziegler, 2015[28]	Arm 1 - placebo	7 weeks	26 (42)	mean: 58.9, SD: 8.6	mean: 7.4, SD: 1.25	mean: 31.3, SD: 5.36	NR	6.1 years	2
Ziegler, 2015[28]	Arm 2 - Pregabalin	7 weeks	34 (49)	mean: 59.6, SD: 8.75	mean: 7.2, SD: 1.11	mean: 33.3, SD: 8.36	NR	5.3 years	5

Evidence Table 4 – KQ2a Pain Continuous Outcomes

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Allen, 2014[1]	Arm 1 - placebo	NRS: 0-10 scale	N: 90, Mean: 6.61, SD: 1.6	13 weeks	N: 89, Mean: NR, SD: NR	Mean change from baseline: -1.83, SD: NR, p: NR	Mean change from baseline: NA (95% CI:NR), SD: NR, Comparator arm: NA, p: NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	NRS: 0-10 scale	N: 63, Mean: 6.44, SD: 1.66	13 weeks	N: 63, Mean: NR, SD: NR	Mean change from baseline: -2.41, SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.084
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	NRS: 0-10 scale	N: 87, Mean: 6.14, SD: 1.62	13 weeks	N: 86, Mean: NR, SD: NR	Mean change from baseline: -2.42, SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.084
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	NRS: 0-10 scale	N: 99, Mean: 6.55, SD: 1.52	13 weeks	N: 99, Mean: NR, SD: NR	Mean change from baseline: -2.93, SD: NR, p: NR	Mean change from baseline: 1.1 (95% CI:NR), SD: NR, Comparator arm: vs Placebo, p: 0.001
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	NRS: 0-10 scale	N: 69, Mean: 6.48, SD: 1.42	13 weeks	N: 68, Mean: NR, SD: NR	Mean change from baseline: -2.74, SD: NR, p: NR	Mean change from baseline: 0.91 (95% CI:NR), SD: NR, Comparator arm: vs Placebo, p: 0.027
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	NRS: 0-10 scale	N: 240, Mean: 3.86, SD: NR	9 months	N: 223, Mean: 3.35, SD: NR	Mean change from baseline: -0.53, SD: NR, p: NR	Mean change from baseline NR Comparator arm: NR, p: NR
Arezzo, 2008[2]	Arm 1 - placebo	NRS: 0-10 scale	N: 85, Mean: 6.58, SD: 1.58	13 weeks	N: 85, Mean: 4.82, SD: NR	NR	

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Arezzo, 2008[2]	Arm 2 - Pregabalin	NRS: 0-10 scale	N: 82, Mean: 6.28, SD: 1.47	13 weeks	N: 82, Mean: 3.54, SD: NR	NR	Mean change from baseline: -1.28 (95% CI:-1.96, -0.60), SD: NR, p: 0.0003
Arezzo, 2008[2]	Arm 1 - placebo	SF-MPQ, Present Pain Intensity: 0-5 scale	N: 85, Mean: NR, SD: NR	12 weeks	N: 85, Mean: NR, SD: NR	NR	
Arezzo, 2008[2]	Arm 2 - Pregabalin	SF-MPQ, Present Pain Intensity: 0-5 scale	N: 82, Mean: NR, SD: NR	12 weeks	N: 82, Mean: NR, SD: NR	NR	Mean change from baseline: -0.34 (95% CI:-0.65, -0.03), SD: NR, p: 0.0311
Arezzo, 2008[2]	Arm 1 - placebo	SF-MPQ, VAS: 0-100 scale	N: 85, Mean: NR, SD: NR	NR	N: 85, Mean: NR, SD: NR	NR	
Arezzo, 2008[2]	Arm 2 - Pregabalin	SF-MPQ, VAS: 0-100 scale	N: 82, Mean: NR, SD: NR	NR	N: 82, Mean: NR, SD: NR	NR	Mean difference from baseline: 11.06 (95% CI:-18.89, -3.22), SD: NR, p: 0.006
Atli, 2005[3]	Arm 1 - placebo	Likert scale, LOCF imputation: 0-10 scale	N: 12, Mean: 6.63, SD: 1.7	14 weeks	N: 12, Mean: 6.03, SD: 1.7	Mean change from baseline: 0.6, SD: 1.4, p: NR	
Atli, 2005[3]	Arm 2 - Zonisamide	Likert scale, LOCF imputation: 0-10 scale	N: 13, Mean: 6.45, SD: 1.1	14 weeks	N: 11, Mean: 4.89, SD: 2.1	Mean change from baseline: 1.56, SD: 1.9, p: NR	p: 0.18

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Atli, 2005[3]	Arm 1 - placebo	VAS, LOCF imputation: 0-100 scale	N: 12, Mean: 63.9, SD: 18.1	14 weeks	N: 12, Mean: 57, SD: 19.9	Mean change from baseline: 6.9, SD: 15.4, p: NR	
Atli, 2005[3]	Arm 2 - Zonisamide	VAS, LOCF imputation: 0-100 scale	N: 13, Mean: 58.9, SD: 9.4	14 weeks	N: 11, Mean: 41.2, SD: 21.2	Mean change from baseline: 17.7, SD: 19, p: NR	p: 0.15
Campbell, 2012[4]	Arm 1 – control placebo	BPI, average pain: 0-10 scale	N: 30, Mean: 6.3, SD: 1.5	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -1.3, SD: 1.7, p: NR	NR Comparator arm: Placebo, p: 0.06
Campbell, 2012[4]	Arm 2 - Clonindine	BPI, average pain: 0-10 scale	N: 33, Mean: 6.5, SD: 1.6	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -2.2, SD: 1.9, p: NR	NR Comparator arm: Placebo, p: 0.06

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Campbell, 2012[4]	Arm 1 - placebo	BPI, functional interference scale-0-70 scale	N: 30, Mean: 37.2, SD: 17.1	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -8.7, SD: 13.2, p: NR	NR Comparator arm: Placebo, p: 0.43
Campbell, 2012[4]	Arm 2 - Clonindine	BPI, functional interference scale-0-70 scale	N: 33, Mean: 37.1, SD: 17.5	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -13, SD: 15.2, p: NR	NR Comparator arm: Placebo, p: 0.43
Campbell, 2012[4]	Arm 1 - placebo	BPI, severity scale-0-40 scale	N: 30, Mean: 25.4, SD: 5.8	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -5.3, SD: 7.8, p: NR	NR Comparator arm: Placebo, p: 0.18
Campbell, 2012[4]	Arm 2 - Clonindine	BPI, severity scale-0-40 scale	N: 33, Mean: 25.1, SD: 7.3	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -7.8, SD: 7.2, p: NR	NR Comparator arm: Placebo, p: 0.18
Campbell, 2012[4]	Arm 1 - placebo	NPRS, average pain severity from diary-NR scale	N: 30, Mean: 6.3, SD: 1.4	12 weeks	N: 30, Mean: NR, SD: NR	Mean change from baseline: -1.4, SD: 1.8, p: NR	NR Comparator arm: Placebo, p: 0.01
Campbell, 2012[4]	Arm 2 - Clonindine	NPRS, average pain severity from diary-NR scale	N: 33, Mean: 6.3, SD: 1.5	12 weeks	N: 33, Mean: NR, SD: NR	Mean change from baseline: -2.6, SD: 2, p: NR	NR Comparator arm: Placebo, p: 0.01

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Freeman, 2007[6]	Arm 1 - placebo	VAS: 0-100 scale	N: 32, Mean: NR, SD: NR	18 weeks	N: 32, Mean: NR, SD: NR	Mean change from baseline: -11.5, SD: 38.9, p: NR	
Freeman, 2007[6]	Arm 2 - Topiramate	VAS: 0-100 scale	N: 35, Mean: NR, SD: NR	18 weeks	N: 35, Mean: NR, SD: NR	Mean change from baseline: -16.2, SD: 27.3, p: NR	p: 0.35
Gao, 2015[7]	Arm 1 - placebo	Weekly mean 24h average pain: 0-10 scale	N: 202, Mean: 5.6, SD: 1.7	12 weeks	N: 173, Mean: NR, SD: NR	Mean change from baseline: -1.97, SD: NR, p: NR	Mean change from baseline: NA (95% CI:NA), SD: NR, Comparator arm: p: NA

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Gao, 2015[7]	Arm 2 - Duloxetine	Weekly mean 24h average pain: 0-10 scale	N:203, Mean:5.7, SD:1.7	12 weeks	N: 172, Mean: NR, SD: NR	Mean change from baseline: -2.4, SD: NR, p: NR	Mean change from baseline: -0.43 (95% CI:(-0.82, -0.04)), SD: NR, Comparator arm: vs Placebo, p: 0.03
Ghasemi, 2014[8]	Arm 1 - placebo	Neuropathy Pain Scale (NPS), Pain Intensity: 0-10 scale	N: 20, Mean: 7.1, SD: 2.2	3 weeks	N: 20, Mean: 7, SD: 2	Mean change from baseline: NR, SD: NR, p: 0.8	Mean change from baseline NR Comparator arm: NA, p: NA
Ghasemi, 2014[8]	Arm 2 - intervention	Neuropathy Pain Scale (NPS), Pain Intensity: 0-10 scale	N: 20, Mean: 6.9, SD: 2.1	3 weeks	N: 20, Mean: 5.1, SD: 2.3	Mean change from baseline: NR, SD: NR, p: <0.001	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.009
Ghasemi, 2014[8]	Arm 1 – control placebo	Neuropathy Pain Scale (NPS), Sharp sensation: 0-10 scale	N: 20, Mean: 5.4, SD: 2.6	3 weeks	N: 20, Mean: 4.9, SD: 2.6	Mean change from baseline: NR, SD: NR, p: 0.1	Mean change from baseline NR Comparator arm: NA, p: NA
Ghasemi, 2014[8]	Arm 2 - intervention	Neuropathy Pain Scale (NPS, sharp sensation: 0-10 scale	N: 20, Mean: 5.4, SD: 2.4	3 weeks	N: 20, Mean: 4.2, SD: 2.7	Mean change from baseline: NR, SD: NR, p: <0.001	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.41
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Box Scale -11 (BS-11)	N: 145, Mean: 6.5, SD: 1.7	12 weeks	N: 145, Mean: NR, SD: NR	Mean change from baseline:-1.5, SD: 2.4, p: NR	Mean change from baseline NR Comparator arm: NA, p: NA
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Box Scale -11 (BS-11)	N: 138, Mean: 6.4, SD: 1.8	12 weeks	N: 138, Mean: NR, SD: NR	Mean change from baseline: -2.1, SD: 2.6, p: NR	Mean change from baseline: 0.55 (95% CI: 0.15, 0.95), p=0.007

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	BPI	N:145, Mean: NR, SD: NR	12 weeks	N:145, Mean: NR, SD: NR	NR	Mean change from baseline NR Comparator arm: NA, p: NA
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	BPI	N: 138, Mean: NR, SD: NR	12 weeks	N: 138, Mean: NR, SD: NR	NR	Mean change from baseline: NR p<0.001
Harati, 1998[10]	Arm 1 - placebo	Pain Intensity Scale (Likert): 0-4 scale	N: 66, Mean: 2.6, SD: 0.1	42 days	N: 64, Mean: 2.2, SD: 0.1	NR	Mean difference from baseline: p: NA
Harati, 1998[10]	Arm 2 - Tramadol	Pain Intensity Scale (Likert): 0-4 scale	N: 65, Mean: 2.5, SD: 0.1	42 days	N: 63, Mean: 1.4, SD: 0.1	NR	Mean change from baseline NR Comparator arm: vs Placebo, p: <0.001
Harati, 1998[10]	Arm 1 - placebo	Pain Relief Rating Scale (Likert): -1-4 scale	N: 66, Mean: NR, SD: NR	42 days	N: 64, Mean: 0.9, SD: 0.2	NR	Mean change from baseline NR Comparator arm: p: NA
Harati, 1998[10]	Arm 2 - Tramadol	Pain Relief Rating Scale (Likert): -1-4 scale	N: 65, Mean: NR, SD: NR	42 days	N: 63, Mean: 2.1, SD: 0.2	NR	Mean change from baseline NR Comparator arm: vs Placebo, p: <0.001

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Jiang, 2011[11]	Arm 1 - Control-Placebo	VAS: 0-100 scale	N: 20, Mean: 75.4, SD: 12.9	4 weeks	N: 14, Mean: NR, SD: NR	Mean change from baseline: -21.29, SD: 35.6, p: NR	P:0.092
Jiang, 2011[11]	Arm 2 - Pregabalin	VAS: 0-100 scale	N: 20, Mean: 70.78, SD: 18.8	4 weeks	N: 15, Mean: NR, SD: NR	Mean change from baseline: -43.27, SD: 32.0, p: NR	P:0.092
Jiang, 2011[11]	Arm 1 - Control-Placebo	BPI, total pain score	N: 20, Mean: 16.9, SD: 7.8	4 weeks	N: 14, Mean: NR, SD: NR	Mean change from baseline: -1.36, SD: 9.01, p: NR	P:0.03
Jiang, 2011[11]	Arm 2 - Pregabalin	BPI, total pain score	N: 20, Mean: 18.1, SD: 9.08	4 weeks	N: 15, Mean: NR, SD: NR	Mean change from baseline: -9.13, SD: 9.63, p: NR	P:0.03
Jiang, 2011[11]	Arm 1 - Control-Placebo	NPS, total pain score	N: 20, Mean: 50.9, SD: 12.35	4 weeks	N: 14, Mean: NR, SD: NR	Mean change from baseline: -10.31, SD: 11.15, p: NR	P:0.053
Jiang, 2011[11]	Arm 2 - Pregabalin	NPS, total pain score	N: 20, Mean: 53.05, SD: 19.64	4 weeks	N: 15, Mean: NR, SD: NR	Mean change from baseline: -27.33, SD: 22.95, p: NR	P:0.053

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	VAS: 0-100 scale	N: 17, Mean: 50.0, SD: 2.93	8 weeks	N: 17, Mean: 3.46, SD: 2.89	NR	P:0.531
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	VAS: 0-100 scale	N: 16, Mean: 44.1, SD: 2.49	8 weeks	N: 16, Mean: 2.88, SD: 2.18	NR	P:0.531
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	NPS	N: 17, Mean: 42.43, SD: 21.41	8 weeks	N: 17, Mean: 31.29, SD: 21.29	NR	P:0.805
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	NPS	N: 16, Mean: 38.46, SD: 20.76	8 weeks	N: 16, Mean: 29.38, SD: 16.07	NR	P:0.805
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	SF-MPQ	N: 17, Mean: 19.18, SD: 8.89	8 weeks	N: 17, Mean: 7.71, SD: 10.16	NR	P:0.953
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	SF-MPQ	N: 16, Mean: 18.06, SD: 9.15	8 weeks	N: 16, Mean: 7.40, SD: 6.19	NR	P:0.953

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Max, 1987[14]	Arm 1 - Control-Placebo	Pain intensity	N: 29, Mean: 1.1, SD: NR	3 weeks	N: 29, Mean: 0.88, SD: NR	NR	NA
Max, 1987[14]	Arm 2 - Amitriptyline	Pain intensity	N: 29, Mean: 0.92, SD: NR	63 weeks	N: 29, Mean: 0.44, SD: NR	NR	Mean difference from baseline: NR, SD: NR, p<0.001 In favor of amitriptyline; only for the 1st part of the crossover trial (full crossover results not reported, & 2nd part was not significant)
Niesters, 2014[15]	Arm 1 - placebo	Conditioned Pain Modulation (CPM): 0-100 scale	N: 12, Mean: 9.1, SD: 5.4	4 weeks	N: 12, Mean: 14.3, SD: 7.2	Mean change from baseline: NR, SD: NR, p: 0.04	NR
Niesters, 2014[15]	Arm 2 - Tapentadol	Conditioned Pain Modulation (CPM): 0-100 scale	N: 12, Mean: 9.1, SD: 5.4	4 weeks	N: 12, Mean: 24.2, SD: 7.7	Mean change from baseline: NR, SD: NR, p: <0.01	Mean difference from baseline:, p: <0.001

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Niesters, 2014[15]	Arm 1 – control – placebo	VAS (NRS): 0-10 scale	N: 12, Mean: 6.5, SD: 0.6	4 weeks	N: 12, Mean: 4.8, SD: 0.7	NR	NR
Niesters, 2014[15]	Arm 2 - Tapentadol	VAS (NRS): 0-10 scale	N: 12, Mean: 6.5, SD: 0.6	4 weeks	N: 12, Mean: 3.9, SD: 0.6	NR	Mean difference from baseline:, p: 0.03
Raskin, 2014[17]	Arm 1 - Control-Placebo	NRS	N:147, Mean: 6.7, SD: 1.3	19 weeks	N:147, Mean: 3.2, SD: 1.9	Mean change from baseline: -3.5, SD: 2.1, p: NR	NR
Raskin, 2014[17]	Arm 2 – Pregabalin	NRS	N:147, Mean: 6.8, SD: 1.2	19 weeks	N:147, Mean: 2.9, SD: 1.7	Mean change from baseline: -3.9, SD: 1.9, p: NR	Comparator arm: placebo; Least squares mean difference in change from baseline -0.32 (95% CI, -0.74 to 0.09, NS) (LOCF data, reported as primary outcome)

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 1 – control – placebo	BPI severity: scale NR	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	BPI severity: scale NR	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.3 (95% CI:-0.96, 0.44), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	BPI severity: scale NR	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.3 (95% CI:-1.06, 0.47), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	BPI severity: scale NR	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.7 (95% CI:-1.29, 0.12), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	BPI severity: scale NR	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.4 (95% CI:-0.28, 1.08), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	NPS 10: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS 10: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.49 (95% CI:-5.96, 6.93), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS 10: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -3.33 (95% CI:-10.3, 3.69), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS 10: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -6.57 (95% CI:-12.0, -1.18), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	NPS 10: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 2.76 (95% CI:-3.55, 9.07), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	NPS 4: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS 4: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.36 (95% CI:-7.49, 6.78), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS 4: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -4.61 (95% CI:-12.4, 3.16), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS 4: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -7.3 (95% CI:-13.3, -1.32), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	NPS 4: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 4.48 (95% CI:-2.51, 11.47), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	NPS 8: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS 8: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.9 (95% CI:-5.50, 7.29), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS 8: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -3.11 (95% CI:-10.1, 3.85), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS 8: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -6.41 (95% CI:-11.8, -1.05), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	NPS 8: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 2.54 (95% CI:-3.72, 8.80), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	NPS: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	NPS: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.49 (95% CI:-6.24, 7.22), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	NPS: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -3.49 (95% CI:-10.8, 3.84), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	NPS: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -6.98 (95% CI:-12.6, -1.34), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	NPS: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 3.74 (95% CI:-2.85, 10.33), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 120, Mean: 6.49, SD: 1.26	16 weeks	N: 120, Mean: NR, SD: NR	Mean change from baseline: -2.09, SD: 2.07, p: NR	Mean difference from baseline: Comparator arm: Placebo, p: NA

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 2- Gabapentin enacarbil, 1200mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 62, Mean: 6.64, SD: 1.47	16 weeks	N: 62, Mean: NR, SD: NR	Mean change from baseline: -2.55, SD: 2.54, p: NR	Mean difference from baseline: -0.35 (95% CI:-1.02, 0.31), SD: NR, Comparator arm: Placebo, p: 0.295
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 56, Mean: 6.26, SD: 1.22	16 weeks	N: 56, Mean: NR, SD: NR	Mean change from baseline: -1.9, SD: 2.05, p: NR	Mean difference from baseline: -0.02 (95% CI:-0.71, 0.66), SD: NR, Comparator arm: Placebo, p: 0.946
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 116, Mean: 6.48, SD: 1.43	16 weeks	N: 116, Mean: NR, SD: NR	Mean change from baseline: -2.54, SD: 2.42, p: NR	Mean difference from baseline: -0.55 (95% CI:-1.10, 0.01), SD: NR, Comparator arm: Placebo, p: 0.105
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	Pain Intensity Numerical Rating Scale (PI-NRS): 0-10 scale	N: 66, Mean: 6.51, SD: 1.27	16 weeks	N: 66, Mean: NR, SD: NR	Mean change from baseline: -1.66, SD: 1.83, p: NR	Mean difference from baseline: 0.43 (95% CI:-0.22, 1.08), SD: NR, Comparator arm: Placebo, p: NA
Rauck, 2013[18]	Arm 1 - placebo	PI-NRS, Daytime average pain: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	PI-NRS, Daytime average pain: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.28 (95% CI:-0.94, 0.38), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	PI-NRS, Daytime average pain: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: 0 (95% CI:-0.68, 0.68), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	PI-NRS, Daytime average pain: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.47 (95% CI:-1.02, 0.08), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	PI-NRS, Daytime average pain: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.57 (95% CI:-0.08, 1.21), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	PI-NRS, Nightime average pain: 0-10 scale	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	PI-NRS, Nightime average pain: 0-10 scale	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.16 (95% CI:-0.84, 0.52), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	PI-NRS, Nightime average pain: 0-10 scale	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.05 (95% CI:-0.76, 0.66), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	PI-NRS, Nightime average pain: 0-10 scale	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.72 (95% CI:-1.29, -0.15), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	PI-NRS, Nightime average pain: 0-10 scale	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.16 (95% CI:-0.51, 0.83), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	24 hour average pain	N: 50, Mean: 6.6, SD: 1.2	8 weeks	N: 50, Mean: NR, SD: NR	Least squares mean change from baseline: -2.1, SE: 0.3, p: NS	Mean change from baseline NR Comparator arm: vs Placebo, p: NA
Rowbotham, 2012[19]	Arm 2 – Duloxetine	24 hour average pain	N: 54, Mean: 6.6, SD: 1.4	8 weeks	N: 54, Mean: NR, SD: NR	Least squares mean change from baseline: -2.8, SE: 0.3, p: 0.05	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.032
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	BPI average pain	N: 50, Mean: 6.5, SD: 1.5	8 weeks	N: 50, Mean: NR, SD: NR	Least squares mean change from baseline: -1.9, SE: 0.3, p: NS	NR
Rowbotham, 2012[19]	Arm 2 – Duloxetine	BPI average pain	N: 56, Mean: 6.4, SD: 1.3	8 weeks	N: 56, Mean: NR, SD: NR	Least squares mean change from baseline: -2.3, SE: 0.3, p: NS	NR
Sandercock, 2012[20]	Arm 1 - Control-Placebo	NRS: 0-10 scale	N: 51, Mean: 6.74, SD: 1.37	4 weeks	N: 49, Mean: NR, SD: NR	Mean change from baseline: -1.3 (95% CI:-1.8, -0..7), SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: NA
Sandercock, 2012[20]	Arm 2 - Gabapentin single dose, 3000mg	NRS: 0-10 scale	N: 46, Mean: 6.71, SD: 1.34	4 weeks	N: 43, Mean: NR, SD: NR	Mean change from baseline: -2.5 (95% CI:-3.0, -1.9), SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.002
Sandercock, 2012[20]	Arm 3 – Gabapentin asymmetric dose, 3000mg	NRS: 0-10 scale	N: 50, Mean: 6.44, SD: 1.51	4 weeks	N: 46, Mean: NR, SD: NR	Mean change from baseline: -1.8 (95% CI:-2.3, -1.2), SD: NR, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: 0.190

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Schwartz, 2015[21]	Arm 1 - placebo	BPI-SF Pain Intensity Subscale: 0-10 scale	N: 343, Mean: NR, SD: NR	12 weeks	N: 343, Mean: NR, SD: NR	Mean change from baseline: 1, SD: 2.22, p: NR	Mean change from baseline NR Comparator arm: NA, p: NA
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	BPI-SF Pain Intensity Subscale: 0-10 scale	N: 360, Mean: NR, SD: NR	12 weeks	N: 360, Mean: NR, SD: NR	Mean change from baseline: 0, SD: 1.87, p: NR	Mean change from baseline NR Comparator arm: vs Placebo, p: <0.001
Schwartz, 2015[21]	Arm 1 - placebo	NRS: 0-10 scale	N: 343, Mean: 3.48, SD: 2.02	12 weeks	N: 343, Mean: 4.76, SD: 2.52	Mean change from baseline: 1.28, SD: 2.41, p: NR	Mean change from baseline: NA (95% CI:NA), SD: NR, Comparator arm: NA, p: NA
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	NRS: 0-10 scale	N: 360, Mean: 3.67, SD: 1.84	12 weeks	N: 360, Mean: 3.77, SD: 2.19	Mean change from baseline: 0.08, SD: 1.87, p: NR	Mean change from baseline: -1.14 (95% CI:(-1.435, -0.838)), SD: NR, Comparator arm: vs Placebo, p: <0.001
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	NRS: 0-10 scale	N: 1040, Mean: 7.29, SD: 1.38	3 weeks	N: NR, Mean: 4.15, SD: 2.1	NR	Mean change from baseline: -3.19 (95% CI:NR), SD:2, Comparator arm: NA, p:NA

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Shaibani, 2012[22]	Arm 1 - placebo	Pain Rating Scale	N: 123, mean: 4.4, SD: 2.5	13 weeks	N: 89, mean: NR, SD: NR	Mean change from baseline: -2.0, SE: 0.05, p: NR	Mean change from baseline: NA , SD: NR, Comparator arm: NA, p: NA
Shaibani, 2012[22]	Arm 2 – Dextromethorphan/ Quinidine (45/30)	Pain Rating Scale	N: 131, mean: 4.9, SD: 2.4	13 weeks	N: 79, mean: NR, SD: NR	Mean change from baseline: -2.6, SE: 0.05, p: NR	Mean change from baseline: NR, SD:NR, Comparator arm: Placebo, p: <0.0001
Shaibani, 2012[22]	Arm 3 - Dextromethorphan/ Quinidine (30/30)	Pain Rating Scale	N: 125, mean: 4.7, SD: .24	13 weeks	N: 74, mean: NR, SD: NR	Mean change from baseline: -2.2, SE: 0.06, p: NR	Mean change from baseline: NR, SD:NR, Comparator arm: Placebo, p: 0.009
Toth, 2012[24]	Arm 1 - placebo	NRS: 0-10 scale	N: 13, Mean: 5.8, SD: 1.6	4 weeks	N: 13, Mean: 5.4, SD: 1.7	Mean change from baseline: 3, SD: 1.5, p: <0.01	NR Comparator arm: NR, p: NR
Toth, 2012[24]	Arm 2 - Nabilone	NRS: 0-10 scale	N: 13, Mean: 5.8, SD: 1.8	4 weeks	N: 13, Mean: 3.5, SD: 1.3	Mean change from baseline: 1.1, SD: 1.2, p: <0.01	NR Comparator arm: NR, p: NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Toth, 2012[24]	Arm 1 – control placebo	VAS, pain severity: 0-100 scale	N: 13, Mean: 65.9, SD: 20.3	4 weeks DAY 28	N: 13, Mean: 54.3, SD: 4.5	Mean change from baseline: NR, SD: NR, p: NS	Mean difference from baseline NR Comparator arm: Placebo, p: <0.05
Toth, 2012[24]	Arm 2 - Nabilone	VAS, pain severity: 0-100 scale	N: 13, Mean: 65.4, SD: 19.1	4 weeks	N: 13, Mean: 35.4, SD: 4	Mean change from baseline: NR, SD: NR, p: NS	Mean difference from baseline NR Comparator arm: Placebo, p: <0.05
Vinik, 2014[26]	Arm 1 - placebo	BPI, pain intensity: 0-10 scale	N: 152, Mean: 6.8, SD: 1.54	15 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: -2.3, SD: 2.33, p: NR	NR
Vinik, 2014[26]	Arm 2 - Tapentadol ER	BPI, pain intensity: 0-10 scale	N: 166, Mean: 6.6, SD: 1.52	15 weeks	N: 147, Mean: NR, SD: NR	Mean change from baseline: -3, SD: 2.16, p: 0.003	NR
Vinik, 2014[26]	Arm 1 - placebo	NPSI paroxysmal pain: 0-10 scale	N: 152, Mean: 2.9, SD: 2.42	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 0.92, SD: 3.02, p: NR	NR
Vinik, 2014[26]	Arm 2 - Tapentadol ER	NPSI paroxysmal pain: 0-10 scale	N: 166, Mean: 2.96, SD: 2.32	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.12, SD: 2.53, p: 0.009	NR
Vinik, 2014[26]	Arm 1 - placebo	NPSI, burning pain: 0-10 scale	N: 152, Mean: 3.11, SD: 2.35	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 1.27, SD: 3.07, p: NR	NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Vinik, 2014[26]	Arm 2 - Tapentadol ER	NPSI, burning pain: 0-10 scale	N: 166, Mean: 3.09, SD: 2.55	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.26, SD: 2.86, p: 0.005	NR
Vinik, 2014[26]	Arm 1 - placebo	NPSI, Evoked pain: 0-10 scale	N: 152, Mean: 2.43, SD: 2.18	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 0.78, SD: 2.64, p: NR	NR
Vinik, 2014[26]	Arm 2 - Tapentadol ER	NPSI, Evoked pain: 0-10 scale	N: 166, Mean: 2.39, SD: 2.23	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.16, SD: 2.15, p: 0.015	NR
Vinik, 2014[26]	Arm 1 - placebo	NPSI, pressing pain: 0-10 scale	N: 152, Mean: 2.44, SD: 2.22	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 1.03, SD: 2.97, p: NR	NR
Vinik, 2014[26]	Arm 2 - Tapentadol ER	NPSI, pressing pain: 0-10 scale	N: 166, Mean: 2.5, SD: 2.2	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 0.15, SD: 2.29, p: 0.01	NR
Vinik, 2014[26]	Arm 1 - placebo	NPSI, total score-NR scale	N: 152, Mean: 28.35, SD: 19.98	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 10.1, SD: 24.38, p: NR	NR

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Vinik, 2014[26]	Arm 2 - Tapentadol ER	NPSI, total score-NR scale	N: 166, Mean: 28.82, SD: 18.94	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: 1.26, SD: 19.8, p: <0.001	NR
Vinik, 2014[26]	Arm 1 - placebo	NRS: 0-10 scale	N: 152, Mean: 3.53, SD: 2.17	12 weeks	N: 152, Mean: NR, SD: NR	Mean change from baseline: 1.3, SD: 2.43, p: NR	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	NRS: 0-10 scale	N: 166, Mean: 3.7, SD: 1.78	12 weeks	N: 166, Mean: NR, SD: NR	Mean change from baseline: 0.28, SD: 2.04, p: NR	Mean change from baseline: -0.95 (95% CI:-1.42, -0.49), SD: NR, p: <0.001
Yuan, 2009[27]	Arm 1 - placebo	VAS	N: 20, Mean: 5.97, SD: 1.51	12 weeks	N: 18, Mean: NR, SD: NR	Mean change from baseline: -0.53, SD: 1.57, p: NR	P:0.024
Yuan, 2009[27]	Arm 2 – Botulinum toxin	VAS	N: 20, Mean: 6.42, SD: 1.11	12 weeks	N: 18, Mean: NR, SD: NR	Mean change from baseline: -2.53, SD: 2.48, p: NR	P:0.024

Evidence Table 4 – KQ2a Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean, SD:	Within arm comparison	Between arm comparison
Ziegler, 2015[28]	Arm 1 - placebo	NRS, mean average pain in 24 hours: 0-10 scale	N: 62, Mean: 6.6, SD: 1.27	6 weeks	N: 57, Mean: 4.34, SD: 2.35	Mean change from baseline: -2.36, SD: NR, p: NR	Mean difference from baseline NR Comparator arm: Placebo, p: NA
Ziegler, 2015[28]	Arm 2 - Pregabalin	NRS, mean average pain in 24 hours: 0-10 scale	N: 70, Mean: 6.6, SD: 1.26	6 weeks	N: 65, Mean: 4.51, SD: 2.17	Mean change from baseline: -2.19, SD: NR, p: NR	Mean difference from baseline NR Comparator arm: Placebo, p: 0.68

Evidence Table 5 – KQ2a Pain Categorical Outcomes

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Allen, 2014[1]	Arm 1 - placebo	89	>50% reduction-% of patients scale	13 week	(26)	NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	63	>50% reduction-% of patients scale	13 week	(35)	NR Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	86	>50% reduction-% of patients scale	13 week	(37)	NR Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	99	>50% reduction-% of patients scale	13 week	(36)	NR Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	68	>50% reduction-% of patients scale	13 week	(32)	NR Comparator arm: Placebo, p: NS
Arezzo, 2008[2]	Arm 1 - placebo	NR	>50% pain reduction-% scale	13 weeks	(49)	NA
Arezzo, 2008[2]	Arm 2 - Pregabalin	NR	>50% pain reduction-% scale	13 weeks	(23)	P <0.001

Evidence Table 5 – KQ2a Pain Categorical Outcomes (continued)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Atli, 2005[3]	Arm 1 - placebo	12	>50% pain reduction-% scale	12 weeks	0(0)	NR
Atli, 2005[3]	Arm 2 - Zonisamide	11	>50% pain reduction-% scale	12 weeks	3(27)	NR
Chad, 1990[5]	Arm 1 – Control - Vehicle	22	≥20% improvement for pain severity	4 weeks	(46)	P=NS
Chad, 1990[5]	Arm 2 - Capsaicin	24	≥20% improvement for pain severity	4 weeks	(71)	P=NS
Chad, 1990[5]	Arm 1 – Control - Vehicle	22	≥20% improvement for pain relief	4 weeks	(41)	NR
Chad, 1990[5]	Arm 2 - Capsaicin	24	≥20% improvement for pain relief	4 weeks	(71)	P<0.05

Evidence Table 5 – KQ2a Pain Categorical Outcomes (continued)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Freeman, 2007[6]	Arm 1 - placebo	32	Categorical Pain Score-0-4 scale	18 weeks	NR	NR
Freeman, 2007[6]	Arm 2 - Topiramate	35	Categorical Pain Score-0-4 scale	18 weeks	NR	NR
Gao, 2015[7]	Arm 1 - placebo	NR	>30% reduction in 24h average pain-% of patients scale	12 week	(49)	
Gao, 2015[7]	Arm 2 - Duloxetine	NR	>30% reduction in 24h average pain-% of patients scale	12 week	(61.5)	% difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: Placebo, p: 0.014
Ghasemi, 2014[8]	Arm 1 - placebo	20	No Pain after Intervention-% of patients scale	3 week	0(0)	NA

Evidence Table 5 – KQ2a Pain Categorical Outcomes (continued)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Ghasemi, 2014[8]	Arm 2 - intervention	20	No Pain after Intervention-% of patients scale	3 week	6(30)	NR Comparator arm: Placebo, p: 0.01
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	17	>50% pain relief	8 weeks	9	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	16	>50% pain relief	8 weeks	6	
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	17	>30% pain relief	8 weeks	10	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	16	>30% pain relief	8 weeks	9	

Evidence Table 5 – KQ2a Pain Categorical Outcomes (continued)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Shaibani, 2012[22]	Arm 1 - placebo	89	>50% pain relief	13 weeks	(39)	
Shaibani, 2012[22]	Arm 2 – Dextromethorphan/Quinidine (45/30)	79	>50% pain relief	13 weeks	(66)	p=0.001 compared to placebo
Shaibani, 2012[22]	Arm 3 - Dextromethorphan/Quinidine (30/30)	74	>50% pain relief	13 weeks	(54)	p=0.06 compared to placebo
Shaibani, 2012[22]	Arm 1 - placebo	89	>30% pain relief	13 weeks	(61)	
Shaibani, 2012[22]	Arm 2 – Dextromethorphan/Quinidine (45/30)	79	>30% pain relief	13 weeks	(83)	p=0.002 compared to placebo
Shaibani, 2012[22]	Arm 3 - Dextromethorphan/Quinidine (30/30)	74	>30% pain relief	13 weeks	(75)	p=0.054 compared to placebo

Evidence Table 5 – KQ2a Pain Categorical Outcomes (continued)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Sandercock, 2012[20]	Arm 1 - Control-Placebo	49	>50% reduction-% of patients scale	4 week	(7.8)	NA
Sandercock, 2012[20]	Arm 2 - Gabapentin single dose, 3000mg	43	>50% reduction-% of patients scale	4 week	(34.8)	NR Comparator arm: Placebo, p: 0.001
Sandercock, 2012[20]	Arm 3 – Gabapentin asymmetric dose, 3000mg	46	>50% reduction-% of patients scale	4 week	(26.0)	NR Comparator arm: Placebo, p: 0.015
Schwartz, 2015[21]	Arm 1 - placebo	343	>30% reduction-% of patients scale	15 week	(43.9)	NA
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	360	>30% reduction-% of patients scale	15 week	(54.4)	NR Comparator arm: Placebo, p: <0.005
Schwartz, 2015[21]	Arm 1 - placebo	343	>50% reduction-% of patients scale	15 week	(28.4)	NA
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	360	>50% reduction-% of patients scale	15 week	(38.9)	NR Comparator arm: Placebo, p: <0.005

Evidence Table 5 – KQ2a Pain Categorical Outcomes (continued)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Tesfaye, 2013[23]	Arm 1 – control - Duloxetine 60mg, then Duloxetine 120mg	67	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	39(58.2)	NR
Tesfaye, 2013[23]	Arm 2 - Duloxetine 60mg, then combination therapy	74	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	48(64.9)	NR
Tesfaye, 2013[23]	Arm 3 - Pregablin 300mg, then combination therapy	91	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	62(68.1)	NR
Tesfaye, 2013[23]	Arm 4 - Pregablin 300mg, then Pregablin 600mg	96	Brief Pain Inventory Modified Short Form (BPI-MSF), ≥2 point reduction in 24-hour average pain: 0-10 scale	18 weeks	66(68.8)	NR
Toth, 2012[24]	Arm 1 - placebo	13	NRS, ≥50% pain reduction: 0-10 scale	5 weeks	1(8)	NR p: NS
Toth, 2012[24]	Arm 2 - Nabilone	13	NRS, ≥50% pain reduction: 0-10 scale	5 weeks	4(31)	NR p: NS

Evidence Table 5 – KQ2a Pain Categorical Outcomes (continued)

Author, year	Arm	N for analysis	Instrument name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Vinik, 2014[26]	Arm 1 - placebo	152	≥30% pain reduction-% scale	12 weeks	69(45.4)	NA
Vinik, 2014[26]	Arm 2 - Tapentadol ER	166	≥30% pain reduction-% scale	12 weeks	92(55.4)	P= 0.032
Yuan, 2009[27]	Arm 1 - placebo	18	≥3 VAS pain reduction	12 weeks	0 (0)	P<0.005
Yuan, 2009[27]	Arm 2 – Botulinum toxin	18	≥3 VAS pain reduction	12 weeks	8 (44.4)	P<0.005
Ziegler, 2015[28]	Arm 1 - placebo	57	NRS, >30% improvement-% scale	6 weeks	28(49)	NA
Ziegler, 2015[28]	Arm 2 - Pregabalin	65	NRS, >30% improvement-% scale	6 weeks	25(38)	Mean change from baseline: NR (95% CI:NR), SD: NR, Comparator arm: Placebo, p: 0.151

Evidence Table 6 – KQ2a Paresthesias

Author, year	Arm	Instrument name	Baseline N, mean, SD	Time point(s)	At time point(s), N mean SD:	Within arm comparison	Between arm comparison
Vinik, 2014[26]	Arm 1 - placebo	NPSI, Paresthesia/dysesthesia: 0-10 scale	N: 152, Mean: 3.64, SD: 2.69	12 weeks	N: 124, Mean: NR, SD: NR	Mean change from baseline: 1.29, SD: 2.95, p: NR	NR
Vinik, 2014[26]	Arm 2 - Tapentadol ER	NPSI, Paresthesia/dysesthesia: 0-10 scale	N: 166, Mean: 3.81, SD: 2.53	12 weeks	N: 137, Mean: NR, SD: NR	Mean change from baseline: -0.01, SD: 2.79, p: <0.001	NR

Evidence Table 7 – KQ2a Quality of life

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Allen, 2014[1]	Arm 1 - placebo	EQ-5D	N: 90, Mean: NR, SD: NR	13 weeks	N: 89, Mean: NR, SD: NR	Mean change from baseline: 0.09, SE: 0.02, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: NA , p: NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	EQ-5D	N: 63, Mean: NR, SD: NR	13 weeks	N: 63, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	EQ-5D	N: 87, Mean: NR, SD: NR	13 weeks	N: 86, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NS
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	EQ-5D	N: 99, Mean: NR, SD: NR	13 weeks	N: 99, Mean: NR, SD: NR	Mean change from baseline: 0.15, SE: 0.02, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: 0.024
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	EQ-5D	N: 69, Mean: NR, SD: NR	13 weeks	N: 68, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Allen, 2014[1]	Arm 1 - placebo	SF-36 Physical component summary score	N: 90, Mean: NR, SD: NR	13 weeks	N: 89, Mean: NR, SD: NR	Mean change from baseline: 3.5, SE: 0.77, SD: NR, p: NR	NA
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	SF-36 Physical component summary score	N: 63, Mean: NR, SD: NR	13 weeks	N: 63, Mean: NR, SD: NR	Mean change from baseline: 6.22, SE: 0.9, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: 0.022
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	SF-36 Physical component summary score	N: 87, Mean: NR, SD: NR	13 weeks	N: 86, Mean: NR, SD: NR	NR	Mean difference from baseline: Comparator arm: Placebo, p: NS

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	SF-36 Physical component summary score	N: 99, Mean: NR, SD: NR	13 weeks	N: 99, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	SF-36 Physical component summary score	N: 69, Mean: NR, SD: NR	13 weeks	N: 68, Mean: NR, SD: NR	NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: NS
Harati, 1998[10]	Arm 1 - placebo	SF-36 Bodily pain	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 41.9, SD: 2.9	NR	NA
Harati, 1998[10]	Arm 2 - Tramadol	SF-36 Bodily pain	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 54.8, SD: 2.6	NR	NR: NR (95% CI:NR), SD: NR, Comparator arm: placebo, p: <0.001
Harati, 1998[10]	Arm 1 - placebo	SF-36 Physical functioning	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 55.1, SD: 4	NR	NA
Harati, 1998[10]	Arm 2 - Tramadol	SF-36 Physical functioning	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: 64.3, SD: 3.8	NR	NR: NR (95% CI:NR), SD: NR, Comparator arm: placebo, p: 0.02
Harati, 1998[10]	Arm 1 - placebo	SF-36 Role-physical	N :NR, Mean: NR, SD: NR	42 days	N: NR, Mean: NR, SD: NR	NR	NA
Harati, 1998[10]	Arm 2 - Tramadol	SF-36 Role-physical	N: NR, Mean: NR, SD: NR	42 days	N: NR, Mean: NR, SD: NR	NR	NR: NR (95% CI:NR), SD: NR, Comparator arm: placebo, p: NS
Raskin, 2006[16]	Arm 1 – routine care	SF-36, Bodily pain	N: 76, mean: NR, SD: NR	52 weeks	N: 68, mean: NR, SD: NR	Mean change from baseline: -3.88, SE: 2.6, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p: NS
Raskin, 2006[16]	Arm 2 - Duloxetine	SF-36, Bodily pain	N: 161, mean: NR, SD: NR	52 weeks	N: 149, mean: NR, SD: NR	Mean change from baseline: -0.05, SE: 1.78, p: NR	Mean difference from baseline: 3.83 (95% CI: -2.07, 9.72), p: NS

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Raskin, 2006[16]	Arm 1 – routine care	SF-36, physical component	N: 76, mean: NR, SD: NR	52 weeks	N: 68, mean: NR, SD: NR	Mean change from baseline: -0.56, SE: 1.06, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p: NS
Raskin, 2006[16]	Arm 2 - Duloxetine	SF-36, physical component	N: 161, mean: NR, SD: NR	52 weeks	N: 149, mean: NR, SD: NR	Mean change from baseline: 1.32, SE: 0.73, p: NR	Mean difference from baseline: 1.87 (95% CI: -0.53, 4.28), p: NS
Raskin, 2006[16]	Arm 1 – routine care	SF-36, role-physical	N: 76, mean: NR, SD: NR	52 weeks	N: 68, mean: NR, SD: NR	Mean change from baseline: 0.12, SE: 4.7, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p: NS
Raskin, 2006[16]	Arm 2 - Duloxetine	SF-36, role-physical	N: 161, mean: NR, SD: NR	52 weeks	N: 149, mean: NR, SD: NR	Mean change from baseline: 1.65, SE: 3.22, p: NR	Mean difference from baseline: 1.53 (95% CI: -9.14, 12.19), p: NS
Raskin, 2006[16]	Arm 1 – routine care	SF-36, physical functioning	N: 76, mean: NR, SD: NR	52 weeks	N: 68, mean: NR, SD: NR	Mean change from baseline: -0.08, SE: 2.77, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p: NS
Raskin, 2006[16]	Arm 2 - Duloxetine	SF-36, physical functioning	N: 161, mean: NR, SD: NR	52 weeks	N: 149, mean: NR, SD: NR	Mean change from baseline: 4.03, SE: 1.9, p: NR	Mean difference from baseline: 4.11 (95% CI: -2.17, 10.39), p: NS
Raskin, 2006[16]	Arm 1 – routine care	EQ-5D	N: 76, mean: NR, SD: NR	52 weeks	N: 68, mean: NR, SD: NR	Mean change from baseline: -0.05, SE: 0.03, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p: NS
Raskin, 2006[16]	Arm 2 - Duloxetine	EQ-5D	N: 161, mean: NR, SD: NR	52 weeks	N: 149, mean: NR, SD: NR	Mean change from baseline: -0.02, SE: 0.02, p: NR	Mean difference from baseline: 0.02 (95% CI: -0.04, 0.09), p: NS

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Raskin, 2014[17]	Overall	QOL-DN- -4-136 scale	N: 665, Mean: 42.6, SD: 22.2	6 weeks	NA	NA	
Raskin, 2014[17]	Arm 1 - Control-Placebo	QOL-DN- -4-136 scale	NR	19 weeks	N: 147, Mean: NR, SD: NR	Mean change from baseline: -14.4, SD: 20.4	P<0.05
Raskin, 2014[17]	Arm 2 – Pregabalin	QOL-DN- -4-136 scale	NR	19 weeks	N: 147, Mean: NR, SD: NR	Mean change from baseline: -20.6, SD: 21.4	P<0.05
Rauck, 2013[18]	Arm 1 - placebo	SF-36 mental component	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-36 mental component	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -2.1 (95% CI:-5.09, 0.90), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-36 mental component	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -1 (95% CI:-4.24, 2.30), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-36 mental component	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.8 (95% CI:-3.34, 1.64), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	SF-36 mental component	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.8 (95% CI:-4.68, 1.17), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 1 - placebo	SF-36 physical component	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-36 physical component	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.3 (95% CI:-1.92, 2.62), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-36 physical component	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.6 (95% CI:-1.88, 3.06), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-36 physical component	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: 1.4 (95% CI:-0.46, 3.31), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	SF-36 physical component	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.6 (95% CI:-1.60, 2.83), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 1 - placebo	SF-MPQ affective	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-MPQ affective	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.02 (95% CI:-0.86, 0.82), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-MPQ affective	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.19 (95% CI:-0.73, 1.10), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-MPQ affective	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.44 (95% CI:-1.14, 0.26), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	SF-MPQ affective	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.37 (95% CI:-0.44, 1.18), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	SF-MPQ sensory	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-MPQ sensory	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.58 (95% CI:-2.88, 1.71), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-MPQ sensory	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.06 (95% CI:-3.56, 1.43), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-MPQ sensory	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.25 (95% CI:-3.15, 0.65), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	SF-MPQ sensory	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 1.52 (95% CI:-0.70, 3.74), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 1 - placebo	SF-MPQ Total	N: 120, Mean: NR, SD: NR	16 weeks	N: 120, Mean: NR, SD: NR	NR	NA
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	SF-MPQ Total	N: 62, Mean: NR, SD: NR	16 weeks	N: 62, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.7 (95% CI:-3.64, 2.24), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	SF-MPQ Total	N: 56, Mean: NR, SD: NR	16 weeks	N: 56, Mean: NR, SD: NR	NR	Mean difference from baseline: -0.9 (95% CI:-4.10, 2.29), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	SF-MPQ Total	N: 116, Mean: NR, SD: NR	16 weeks	N: 116, Mean: NR, SD: NR	NR	Mean difference from baseline: -1.71 (95% CI:-4.14, 0.73), SD: NR, Comparator arm: Placebo, p: NR
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	SF-MPQ Total	N: 66, Mean: NR, SD: NR	16 weeks	N: 66, Mean: NR, SD: NR	NR	Mean difference from baseline: 1.84 (95% CI:-1.00, 4.69), SD: NR, Comparator arm: Placebo, p: NR

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	SF-36 Physical component	N: 49, Mean: 33.2, SD: 6.9	8 weeks	N: 49, Mean: NR, SD: NR	Least squares mean difference from baseline: 3.8 SE: 0.9, p: NR	NR
Rowbotham, 2012[19]	Arm 2 – Duloxetine	SF-36 Physical component	N: 55, Mean: 35.2, SD: 7.4	8 weeks	N: 55, Mean: NR, SD: NR	Least squares mean difference from baseline: 6.8, SE: 0.8, p: 0.05	NR
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	SF-36 Mental component	N: 49, Mean: NR, SD: NR	8 weeks	N: 49, Mean: NR, SD: NR	Mean difference from baseline: 2.8, SD: 1.2, p: NR	NR
Rowbotham, 2012[19]	Arm 2 – Duloxetine	SF-36 Mental component	N: 55, Mean: NR, SD: NR	8 weeks	N: 55, Mean: NR, SD: NR	Mean difference from baseline: 2.3, SD: 1.2, p: NS	NR
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	EQ-5D	N: 49, Mean: 0.66, SD: 0.16	8 weeks	N: 49, Mean: NR, SD: NR	Least squares mean difference from baseline: 0.07, SE: 0.02, p: NR	NR
Rowbotham, 2012[19]	Arm 2 – Duloxetine	EQ-5D	N: 55, Mean: 0.67, SD: 0.16	8 weeks	N: 55, Mean: NR, SD: NR	Least squares mean difference from baseline: 0.07, SE: 0.02, p: NS	NR
Schwartz, 2015[21]	Arm 1 - placebo	EQ-5D	N: 343, Mean: NR, SD: NR	12 weeks	N: 343, Mean: NR, SD: NR	NR	Mean difference from baseline: NA (95% CI:NA), SD: NR, Comparator arm: NA, p: NA

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	EQ-5D	N: 360, Mean: NR, SD: NR	12 weeks	N: 360, Mean: NR, SD: NR	NR	Mean difference from baseline: 0.09 (95% CI:(0.056, 0.122)), SD: NR, Comparator arm: Placebo, p: <0.001
Schwartz, 2015[21]	Arm 1 - placebo	SF-36 Bodily pain	N: 343, Mean: NR, SD: NR	12 weeks	N: 343, Mean: NR, SD: NR	Mean change from baseline: -6.2, SE: NR, SD: NR, p: NR	NA
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	SF-36 Bodily pain	N: 360, Mean: NR, SD: NR	12 weeks	N: 360, Mean: NR, SD: NR	Mean change from baseline: -0.2, SE: NR, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: Placebo, p: <0.001
Schwartz, 2015[21]	Arm 1 - placebo	SF-36 Physical component summary score	N: 343, Mean: NR, SD: NR	12 weeks	N: 343, Mean: NR, SD: NR	Mean change from baseline: -2.3, SE: NR, SD: NR, p: NR	NA
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	SF-36 Physical component summary score	N: 360, Mean: NR, SD: NR	12 weeks	N: 360, Mean: NR, SD: NR	Mean change from baseline: -0.1, SE: NR, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: <0.05
Schwartz, 2015[21]	Arm 1 - placebo	SF-36 Physical functioning	N: 343, Mean: NR, SD: NR	12 weeks	N: 343, Mean: NR, SD: NR	Mean change from baseline: -2.4, SE: NR, SD: NR, p: NR	NA
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	SF-36 Physical functioning	N: 360, Mean: NR, SD: NR	12 weeks	N: 360, Mean: NR, SD: NR	Mean change from baseline: 0.1, SE: NR, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: <0.05
Schwartz, 2015[21]	Arm 1 - placebo	SF-36 Role-physical	N: 343, Mean: NR, SD: NR	12 weeks	N: 343, Mean: NR, SD: NR	Mean change from baseline: -7.3, SE: NR, SD: NR, p: NR	NA

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	SF-36 Role-physical	N: 360, Mean: NR, SD: NR	12 weeks	N: 360, Mean: NR, SD: NR	Mean change from baseline: 0.6, SE: NR, SD: NR, p: NR	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: vs placebo, p: <0.001
Toth, 2012[24]	Arm 1 - placebo	EQ-5D index score	N: 13, Mean: 0.58, SD: 0.2	4 weeks	N: 13, Mean: 0.6, SD: 0.08	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline: Comparator (95% CI:NR), SD: NR, Comparator arm: Placebo, p: <0.05
Toth, 2012[24]	Arm 2 - Nabilone	EQ-5D index score	N: 13, Mean: 0.58, SD: 0.2	4 weeks	N: 13, Mean: 0.74, SD: 0.03	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline: NR (95% CI:NR), SD: NR, Comparator arm: Placebo, p: <0.05
Toth, 2012[24]	Arm 1 - placebo	EQ-5D utility score	N: 13, Mean: 58.4, SD: 16.7	4 weeks	N: 13, Mean: 61.4, SD: 6.7	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline:, Comparator arm: Placebo, p: NS
Toth, 2012[24]	Arm 2 - Nabilone	EQ-5D utility score	N: 13, Mean: 55.8, SD: 17.2	4 weeks	N: 13, Mean: 72.6, SD: 4.7	Mean change from baseline: NR, SE: NR, SD: NR, p: NS	Mean difference from baseline: Comparator arm: Placebo, p: NS
Wernicke, 2007[25]	Arm 1 – routine care	SF-36, physical component summary	N: 96, Mean: NR, SD: NR	52 weeks	N: 86, Mean: NR, SD: NR	Mean change from baseline: -1.26, SE: 0.94, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p:NA
Wernicke, 2007[25]	Arm 2 - Duloxetine	SF-36, physical component summary	N: 197, Mean: NR, SD: NR	52 weeks	N: 189, Mean: NR, SD: NR	Mean change from baseline: 1.2, SE: 0.63, p: NR	Mean difference from baseline: 2.47 (95% CI: 0.29,4.65), p:<0.05

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Wernicke, 2007[25]	Arm 1 – routine care	SF-36, Physical functioning	N: 96, Mean: NR, SD: NR	52 weeks	N: 86, Mean: NR, SD: NR	Mean change from baseline: -4.84, SE: 2.27, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p:NA
Wernicke, 2007[25]	Arm 2 - Duloxetine	SF-36, Physical functioning	N: 197, Mean: NR, SD: NR	52 weeks	N: 189, Mean: NR, SD: NR	Mean change from baseline: 0.87, SE: 1.51, p: NR	Mean difference from baseline: 5.71 (95% CI: 0.45,10.96), p:<0.05
Wernicke, 2007[25]	Arm 1 – routine care	SF-36, role physical	N: 96, Mean: NR, SD: NR	52 weeks	N: 86, Mean: NR, SD: NR	Mean change from baseline: -6.13, SE: 4.37, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p:NA
Wernicke, 2007[25]	Arm 2 - Duloxetine	SF-36, role physical	N: 197, Mean: NR, SD: NR	52 weeks	N: 189, Mean: NR, SD: NR	Mean change from baseline: 2.46, SE: 2.9, p: NR	Mean difference from baseline: 8.59 (95% CI: 8.69), p:>0.05
Wernicke, 2007[25]	Arm 1 – routine care	SF-36, bodily pain	N: 96, Mean: NR, SD: NR	52 weeks	N: 86, Mean: NR, SD: NR	Mean change from baseline: -3.85, SE: 2.27, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p:NA
Wernicke, 2007[25]	Arm 2 - Duloxetine	SF-36, bodily pain	N: 197, Mean: NR, SD: NR	52 weeks	N: 189, Mean: NR, SD: NR	Mean change from baseline: 3.27, SE: 1.5, p: NR	Mean difference from baseline: 7.12 (95% CI: 1.88, 12.36), p:<0.01
Wernicke, 2007[25]	Arm 1 – routine care	EQ-5D	N: 96, Mean: NR, SD: NR	52 weeks	N: 86, Mean: NR, SD: NR	Mean change from baseline: -0.04, SE: 0.02, p: NR	Mean difference from baseline: Comparator (95% CI: NA), p:NA
Wernicke, 2007[25]	Arm 2 - Duloxetine	EQ-5D	N: 197, Mean: NR, SD: NR	52 weeks	N: 189, Mean: NR, SD: NR	Mean change from baseline: 0, SE: 0.01, p: NR	Mean difference from baseline: 0.04 (95% CI: -0.01, 0.09), p:>0.05

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Vinik, 2014[26]	Arm 1 - placebo	EQ-5D health status index	N: 152, Mean: 0.71, SD: 0.16	12 weeks	N: 152, Mean: NR, SD: NR	Mean change from baseline: -0.1, SD: 0.26, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[26]	Arm 2 - Tapentadol ER	EQ-5D health status index	N: 166, Mean: 0.7, SD: 0.14	12 weeks	N: 166, Mean: NR, SD: NR	Mean change from baseline: 0, SD: 0.2, p: NR	Mean difference from baseline: 0.1 (95% CI:0.05, 0.16), p: <0.001
Vinik, 2014[26]	Arm 1 - placebo	SF-36, Bodily pain	N: 152, Mean: 44.2, SD: 7.34	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -3.9, SD: 8.8, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[26]	Arm 2 - Tapentadol ER	SF-36, Bodily pain	N: 166, Mean: 42.4, SD: 7.03	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0, SD: 7.55, p: NR	Mean difference from baseline: 3 (95% CI:1.24, 4.69), p: <0.001

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Vinik, 2014[26]	Arm 1 - placebo	SF-36, physical component	N: 152, Mean: 40.1, SD: 8.87	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -2.3, SD: 6.4, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[26]	Arm 2 - Tapentadol ER	SF-36, physical component	N: 166, Mean: 39.1, SD: 8.52	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0.1, SD: 6.52, p: NR	Mean difference from baseline: 2.1 (95% CI:0.67, 3.57), p: 0.004
Vinik, 2014[26]	Arm 1 - placebo	SF-36, physical functioning	N: 152, Mean: 38.2, SD: 11.35	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -1.7, SD: 7.44, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[26]	Arm 2 - Tapentadol ER	SF-36, physical functioning	N: 166, Mean: 37.3, SD: 10.49	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0.1, SD: 7.5, p: NR	Mean difference from baseline: 1.5 (95% CI:-0.21, 3.23), p: 0.085
Vinik, 2014[26]	Arm 1 - placebo	SF-36, role-physical	N: 152, Mean: 41.9, SD: 10.33	12 weeks	N: 131, Mean: NR, SD: NR	Mean change from baseline: -2.1, SD: 7.14, p: NR	Mean difference from baseline: Comparator (95% CI:NA), p: NA
Vinik, 2014[26]	Arm 2 - Tapentadol ER	SF-36, role-physical	N: 166, Mean: 41.7, SD: 9.89	12 weeks	N: 146, Mean: NR, SD: NR	Mean change from baseline: 0.8, SD: 8.12, p: NR	Mean difference from baseline: 2.6 (95% CI:0.85, 4.29), p: 0.004
Yuan, 2009[27]	Arm 1 - placebo	SF-36, physical component score	N:20, Mean: 33.8, SD: 4.17	12 weeks	N:18, Mean: 39.8, SD: 18.3	Mean change from baseline: -1.06, SD: 7.83, p: NR	P:0.072
Yuan, 2009[27]	Arm 2 – Botulinum toxin	SF-36, physical component score	N:20, Mean: 39.05, SD: 18.1	12 weeks	N:18, Mean: 42.2, SD: 16.1	Mean change from baseline: -0.35, SD: 4.2, p: NR	P:0.072

Evidence Table 7 – KQ2a Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, mean SD	Time point(s)	At time point(s), N mean SD	Within arm comparison	Between arm comparison
Yuan, 2009[27]	Arm 1 - placebo	SF-36, mental component score	N:20, Mean: 64.4, SD: 17.4	12 weeks	N:18, Mean: 60.6, SD: 19.5	Mean change from baseline:-0.93, SD: 1.91, p: NR	P:0.072
Yuan, 2009[27]	Arm 2 – Botulinum toxin	SF-36, mental component score	N:20, Mean: 60.9, SD: 20.4	12 weeks	N:18, Mean: 64.1, SD: 23.5	Mean change from baseline: 0.37, SD: 6.19, p: NR	P:0.072
Ziegler, 2015[28]	Arm 1 - placebo	EQ-5D-5L, weighted index score	N: 57, Mean: 0.7, SD: 0.14	6 weeks	N: 57, Mean: NR, SD: NR	Mean change from baseline: 0.07, SE: 0.02, SD: NR, p: NR	NA
Ziegler, 2015[28]	Arm 2 - Pregabalin	EQ-5D-5L, weighted index score	N: 65, Mean: 0.6, SD: 0.15	6 weeks	N: 65, Mean: NR, SD: NR	Mean change from baseline: 0.07, SE: 0.02, SD: NR, p: NR	Mean difference from baseline: Comparator arm: Placebo, p: NS
Ziegler, 2015[28]	Arm 1 - placebo	NePIQoL	N: 57, Mean: 127.3, SD: 28.74	6 weeks	N: 57, Mean: NR, SD: NR	Mean change from baseline: -2.97, SE: 0.69, SD: NR, p: NR	NA
Ziegler, 2015[28]	Arm 2 - Pregabalin	NePIQoL	N: 65, Mean: 128.8, SD: 23.7	6 weeks	N: 65, Mean: NR, SD: NR	Mean change from baseline: -2.84, SE: 0.65, SD: NR, p: NR	Mean difference from baseline: Comparator arm: Placebo, p: NS

Evidence Table 8 – KQ2a Adverse effects

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Allen, 2014[1]	Arm 1 - placebo	Dizziness	7	7.8	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Dizziness	1	1.6	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Dizziness	7	8	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Dizziness	18	18.2	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Dizziness	18	26.1	
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	Dizziness	NR	12.2	
Allen, 2014[1]	Arm 1 - placebo	Dry mouth	2	2.2	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Dry mouth	2	3.2	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Dry mouth	4	4.6	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Dry mouth	6	6.1	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Dry mouth	9	13	
Allen, 2014[1]	Arm 1 - placebo	Fatigue	4	4.4	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Fatigue	4	6.3	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Fatigue	6	6.9	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Fatigue	8	8.1	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Fatigue	8	11.6	
Allen, 2014[1]	Arm 1 - placebo	Nausea	2	2.2	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Nausea	9	14.3	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Nausea	11	12.6	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Nausea	27	27.3	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Nausea	12	17.4	
Allen, 2014[1]	Arm 1 - placebo	Overall	68	75.6	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Overall	47	74.6	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Overall	65	74.7	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Overall	82	82.8	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Overall	63	91.3	
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	Overall	NR	80.2	
Allen, 2014[1]	Arm 1 - placebo	Vomiting	2	2.2	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	Vomiting	3	4.8	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	Vomiting	3	3.4	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	Vomiting	10	10.1	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	Vomiting	2	2.9	
Arezzo, 2008, 2014	Arm 1 - placebo	Any AE	NR	78	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Any AE	NR	84	
Arezzo, 2008, 2014	Arm 1 - placebo	Dizziness	5	5.9	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Dizziness	27	32.9	
Arezzo, 2008, 2014	Arm 1 - placebo	Peripheral edema	27	31.8	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Peripheral edema	30	36.6	
Arezzo, 2008, 2014	Arm 1 - placebo	Somnolence	5	5.9	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Somnolence	11	13.4	
Arezzo, 2008, 2014	Arm 1 - placebo	Weight gain	1	1.2	
Arezzo, 2008, 2014	Arm 2 - Pregabalin	Weight gain	12	14.6	
Atli, 2005[3]	Arm 1 - placebo	Any AE	10	83.3	
Atli, 2005[3]	Arm 2 - Zonisamide	Any AE	11	91.7	
Atli, 2005[3]	Arm 1 - placebo	Cardiovascular	1	8.3	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Atli, 2005[3]	Arm 2 - Zonisamide	Cardiovascular	3	25	
Atli, 2005[3]	Arm 1 - placebo	Dermatological	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Dermatological	4	33.3	
Atli, 2005[3]	Arm 1 - placebo	Dizziness	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Dizziness	3	25	
Atli, 2005[3]	Arm 1 - placebo	Drowsiness	2	16.7	
Atli, 2005[3]	Arm 2 - Zonisamide	Drowsiness	2	16.7	
Atli, 2005[3]	Arm 1 - placebo	Gastrointestinal	NR	NR	
Atli, 2005[3]	Arm 2 - Zonisamide	Gastrointestinal	NR	NR	P: 0.04
Atli, 2005[3]	Arm 1 - placebo	Headache	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Headache	2	16.7	
Atli, 2005[3]	Arm 1 - placebo	Musculoskeletal	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Musculoskeletal	3	25	
Atli, 2005[3]	Arm 1 - placebo	Neurological	6	50	
Atli, 2005[3]	Arm 2 - Zonisamide	Neurological	8	66.7	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Atli, 2005[3]	Arm 1 – CONTROL – placebo	Respiratory	3	25	
Atli, 2005[3]	Arm 2 - Zonisamide	Respiratory	4	33.3	
Atli, 2005[3]	Arm 1 - placebo	Restlessness/Insomnia	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Restlessness/Insomnia	3	25	
Atli, 2005[3]	Arm 1 - placebo	Special senses	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Special senses	2	16.7	
Atli, 2005[3]	Arm 1 - placebo	Urinary	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	Urinary	3	25	
Atli, 2005[3]	Arm 1 - placebo	Weight change	1	8.3	
Atli, 2005[3]	Arm 2 - Zonisamide	Weight change	3	25	
Campbell, 2012[4]	Arm 1 - placebo	Administration site	2	2.2	
Campbell, 2012[4]	Arm 2 - Clonidine	Administration site	1	1.1	
Campbell, 2012[4]	Arm 1 - placebo	Musculoskeletal	2	2.2	
Campbell, 2012[4]	Arm 2 - Clonidine	Musculoskeletal	0	0	
Campbell, 2012[4]	Arm 1 - placebo	Nervous system	2	2.2	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Campbell, 2012[4]	Arm 2 - Clonidine	Nervous system	2	2.2	
Campbell, 2012[4]	Arm 1 - placebo	Psychiatric disorders	1	1.1	
Campbell, 2012[4]	Arm 2 - Clonidine	Psychiatric disorders	0	0	
Campbell, 2012[4]	Arm 1 - placebo	Respiratory disorders	0	0	
Campbell, 2012[4]	Arm 2 - Clonidine	Respiratory disorders	1	1.1	
Campbell, 2012[4]	Arm 1 - placebo	Skin disorders	5	5.6	
Campbell, 2012[4]	Arm 2 - Clonidine	Skin disorders	0	0	
Freeman, 2007[6]	Arm 1 - placebo	Abnormal vision	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Abnormal vision	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Anorexia	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Anorexia	7	20	
Freeman, 2007[6]	Arm 1 - placebo	Back pain	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Back pain	4	11	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Freeman, 2007[6]	Arm 1 - placebo	Diarrhea	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Diarrhea	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Fatigue	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Fatigue	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Headache	7	22	
Freeman, 2007[6]	Arm 2 - Topiramate	Headache	5	14	
Freeman, 2007[6]	Arm 1 - placebo	Nausea	5	16	
Freeman, 2007[6]	Arm 2 - Topiramate	Nausea	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Paresthesia	3	9	
Freeman, 2007[6]	Arm 2 - Topiramate	Paresthesia	7	20	
Freeman, 2007[6]	Arm 1 - placebo	Somnolence	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Somnolence	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Taste perversion	0	0	
Freeman, 2007[6]	Arm 2 - Topiramate	Taste perversion	5	14	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Freeman, 2007[6]	Arm 1 - placebo	Upper respiratory tract infection	4	13	
Freeman, 2007[6]	Arm 2 - Topiramate	Upper respiratory tract infection	3	9	
Freeman, 2007[6]	Arm 1 - placebo	Vomiting	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Vomiting	4	11	
Freeman, 2007[6]	Arm 1 - placebo	Weight decrease	2	6	
Freeman, 2007[6]	Arm 2 - Topiramate	Weight decrease	5	14	
Gao, 2015[7]	Arm 1 - placebo	Nausea	7	3.5	P: 0.01
Gao, 2015[7]	Arm 2 - Duloxetine	Nausea	21	10.4	
Gao, 2015[7]	Arm 1 - placebo	Pts with > 1 TEAE	72	35.6	
Gao, 2015[7]	Arm 2 - Duloxetine	Pts with > 1 TEAE	94	46.5	P: 0.034
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Any AE	119	71	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Any AE	147	88	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Gastrointestinal disorders	45	27	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Gastrointestinal disorders	91	54	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Fatigue	14	8	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Fatigue	31	18	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Infections and infestations	30	18	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Infections and infestations	60	30	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Injury, poisoning and procedural complications	16	10	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Injury, poisoning and procedural complications	12	7	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Investigations	16	10	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Investigations	17	10	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Muscoskeletal and connective tissue disorders	26	16	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Muscoskeletal and connective tissue disorders	31	18	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Nervous system disorders	39	23	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Nervous system disorders	81	48	
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Physciatric disorders	16	10	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Physciatric disorders	29	17	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Hanna, 2008[9]	Arm 1 – Control – Placebo + Gabapentin	Skin and subcutaneous tissue disorders	19	11	
Hanna, 2008[9]	Arm 2 – Oxycodon + Gabapentin	Skin and subcutaneous tissue disorders	34	20	
Harati, 1998[10]	Arm 1 - placebo	Constipation	2	3	
Harati, 1998[10]	Arm 2 - Tramadol	Constipation	14	22	
Harati, 1998[10]	Arm 1 - placebo	Headache	3	5	
Harati, 1998[10]	Arm 2 - Tramadol	Headache	11	17	
Harati, 1998[10]	Arm 1 - placebo	Nausea	2	3	
Harati, 1998[10]	Arm 2 - Tramadol	Nausea	15	23	
Harati, 1998[10]	Arm 1 - placebo	Rhinitis	8	12	
Harati, 1998[10]	Arm 2 - Tramadol	Rhinitis	3	5	
Harati, 1998[10]	Arm 1 - placebo	Somnolence	4	6	
Harati, 1998[10]	Arm 2 - Tramadol	Somnolence	8	12	
Jiang, 2011[11]	Arm 1 - Control-Placebo	Dizziness	0	0	
Jiang, 2011[11]	Arm 2 - Pregabalin	Dizziness	2	10	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	Any skin reaction	0	0	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	Any skin reaction	5	14.7	
Kulkantrakorn, 2013[13]	Arm 1 - Control-Placebo	Hypertension	12	36.4	
Kulkantrakorn, 2013[13]	Arm 2 - Capsaicin	Hypertension	11	33.3	
Max, 1987[14]	Arm 1 - Control-Placebo	Dry mouth	20		
Max, 1987[14]	Arm 2 - Amitriptyline	Dry mouth	26		
Max, 1987[14]	Arm 1 - Control-Placebo	Sedation	12		
Max, 1987[14]	Arm 2 - Amitriptyline	Sedation	19		
Max, 1987[14]	Arm 1 - Control-Placebo	Dizziness	3		
Max, 1987[14]	Arm 2 - Amitriptyline	Dizziness	8		

Evidence Table 8 – KQ2a Adverse effects

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Rauck, 2013[18]	Arm 1 - placebo	Any AE	79	66	
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	Any AE	45	73	
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	Any AE	38	68	
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	Any AE	86	74	
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	Any AE	47	71	
Rauck, 2013[18]	Arm 1 - placebo	Dizziness	7	6	
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	Dizziness	9	15	
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	Dizziness	8	14	
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	Dizziness	16	14	
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	Dizziness	9	14	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Rauck, 2013[18]	Arm 1 - placebo	Nausea	9	8	
Rauck, 2013[18]	Arm 2 – Gabapentin enacarbil, 1200mg	Nausea	7	11	
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	Nausea	4	7	
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	Nausea	7	6	
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	Nausea	3	5	
Rauck, 2013[18]	Arm 1 - placebo	Peripheral edema	5	4	
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	Peripheral edema	2	3	
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	Peripheral edema	0	0	
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	Peripheral edema	11	9	
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	Peripheral edema	11	17	
Rauck, 2013[18]	Arm 1 - placebo	Somnolence	5	4	
Rauck, 2013[18]	Arm 2 - Gabapentin enacarbil, 1200mg	Somnolence	2	3	
Rauck, 2013[18]	Arm 3 - Gabapentin enacarbil, 2400mg	Somnolence	7	13	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Rauck, 2013[18]	Arm 4 - Gabapentin enacarbil, 3600mg	Somnolence	14	12	
Rauck, 2013[18]	Arm 5 - Pregabalin, 300mg	Somnolence	9	14	
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	Any AE	32	62.7	
Rowbotham, 2012[19]	Arm 2 – Duloxetine	Any AE	42	73.7	
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	Nausea	2	3.9	
Rowbotham, 2012[19]	Arm 2 – Duloxetine	Nausea	9	15.8	
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	Fatigue	2	3.9	
Rowbotham, 2012[19]	Arm 2 – Duloxetine	Fatigue	7	12.3	
Sandercock, 2012[20]	Arm 1 - Control-Placebo	Any AE	20	39.2	
Sandercock, 2012[20]	Arm 2 - Gabapentin single dose, 3000mg	Any AE	27	57.4	
Sandercock, 2012[20]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Any AE	23	46.9	
Sandercock, 2012[20]	Arm 1 - Control-Placebo	Dizziness	0	0	
Sandercock, 2012[20]	Arm 2 - Gabapentin single dose, 3000mg	Dizziness	8	17.0	
Sandercock, 2012[20]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Dizziness	6	12.2	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Sandercock, 2012[20]	Arm 1 - Control-Placebo	Somnolence	0	0	
Sandercock, 2012[20]	Arm 2 - Gabapentin single dose, 3000mg	Somnolence	6	12.8	
Sandercock, 2012[20]	Arm 3 – Gabapentin asymmetric dose, 3000mg	Somnolence	2	4.1	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	Constipation	116	11.2	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	Dizziness	168	16.2	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	General disorders and administration site conditions	156	15	
Schwartz, 2015[21]	Arm 1 - placebo	GI Disorders	61	17.8	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	GI Disorders	125	34.7	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	GI Disorders	423	40.7	
Schwartz, 2015[21]	Arm 1 - placebo	MSK and connective tissue disorders	44	12.8	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	MSK and connective tissue disorders	46	12.8	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	N	236	22.7	
Schwartz, 2015[21]	Arm 1 - placebo	Nausea	27	7.9	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	Nausea	61	16.9	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Schwartz, 2015[21]	Arm 1 - placebo	Nervous system disorders	44	12.8	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	Nervous system disorders	72	20	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	Nervous system disorders	402	38.7	
Schwartz, 2015[21]	Arm 1 - placebo	Overall	192	56	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	Overall	269	74.7	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	Overall	760	73.1	
Schwartz, 2015[21]	Arm 1 - placebo	Psychiatric disorders	31	9	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	Psychiatric disorders	55	15.3	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	Skin and subcutaneous tissue disorders	124	11.9	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	Somnolence	137	13.2	
Shaibani, 2012[22]	Arm 1 - placebo	Any AE	98	79.7	
Shaibani, 2012[22]	Arm 2 – Dextromethorphan/Quinidine (45/30)	Any AE	119	90.8	
Shaibani, 2012[22]	Arm 3 - Dextromethorphan/Quinidine (30/30)	Any AE	97	78.2	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Toth, 2012[24]	Arm 1 - placebo	Any AE	6	46	
Toth, 2012[24]	Arm 2 - Nabilone	Any AE	7	13	
Vinik, 2014[26]	Arm 1 - placebo	Any AE	93	61.2	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	Any AE	132	79.5	
Vinik, 2014[26]	Arm 1 - placebo	Dizziness	3	2	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	Dizziness	12	7.2	
Vinik, 2014[26]	Arm 1 - placebo	Headache	8	5.3	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	Headache	4	2.4	
Vinik, 2014[26]	Arm 1 - placebo	Nausea	15	9.9	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	Nausea	35	21.1	
Vinik, 2014[26]	Arm 1 - placebo	Somnolence	1	0.7	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	Somnolence	10	6	
Vinik, 2014[26]	Arm 1 - placebo	Vomiting	7	4.6	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	Vomiting	21	12.7	

Evidence Table 8 – KQ2a Adverse effects (continued)

Author, year	Select arm	Adverse effect	Patients with outcomes, n	Patients with outcomes, %	Comments
Ziegler, 2015[28]	Arm 1 - placebo	Any AE	NR	55	
Ziegler, 2015[28]	Arm 2 - Pregabalin	Any AE	NR	54	
Ziegler, 2015[28]	Arm 1 - placebo	Peripheral Edema	0	0	
Ziegler, 2015[28]	Arm 2 - Pregabalin	Peripheral Edema	7	10	P: <0.05

Evidence Table 9 – KQ2a Drop outs

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Allen, 2014[1]	Arm 1 - placebo	5	5.6	
Allen, 2014[1]	Arm 2 - Desvenlafaxine 50mg	8	12.7	
Allen, 2014[1]	Arm 3 - Desvenlafaxine 100mg	7	8	
Allen, 2014[1]	Arm 4 - Desvenlafaxine 200mg	21	21.2	
Allen, 2014[1]	Arm 5 - Desvenlafaxine 400mg	21	30.4	
Allen, 2014[1]	Arm 6 - Desvenlafaxine Open Label	37	15.6	
Arezzo, 2008[2]	Arm 1 - placebo	15	17.6	
Arezzo, 2008[2]	Arm 2 - Pregabalin	21	25.6	
Atli, 2005[3]	Arm 1 - placebo	0	0	
Atli, 2005[3]	Arm 2 - Zonisamide	5	38.5	
Campbell, 2012[4]	Arm 1 - placebo	3	NR	
Campbell, 2012[4]	Arm 2 - Clonidine	1	NR	
Freeman, 2007[6]	Arm 1 - placebo	3	9	
Freeman, 2007[6]	Arm 2 - Topiramate	4	12	

Evidence Table 9 – KQ2a Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Gao, 2015[7]	Arm 1 - placebo	8	4	
Gao, 2015[7]	Arm 2 - Duloxetine	17	8.4	P = 0.097
Ghasemi, 2014[8]	Arm 1 - placebo	0	0	
Ghasemi, 2014[8]	Arm 2 - intervention	0	0	
Harati, 1998[10]	Arm 1 - placebo	1	NR	
Harati, 1998[10]	Arm 2 - Tramadol	9	NR	
Jiang, 2011[11]	Arm 1 - Control-Placebo	0	0	
Jiang, 2011[11]	Arm 2 - Pregabalin	3	15	
Max, 1987[14]	Overall	5	NR	
Raskin, 2006[16]	Arm 1 – routine care	NR	2.6	
Raskin, 2006[16]	Arm 2 - Duloxetine	NR	9.3	
Raskin, 2014[17]	Arm 1 - Control-Placebo	11		
Raskin, 2014[17]	Arm 2 – Pregabalin	8		
Rowbotham, 2012[19]	Arm 1 - Control-Placebo	3	5.9	
Rowbotham, 2012[19]	Arm 2 – Duloxetine	11	19.3	

Evidence Table 9 – KQ2a Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Schwartz, 2015[21]	Arm 1 – control – placebo	28	8.2	
Schwartz, 2015[21]	Arm 2 - Tapentadol ER	51	14.2	
Schwartz, 2015[21]	Arm 3 - Tapentadol ER Open Label	169	16.3	
Shaibani, 2012[22]	Arm 1 - placebo	13	10.6	
Shaibani, 2012[22]	Arm 2 – Dextromethorphan/Quinidine (45/30)	33	25.2	
Shaibani, 2012[22]	Arm 3 - Dextromethorphan/Quinidine (30/30)	25	20.2	
Vinik, 2014[26]	Arm 1 - placebo	13	8.6	
Vinik, 2014[26]	Arm 2 - Tapentadol ER	23	13.8	
Ziegler, 2015[28]	Arm 1 - placebo	2	3	
Ziegler, 2015[28]	Arm 2 - Pregabalin	4	6	

Evidence Table 10 – KQ2a Summary of findings from Griebler et al. (2014) review

	Intervention	Number of Studies
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Venlafaxine	2
	Duloxetine	5
Topical Agents	Capsaicin	2
Tricyclic antidepressants (TCAs)	Imipramine	2
	Amitriptyline	1
	Desipramine	2
Anticonvulsants	Carbamazepine	1
	Gabapentin	3
	Lamotrigine	2
	Valproic acid	2
	Topiramate	2
	Pregabalin	6
	Oxcarbazepine	3
	Lamotrigine	1
N-methyl-D-aspartate receptor antagonists	Dextromethorphan	2
Lacosamide	Lacosamide	4

Evidence Table 10 – KQ2a Summary of findings from Griebler et al. (2014) review (continued)

	Intervention	Number of Studies
Opiates	Oxycodone	3
	Tramadol/ Acetaminophen	1
	Tapentadol ER	1
Class IB antiarrhythmics	Mexiletine	5
Trials Comparing Medications of Different Classes	Imipramine vs. Paroxetine	1
	Amitriptyline vs. Topical Capsaicin 0.075%	1
	Amitriptyline vs. Maprotiline vs. Placebo	1
	Gabapentin vs. Amitriptyline	1

Evidence Table 10 – KQ2a Summary of findings from Griebler et al. (2014) review (continued)

	Intervention	Number of Studies
	Venlafaxine vs. Carbamazepine	1
	Amitriptyline vs. Lamotrigine	1
	Pregabalin vs. Amitriptyline	1
	Amitriptyline vs. Duloxetine vs. Pregabalin	1

Evidence Table 10 – KQ2a Summary of findings from Griebler et al. (2014) review (continued)

Network Meta-Analysis Findings
All results are from network meta-analysis: Placebo-Controlled Comparisons by Drug Class within 3 months of treatment: • SNRIs were superior to placebo (SMD, -1.36 [CrI, -1.77 to -0.95]), • TCAs were superior to placebo (SMD, -0.78 [CrI, -1.24 to -0.33]) • Anticonvulsants were superior to placebo (SMD, -0.67 [CrI, -0.97 to -0.37]) • Topical capsaicin 0.075% was superior to placebo (SMD, -0.91 [CrI, -1.18 to -0.08]) • There was no difference with opioids, dextromethorphan, mexiletine, or lacosamide (a newer anticonvulsant) Placebo-Controlled Comparisons for key individual drugs within 3 months of treatment: Anticonvulsants: • Pregabalin was superior to placebo (SMD, -0.55 [CrI, -0.94 to -0.15]) • Gabapentin did not differ from placebo (SMD, -0.58 [CrI, -1.54 to 0.09]) • Topiramate did not differ from placebo (SMD, -0.45 [CrI, -1.98 to 1.08]) • Carbamazepine was superior to placebo (SMD, -1.57 [CrI, -2.83 to -0.31]) (only one study) SNRIs: • Venlafaxine was superior to placebo (SMD, -1.53 [CrI, -2.41 to -0.65]) • Duloxetine was superior to placebo (SMD, -1.33 [CrI, -1.82 to -0.86]) Tricyclic antidepressants: • Amitriptyline was superior to placebo (SMD, -0.72 [CrI, -1.35 to -0.08]) (only one study) Drug-Drug Comparisons: • SNRIs reduced pain more than did anticonvulsants (SMD, -0.69 [CrI, -1.17 to -0.21]) • Anticonvulsants did not differ from TCAs (SMD, 0.00 [CrI, -0.17 to 0.17])

Evidence Table 11 – KQ2a list of additional outcomes from Griebler et al. (2014)

Author, year	Pain	Paresthesias	Numbness	Quality of life	Adverse effects	Dropouts due to adverse effects
Backonja, 1998[29]				X		x
Bansal, 2009[30]						x
Beydoun, 2006[31]				X		x
Boyle, 2012[32]				X		x
Capsaicin study group, 1991[33]						x
Dejgard, 1988[34]		x				
Dogra, 2005[35]				X		x
Eisenberg, 2001[36]						x
Freeman, 2007[37]				X		x
Freynhagen, 2005[38]						x
Gao, 2010[39]				X		x
Gimbel, 2003[40]				X		x
Goldstein, 2005[41]				X		x
Grosskopf, 2006[42]				x		x
Jia, 2006[43]						x
Jose, 2007[44]						x
Kochar, 2002[45]						x
Kochar, 2004[46]						x
Kvinesdal, 1984[47]		x				
Lesser, 2004[48]				x		x
Max, 1991[49]						x
Max, 1992[50]						x
McCleane, 1999[51]			x	x		x
Raskin, 2004[52]				x		x

Evidence Table 11 – KQ2a list of additional outcomes from Griebler et al. (2014) (continued)

Author, year	Pain	Paresthesias	Numbness	Quality of life	Adverse effects	Dropouts due to adverse effects
Raskin, 2005[53]						x
Rauck, 2007[54]				x		x
Richter, 2005[55]				x		x
Rosenstock, 2004[56]				x		x
Rowbotham, 2004[57]						x
Sang, 2002[58]				x		
Satoh, 2011[59]		x	x	x		x
Scheffler, 1991[60]						x
Schwartz, 2011[61]						x
Shaibani, 2009[62]						x
Simpson, 2001[63]				x		
Sindrup, 1989[64]		x				
Sindrup, 1990[65]		x	x			
Tandan, 1992[66]						x
Thienel, 2004[67]						x
Tolle, 2008[68]				x		x
Vinik, 2007[69]						x
Vrethem, 1997[70]						x
Watson, 2003[71]						x
Wernicke, 2006[72]				x		x
Wilton, 1974[73]			x			
Wright, 1997[74]		x				x
Wymer, 2009[75]						x
Ziegler, 2010[76]						x

Evidence Table 12 – KQ2a list of additional numbness outcomes from Griebler et al. (2014)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
McCleane, 1999[51]	Overall-	Numbness	N:100, Mean:3.98, SD: NR	56 days	N:NR, Mean: NR, SD:NR		
McCleane, 1999[51]	Arm 1- Placebo	Numbness	N:50, Mean: NR, SD:NR	56 days	N:38, Mean: NR, SD:NR	Mean change from baseline:-0.14 (95% CI:), p:NS	
McCleane, 1999[51]	Arm 2- Lamotrigine	Numbness	N:50, Mean: NR, SD:NR	56 days	N:36, Mean: NR, SD:NR	Mean change from baseline:-0.02 (95% CI:), p:NS	
Satoh, 2011[59]	Arm 1- Placebo	Numbness	N:135, Mean: NR, SD:NR	14 weeks	N:135, Mean: NR, SD:NR	Mean change from baseline: (95% CI:), p:NS	p:NS
Satoh, 2011[59]	Arm 2- Pregabalin, 300 mg/day	Numbness	N:134, Mean: NR, SD:NR	14 weeks	N:134, Mean: NR, SD:NR	Mean change from baseline: (95% CI:), p:0.0072	p:NS
Satoh, 2011[59]	Arm 3- Pregabalin, 600 mg/day	Numbness	N:45, Mean: NR, SD:NR	14 weeks	N:45, Mean: NR, SD:NR	Mean change from baseline: (95% CI:), p:NS	p:NS
Sindrup, 1990[65]	Arm 1- Placebo	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:0.04, SD: NR		

Evidence Table 12 – KQ2a list of additional numbness outcomes from Griebler et al. (2014) (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Sindrup, 1990[65]	Arm 2-Paroxetine	Paraesthesia	N:20, Mean:NR, SD:NR	6 weeks	N:20, Mean:0.03, SD: NR		
Sindrup, 1990[65]	Arm 3-Imipramine	Paraesthesia	N:20, Mean:NR, SD:NR	6 weeks	N:20, Mean:0.02, SD: NR		
Wilton, 1974[73]	Arm 1-Placebo	Numbness	N:40, Mean:4.62, SD:0.88	1 week	N:40, Mean:2.18, SD:0.78		
Wilton, 1974[73]	Arm 2-Tegretol	Numbness	N:40, Mean:5.92, SD:0.76	1 week	N:40, Mean:2.01, SD:0.63		

Evidence Table 13 – KQ2a list of additional (Parasthesias) outcomes from Griebler et al. (2014)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Dejgard, 1988[34]	Overall-	Paraesthesia	N:19, Mean:1.9, SD:0.8		N:16, Mean:, SD: NR		
Dejgard, 1988[34]	Arm 1-Placebo	Paraesthesia	N:19, Mean: NR, SD:NR	26 weeks	N:16, Mean:1.8, SD:0.8		p:<0.03
Dejgard, 1988[34]	Arm 2-Mexiltetine	Paraesthesia	N:19, Mean: NR, SD:NR	26 weeks	N:16, Mean:0.9, SD:0.7		p:<0.03
Kvinesdal, 1984[47]	Arm 1-Placebo	Six item scale, includes paraethesia	N:12, Mean: NR, SD:NR	5 weeks	N:12, Mean: NR, SD:NR		p:<0.10
Kvinesdal, 1984[47]	Arm 2-Imipramine	Six item scale, includes paraethesia	N:12, Mean: NR, SD:NR	5 weeks	N:12, Mean: NR, SD:NR		p:<0.10
Satoh, 2011[59]	Arm 1-Placebo		N:135, Mean: NR, SD:NR	14 weeks	N:135, Mean: NR, SD:NR	Mean change from baseline: p:NS	
Satoh, 2011[59]	Arm 2-Pregabalin, 300 mg/day		N:134, Mean: NR, SD:NR	14 weeks	N:134, Mean: NR, SD:NR	Mean change from baseline: p:nS	

Evidence Table 13 – KQ2a list of additional (Parasthesias) outcomes from Griebler et al. (2014) (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Satoh, 2011[59]	Arm 3-Pregabalin, 600 mg/day		N:45, Mean: NR, SD:NR	14 weeks	N:45, Mean: NR, SD:NR	Mean change from baseline: p:0.0093	
Sindrup, 1989[64]	Arm 1-Placebo	Six item scale, includes paraethesia	N:9, Mean:, SD:		NR		p:<0.01
Sindrup, 1989[64]	Arm 2-Imipramine	Six item scale, includes paraethesia	N:9, Mean:, SD:		NR		p:<0.01
Sindrup, 1990[65]	Arm 1-Placebo	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:1.48, SD: NR		
Sindrup, 1990[65]	Arm 2-Paroxetine	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:0.52, SD: NR		p:<0.05
Sindrup, 1990[65]	Arm 3-Imipramine	Paraesthesia	N:20, Mean: NR, SD:NR	6 weeks	N:20, Mean:0.49, SD: NR	(95% CI:1, 4.5), p:NR	p:<0.05
Wright, 1997[74]	Arm 1-Placebo	FIS	N:16, Mean:11, SD:	3 weeks	N:15, Mean:6, SD: NR	Median change from baseline:2 (95% CI:2, 6), p:NR	

Evidence Table 13 – KQ2a list of additional (Parasthesias) outcomes from Griebler et al. (2014) (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Wright, 1997[74]	Arm 2-Mexiltetine	FIS, includes paresthesia	N:15, Mean:9.5, SD:	3 weeks	N:14, Mean:4.5, SD: NR	Median change from baseline:5.5 (95% CI:), p:NR	

Evidence Table 14 – Griebler Review Quality of life

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Backonja, 1998[29]	Arm 1-Placebo	SF-36	N:81, Mean: NR, SD:NR				Mean difference from baseline: (95% CI:) Comparator: , p:NS
Backonja, 1998[29]	Arm 2-Gabapentin	SF-36	N:84, Mean: NR, SD:NR			Mean difference from baseline: NR, SE:, p:0.01	Mean difference from baseline: (95% CI:) Comparator: , p:NS
Beydoun, 2006[31]	Arm 1-Placebo	SF-36	N:89, Mean: NR, SD:NR	12 weeks			p:NS
Beydoun, 2006[31]	Arm 2-Oxcarbazepine, 600mg	SF-36	N:83, Mean: NR, SD:NR	12 weeks			p:NS
Beydoun, 2006[31]	Arm 3-Oxcarbazepine, 1200mg	SF-36	N:87, Mean: NR, SD:NR	12 weeks			p:NS
Beydoun, 2006[31]	Arm 4-Oxcarbazepine, 1800mg	SF-36	N:88, Mean: NR, SD:NR	12 weeks			p:NS
Boyle, 2012[32]	Arm 1-Pregabalin	SF-36	N:27, Mean: NR, SD:NR	36 days	N:27, Mean:31.1, SD:10.9		p:NS
Boyle, 2012[32]	Arm 2-Duloxetine	SF-36	N:28, Mean: NR, SD:NR	36 days	N:28, Mean:36.6, SD:9.4		p:NS
Boyle, 2012[32]	Arm 3-Amitriptyline	SF-36	N:28, Mean: NR, SD:NR	36 days	N:28, Mean:38.5, SD:8.8		p:NS
Dogra, 2005[35]	Arm 1-Placebo	SF-36	N:77, Mean: NR, SD:NR	14 weeks	N:70, Mean:50.2, SD:NR		p:0.03
Dogra, 2005[35]	Arm 2-Oxcarbazepine	SF-36	N:69, Mean: NR, SD:NR	14 weeks	N:55, Mean:47.2, SD:NR		p:0.03

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Freeman, 2007[37]	Arm 1-Placebo	SF-36, physical functioning	N:134, Mean:46, SD:25.37	66 days	N:134, Mean:52.1, SD:26.09	Mean difference from baseline:6.1, SE:, p:0.082	
Freeman, 2007[37]	Arm 2-Tramadol/APAP	SF-36, physical functioning	N:143, Mean:47.9, SD:26.24	66 days	N:143, Mean:57.4, SD:29.44	Mean difference from baseline:9.5, SE:, p:0.082	
Freeman, 2007[37]	Arm 1-Placebo	SF-36, Role-physical	N:134, Mean:33.7, SD:38.07	66 days	N:134, Mean:54.7, SD:40.96	Mean difference from baseline:21.1, SE:, p:0.916	
Freeman, 2007[37]	Arm 2-Tramadol/APAP	SF-36, Role-physical	N:143, Mean:35.5, SD:38.67	66 days	N:143, Mean:55.1, SD:41.6	Mean difference from baseline:19.6, SE:, p:0.916	
Freeman, 2007[37]	Arm 1-Placebo	SF-36, physical component summary	N:134, Mean:32, SD:9.15	66 days	N:134, Mean:36.3, SD:9.91	Mean difference from baseline:4.3, SE:, p:0.063	
Freeman, 2007[37]	Arm 2-Tramadol/APAP	SF-36, physical component summary	N:143, Mean:31.3, SD:9.85	66 days	N:143, Mean:37.4, SD:10.77	Mean difference from baseline:6.1, SE:, p:0.063	
Gao, 2010[39]	Arm 1-Placebo	EQ-5D (US)	N:109, Mean: NR, SD:NR	14 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:0.1, SE:, p:0.207	

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Gao, 2010[39]	Arm 2-Duloxetine	EQ-5D (US)	N:106, Mean: NR, SD:NR	14 weeks	N:106, Mean: NR, SD:NR	Mean difference from baseline:0.12, SE:, p:0.207	
Gimbel, 2003[40]	Arm 1-Placebo	SF-36	N:77, Mean: NR, SD:NR	42 days	N:77, Mean: NR, SD:NR		p:NS
Gimbel, 2003[40]	Arm 2-CR Oxycodone	SF-36	N:82, Mean: NR, SD:NR	42 days	N:82, Mean: NR, SD:NR		p:NS
Gimbel, 2003[40]	Arm 1-Placebo	Rand Mental Health Survey	N:77, Mean: NR, SD:NR	42 days	N:77, Mean: NR, SD:NR		p:NS
Gimbel, 2003[40]	Arm 2-CR Oxycodone	Rand Mental Health Survey	N:82, Mean: NR, SD:NR	42 days	N:82, Mean: NR, SD:NR		p:NS
Goldstein, 2005[41]	Arm 1-Placebo	SF-36, physical functioning	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:3.94, SE:, p:NS	
Goldstein, 2005[41]	Arm 2-Duloxetine, 20 mg/d	SF-36, physical functioning	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:3.67, SE:, p:NS	
Goldstein, 2005[41]	Arm 3-Duloxetine, 60 mg/d	SF-36, physical functioning	N:114, Mean: NR, SD:NR	12 weeks	N:114, Mean: NR, SD:NR	Mean difference from baseline:5.86, SE:, p:NS	
Goldstein, 2005[41]	Arm 4-Duloxetine, 120 mg/d	SF-36, physical functioning	N:113, Mean: NR, SD:NR	12 weeks	N:113, Mean: NR, SD:NR	Mean difference from baseline:5.85, SE:, p:NS	

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Goldstein, 2005[41]	Arm 1-Placebo	SF-36, bodily pain	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:10.32, SE:, p:<0.01	
Goldstein, 2005[41]	Arm 2-Duloxetine, 20 mg/d	SF-36, bodily pain	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:13.22, SE:, p:<0.01	
Goldstein, 2005[41]	Arm 3-Duloxetine, 60 mg/d	SF-36, bodily pain	N:114, Mean: NR, SD:NR	12 weeks	N:114, Mean: NR, SD:NR	Mean difference from baseline:18, SE:, p:<0.01	
Goldstein, 2005[41]	Arm 4-Duloxetine, 120 mg/d	SF-36, bodily pain	N:113, Mean: NR, SD:NR	12 weeks	N:113, Mean: NR, SD:NR	Mean difference from baseline:18.32, SE:, p:<0.01	
Goldstein, 2005[41]	Arm 1-Placebo	EQ-5D	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:0.08, SE:, p:<0.05	
Goldstein, 2005[41]	Arm 2-Duloxetine, 20 mg/d	EQ-5D	N:115, Mean: NR, SD:NR	12 weeks	N:115, Mean: NR, SD:NR	Mean difference from baseline:0.1, SE:, p:<0.05	
Goldstein, 2005[41]	Arm 3-Duloxetine, 60 mg/d	EQ-5D	N:114, Mean: NR, SD:NR	12 weeks	N:114, Mean: NR, SD:NR	Mean difference from baseline:0.13, SE:, p:<0.05	

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Goldstein, 2005[41]	Arm 4-Duloxetine, 120 mg/d	EQ-5D	N:113, Mean: NR, SD:NR	12 weeks	N:113, Mean: NR, SD:NR	Mean difference from baseline:0.13, SE:, p:<0.05	
Grosskopf, 2006[42]	Arm 1-Placebo	SF-36	N:70, Mean: NR, SD:NR	16 weeks	N:70, Mean: NR, SD:NR		p:NS
Grosskopf, 2006[42]	Arm 2-Oxcarbazepine	SF-36	N:71, Mean: NR, SD:NR	16 weeks	N:71, Mean: NR, SD:NR		p:NS
Lesser, 2004[48]	Arm 1-Placebo	SF-36, social domain	N:97, Mean: NR, SD:NR	5 weeks	N:88, Mean: NR, SD:NR		p:NS
Lesser, 2004[48]	Arm 2-Pregabalin, 75 mg/day	SF-36, social domain	N:77, Mean: NR, SD:NR	5 weeks	N:67, Mean: NR, SD:NR		p:NS
Lesser, 2004[48]	Arm 3-Pregabalin, 300 mg/day	SF-36, social domain	N:81, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.05
Lesser, 2004[48]	Arm 4-Pregabalin, 600 mg/day	SF-36, social domain	N:82, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.01
Lesser, 2004[48]	Arm 1-Placebo	SF-36, bodily pain	N:97, Mean: NR, SD:NR	5 weeks	N:88, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:NS
Lesser, 2004[48]	Arm 2-Pregabalin, 75 mg/day	SF-36, bodily pain	N:77, Mean: NR, SD:NR	5 weeks	N:67, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:NS
Lesser, 2004[48]	Arm 3-Pregabalin, 300 mg/day	SF-36, bodily pain	N:81, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.005

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Lesser, 2004[48]	Arm 4-Pregabalin, 600 mg/day	SF-36, bodily pain	N:82, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.0005
Lesser, 2004[48]	Arm 1-Placebo	SF-36, vitality	N:97, Mean: NR, SD:NR	5 weeks	N:88, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:NS
Lesser, 2004[48]	Arm 2-Pregabalin, 75 mg/day	SF-36, vitality	N:77, Mean: NR, SD:NR	5 weeks	N:67, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.05
Lesser, 2004[48]	Arm 3-Pregabalin, 300 mg/day	SF-36, vitality	N:81, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.01
Lesser, 2004[48]	Arm 4-Pregabalin, 600 mg/day	SF-36, vitality	N:82, Mean: NR, SD:NR	5 weeks	N:70, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:NS
McCleane, 1999[51]	Overall-	VAS score, Quality of life	N:100, Mean:4.68, SD:NR	56 days	N:, Mean: NR, SD:NR		
McCleane, 1999[51]	Arm 1-Placebo	VAS score, Quality of life	N:50, Mean: NR, SD:NR	56 days	N:38, Mean: NR, SD:NR	Mean difference from baseline:-0.15, SE:, p:NS	
McCleane, 1999[51]	Arm 2-Lamotrigine	VAS score, Quality of life	N:50, Mean: NR, SD:NR	56 days	N:36, Mean: NR, SD:NR	Mean difference from baseline:-0.38, SE:, p:NS	
Raskin, 2004[52]	Arm 1-Placebo	SF-36, physical functioning	N:109, Mean:32.4, SD:8.7	12 weeks	N:109, Mean:34.9, SD:9.4		Mean difference from baseline: (95% CI:) Comparator: , p:0.066

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Raskin, 2004[52]	Arm 2-Topiramate	SF-36, physical functioning	N:208, Mean:33.2, SD:9.8	12 weeks	N:208, Mean:32.4, SD:8.7		Mean difference from baseline: (95% CI:) Comparator: , p:0.066
Rauck, 2007[54]	Arm 1-Placebo	SF-36, bodily pain	N:59, Mean: NR, SD:NR	10 weeks	N:48, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:0.022
Rauck, 2007[54]	Arm 2-Lacosamide	SF-36, bodily pain	N:60, Mean: NR, SD:NR	10 weeks	N:46, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:0.022
Rauck, 2007[54]	Arm 1-Placebo	SF-36, vitality	N:59, Mean: NR, SD:NR	10 weeks	N:48, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:0.024
Rauck, 2007[54]	Arm 2-Lacosamide	SF-36, vitality	N:60, Mean: NR, SD:NR	10 weeks	N:46, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:0.024
Richter, 2005[55]	Arm 1-Placebo	SF-36, bodily pain	N:85, Mean: NR, SD:NR	6 weeks	N:85, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.0106
Richter, 2005[55]	Arm 2-Pregabalin, 150 mg/day	SF-36, bodily pain	N:79, Mean: NR, SD:NR	6 weeks	N:79, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.0106
Richter, 2005[55]	Arm 3-Pregabalin, 600 mg/day	SF-36, bodily pain	N:82, Mean: NR, SD:NR	6 weeks	N:82, Mean: NR, SD:NR		Mean difference from baseline: (95% CI:) Comparator: , p:<0.0106
Rosenstock, 2004[56]	Arm 1-Placebo	SF-36, bodily pain	N:70, Mean: NR, SD:NR	8 weeks	N:61, Mean:46.96, SD:2.37		Mean difference from baseline:6.87 (95% CI:0.70, 13.04) Comparator: Placebo, p:0.0294

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Rosenstock, 2004[56]	Arm 2-Pregabalin	SF-36, bodily pain	N:76, Mean: NR, SD:NR	8 weeks	N:62, Mean:53.83, SD:2.24		
Rosenstock, 2004[56]	Arm 1-Placebo	SF-36, mental health	N:70, Mean: NR, SD:NR	8 weeks	N:61, Mean:72.36, SD:1.97		Mean difference from baseline:3.47 (95% CI:-1.73, 8.66) Comparator: Placebo, p:0.1893
Rosenstock, 2004[56]	Arm 2-Pregabalin	SF-36, mental health	N:76, Mean: NR, SD:NR	8 weeks	N:62, Mean:75.82, SD:1.9		
Rosenstock, 2004[56]	Arm 1-Placebo	SF-36, vitality	N:70, Mean: NR, SD:NR	8 weeks	N:61, Mean:43.57, SD:2.05		Mean difference from baseline:3.24 (95% CI:-2.13, 8.61) Comparator: Placebo, p:0.2343
Rosenstock, 2004[56]	Arm 2-Pregabalin	SF-36, vitality	N:76, Mean: NR, SD:NR	8 weeks	N:62, Mean:46.82, SD:1.96		
Sang, 2002[58]	Arm 1-Placebo	SF-36	N:19, Mean: NR, SD:NR	9 weeks	N:19, Mean: NR, SD:NR		p:NS
Sang, 2002[58]	Arm 2-Dextromethorpan	SF-36	N:19, Mean: NR, SD:NR	9 weeks	N:19, Mean: NR, SD:NR		Mean difference from baseline: NR (95% CI:) Comparator: Placebo, p:<0.05
Sang, 2002[58]	Arm 3-Memantine	SF-36	N:19, Mean: NR, SD:NR	9 weeks	N:19, Mean: NR, SD:NR		p:NS
Satoh, 2011[59]	Arm 1-Placebo	SF-36	N:135, Mean: NR, SD:NR	14 weeks	N:135, Mean: NR, SD:NR		p:NS
Satoh, 2011[59]	Arm 2-Pregabalin, 300 mg/day	SF-36	N:134, Mean: NR, SD:NR	14 weeks	N:134, Mean: NR, SD:NR		p:NS

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Satoh, 2011[59]	Arm 3-Pregabalin, 600 mg/day	SF-36	N:45, Mean: NR, SD:NR	14 weeks	N:45, Mean: NR, SD:NR		Mean difference from baseline: NR (95% CI:) Comparator: Placebo, p:<0.05
Simpson, 2001[63]	Arm 1-Placebo	SF-36, bodily pain	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean: NR, SD:NR		
Simpson, 2001[63]	Arm 2-Gabapentin+venlafaxine	SF-36, bodily pain	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean:90, SD:NR		
Simpson, 2001[63]	Arm 1-Placebo	SF-36, mental health	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean: NR, SD:NR		
Simpson, 2001[63]	Arm 2-Gabapentin+venlafaxine	SF-36, mental health	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean:75, SD:NR		
Simpson, 2001[63]	Arm 1-Placebo	SF-36, vitality	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean: NR, SD:NR		
Simpson, 2001[63]	Arm 2-Gabapentin+venlafaxine	SF-36, vitality	N:30, Mean: NR, SD:NR	8 weeks	N:30, Mean:65, SD:NR		
Tolle, 2008[68]	Arm 1-Placebo	EQ-5D	N:96, Mean: NR, SD:NR	12 weeks	N:90, Mean: NR, SD:NR		
Tolle, 2008[68]	Arm 2-Pregabalin, 150 mg/day	EQ-5D	N:99, Mean: NR, SD:NR	12 weeks	N:92, Mean: NR, SD:NR		Mean difference from baseline:0.1 (95% CI:0.03, 0.16) Comparator: , p:0.0092
Tolle, 2008[68]	Arm 3-Pregabalin, 300 mg/day	EQ-5D	N:99, Mean: NR, SD:NR	12 weeks	N:92, Mean: NR, SD:NR		Mean difference from baseline:0.08 (95% CI:0.01, 0.14) Comparator: , p:0.0263

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Tolle, 2008[68]	Arm 4-Pregabalin, 600 mg/day	EQ-5D	N:101, Mean: NR, SD:NR	12 weeks	N:90, Mean: NR, SD:NR		Mean difference from baseline:0.14 (95% CI:0.07, 0.20) Comparator: , p:0.003
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, Physical functioning	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:3.64, SE:1.9, p:NS	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, Physical functioning	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:11.96, SE:1.81, p:<0.01	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, Physical functioning	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:11.2, SE:11.2, p:<0.01	
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, role physical	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:12.14, SE:3.77, p:NS	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, role physical	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:22.85, SE:3.63, p:<0.05	

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, role physical	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:25.01, SE:3.67, p:<0.05	
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, role emotional	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:2.13, SE:3.44, p:NS	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, role emotional	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:10.66, SE:3.32, p:NS	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, role emotional	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:9, SE:3.35, p:NS	
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, bodily pain	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:12.17, SE:2.1, p:NS	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, bodily pain	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:15.3, SE:1.98, p:NS	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, bodily pain	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:20.59, SE:2.04, p:<0.01	

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, vitality	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:2.79, SE:1.78, p:NS	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, vitality	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:8.47, SE:1.73, p:<0.05	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, vitality	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:6.36, SE:1.74, p:NS	
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, mental health	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:-0.31, SE:1.52, p:NS	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, mental health	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:1.63, SE:1.48, p:NS	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, mental health	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:3.82, SE:1.49, p:<0.05	
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, Physical component	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:3.67, SE:0.78, p:NS	

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, Physical component	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:6.85, SE:0.76, p:<0.01	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, Physical component	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:7.46, SE:0.77, p:<0.001	
Wernicke, 2006[72]	Arm 1-Placebo	SF-36, Mental component	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:-0.29, SE:0.83, p:NS	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	SF-36, Mental component	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:0.77, SE:0.81, p:NS	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	SF-36, Mental component	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:1.09, SE:0.82, p:NS	
Wernicke, 2006[72]	Arm 1-Placebo	EQ-5D	N:108, Mean: NR, SD:NR	12 weeks	N:101, Mean: NR, SD:NR	Mean difference from baseline:0.08, SE:0.02, p:NS	

Evidence Table 14 – Griebler Review Quality of life (continued)

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	EQ-5D	N:114, Mean: NR, SD:NR	12 weeks	N:109, Mean: NR, SD:NR	Mean difference from baseline:0.15, SE:0.02, p:<0.05	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	EQ-5D	N:112, Mean: NR, SD:NR	12 weeks	N:108, Mean: NR, SD:NR	Mean difference from baseline:0.15, SE:0.02, p:<0.05	

Evidence Table 15 – Griebler Review Drop outs

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Backonja, 1998[29]	Arm 1-Placebo	5	6.17	
Backonja, 1998[29]	Arm 2-Gabapentin	7	8.33	
Bansal, 2009[30]	Arm 1-Pregabalin	9	40.91	
Bansal, 2009[30]	Arm 2-Amitriptyline	21	95.45	
Beydoun, 2006[31]	Arm 1-Placebo	6	6.74	
Beydoun, 2006[31]	Arm 2-Oxcarbazepine, 600mg	9	10.84	
Beydoun, 2006[31]	Arm 3-Oxcarbazepine, 1200mg	20	22.99	
Beydoun, 2006[31]	Arm 4-Oxcarbazepine, 1800mg	36	40.91	
Boyle, 2012[32]	Arm 1-Pregabalin	6	22.22	
Boyle, 2012[32]	Arm 2-Duloxetine	3	10.71	
Boyle, 2012[32]	Arm 3-Amitriptyline	1	3.57	
Capsaicin study group, 1991[33]	Arm 1-Vehicle	8	5.80	
Capsaicin study group, 1991[33]	Arm 2-Capsaicin	17	12.23	

Evidence Table 15 – Griebler Review Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Dogra, 2005[35]	Arm 1-Placebo	6	7.79	
Dogra, 2005[35]	Arm 2-Oxcarbazepine	19	27.54	
Eisenberg, 2001[36]	Arm 1-Placebo	2	7.69	
Eisenberg, 2001[36]	Arm 2-Lamotrigine	2	7.41	
Freeman, 2007[37]	Arm 1-Placebo	10	6.54	
Freeman, 2007[37]	Arm 2-Tramadol/APAP	13	8.13	
Freynhagen, 2005[38]	Arm 1-Placebo	5	7.69	
Freynhagen, 2005[38]	Arm 2-PGB fixed dose	33	25	
Freynhagen, 2005[38]	Arm 3-PGB flexible dose	24	17.02	
Gao, 2010[39]	Arm 1-Placebo	4	3.67	
Gao, 2010[39]	Arm 2-Duloxetine	15	13.76	
Gimbel, 2003[40]	Arm 1-Placebo	4	5.19	
Gimbel, 2003[40]	Arm 2-CR Oxycodone	7	8.54	
Grosskopf, 2006[42]	Arm 1-Placebo	4	5.71	

Evidence Table 15 – Griebler Review Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Grosskopf, 2006[42]	Arm 2-Oxcarbazepine	18	25.35	
Jia, 2006[43]	Arm 1-Venlafaxine	4	6.06	
Jia, 2006[43]	Arm 2-Carbamazepine	2	3.03	
Jose, 2007[44]	Arm 1-Amitriptyline	19	63.33	
Jose, 2007[44]	Arm 2-Lamotrigine	8	34.78	
Kochar, 2002[45]	Arm 1-Placebo	0	0	
Kochar, 2002[45]	Arm 2-Sodium Valproate	1	3.45	
Kochar, 2004[46]	Arm 1-Placebo	0	0.00	
Kochar, 2004[46]	Arm 2-Sodium Valproate	1	4.76	
Lesser, 2004[48]	Arm 1-Placebo	1	1.03	
Lesser, 2004[48]	Arm 2-Pregabalin, 75 mg/day	0	0.00	
Lesser, 2004[48]	Arm 3-Pregabalin, 300 mg/day	0	0.00	
Lesser, 2004[48]	Arm 4-Pregabalin, 600 mg/day	0	0.00	
Max, 1991[49]	Arm 1-Placebo	2	10.00	

Evidence Table 15 – Griebler Review Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Max, 1991[49]	Arm 2-Desipramine	2	10.00	
Max, 1992[50]	Arm 1-Placebo-Fluoxetine	5	9.26	
Max, 1992[50]	Arm 2-Desipramine-Amitriptyline	14	25.93	
McCleane, 1999[51]	Arm 1-Placebo	8	16.00	
McCleane, 1999[51]	Arm 2-Lamotrigine	10	20.00	
Raskin, 2004[52]	Arm 1-Placebo	9	8.26	
Raskin, 2004[52]	Arm 2-Topiramate	52	25.00	
Raskin, 2005[53]	Arm 1-Placebo	3	2.59	
Raskin, 2005[53]	Arm 2-Duloxetine, 60mg/day	5	4.31	
Raskin, 2005[53]	Arm 3-Duloxetine, 120mg/day	14	12.07	
Rauck, 2007[54]	Arm 1-Placebo	3	5.08	
Rauck, 2007[54]	Arm 2-Lacosamide	5	8.33	
Richter, 2005[55]	Arm 1-Placebo	4	4.71	
Richter, 2005[55]	Arm 2-Pregabalin, 150 mg/day	2	2.53	

Evidence Table 15 – Griebler Review Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Richter, 2005[55]	Arm 3-Pregabalin, 600 mg/day	7	8.54	
Rosenstock, 2004[56]	Arm 1-Placebo	8	11.43	
Rosenstock, 2004[56]	Arm 2-Pregabalin	21	27.63	
Rowbotham, 2004[57]	Arm 1-Placebo	3	3.75	
Rowbotham, 2004[57]	Arm 2-Venlafaxine 75mg	6	7.50	
Rowbotham, 2004[57]	Arm 3-Venlafaxine 150/225mg	8	9.76	
Satoh, 2011[59]	Arm 1-Placebo	2	1.48	
Satoh, 2011[59]	Arm 2-Pregabalin, 300 mg/day	4	2.99	
Satoh, 2011[59]	Arm 3-Pregabalin, 600 mg/day	8	17.78	
Scheffler, 1991[60]	Arm 1-Vehicle	2	7.69	
Scheffler, 1991[60]	Arm 2-Capsaicin	9	32.14	
Schwartz, 2011[61]	Arm 1-Placebo	15	7.65	
Schwartz, 2011[61]	Arm 2-Tapentadol ER	29	14.57	
Shaibani, 2009[62]	Arm 1-Placebo	9	13.85	

Evidence Table 15 – Griebler Review Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Shaibani, 2009[62]	Arm 2-Lacosamide, 200mg/day	17	12.06	
Shaibani, 2009[62]	Arm 3-Lacosamide, 400mg/day	30	24.00	
Shaibani, 2009[62]	Arm 4-Lacosamide, 600mg/day	58	42.34	
Tandan, 1992[66]	Arm 1-Vehicle	1	4.55	
Tandan, 1992[66]	Arm 2-Capsaicin	1	4.55	
Thienel, 2004[67]	Arm 1-Placebo	32	8.33	
Thienel, 2004[67]	Arm 2-Topiramate, 100mg/day	41	16.21	
Thienel, 2004[67]	Arm 3-Topiramate, 200mg/day	93	25.00	
Thienel, 2004[67]	Arm 4-Topiramate, 400mg/day	79	30.38	
Tolle, 2008[68]	Arm 1-Placebo	3	3.13	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)
Tolle, 2008[68]	Arm 2-Pregabalin, 150 mg/day	5	5.05	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)
Tolle, 2008[68]	Arm 3-Pregabalin, 300 mg/day	11	11.11	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)

Evidence Table 15 – Griebler Review Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Tolle, 2008[68]	Arm 4-Pregabalin, 600 mg/day	13	12.87	The NNH for one discontinuation due to AEs was 10.3 (95% confidence interval 5.8, 42)
Vinik, 2007[69]	Arm 1-Placebo	4	4.44	
Vinik, 2007[69]	Arm 2-Lamotrigine, 200 mg/day	5	5.56	
Vinik, 2007[69]	Arm 3-Lamotrigine, 300 mg/day	8	8.89	
Vinik, 2007[69]	Arm 4-Lamotrigine, 400 mg/day	10	11.11	
Vrethem, 1997[70]	Arm 1-Placebo	NR	NR	
Vrethem, 1997[70]	Arm 2-Amitriptyline	3	15.79	
Vrethem, 1997[70]	Arm 3-Maprotiline	2	10.53	
Watson, 2003[71]	Arm 1-Placebo	1	9.09	
Watson, 2003[71]	Arm 2-CR Oxycodone	7	70.00	
Wernicke, 2006[72]	Arm 1-Placebo	8	7.41	
Wernicke, 2006[72]	Arm 2-Dutoxetine, 60mg	17	14.91	
Wernicke, 2006[72]	Arm 3-Dutoxetine, 120mg	20	17.86	

Evidence Table 15 – Griebler Review Drop outs (continued)

Author, year	Select arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Wright, 1997[74]	Arm 1-Placebo	2	12.50	
Wright, 1997[74]	Arm 2-Mexiltetine	2	13.33	
Wymer, 2009[75]	Arm 1-Placebo	8	8.60	
Wymer, 2009[75]	Arm 2-Lacosamide, 200mg/day	8	8.60	
Wymer, 2009[75]	Arm 3-Lacosamide, 400mg/day	21	23.08	
Wymer, 2009[75]	Arm 4-Lacosamide, 600mg/day	37	39.78	
Ziegler, 2010[76]	Arm 1-Placebo	NR	NR	
Ziegler, 2010[76]	Arm 2-Lacosamide, 400mg/day slow titration	NR	13	
Ziegler, 2010[76]	Arm 3-Lacosamide, 400mg/day standard titraion	NR	8.20	
Ziegler, 2010[76]	Arm 4-Lacosamide, 600mg/day	NR	NR	

KQ2b

Evidence Table 16 – KQ2b Supplements Study Characteristics

Author, year Trial name	Study design Site(s)	Funding source	Start year of recruitment End year of recruitment	Run- in period	Study intervention Drug dosage (mg daily) Drug administration route
Ziegler, 2011[77] The Nathan 1 Trial	Parallel randomized controlled trial Multiple center: US, Canada and Europe	Industry MEDA GmbH & Co. KG, Bad Homburg, Germany	Not reported	Yes	Alpha-lipoic acid 600 Oral
Ziegler, 2006[78] SYDNEY 2 Trial	Parallel randomized controlled trial Multiple center: Israel and Russia	Industry, MEDA Pharma, Bad Homburg, Germany	Not reported	Yes	Alpha-lipoic acid 600 Oral
Ziegler, 1999[79] ALADIN III	Parallel randomized controlled trial Multiple center: Europe, 71 centers in Germany	Industry	Not reported	No	Alpha-lipoic acid 600mg x 3 weeks then 1800mg (IV x 3 weeks then PO) Intravenous
Ziegler, 1996[80] ALADIN	Parallel randomized controlled trial, Multiple center: Europe, 38 centers in Germany	Industry	Not reported	No	Alpha-lipoic acid 1200,600,100 (Received on weekdays only) Intravenous
Ametov, 2003[81] SYDNEY Trial	Parallel randomized controlled trial, Single center: Europe	Industry ASTA Medica	Not reported	Yes	Alpha-lipoic acid 600 Intravenous
Ruhnau, 1999[82] ORPIL	Parallel randomized controlled trial Single center: Europe	Industry, ASTA Medica	Not reported	No	Alpha-lipoic acid 1800 (Given 14 days total, 5 days/ week) Oral
De Grandis, 2002*[83]	Parallel randomized controlled trial Multiple center: Europe	Industry, Sigma Tau	Not reported	Yes	Acetyl-L-carnitine 2000 Oral

* Received 1000mg IM BID X 10 days

Evidence Table 17 – KQ2b Supplements Patients Characteristics

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: n (%)
Ziegler, 2011[77]	Arm 1: ALA, N: 233	4 years	Female: (33.9) Age: mean: 53.3, SD: 8.3	HbA1c: mean: 8.9, SD:1.8 BMI: mean: 29.7, SD: 6.1	3 Years	(3)
Ziegler, 2011[77]	Arm 2: placebo, N: 227	4 years	Female: (33) Age: mean: 53.9, SD: 7.6	HbA1c: mean: 8.8, SD: 1.9 BMI: mean: 29.8, SD: 6.1	3.2 Years	(3)
Ziegler, 2006[78]	Arm 1: placebo, N: 43	5 weeks	Female: (65) Age: mean: 57, SD: 11	HbA1c: mean: 7.53, SD: 1.18 BMI: mean: 29.1, SD: 4.4	4.9 Years	(0)
Ziegler, 2006[78]	Arm 2: ALA600, N: 45	5 weeks	Female: (56) Age: mean: 56, SD: 12	HbA1c: mean: 7.58, SD: 1.09 BMI: mean: 28.7, SD: 3.9	4.8 Years	(0)
Ziegler, 2006[78]	Arm 3: ALA1200, N: 47	5 weeks	Female: (60) Age: mean: 59, SD: 12	HbA1c: mean: 7.85, SD: 1.31 BMI: mean: 30.9, SD: 4.5	5 Years	(0)

Evidence Table 17 – KQ2b Supplements Patients Characteristics (continued)

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: n (%)
Ziegler, 2006[78]	Arm 4: ALA1800, N: 46	5 weeks	Female: (59) Age: mean: 59, SD: 9	HbA1c: mean: 7.81, SD: 1.14 BMI: mean: 28.4, SD: 4.8	4.9 Years	(0)
Ziegler, 1999[79]	Arm 1: A-A, N: 165	7 months	Female: (54.5) Age: mean: 56.5, SD: 7.1	HbA1c: mean: 8.5, SD: 1.9 BMI: mean: 29, SD: 4.8	37.7 Months	(43)
Ziegler, 1999[79]	Arm 2: A-P, N: 173	7 months	Female: (45.7) Age: mean: 57, SD: 6.2	HbA1c: mean: 8.7, SD: 1.8 BMI: mean: 28.8, SD: 4.2	35.1 Months	(45)
Ziegler, 1999[79]	Arm 3: P-P, N: 165	7 months	Female: (49.7) Age: mean: 57.3, SD: 5.5	HbA1c: mean: 8.7, SD: 1.8 BMI: mean: 29.5, SD: 4.8	38 Months	(38)
Ziegler, 1996[80]	Arm 1: ALA 1200, N: 86	19 days	Female: (60) Age: mean: 59.2, SD: 7.7	HbA1c: mean: 8.8, SD: 1.9 BMI: mean: 29.2, SD: 4.8	3.3 Years	(21)

Evidence Table 17 – KQ2b Supplements Patients Characteristics (continued)

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: n (%)
Ziegler, 1996[80]	Arm 2: ALA 600, N: 77	19 days	Female : (63) Age: mean: 57.5, SD: 8.7	HbA1c: mean: 9.2, SD: 2.5 BMI: mean: 27.7, SD: 4.9	2.8 Years	(14)
Ziegler, 1996[80]	Arm 3: ALA 100, N: 81	19 days	Female: (49) Age: mean: 58.7, SD: 7.9	HbA1c: mean: 9, SD: 2.1 BMI: mean: 27.8, SD: 4.4	2.8 Years	(15)
Ziegler, 1996[80]	Arm 4: placebo, N: 82	19 days	Female: (65) Age: mean: 60.2, SD: 7.7	HbA1c: mean: 9.4, SD: 2.6 BMI: mean: 29.7, SD: 4.9	3.4 Years	(16)
Ametov, 2003**[81]	Arm 1: placebo, N: 60	3 weeks	Female: 36 (72) Age: mean: 55.4, SD: 8.66	HbA1c: NR BMI: mean: 29.3, SD: 5.23	3.4 Years	3.3(2)
Ametov, 2003[81]	Arm 2: ALA, N: 60	3 weeks	Female: 46 (77) Age: mean: 56.8, SD: 9.65	HbA1c: NR BMI: mean: 29.4, SD: 4.93	3.7 Years	0(0)

Evidence Table 17 – KQ2b Supplements Patients Characteristics (continued)

Author, year	Arm name, N at enrollment	Actual length of mean follow-up	Female, n (%) Age	HbA1c, BMI	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: n (%)
Ruhnau, 1999[82]	Arm 1: TA, N: 12	3 weeks	Female: 6 (50) Age: mean: 60.5, SD: 6.9	HbA1c: mean: 7.7, SD: 1.3 BMI: mean: 29.6, SD: 4	4.1 Years	8.3(1)
Ruhnau, 1999[82]	Arm 2: placebo, N: 12	3 weeks	Female: 6 (50) Age: mean: 62.1, SD: 4.5	HbA1c: mean: 7.1, SD: 1.8 BMI: mean: 28.5, SD: 3.9	3.8 Years	8.3(1)
De Grandis, 2002[83]	Arm 1: LAC, N: 167	1 year	Female: 62 Age: NR	NR	NR	12(20)
De Grandis, 2002[83]	Arm 2: placebo, N: 166	1 year	Female: 66 Age: NR	NR	NR	11.4(19)

*Race is not reported
** Higher ration of men to women in placebo group, Figure 2 with the results is not in the article; ITT analysis
RefID 4763: "No significant differences were noted for any of the parameters listed, except for treatment with oral antidiabetic agens (p=0.018) and BMI (p=0.036), Not clear difference between WHICH groups

Evidence Table 18– KQ2b Supplements Pain Continuous Outcomes

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at timepoint(s)	Within arm comparison	NOTES
*Ziegler, 2006[78]	Arm 1: placebo	TSS Stabbing Pain	N: 43, mean: 2.21, SD: 0.77	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -0.83, SD:1.14 ALA600 vs placebo, p: <0.05	
Ziegler, 2006[78]	Arm 2: ALA600	TSS Stabbing Pain	N: 45, mean: 2.32, SD: 0.94	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -1.4, SD: 1.15 ALA1200 vs placebo, p: <0.05	
Ziegler, 2006[78]	Arm 3: ALA1200	TSS Stabbing Pain	N: 47, mean: 2.38, SD: 0.89	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -1.56, SD: 1.07 ALA1800 vs placebo, p: <0.05	
Ziegler, 2006[78]	Arm 4: ALA1800	TSS Stabbing Pain	N: 46, mean: 2.03, SD: 0.88	5 weeks		Mean change from baseline: -1.46, SD: 1.2	
Ametov, 2003[81]	Arm 1: placebo	NSC(LL) Pain- severity	N: 58, mean: 10.6, SD: NR	3 weeks	N: 58, mean: NR, SD: NR	Mean change from baseline: -4.6, SD: NR	
Ametov, 2003[81]	Arm 2: ALA	NSC(LL) Pain- severity	N: 60, mean: 10, SD: NR	3 weeks	N: 60, mean: NR, SD: NR	Mean change from baseline: -7.3, SD: NR	
Ruhnau, 1999[82]	Arm 2: placebo	TSS pain -points	N: 11, mean: 1.47, SD: 0.54	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: 0.79, SD: 0.81	
Ruhnau, 1999[82]	Arm 1: TA	TSS pain-points	N: 11, mean: 1.69, SD: 0.58	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: -1.39, SD: 0.84 Mean change from baseline placebo p: 0.099	
De Grandis, 2002[83]	Arm 2: placebo	VAS-mm	N: 166, mean: 44.68, SD: 3.4	Month 12	N: 95, mean: 40.87, SD: 4	Mean change from baseline: -3.5, SD: 11	

Evidence Table 18 – KQ2b Supplements Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at timepoint(s)	Within arm comparison	NOTES
De Grandis, 2002[83]	Arm 1: LAC	VAS-mm	N: 167, mean: 45.37, SD: 2.9	Month 12	N: 104, mean: 25.16, SD: 4.6	Mean change from baseline: -19.3, SD: 20.9 Mean change from baseline placebo p:<0.01	Data from figure 1

* Burning also reported but not abstracted

Evidence Table 19 – KQ2b Supplements Composite Outcomes Categorical TSS

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at time point(s)	Within arm comparison	NOTES
Ziegler, 2011[77]	Arm 2: placebo	TSS Total (COMPOSITE, NOT PAIN)	N: 224, mean: 2.6, SD: 1.8	4 years	N:207,mean:NR,SD:NR	Mean change from baseline:-0.21,SD:2.45	
Ziegler, 2011[77]	Arm 1:ALA	TSS Total (COMPOSITE, NOT PAIN)	N: 230, mean: 2.4, SD: 1.9	4 years	N: 215, mean: NR, SD: NR	Mean change from baseline: -0.22, SD: 2.42 Mean change from baseline1 vs 2 p: NS	
Ziegler, 2006[78]	Arm 1: placebo	TSS Total (COMPOSITE, NOT PAIN)	N: 43, mean: 9.27, SD: 1.56	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -2.92, SD: 3.18 ALA600 vs placebo, p: <0.05	
Ziegler, 2006[78]	Arm 2: ALA600	TSS Total (COMPOSITE, NOT PAIN)	N: 45, mean: 9.44, SD: 1.86	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.85, SD: 3.03 ALA1200 vs placebo, p: <0.05	
Ziegler, 2006[78]	Arm 3: ALA1200	TSS Total (COMPOSITE, NOT PAIN)	N: 47, mean: 9.4, SD: 1.64	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.5, SD: 3.28 ALA1800 vs placebo, p: <0.05	
Ziegler, 2006[78]	Arm 4: ALA1800	TSS Total (COMPOSITE, NOT PAIN)	N: 46, mean: 9.02, SD: 1.61	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.7, SD: 3.54	
Ziegler, 1999[79]	Arm 2: placebo	TSS Total	N: 165, mean: 8.4, SD: 3.2	19 days	N: 165, mean: NR, SD: NR	Median change from baseline: -3, SD: NR ALA vs placebo, p:0.447 Median change from baseline - range reported: -12.3, 8. Post-hoc analysis with AUC - p=0.033	

Evidence Table 19 – KQ2b Supplements Composite Outcomes Categorical TSS (continued)

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at time point(s)	Within arm comparison	NOTES
Ziegler, 1999[79]	Arm 1: ALA	TSS Total	N: 338, mean: NR, SD: NR	19 days	N: 338, mean: NR, SD: NR	Median change from baseline: -3.7, SD: NR Median change from baseline - range reported: -12.6, 5.	Note that in this study, Arm 1 and Arm 2 are used for the initial period, and then this is split into 3 arms for the longer-term study. Here we are reporting the initial period separately
Ziegler, 1999[79]	Arm 1: A-A	TSS Total	N: 165, mean: 8.1, SD: 3	7 months	N: 165, mean: NR, SD: NR	Median change from baseline: -3.98,SD: NR Median change from baseline - range reported: -12.64, 5.66	
Ziegler, 1999[79]	Arm 2 :A-P	TSS Total	N: 173, mean: 8.3, SD: 2.9	7 months	N: 173, mean: NR, SD: NR	Median change from baseline: -3.99, SD: NR Median change from baseline - range reported: -12.31, 5.33	
Ziegler, 1999[79]	Arm 3: P-P	TSS Total	N: 165, mean: 8.4, SD: 3.2	7 months	N: 165, mean: NR, SD: NR	Median change from baseline: -3.98, SD: NR Median change from baseline - range reported: -12.32, 8.32	
Ziegler, 1996[80]	Arm 4: placebo	TSS Total	N: 66, mean: NR, SD: NR	19 days	N: 66, mean: NR, SD: NR	Mean change from baseline: -2.5, SD: 3.2	Data taken from figure 1
Ziegler, 1996[80]	Arm 3: ALA100	TSS Total	N: 66, mean: NR, SD: NR	19 days	N: 66, mean: NR, SD: NR	Mean change from baseline: -3.3, SD: 2.8 P: NS	Data taken from figure 1

Evidence Table 19 – KQ2b Supplements Composite Outcomes Categorical TSS (continued)

Author, year	Arm	Instrument name	Baseline outcome	Time point(s)	Outcome at time point(s)	Within arm comparison	NOTES
Ziegler, 1996[80]	Arm 2: ALA600	TSS Total	N: 63, mean: NR, SD: NR	19 days	N: 63, mean: NR, SD: NR	Mean change from baseline -4.9, SD: 4.1 p: <0.05	Data taken from figure 1
Ziegler, 1996[80]	Arm 1: ALA1200	TSS Total	N: 65, mean: NR, SD: NR	19 days	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.4, SD: 3.7 p:<0.05	Data taken from figure 1
Ruhnau, 1999[82]	Arm 2: placebo	TSS Total-points	N: 11, mean: 8.18, SD: 0.89	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: -1.94, SD: 1.5	
Ruhnau, 1999[82]	Arm 1: TA	TSS Total-points (COMPOSITE)	N: 11, mean: 7.99, SD: 0.97	Day 19	N: 11, mean: NR, SD: NR	Mean change from baseline: -3.75, SD: 1.88 Mean change from baseline placebo p: 0.021	
Ametov, 2003[81] Sydney trial	Arm 1: placebo	TSS -points	N: 60, mean: 8.2, SD: 1.06	3 weeks	N: 58, mean: 6.4, SD: 1.97	Mean change from baseline: -1.83, SD: 1.97	Data taken from figure 2
Ametov, 2003[81]	Arm 2: ALA	TSS-points (COMPOSITE)	N: 60, mean: 8.8, SD: 1.02	3 weeks	N: 60, mean: 3, SD: 1.38	Mean change from baseline: -5.72, SD: 1.53 p: <0.001	

Evidence Table 20 – KQ2b Supplements NSC Severity

**Ziegler, 2006[78]	Arm 1: placebo	NSC(COMPOSITE NOT PAIN) Severity	N: 43, mean: 14.1, SD: 4.3	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -4.9, SD: 4.3
Ziegler, 2006	Arm 2: ALA600	NSC Severity	N: 45, mean: 14.4, SD: 4.4	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -7.4, SD: 4.6 ALA600 vs placebo, p: <0.05
Ziegler, 2006[78]	Arm 3: ALA1200	NSC Severity	N: 47, mean: 14.7, SD: 4.5	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -7.2, SD: 5 ALA1200 vs placebo, p: <0.05
Ziegler, 2006[78]	Arm 4: ALA1800	NSC Severity	N: 46, mean: 13.5, SD: 3.5	5 weeks	N: NR, mean: NR, SD: NR	Mean change from baseline: -7.6, SD: 4.2 ALA1800 vs placebo, p: <0.05

** Study also reported NSC number of symptoms and change score

Evidence Table 21 – KQ2b Supplements Pain Categorical Outcomes

Author, year	Arm	Instrument Name	N for analysis	Time point	Patients with outcomes, n, %	Between arm comparison
Ziegler, 2006[78]	Arm 1: placebo	TSS: >50% reduction	NR	5 weeks	n: NR, %: 26	% difference from baseline: 26
Ziegler, 2006[78]	Arm 2: ALA600	TSS: >50% reduction	NR	5 weeks	n: NR, %: 62	% difference from baseline: 62, ALA600 vs placebo, p: <0.05
Ziegler, 2006[78]	Arm 3: ALA1200	TSS: >50% reduction	NR	5 weeks	n: NR, %: 50	% difference from baseline: 50, ALA1200 vs placebo, p: <0.05
Ziegler, 2006[78]	Arm 4: ALA1800	TSS: >50% reduction	NR	5 weeks	n: NR, %: 56	% difference from baseline:56, ALA1800 vs placebo, p:<0.05
Ziegler, 1996[80]	Arm 4:placebo	TSS: >30% reduction	66	19 days	n: 38, %: 57.6	NR
Ziegler, 1996[80]	Arm 3: ALA100	TSS: >30% reduction	66	19 days	n: 43, %: 65.2	NR
Ziegler, 1996[80]	Arm 2: ALA600	TSS: >30% reduction	63	19 days	n: 52, %: 82.5	ALA600 vs placebo, p: 0.002
Ziegler, 1996[80]	Arm 1: ALA1200	TSS: >30% reduction	65	19 days	n: 46, %: 70.8	NS (Not reported as NS but assume these were)

Evidence Table 22 – KQ2b Supplements Paresthesia's Continuous Outcomes

Author, year	Arm	Instrument Name	Baseline N Mean SD	Time point(s)	N at time point(s)	Within arm comparison	Between arm comparison	Comments
Ziegler, 2006[78]	Arm 1: placebo	TSS Paresthesia	N: 43, mean: 2.21, SD: 0.63	5 weeks	N: NR	Mean change from baseline: -.8, SD: 1.17		Instrument name is TSS, subscale parethesia
	Arm 2: ALA600	TSS Paresthesia	N: 45, mean: 2.32, SD: 0.8	5 weeks	N: NR	Mean change from baseline: -1.16, SD: 1.26	Mean change from baseline: ALA600 vs placebo, p: NS	
	Arm 3: ALA1200	TSS Paresthesia	N: 47, mean: 2.12, SD: 0.8	5 weeks	N: NR	Mean change from baseline: -0.85, SD: 1.21	Mean change from baseline: ALA1200 vs placebo, p: NS	
	Arm 4: ALA1800	TSS Paresthesia	N: 46, mean: 2.17, SD: 0.69	5 weeks	N: NR	Mean change from baseline: -1.12, SD: 1.2	Mean change from baseline: ALA1800 vs placebo, p: NS	
Ziegler, 1996[80]	Arm 4: placebo	TSS Paresthesia	N: 66, mean: 1.98, SD: 1.12	19 days	N: NR	Mean change from baseline: 0.8	Mean change from baseline: NA	Data taken from figure 2
Ziegler, 1996[80]	Arm 3: ALA100	TSS Paresthesia	N: 66, mean: 2.04, SD: 1.3	19 days	N: NR	Mean change from baseline: 1	Mean change from baseline: placebo, p: NS	Data taken from figure 2
Ziegler, 1996[80]	Arm 2: ALA600	TSS Paresthesia	N: 63, mean: 1.93, SD: 1.23	19 days	N: NR	Mean change from baseline: 1.4	Mean change from baseline: ALA600 vs placebo, p: <0.05	Data taken from figure 2
Ziegler, 1996[80]	Arm 1: ALA1200	TSS Paresthesia	N: 65, mean: 2.06, SD: 1.08	19 days	N: NR	Mean change from baseline: 1.2	Mean change from baseline: ALA1200 vs placebo, p: <0.05	Data taken from figure 2
Ametov, 2003[81]	Arm 1: placebo	NSC(LL) Positive Sensation—severity NR	N: 58, mean: 12.9, SD: NR	3 weeks	N: 58	mean change from baseline: -5, SD: NR	Mean change from baseline: NA	
Ametov, 2003[81]	Arm 2: ALA	NSC(LL) Positive Sensation—severity NR	N: 60, mean: 12.2, SD: NR	3 weeks	N: 60	mean change from baseline: -8.3, SD: NR	Mean change from baseline: placebo, p: <0.001	Not totally sure what this is but appears to be paresthesia
Ruhnau, 1999[82]	Arm 2: placebo	TSS paresthesia, points	N: 11, mean: 2, SD: 0.74	Day 19	N: 11	Mean change from baseline: -0.51,SD: 0.98		
Ruhnau, 1999[82]	Arm 1: TA	TSS paresthesia, points	N: 11, mean: 1.91, SD: 0.57	Day 19	N: 11	Mean change from baseline: -0.82, SD: 0.6	Mean change from baseline: placebo, p: 0.517	

Evidence Table 23 – KQ2b Supplements Numbness Continuous

Author, year	Arm	Instrument Name	Baseline N Mean SD	Time point(s)	N at time point(s)	Within arm comparison
Ziegler, 2006[78]	Arm 1: placebo	TSS Numbness	N: 43, mean: 2.74, SD: 0.67	5 weeks	NR	Mean change from baseline: -0.79, SD: 1.09 Mean change from baseline: ALA600 vs placebo, p: NS
	Arm 2: ALA600	TSS Numbness	N: 45, mean: 2.58, SD: 0.67	5 weeks	NR	Mean change from baseline: -0.97, SD: 1.06
	Arm 3: ALA1200	TSS Numbness	N: 47, mean: 2.73, SD: 0.66	5 weeks	NR	Mean change from baseline: -0.99, SD: 1.13 Mean change from baseline: ALA1200 vs placebo, p: NS
	Arm 4: ALA1800	TSS Numbness	N: 46, mean: 2.67, SD: 0.72	5 weeks	NR	Mean change from baseline: -0.98, SD: 1.16 Mean change from baseline: ALA1800 vs placebo, p: NS
Ziegler, 1996[80]	Arm 4: placebo	TSS Numbness	N: 63, mean: 1.89, SD: 1.32	19 days	NR	Mean change from baseline: 0.7, (Data taken from figure 2)
Ziegler, 1996[80]	Arm 3: ALA100	TSS Numbness	N: 63, mean: 1.95, SD: 1.34	19 days	NR	Mean change from baseline: 0.7, p: NS
Ziegler, 1996[80]	Arm 2: ALA600	TSS Numbness	N: 63, mean: 2.17, SD: 1.28	19 days	NR	Mean change from baseline: 1.1, SD: NR ALA600 vs placebo, p: <0.05
Ziegler, 1996[80]	Arm 1: ALA1200	TSS Numbness	N: 65, mean: 2.04, SD: 1.24	19 days	NR	Mean change from baseline: 1.1, SD: NR Mean change from baseline: ALA1200 vs placebo, p: <0.05
Ametov, 2003[81]	Arm 1: placebo	NSC(LL) Negative Sensation—severity	N: 58, mean: 3.5, SD: NR	3 weeks	58	mean change from baseline: -0.7, SD: NR

Evidence Table 23 – KQ2b Supplements Numbness Continuous (continued)

Author, year	Arm	Instrument Name	Baseline N Mean SD	Time point(s)	N at time point(s)	Within arm comparison
Ametov, 2003[81]	Arm 2: ALA	NSC(LL) Negative Sensation—severity	N: 60, mean: 2.7, SD: NR	3 weeks	60	mean change from baseline: -1.2, SD: NR Mean change from baseline: placebo, p: 0.043 Not totally sure what this is but appears to be numbness
Ruhnau, 1999[82]	Arm 2: placebo	TSS numbness-points	N: 11, mean: 2.61, SD: 0.13	Day 19	11	Mean change from baseline: 0, SD: 0
Ruhnau, 1999[82]	Arm 1: TA	TSS numbness - points	N: 11, mean: 2.36, SD: 0.5	Day 19	11	Mean change from baseline: -0.12, SD: 0.92 Mean change from baseline: placebo, p: 0.67

Evidence Table 24 – KQ2b Supplements Adverse Effects

Author, year	Arm	Adverse effect	N for analysis	Time point (s)	Patients with outcomes, n, %	Results
Ametov, 2003[81]	Arm 1: placebo	NR	NR	NR	n: NR, %: NR	NR
Ametov, 2003[81]	Arm 2: ALA	NR	NR	NR	n: NR, %: NR	NR
Ruhnau, 1999[82]	Arm 1: TA	NR	NR	NR	n: NR, %: NR	NR
Ruhnau, 1999[82]	Arm 2: placebo	NR	NR	NR	n: NR, %: NR	Not reported - only adverse events (1 pt had MI)
Ziegler, 1996[80]	Arm 1: ALA1200	Total	86	NR	n: 28, %: 32.6	NR
Ziegler, 1996[80]	Arm 2: ALA600	Total	77	NR	n: 14, %: 18.2	NR
Ziegler, 1996[80]	Arm 3: ALA100	Total	81	NR	n: 11, %: 13.6	NR
Ziegler, 1996[80]	Arm 4: placebo	Total	82	NR	n: 17, %: 20.7	NR
Ziegler, 1996[80]	Arm 1: ALA1200	Headache	86	NR	n: 5, %: NR	NR
Ziegler, 1996[80]	Arm 2: ALA600	Headache	77	NR	n: 6, %: NR	NR
Ziegler, 1996[80]	Arm 3: ALA100	Headache	81	NR	n: 6, %: NR	NR
Ziegler, 1996[80]	Arm 4: placebo	Headache	82	NR	n: 8, %: NR	NR
Ziegler, 1996[80]	Arm 1: ALA1200	Nausea	86	NR	n: 13, %: NR	NR
Ziegler, 1996[80]	Arm 2: ALA600	Nausea	77	NR	n: 2, %: NR	NR
Ziegler, 1996[80]	Arm 3: ALA100	Nausea	81	NR	n: 1, %: NR	NR
Ziegler, 1996[80]	Arm 4: placebo	Nausea	82	NR	n: 1, %: NR	NR
Ziegler, 1996[80]	Arm 1: ALA1200	Vomiting	86	NR	n: 8, %: NR	ALA1200 vs other groups, p: <0.05
Ziegler, 1996[80]	Arm 2: ALA600	Vomiting	77	NR	n: 0, %: NR	NR
Ziegler, 1996[80]	Arm 3: ALA100	Vomiting	81	NR	n: 0, %: NR	NR
Ziegler, 1996[80]	Arm 4: placebo	Vomiting	82	NR	n: 0, %: NR	NR
Ziegler, 1999[79]	Arm 1: ALA	Total	341	19 days	n: 72, %: 21.1	significant difference between groups

Evidence Table 24 – KQ2b Supplements Adverse Effects (continued)

Author, year	Arm	Adverse effect	N for analysis	Time point (s)	Patients with outcomes, n, %	Results
Ziegler, 1999[79]	Arm 2: placebo	Total	168	19 days	n: 41, %: 24.4	significant difference between groups
Ziegler, 1999[79]	Arm 1: A-A	Total	167	7 months	n: 77, %: 46.1	significant difference between groups
Ziegler, 1999[79]	Arm 2: A-P	Total	174	7months	n: 66, %: 37.9	significant difference between groups
Ziegler, 1999[79]	Arm 3: P-P	Total	168	7months	n: 75, %: 44.6	significant difference between groups
Ziegler, 2006[78]	Arm 1: placebo	Nausea	43	NR	n: 0, %: 0	
Ziegler, 2006[78]	Arm 2: ALA600	Nausea	45	NR	n: 6, %: 13	ALA600 vs placebo, p: <0.05
Ziegler, 2006[78]	Arm 3: ALA1200	Nausea	47	NR	n: 10, %: 21	ALA1200 vs placebo, p: <0.05
Ziegler, 2006[78]	Arm 4: ALA1800	Nausea	46	NR	n: 22, %: 48	ALA1800 vs placebo, p: <0.05
Ziegler, 2006[78]	Arm 1: placebo	Overall	43	NR	n: 9, %: 21	
Ziegler, 2006[78]	Arm 2: ALA600	Overall	45	NR	n: 12, %: 27	ALA600 vs placebo, p: 0.53
Ziegler, 2006[78]	Arm 3: ALA1200	Overall	47	NR	n: 20, %: 43	ALA1200 vs placebo, p: 0.03
Ziegler, 2006[78]	Arm 4: ALA1800	Overall	46	NR	n: 25, %: 54	ALA1800 vs placebo, p: 0.001
Ziegler, 2006[78]	Arm 1: placebo	Vertigo	43	NR	n: 0, %: 0	
Ziegler, 2006[78]	Arm 2: ALA600	Vertigo	45	NR	n: 2, %: 4	ALA600 vs placebo, p: NS
Ziegler, 2006[78]	Arm 3: ALA1200	Vertigo	47	NR	n: 2, %: 4	ALA1200 vs placebo, p: NS
Ziegler, 2006[78]	Arm 4: ALA1800	Vertigo	46	NR	n: 5, %: 11	ALA1800 vs placebo, p: 0.056
Ziegler, 2006[78]	Arm 1: placebo	Vomiting	43	NR	n: 0, %: 0	
Ziegler, 2006[78]	Arm 2: ALA600	Vomiting	45	NR	n: 1, %: 2	ALA600 vs placebo, p: NS
Ziegler, 2006[78]	Arm 3: ALA1200	Vomiting	47	NR	n: 2, %: 4	ALA1200 vs placebo, p: NS
Ziegler, 2006[78]	Arm 4: ALA1800	Vomiting	46	NR	n: 12, %: 26	ALA1800 vs placebo, p: <0.05

Evidence Table 25 – KQ2b Supplements Drop Outs

Author, year	Arm	Dropouts due to adverse effects, n , %	Comments
Ziegler, 2011[77]	Arm 2: placebo	n: 1, %: 0.7	
	Arm 1: ALA	n: 2, %: 0.9	Adverse effects not reported - only events by system (eg, cardiovascular) that occurred over course of the study
Ziegler, 2006[78]	Overall	n: 12, %: 6.6	
	Arm 1: placebo	n: 1, %: 2.3	
	Arm 2: ALA600	n: 0, %: 0	
	Arm 3: ALA1200	n: 5, %: 10.6	
	Arm 4: ALA1800	n: 6, %: 13	
Ziegler, 1999[79]	Arm 1: A-A	n: 4, %: 2.7	
	Arm 2: A-P	n: 1, %: 0.6	
	Arm 3: P-P	n: 6, %: 3.6	

Evidence Table 25 – KQ2b Supplements Drop Outs (continued)

Author, year	Arm	Dropouts due to adverse effects, n , %	Comments
Ziegler, 1996[80]	Arm 4: placebo	n: 1, %: 1.5	
	Arm 3: ALA100	n: 1, %: 1.5	
	Arm 2: ALA600	n: 1, %: 1.6	
	Arm 1: ALA1200	n: 5, %: 7.7	
Ametov, 2003[81]	Arm 1: placebo	n: 2, %: 1.6	Very difficult to interpret drop outs and AEs
Ametov, 2003[81]	Arm 2: ALA	n: 0, %: 0	
Ruhnau, 1999[82]	Arm 2: placebo	n: 1, %: 9.1	MI
Ruhnau, 1999[82]	Arm 1: TA	n: 1, %: 9.1	Lack of efficacy
De Grandis, 2002[83]	Arm 2: placebo	n: 2, %: 1.9	Multiple reasons

Evidence Table 25 – KQ2b Supplements Drop Outs (continued)

Author, year	Arm	Dropouts due to adverse effects, n , %	Comments
De Grandis, 2002[83]	Arm 1: LAC	n: 6, %: 6.3	LAC 15, placebo 10 dropouts not due to AEs

Evidence Table 26 – KQ2b Acupuncture Study Characteristics

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Garrow, 2014[84]	Parallel randomized controlled trial Single center: Europe	Government	2008-2010	No

Evidence Table 27 – KQ2b Acupuncture Interventions Characteristics

Author, year	Arm	Time per session Total number of sessions
Garrow, 2014[84]	Arm 1 - Sham	10 weeks 45 min per session, 1 session per week
Garrow, 2014[84]	Arm 2 - Acupuncture	10 weeks 45 min per session, 1 session per week

Evidence Table 28 – KQ2b Acupuncture Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Garrow, 2014[84]	Arm 1 - Sham	10 weeks	(29)	mean: 63, SD: 10.8	NR	NR	NR	NR	10
Garrow, 2014[84]	Arm 2 - Acupuncture	10 weeks	(33)	mean: 68, SD: 11.1	NR	NR	NR	NR	4

Evidence Table 29 – KQ2b Acupuncture Pain Continuous Outcomes

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	at time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Garrow, 2014[84]	Arm 1 - Sham	VAS	N: 21, Mean: 67, SD: 19	10 weeks	N: 21, Mean: 62, SD: 23	Mean change from baseline: -5 (95% CI:-11,1.1)	
Garrow, 2014[84]	Arm 2 - Acupuncture	VAS	N: 24, Mean: 73, SD: 24	10 weeks	N:24, Mean:58, SD:26	Mean change from baseline: -15 (95% CI:-26,-3.5)	Change score: 7 (95% CI:-4, 19), p: NS

Evidence Table 30 – KQ2b Acupuncture Quality of Life

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	at time point(s), N Mean SD	Within arm comparison	Between arm comparison
Garrow, 2014[84]	Arm 1 - Sham	SF-36 physical component score	N: 21, Mean: 32.1, SD: 9.8	10 weeks	N: 21, Mean: 31.5, SD: 10.3	Mean difference from baseline: -0.6 (95% CI:-2.7, 1.5)	Mean difference from baseline: -2.2 (95% CI:-5.2,0.77), Comparator: Sham, p: NS
Garrow, 2014[84]	Arm 2 - Acupuncture	SF-36 physical component score	N: 24, Mean: 31.9, SD: 9.2	10 weeks	N: 24, Mean: 33.6, SD: 8.7	Mean difference from baseline: 1.6 (95% CI:-0.7, 3.9)	Mean difference from baseline: -2.2 (95% CI:-5.2,0.77), Comparator: Sham, p: NS
Garrow, 2014[84]	Arm 1 - Sham	SF-36 bodily pain score	N: 21, Mean: 27.7, SD: 16.9	10 weeks	N: 21, Mean: 33.9, SD: 20.9	Mean change from baseline: 6.3 (95% CI:-4.8, 17.5)	Mean change from baseline: -1.2 (95% CI:-10.8, 8.4), Comparator: Sham, p: NS
Garrow, 2014[84]	Arm 2 - Acupuncture	SF-36 bodily pain score	N: 24, Mean: 37.7, SD: 27.4	10 weeks	N: 24, Mean: 40.2, SD: 20.2	Mean change from baseline: 2.5 (95% CI:-5.8, 10.7)	Mean change from baseline: -1.2 (95% CI:-10.8, 8.4), Comparator: Sham, p: NS

Evidence Table 31 – KQ2b Acupuncture Adverse Events

Author, year	Select Arm	Adverse events	N for analysis	Patients with adverse events, N (%)
Garrow, 2014[84]	Arm 1 - Sham		21	1(4.76)
Garrow, 2014[84]	Arm 2 - Acupuncture		24	2(8.33)

Evidence Table 32 – KQ2b Cognitive Therapy Study Characteristics

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Otis, 2013[85]	Parallel randomized controlled trial Single center: North America	Government	NR	No

Evidence Table 33 – KQ2b Cognitive Therapy Interventions Characteristics

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:
Otis, 2013[85]	Arm 1 - Control (treatment as usual)	Usual treatment therapy determined by participant's primary care provider.
Otis, 2013[85]	Arm 2 - Cognitive behavioral therapy (CBT)	Cognitive behavioral pain management therapy given weekly for 11 sessions

Evidence Table 34 – KQ2b Cognitive Therapy Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
Otis, 2013[85]	Arm 1 - Control (treatment as usual), 8	4 months	0(0)	63.38	NR	NR	NR	NR	0
Otis, 2013[85]	Arm 2 - Cognitive behavioral therapy (CBT), 11	4 months	0(0)	62.50	NR	NR	NR	NR	3

Evidence Table 35 – KQ2b Cognitive Therapy Pain Continuous Outcomes

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Otis, 2013[85]	Arm 1 - Control (treatment as usual)	WHYMPI	N: 8, Mean: 3.8, SD: 0.9	4 months	N: 8, Mean: 3.7, SD: 0.9	NR	
Otis, 2013[85]	Arm 2 - Cognitive behavioral therapy (CBT)	WHYMPI	N: 11, Mean: 3.9, SD: 1.4	4 months	N: 8, Mean: 2.8, SD: 1.3	NR	Mean change from baseline: -0.54, Comparator arm: control, p: <0.05

Evidence Table 36 – KQ2b Electrical Stimulation Study Characteristics

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
Lacigova, 2013[86]	Crossover randomized controlled trial Single center: Europe	Academics	NR-NR	No	
Gossrau, 2011[87]	Parallel randomized controlled trial Single center: Europe	NR	NR-NR	No	
Forst, 2004[88]	Parallel randomized controlled trial NR: Europe	NR	NR-NR	No	
Hamza, 2000[89]	Crossover randomized controlled trial NR: North America	Non-profit	NR-NR	1 week	
Oyibo, 2004[90]	Crossover randomized controlled trial NR: Europe	Industry	NR-NR	4 weeks	
Kumar, 1998[91]	Parallel randomized controlled trial NR: North America	Industry	NR-NR	Yes	Amitryptiline run in
Kumar, 1997[92]	Parallel randomized controlled trial NR: North America	Industry	NR-NR	NR	

Evidence Table 37 – KQ2b Electrical Stimulation Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N	Comments
Lacigova, 2013[86]	Arm 1 – Control - Sham, 32	80 days	11 (NR)	mean: 62, SD: 7.2	NR	NR	NR	5.3 Years	2	
Lacigova, 2013[86]	Arm 2 - Mesodiencephalic moedulation (MDM), 32	80 days	11 (NR)	mean: 62, SD: 7.2	NR	NR	NR	5.3 Years	2	
Gossrau, 2011[87]	Arm 1 - Placebo, 19	8 weeks	NR (NR)	mean: 65.95, SD: 7.05	%mean: 7.02, SD: 0.84	mean: 29.86, SD: 4.09	58.12	NR	0	
Gossrau, 2011[87]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation), 21	8 weeks	NR (NR)	mean: 67.91, SD: 12.13	%mean: 7.04, SD: 0.71	mean: 29.05, SD: 3.64	46.31	NR	1	
Forst, 2004[88]	Arm 1 – Control - Sham, 11	12 weeks	3 (NR)	mean: 59.4, SD: 8.6	%mean: 6.5, SD: 0.7	mean: NR, SD: NR	NR	NR	4	
Forst, 2004[88]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS), 13	12 weeks	6 (0.5)	mean: 57.6, SD: 11.5	%mean: 6.6, SD: 0.9	NR	NR	NR	1	
Hamza, 2000[89]	Overall - , 50	3 weeks	28 (NR)	mean: 55, SD: 9	NR	NR	NR	NR	NR	
Oyibo, 2004[90]	Overall - , 30	6 weeks	7 (NR)	mean: 57.7, SD: 10.7	%mean: 8.3, SD: 1.4	NR	NR	4 Years	16	
Kumar, 1998[91]	Arm 1 – Control - Sham, 9	12 weeks	3 (NR)	mean: 58, SD: 4	NR	mean: 32.4, SD: 2.9	NR	21 Months	NR	Only counted from electrotherapy portion of the study. Participants for electrotherapy session selected from patients with no improvement in the amitriptyline therapy session.

Evidence Table 37 – KQ2b Electrical Stimulation Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N	Comments
Kumar, 1998[91]	Arm 2 - Electrotherapy, 14	12 weeks	10 (NR)	mean: 59, SD: 2	NR	mean: 32.4, SD: 1.8	NR	22 Months	NR	Only counted from electrotherapy portion of the study. Participants for electrotherapy session selected from patients with no improvement in the amitriptyline therapy session.
Kumar, 1997[92]	Arm 1 - Sham, 13	4 weeks	8 (NR)	mean: 59, SD: 3	NR	mean: 30.5, SD: 1.8	NR	22 Months	NR	
Kumar, 1997[92]	Arm 2 - Transcutaneous electrostimulation, 18	4 weeks	11 (NR)	mean: 53, SD: 4	NR	mean: 29.2, SD: 2.9	NR	16 Months	NR	

Evidence Table 38 – KQ2b Electrical Stimulation Interventions Characteristics

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:
Lacigova, 2013[86]	Arm 1 – Control - Sham	NR
Lacigova, 2013[86]	Arm 2 - Mesodiencephalic moedulation (MDM)	Voltage: Rectangular pulse: 230V, Pulse: NR, Current: 4mA-8mA, 10mA max, session: Twice daily treatment first 3 days, then daily for the remaining 10 days. Total 13 days, frequency: 50 Hz
Gossrau, 2011[87]	Arm 1 - Placebo	NA
Gossrau, 2011[87]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation)	Voltage: NR, Pulse: NR, Current: 30-40uA, session: 30 min/ 13 sessions, frequency: 2 Hz
Forst, 2004[88]	Arm 1 - Sham	NA
Forst, 2004[88]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	Voltage: NR, Pulse: NR, Current: 5-70mA, session: 30 min, frequency: 4Hz
Hamza, 2000[89]	Arm 1 - Sham	NA
Hamza, 2000[89]	Arm 2 - Percutaneous Electrical Nerve Stimulation (PENS)	Voltage: Biphasic pulse, Pulse: 0.5ms, Current: 25mA, session: 30 min ,frequency: 15-30 Hz per 3s
Oyibo, 2004[90]	Arm 1 - Sham: wear stocking with electrodes but given insignificant current	Voltage: 5V, Pulse: NR, Current: NR, session: NR, frequency: NR

Evidence Table 38 – KQ2b Electrical Stimulation Interventions Characteristics (continued)

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:
Oyibo, 2004[90]	Arm 2 - Wear silver plated nylon-dacron stocking with electrodes	Voltage: 50V, Pulse: 80-80 pulses, Current: 50uA, session: NR, frequency: NR
Oyibo, 2004[90]	Arm 1 - Sham	
Oyibo, 200[90]	Arm 2 - Stocking electrodes	
Kumar, 1998[91]	Arm 1 - Sham: machine had inactive output terminals	
Kumar, 1998[91]	Arm 2 - Given working electrotherapy H-wave machines	Voltage: ≤35V, Pulse: Biphasic pulse: 4ms, Current: <35mA, session: NR, frequency: 2-70Hz
Kumar, 1997[92]	Arm 1 - Sham: machine had inactive output terminals	
Kumar, 1997[92]	Arm 2 - Transcutaneous electrostimulation: Given working electrotherapy H-wave machines	Voltage: ≤35V, Pulse: Biphasic pulse: 4ms, Current: <35mA, session: 30 min per day, frequency: 2-70Hz

Evidence Table 39 – KQ2b Electrical Stimulation Pain Continuous Outcomes

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Forst, 2004[88]	Arm 1 – Control - Sham	VAS: 0-10 scale	N: 7, Mean: 15.3, SD: 8.5	12 weeks	N: 7, Mean: 15, SD: 11.8		
Forst, 2004[88]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	VAS: 0-10 scale	N: 12, Mean: 19.8, SD: 5	12 weeks	N: 12, Mean: 17.8, SD: 8.8		
Kumar, 1998[91]	Arm 1 – Control - Sham: machine had inactive output terminals	Pain scale (tool NR): 0-5 scale	N: 9, Mean: 2.8, SD: 0.3	12 weeks	N: 9, Mean: 1.9, SD: 0.5	Mean change from baseline: -0.9, SD: 0.3, p: <0.03	
Kumar, 1998[91]	Arm 2 - Given working electrotherapy H-wave machines	Pain scale (tool NR): 0-5 scale	N: 14, Mean: 3.2, SD: 0.2	12 weeks	N: 14, Mean: 1.4, SD: 0.4	Mean change from baseline: -1.8, SD: 0.3, p: <0.01	Mean change from baseline: , Comparator arm: Sham p:<0.03
Kumar, 1997[92]	Arm 1 – Control - Sham	Pain scale (tool NR): 0-5 scale	N: 13, Mean: 2.92, SD: 0.13	4 weeks	N: 13, Mean: 2.38, SD: 0.26	Mean change from baseline: -0.54, SD: 0.21, p: <0.04	% change from baseline: -27, Comparator arm: Sham, SD: 10, p: <0.05
Kumar, 1997[92]	Arm 2 - Transcutaneous electrostimulation	Pain scale (tool NR): 0-5 scale	N: 18, Mean: 3.17, SD: 0.12	4 weeks	N: 18, Mean: 1.44, SD: 0.25	Mean change from baseline: p: <0.01	% change from baseline:- 52, Comparator arm:, SD: 7, p: NR
Hamza, 2000[89]	Arm 1 – Control - Sham	VAS-10 cm	N: 50, Mean: 5.2, SD: 1.6	3 weeks	N: 50, Mean: 4.8, SD: 1.2		Mean change from baseline: , Comparator arm: , p: <0.05
Hamza, 2000[89]	Arm 2 - Percutaneous Electrical Nerve Stimulation (PENS)	VAS-10 cm	N: 50, Mean: 6.2, SD: 1.3	3 weeks	N: 50, Mean: 2.6, SD: 0.9	Mean change from baseline:, p: <0.05	Mean change from baseline: , Comparator arm: Sham, p: <0.05
Lacigova, 2013[86]	Arm 1 – Control - Sham	VAS: 0-10 scale	N: 32, Mean: 4.3, SD: 1.9	30 days	N: 32, Mean: 4.1, SD: 1.8	Mean change from baseline: 0	
Lacigova, 2013[86]	Arm 2 - Mesodiencephalic moedulation (MDM)	VAS: 0-10 scale	N: 32, Mean: 4.4, SD: 1.4	30 days	N: 32, Mean: 4, SD: 2.1	Mean change from baseline: -0.4	Mean change from baseline: , Comparator arm: Sham, p: 0.46

Evidence Table 39 – KQ2b Electrical Stimulation Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Oyibo, 2004[90]	Arm 1 – Control - Sham	VAS-10 cm	N: 14, Mean: 7.1 (95% CI: 5.6-8.7), SD: NR	6 weeks	N: 14, Mean: 3.6 (95% CI: 1.8-6.0), SD: NR	Mean change from baseline: , p: 0.02	Median change from baseline: 49.2
Oyibo, 2004[90]	Arm 2 - Stocking electrodes	VAS-10 cm	N: 14, Mean: 6.2 (95% CI: 3.9-8.4), SD: NR	6 weeks	N: 14, Mean: 3.1 (95% CI: 1.0-5.1), SD: NR	Mean change from baseline: , p: 0.003	Median change from baseline: 40.1, Comparator arm: control, SD: NR, p: 0.7
Gossrau, 2011[87]	Arm 1 - placebo	Neuropathic pain score (NPS)	N: 19, Mean: 43.42, SD: 13.3	4 weeks	N: 19, Mean: 32.74, SD: 17.2	:,	Mean change from baseline:, Comparator arm: , p: >0.18
Gossrau, 2011[87]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation)	Neuropathic pain score (NPS)	N: 21, Mean: 43.18, SD: 12.9	4 weeks	N: 21, Mean: 36.23, SD: 15		Mean change from baseline: , Comparator arm: placebo, p:> 0.18

Evidence Table 40 – KQ2b Electrical Stimulation Pain Categorical Outcomes

Author, year	Arm	N for analysis	Instrument Name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
Gossrau, 2011[87]	Arm 1 - Placebo	19	Neuropathic pain score, >=30% reduction	4 weeks	10	
Gossrau, 2011[87]	Arm 2 - micro-TENS (Microcurrent Transcutaneous Electric Nerve Stimulation)	21	Neuropathic pain score, >=30% reduction	4 weeks	6	% change from baseline, comparator arm: Placebo, p: >.09

Evidence Table 41 – KQ2b Electrical Stimulation Composite Pain Outcomes

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Lacigova, 2013[86]	Arm 1 – Control - Sham	Total symptom score	N: 32, Mean: 6.6, SD: 2.8	30 days	N: 32, Mean: 5.7, SD: 2.9	Mean change from baseline: -0.34	
Lacigova, 2013[86]	Arm 2 - Mesodiencephalic moedulation (MDM)	Total symptom score	N: 32, Mean: 6.9, SD: 2.8	30 days	N: 32, Mean: 5.2, SD: 3	Mean change from baseline: -1.5	Mean change from baseline: , Comparator arm: sham, p: 0.9

Evidence Table 42 – KQ2b Electrical Stimulation Paresthesia's

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison
Forst, 2004[88]	Arm 1 - Control	NTSS-6, prickling sensation	N: 7, Mean: 2.14, SD: 0.73	12 weeks	N: 7, Mean: 1.81, SD: 1.11	Mean change from baseline p: NS
Forst, 2004[88]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	NTSS-6, prickling sensation	N: 12, Mean: 2.14, SD: 0.91	12 weeks	N: 12, Mean: 1.61, SD: 0.97	Mean change from baseline p: NS

Evidence Table 43 – KQ2b Electrical Stimulation Numbness

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison
Forst, 2004[88]	Arm 1 – Control	NTSS-6, prickling sensation	N: 7, Mean: 1.86, SD: 1.47	12 weeks	N: 7, Mean: 1.47, SD: 1.44	Mean change from baseline p: NS
Forst, 2004[88]	Arm 2 - Transcutaneous electrical nerve stimulation (TENS)	NTSS-6, prickling sensation	N: 12, Mean: 2.19, SD: 1.05	12 weeks	N: 12, Mean: 1.86, SD: 1	Mean change from baseline p: NS

Evidence Table 44 – KQ2b Electrical Stimulation Quality of Life

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
Hamza, 2000[89]	Arm 1 – Control - Sham	SF-36, physical component	N: 50, Mean: 31.2, SD: 7.3	3 weeks	N: 50, Mean: 32.4, SD: 7.5	Mean difference from baseline: , p: <0.05	Mean difference from baseline, Comparator arm: , p: <0.05
Hamza, 2000[89]	Arm 2 - Percutaneous Electrical Nerve Stimulation (PENS)	SF-36, physical component	N: 50, Mean: 31.2, SD: 7.3	3 weeks	N: 50, Mean: 36.8, SD: 6.7	Mean difference from baseline: , p: <0.01	Mean difference from baseline, Comparator arm: Sham, p: <0.05
Lacigova, 2013[86]	Arm 1 – Control - Sham	SF-36, physical component	N: 32, Mean: NR, SD: NR	30 days	N: 32, Mean: NR, SD: NR	Mean difference from baseline: -2,	
Lacigova, 2013[86]	Arm 2 - Mesodiencephalic moedulation (MDM)	SF-36, physical component	N: 32, Mean: NR, SD: NR	30 days	N: 32, Mean: NR, SD: NR	Mean difference from baseline: 2.5	Mean difference from baseline, Comparator arm: Sham, p: <0.01

Evidence Table45 – KQ2b Electrical Stimulation Drop Outs

Author, year	Select Arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Oyibo, 2004[90]	Overall	4		Combined with "inconvenient"

Evidence Table 46 – KQ2b Spinal Cord Study Characteristics

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?	Comments
de Vos, 2014[93]	Parallel randomized controlled trial Multiple center: Europe	Industry	2008-2012	Yes	A trial stimulation period of 7 days maximum was allowed to test whether a patient responded positively to SCS
Slangen, 2014[94]	Parallel randomized controlled trial Multiple center: Europe	Industry	2010-2013	Yes	After a 2-week trial stimulation, the spinal cord stimulator (Synergy Versitrel or PrimeAdvanced; Medtronic) was im- planted if the NRS for the intensity of pain during daytime or nighttime for the last 4 days of the trial period was at least 50% lower than the baseline score, or if there was a score of 6 or higher (“much improved” or “very much improved”) on the PGIC scale for pain and sleep

Evidence Table 47 – KQ2b FERMS Study Characteristics

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR	Was run-in period reported?
Bosi, 2013[95]	Parallel randomized controlled trial Multiple center - Europe	Industry	NR	NR
Bosi, 2005[96]	Crossover randomized controlled trial Multiple center - Europe	Industry	2001-2003	NR
Onesti, 2013[97]	Crossover randomized controlled trial Single center - Europe	No funding	NR	NR
Weintraub, 2009[98]	Parallel randomized controlled trial Multiple center – North America	NR	2005 -2007	NR

Evidence Table 48 – KQ2b FERMS Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c , %	BMI	Comments
Bosi, 2013[95]	Arm 1: Placebo, 51	51 weeks	(39)	mean: 61.3, SD: 8.3	mean: 7.6, SD: 1.2	Mean: 28.5, SD: 4.8	
Bosi, 2013[95]	Arm 2: Frequency-modulated electromagnetic neural stimulation (FREMS), 50	51 weeks	(28)	mean: 59 SD: 10.6	mean: 7.9, SD: 1.2	Mean: 28.8, SD: 4.8	
Bosi, 2005[96]	Arm 1: Sequence 1 - placebo 1st, 15	4 months		mean: 63.1, SD: 3.1	mean: 8.3, SD: 0.4		Participant characteristics reported as sequence 1 and sequence 2 (based on intervention randomization in crossover study). Was not reported by overall or individual arms.
Bosi, 2005[96]	Arm 2: Sequence 2 - FREMS 1st, 16	4 months		mean: 59.2, SD: 3.1	mean: 8.2, SD: 0.3		Participant characteristics reported as sequence 1 and sequence 2 (based on intervention randomization in crossover study). Was not reported by overall or individual arms.
Onesti, 2013[97]	Arm 1: Real-sham (Arm1 given real rTMS, then sham rTMS), 11	9 weeks	4	mean: 70.7, Range: NR, SD: 9.5	NR		

Evidence Table 48 – KQ2b FERMS Participants Characteristics (continued)

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c , %	BMI	Comments
Onesti, 2013[97]	Arm 2: Sham-real (Arm2 given sham rTMS, then real rTMS, 12	9 weeks	5	mean: 70.6, SD: 7.9	NR		
Weintraub, 2009[98]	Arm 1: Sham, 118	3 months	(55.8)	mean: 60.6, Range: 21-83, SD: 12.4	mean: 7.4, SD: 1.8		Participant characteristics based on those who completed study
Weintraub, 2009[98]	Arm 2: Pulsed electromagnetic fields (PEMF), 107	3 months	(56.7)	mean: 61.1, Range: 33-87, SD: 10.4	mean: 7.5, SD: 1.8		Participant characteristics based on those who completed study

Evidence Table 49 – KQ2b FERMS Interventions Characteristics

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:	Comments
Bosi, 2013[95]	Arm 1 - Placebo	Voltage: NA, Pulse: NR, Current: NA, Session: 30 min, Frequency: NA	
Bosi, 2013[95]	Arm 2 – Frequency - modulated electromagnetic neural stimulation	Voltage: Max -300V, followed by smaller voltage 0.9-999 ms, Pulse: biphsic asymmetrical pulses, 10-100us, Current: NR, Session: 30 min, Frequency:1-1000 Hz	
Bosi, 2005[96]	Arm 1 - Placebo	Voltage: NA, Pulse: NR, Current: NA, Session: 30 min, Frequency: NA	
Bosi, 2005[96]	Arm 2 – Frequency - modulated electromagnetic neural stimulation	Voltage:0-255 V, Pulse: monophasic negative asymmetrical, 10-40 us , Current: NR, Session: 30 min, Frequency:1-50 Hz	
Onesti, 2013[97]	Arm 1 – Real - sham (Arm1 given real rTMS, then sham rTMS) (rTMS = repetitive transcranial magnetic stimulation)	Voltage: NR, Pulse: NR, Current: NR, Session: 30 consective trains of 50 stimuli at 100% resting motor, separated by intertrain intervals lasting 30 seconds, Frequency: 20 HZ	Sham treatment used a sham coil with negligible electric field.
Onesti, 2013[97]	Arm 2 – Sham - real (Arm2 given sham rTMS, then real rTMS) (rTMS = repetitive transcranial magnetic stimulation)	Voltage: NR, Pulse: NR, Current: NR, Session: 30 consective trains of 50 stimuli at 100% resting motor, separated by intertrain intervals lasting 30 seconds, Frequency: 20 HZ	Sham treatment used a sham coil with negligible electric field.
Weintraub, 2009[98]	Arm 1 - Sham	Voltage: NR, Pulse: NR, Current: NR, Session: Participant self administered 2 hours per day (in 10-30 minute sessions) for 3 months Frequency: NR	voltage = 6 volt DC motor (1800 G magnetic sphere unit)

Evidence Table 49 – KQ2b FERMS Interventions Characteristics (continued)

Author, year	Arm	Voltage Pulse Current Session: duration of session frequency:	Comments
Weintraub, 2009[98]	Arm 2 - Pulsed electromagnetic fields (PEMF)	Voltage: NR, Pulse: NR, Current: NR, Session: Participant self administered 2 hours per day (in 10-30 minute sessions) for 3 months Frequency: NR	voltage = 6 volt DC motor (1800 G magnetic sphere unit)

Evidence Table 50 – KQ2b FERMS Pain Continuous Outcomes

Author, year	Arm	Instrument Name, Outcome unit- IF APPLICABLE	Baseline N Mean SD	Time point (s)	Nat time point(s), N Mean SD	Within arm comparison	Between arm comparison
Bosi, 2013[95]	Arm 1 - placebo	VAS, daytime pain score,0-100 scale	N 51, Mean: 40.9, SD: 24	3 weeks	N 45, Mean: 31.5, SD: 3.5	NR	NR
Bosi, 2013[95]	Arm 2 - FREMS	VAS, daytime pain score,0-100 scale	N 50, Mean: 31.6, SD: 26.3	3 weeks	N 47, Mean: 19.1, SD: 3.2	NR	Comparator arm-placebo, pvalue: <0.001
Bosi, 2013[95]	Arm 1 - placebo	VAS, daytime pain score,0-100 scale	N 51, Mean: 40.9, SD: 24	51 weeks	N 36, Mean: 22.5, SD: 6.9	NR	NA
Bosi, 2013[95]	Arm 2 - FREMS	VAS, daytime pain score,0-100 scale	N 50, Mean: 31.6, SD: 26.3	51 weeks	N 39, Mean: 25.7, SD: 4.1	NR	Comparator arm-placebo, p value: "not detectable" Pain significantly decreased at end of each treatment cycle but then back to baseline by beginning of next; endpoint was 14 weeks after completion of last cycle; note that placebo VAS scores gradually decreased over study period
Bosi, 2004[96]	Arm 1 - placebo	VAS, daytime pain score,	N 31, Mean: 31.2, SD: 3.9	30 weeks	N 31, Mean: 31.9, SD: 4.2		NR
Bosi, 2004[96]	Arm 2 - FREMS	VAS, daytime pain score,	N 31, Mean: 37.1, SD: 5.3	30 weeks	N 31, Mean: 26.2, SD: 3.9	p value: 0.0025	NR Statistics between groups not reported
Onesti, 2013[97]	Arm 1 – Real - sham (Arm1 given real rTMS, then sham rTMS)	VAS,NR, presume 0-100	N 11, Mean: 68.64, SD: 5.5	3 weeks (T2)	N 11, Mean: 47.81, SD: NR	% change from baseline--0.43	Time x group effect -5.46, Comparator arm-NR, pvalue:0.005 Note this is the timex group effect seen at end of the 1st crossover period; also report that values decreased in real perio d significant at <0.01 and in sham did not decrease

Evidence Table 50 – KQ2b FERMS Pain Continuous Outcomes (continued)

Author, year	Arm	Instrument Name, Outcome unit- IF APPLICABLE	Baseline N Mean SD	Time point (s)	Nat time point(s), N Mean SD	Within arm comparison	Between arm comparison
Onesti, 2013[97]	Arm 2 – Sham - real (Arm2 given sham rTMS, then real rTMS	VAS,NR, presume 0-100	N 12, Mean: 63.75, SD: 7.6	3 weeks (T2)	N 12, Mean: 59.33, SD: NR	% change from baseline--0.07	Time x group effect (F) -, Comparator arm-NR, pvalue:
Weintraub, 2009[98]	Arm 1 - Sham	VAS,0-10 scale	N 104, Mean: 5.45, SD: 2.09	3 months	N 104, Mean: 4.13, SD: 2.47	NS	
Weintraub, 2009[98]	Arm 2 - Pulsed electromagnetic fields (PEMF)	VAS,0-10 scale	N 90, Mean: 5.59, SD: 2.26	3 months	N 90, Mean: 4.05, SD: 2.71	NS	Between group difference likely also not significant
Weintraub, 2009[98]	Arm 1 - Sham	NPS 10,0-100 scale	N 104, Mean: 56.53, SD: 18.25	3 months	N 104, Mean: 44.21, SD: 20.85	NS	
Weintraub, 2009[98]	Arm 2 - Pulsed electromagnetic fields (PEMF)	NPS 10,0-100 scale	N 90, Mean: 60.35, SD: 17.83	3 months	N 90, Mean: 45.2, SD: 21.18	NS	Between group difference likely also not significant

Evidence Table 51 – KQ2b FERMS Quality of Life

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
Bosi, 2004[96]	Arm 1 - placebo	SF-36 total	N: 31, Mean: 104.4, SD: 1.5	30 weeks	N: 31, Mean: 105.9, SD: 1.5	NS	NR
Bosi, 2004[96]	Arm 2 - Frequency-modulated electromagnetic neural stimulation (FREMS)	SF-36 total	N: 31, Mean: 103.7, SD: 1.5	30 weeks	N: 31, Mean: 105.6, SD: 1.3	NS	NR

Evidence Table 52 – KQ2b FERMS Drop Outs

Author, year	Arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %
Bosi, 2013[95]	Arm 1 - placebo	0	NR
Bosi, 2013[95]	Arm 2 - FREMS	0	NR
Bosi, 2004[96]	Arm 1 - placebo	0	
Bosi, 2004[96]	Arm 2 - FREMS	0	
Weintraub, 2009[98]	Arm 1 - Sham	2	NR
Weintraub, 2009[98]	Arm 2 - Pulsed electromagnetic fields (PEMF)	2	NR

Evidence Table 53 – KQ2b Surgical Decompression Study Characteristics

Author, year	Study Design Study site	Funding source	Recruitment Start YEAR - End YEAR
van Maurik, 2015[99] and van Maurik, 2014[100] Lower Extremity Nerve Entrapment Study	Parallel randomized controlled trial Single center: Europe	Non-profit	2010-2013

Evidence Table 54 – KQ2b Surgical Decompression Interventions Characteristics

Author, year	Arm	Comments
van Maurik, 2015[99] and van Maurik, 2014[100]	Arm 1 - Control (usual care)	Randomization of limbs. Control limb did not undergo surgical decompression
van Maurik, 2015[99] and van Maurik, 2014[100]	Arm 2 - Surgical decompression	Randomization of limbs. Decompression of the lower extremity nerves in one limb, i.e. of the tibial nerve at the ankle site, the common peroneal, deep peroneal and superficial peroneal nerve,

Evidence Table 55 – KQ2b Surgical Decompression Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Number of withdrawals and/or losses to follow-up: N
van Maurik, 2015[99] and van Maurik, 2014[100]	Overall, 42	1 year	14 (35)	mean: 61.7, SD: 10.2	NR	Mean: 29 SD: 4.2	4

Evidence Table 56 – KQ2b Surgical Decompression Pain Continuous Outcome

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Comments
van Maurik, 2015[99] and van Maurik, 2014[100]	Arm 1 - Control	Pain, Visual Analogue Scale	N: 38, Mean: 6.1,	12 months	N: 38, Mean: 5.3	p: NS	42.5% had clinically important difference change of >2.9 on VAS
van Maurik, 2015[99] and van Maurik, 2014[100]	Arm 2 - Intervention	Pain, Visual Analogue Scale	N: 38, Mean: 6.1,	12 months	N: 38, Mean: 3.5	p: <0.001	

Evidence Table 57 – KQ2b Surgical Decompression Quality of Life

Author, year	Arm	Instrument	Baseline N Mean	Time point(s)	At time point(s) N Mean	Comment
van Maurik, 2015[99]	Arm 1 - Control	SF-36-Physical Functioning	N: 38, Mean: 56.4	12 months	N: 8, Mean: 55	QOL scores are same for both arms as these are the same people
van Maurik, 2015[99]	Arm 2 - Intervention	SF-36-Physical Functioning	N: 38, Mean: 56.4	12 months	N: 8, Mean: 55	
van Maurik, 2015[99]	Arm 1 - Control	SF-36-Role-physical	N: 38, Mean: 40.6	12 months	N: 8, Mean: 35.1	
van Maurik, 2015[99]	Arm 2 - Intervention	SF-36-Role-physical	N: 38, Mean: 40.6	12 months	N: 38, Mean: 35.1	
van Maurik, 2015[99]	Arm 1 - Control	SF-36-Bodily pain	N: 38, Mean: 46.4	12 months	N: 38, Mean:5 0.5	
van Maurik, 2015[99]	Arm 2 - Intervention	SF-36-Bodily pain	N: 38, Mean: 46.4	12 months	N: 38, Mean: 50.5	
van Maurik, 2015[99]	Arm 1 - Control	SF-36-Physical composite score	N: 38, Mean: 36.5	12 months	N: 38, Mean: 36.1	
van Maurik, 2015[99]	Arm 2 - Intervention	SF-36-Physical composite score	N: 38, Mean: 36.5	12 months	N: 38, , Mean: 36.1	
van Maurik, 2015[99]	Arm 1 - Control	EQ-5D index score	N: 38, Mean: 0.6	12 months	N: 38, Mean: 0.62	
van Maurik, 2015[99]	Arm 2 - Intervention	EQ-5D index score	N: 38, Mean: 0.6	12 months	N: 38, Mean: 0.62	

Evidence Table 58 – KQ2b Spinal Cord Interventions Characteristics

Author, Year	Arm	Voltage Pulse Current Session: duration of session frequency:	Comments
de Vos, 2014[93]	Arm 1 - Control (No SCS)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.
de Vos, 2014[93]	Arm 2 - Spinal cord stimulation (SCS)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.
Slangen, 2014[94]	Arm 1 - Control-Best medical treatment (BMT)(Control)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	NR	Details on SCS intervention not reported. Only on placement of electrodes, but nothing on frequency, voltage, duration etc.

Evidence Table 59 – KQ2b Spinal Cord Participants Characteristics

Author, year	Arm, N at enrollment	Actual length of follow-up-MEAN unit for follow-up	Women, n (%)	Age, years:	HbA1c	BMI	Duration of pain	Duration of neuropathic symptoms	Number of withdrawals and/or losses to follow-up: N
de Vos, 2014[93]	Arm 1 - Control, 20	6 months	7 (NR)	mean: 61, SD: 12	NR	NR	7 Years	NR	2
de Vos, 2014[93]	Arm 2 - Spinal cord stimulation (SCS), 40	6 months	15 (NR)	mean: 58, SD: 11	NR	NR	7 Years	NR	4
Slangen, 2014[94]	Arm 1 – Control - Best medical treatment (BMT)(Control),14	6 months	5 (36)	mean: 56.5, SD: 8	%mean: 8.4, SD: 2.7	mean: 30.3, SD: 5.4	4.9 Years	NR	0
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS),22	6 months	7 (32)	mean: 57.1, SD: 12.4	%mean: 8.3, SD: 2	mean: 29, SD: 4.3	6 Years	NR	3

Evidence Table 60 – KQ2b Spinal Cord Pain Continuous Outcomes

Author, year	Arm	Instrument Name	Baseline N, Mean, SD	Time point(s)	At time point(s), N Mean SD:	Within arm comparison	Between arm comparison
de Vos, 2014[93]	Arm 1 – Control - Control	VAS: 0-100 scale	N: 20, Mean: 67, SD: 18	3 months	N: 20, Mean: 70.6, SD: 14.2	NR	
de Vos, 2014[93]	Arm 2 - Spinal cord stimulation (SCS)	VAS: 0-100 scale	N: 40, Mean: 73, SD: 16	3 months	N: 40, Mean: 28.9, SD: 57.8	NR	
de Vos, 2014[93]	Arm 1 – Control - Control	VAS: 0-100 scale	N: 20, Mean: 67, SD: 18	6 months	N: 20, Mean: 67, SD: 21	Mean change from baseline: 0, SD: 20,p: NS	
de Vos, 2014[93]	Arm 2 - Spinal cord stimulation (SCS)	VAS: 0-100 scale	N: 40, Mean: 73, SD: 16	6 months	N: 40, Mean: 31, SD: 28	Mean change from baseline: 42, SD: 31, p: <0.001	Mean change from baseline: , Comparator arm: placebo, p: <0.001
Slangen, 2014[94]	Arm 1 - Control- Best medical treatment (BMT)(Control)	Modified Brief Pain Inventory, Pain Severity Index-	N: 14, Mean: 6.3, SD: 1.8	6 months	N: 14, Mean: 6.5, SD: 2.1		
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	Modified Brief Pain Inventory, Pain Severity Index-	N: 22, Mean: 7.1, SD: 1.5	6 months	N: 19, Mean: 4, SD: 2.8		Mean change from baseline: , Comparator arm: BMT, p: <0.001
Slangen, 2014[94]	Arm 1 – Control - Best medical treatment (BMT)(Control)	Neuropathic Pain Scale (NPS), intensity-	N: 14, Mean: 7.6, SD: 1.5	6 months	N: 14, Mean: 7.3, SD: 2		
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	Neuropathic Pain Scale (NPS), intensity-	N: 22, Mean: 8.2, SD: 1.5	6 months	N: 19, Mean: 4.3, SD: 3		Mean change from baseline: , Comparator arm: BMT, p: <0.001

Evidence Table 61 – KQ2b Spinal Cord Pain Categorical Outcomes

Author, year	Arm	N for analysis	Instrument Name	Time point	n (%) of PATIENTS with outcomes	Between arm comparison
de Vos, 2014[93]	Arm 1 - Control	20	VAS, >50% pain reduction	6 months	1 (5)	
de Vos, 2014[93]	Arm 2 - Spinal cord stimulation (SCS)	40	VAS, >50% pain reduction	6 month	25 (60)	% change from baseline, comparator arm: control, p: <0.001
Slangen, 2014[94]	Arm 1 – Control - Best medical treatment (BMT)(Control)	14	Numeric rating scale (NRS), ≥50% reduction day	6 months	0 (0)	
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	19	Numeric rating scale (NRS), ≥50% reduction day	6 months	9 (41)	% change from baseline, comparator arm: BMT, p: <0.001

Evidence Table 62 – KQ2b Spinal Cord Quality of Life

Author, year	Arm	Instrument	Baseline N, Mean SD	Time point(s)	At time point(s), N Mean SD	Within arm comparison	Between arm comparison
de Vos, 2014[93]	Arm 1 - Control-Control	MPQ QOL score	N: 20, Mean: 15, SD: 6	6 months	N: 20, Mean: 14, SD: 6	Mean difference from baseline: , p: NS	
de Vos, 2014[93]	Arm 2 - Spinal cord stimulation (SCS)	MPQ QOL score	N: 40, Mean: 16, SD: 5	6 months	N: 40, Mean: 8, SD: 7	Mean difference from baseline:, p: <0.001	Mean difference from baseline, Comparator arm: control, p: <0.001
de Vos, 2014[93]	Arm 1 – Control - Control	EQ-5D	N: 20, Mean: 46, SD: 17	6 months	N: 20, Mean: 41, SD: 20	Mean difference from baseline: , p: NS	
de Vos, 2014[93]	Arm 2 - Spinal cord stimulation (SCS)	EQ-5D	N: 40, Mean: 50, SD: 19	6 months	N: 40, Mean: 61, SD: 22	Mean difference from baseline: , p: <0.05	Mean difference from baseline, Comparator arm: control, p: <0.01
Slangen, 2014[94]	Arm 1 – Control - Best medical treatment (BMT)(Control)	EQ-5D, current health0-100	N: 14, Mean: 54.6, SD: 16.7	6 months	N: 14, Mean: 56.5, SD: 14.2		
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	EQ-5D, current health0-100	N: 22, Mean: 53.9, SD: 18.5	6 months	N: 19, Mean: 57.6, SD: 24.3		Mean difference from baseline, Comparator arm: BMT, p: NS
Slangen, 2014[94]	Arm 1 – Control - Best medical treatment (BMT)(Control)	SF-36, physical component	N: 14, Mean: 31.7, SD: 7.9	6 months	N: 14, Mean: 30.5, SD: 7.4		
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)	SF-36, physical component	N: 22, Mean: 27.9, SD: 7.5	6 months	N: 19, Mean: 32.3, SD: 10.5		Mean difference from baseline, Comparator arm: BMT, p: NS

Evidence Table 63 – KQ2b Spinal Cord Drop Outs

Author, year	Select Arm	Dropouts due to adverse effects, N	Dropouts due to adverse effects, %	Comments
Slangen, 2014[94]	Arm 1 - Best medical treatment (BMT)(Control)		0	
Slangen, 2014[94]	Arm 2 - Best medical treatment + Spinal Cord Stimulation (SCS)		1	Infection; also one patient died from dural puncture

Evidence Table 64 – KQ2A Risk of Bias – RCTs

RefID	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome: outcome assessor blinded by critical outcomes (xxx)	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Harati, 1998[10]	Low	Unclear	Low	Unclear		Unclear	Unclear	Unclear	Unclear
Ziegler, 2015[28]	Low	Low	Low	Unclear		Unclear	Unclear	Unclear	Unclear
Gao, 2015[7]	Unclear	Unclear	Unclear	Unclear		Low	Low	Unclear	Unclear
Karmakar, 2014[12]	Low	Unclear	Low	Unclear		Low	Unclear	Unclear	Unclear
Allen, 2014[1]	Low	Unclear	Unclear	Unclear		Unclear	Low	Unclear	Unclear
Ghasemi, 2014[8]	Unclear	Unclear	Unclear	Low		Unclear	Unclear	Unclear	Unclear
Niesters, 2014[15]	Low	Low	Low	Low		Unclear	Unclear	Unclear	Unclear
Tesfaye, 2013[23]	Low	Low	Low	Unclear		High	Unclear	Unclear	High
Rauck, 2013[18]	Low	Unclear	Low	Unclear		Low	Unclear	Unclear	Unclear
Toth, 2012[24]	Low	Low	Low	Low		Low	Unclear	Unclear	Unclear
Campbell, 2012[4]	Unclear	Unclear	Unclear	Unclear		Unclear	Unclear	Unclear	Unclear
Vinik, 2014[26]	Low	Unclear	Unclear	Unclear		Low	Unclear	Unclear	Unclear
Arezzo, 2008[2]	Low	Low	Low	Unclear		Low	Unclear	Unclear	Unclear
Freeman, 2007[6]	Low	Unclear	Unclear	Low		Unclear	Unclear	Unclear	Unclear
Atli, 2005[3]	Unclear	Unclear	Unclear	Unclear		Unclear	Unclear	Unclear	Unclear
Chad, 1990[5]	Unclear	Unclear	Unclear	Unclear		Unclear	Unclear	Low	Unclear
Hanna, 2008[9]	Unclear	Low	Low	Low		Low	Low	Low	Low
Jiang, 2011[11]	Unclear	Unclear	Unclear	Unclear		Low	Unclear	Unclear	Unclear
Kulkantrakorn, 2013[13]	Low	Low	Low	Unclear		Low	Unclear	Unclear	Low
Max, 1987[14]	Unclear	Unclear	Low	Low		Low	Low	Low	Unclear
Raskin, 2014[17]	Low	Unclear	Unclear	Unclear		Low	Low	Unclear	Unclear
Rowbotham, 2012[19]	Unclear	Unclear	Unclear	Unclear		Low	Low	Low	Unclear
Sandercock, 2012[20]	Unclear	Unclear	Unclear	Unclear		Unclear	Unclear	Unclear	Unclear
Shaibani, 2012[22]	High	Unclear	Low	Unclear		Low	Low	Unclear	Unclear
Yuan, 2009[27]	Unclear	Unclear	Unclear	Low		Low	Unclear	Unclear	Unclear

Evidence Table 65 – KQ2B Risk of Bias – RCTs

RefID	Random sequence generation	Allocation concealment	Blinding of personnel	Blinding of outcome assessors	Assessing blinding by outcome: outcome assessor blinded by critical outcomes (xxx)	Incomplete outcome data	Selective reporting of outcomes	Other sources of bias	Overall quality
Electrical Stimulation									
Lacigova, 2013[86]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	Unclear
Gossrau, 2011[87]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Forst, 2004[88]	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Hamza, 2000[89]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Oyibo, 2004[90]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Kumar, 1998[91]	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Kumar, 1997[92]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
Spinal Cord									
de Vos[93]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Slangen, 2014[94]	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low
FREMS									
Bosi, 2013[95]	Low	Low	Low	Low	Unclear	Low	Unclear	Low	Low
Bosi, 2005[96]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low
Onesti, 2013[97]	Low	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low
Weintraub, 2009[98]	Unclear	Low	Low	Low	Unclear	Low	Unclear	Low	Low
Supplements									
Ziegler, 1996[80]	Low	Unclear	Low	Unclear	Unclear	High	Low	Unclear	Unclear
Ziegler, 1999[79]	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Ruhnau, 1999[82]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	High	Low	Unclear
Ametov, 2003[81]	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Low	Unclear
Ziegler, 2006[78]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Ziegler, 2011[77]	Low	Low	Unclear	Unclear	Unclear	High	Unclear	Low	High
De Grandis, 2002[83]	Low	Low	Unclear	Unclear	Unclear	High	Low	Low	Unclear
Acupuncture									
Garrow, 2014[84]	Low	Low	Low	Unclear	Unclear	Unclear	Low	Low	Low
Cognitive									
Otis, 2013[85]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear
Surgical Decompression									
Macare van Maurik, 2015[99]	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

Table 66. KQ1a - Pharmacologic treatment for the prevention of diabetic foot ulcers and lower extremity amputations: Strength of evidence domains

Key Outcomes Strength of evidence	Study Design: No. Studies (N)[a]	Study limitation	Directness	Consistency	Precision	Reporting Bias	Other issues	Key Findings
Diabetic foot ulcers								
Intensive vs. standard glycemic control Overall strength of evidence: Low	2 RCTs in people with Type 1 DM n=1,329 2 RCTs in people with Type 2 DM n=1,326	Moderate[a]	Direct	Consistent	Imprecise	None	Few event rates.	Two RCTs reported that intensive glycemic control prevented more foot ulcers (OR 0.25 95%CI, 0.06 to 1.01 and 0.36, 95% CI 0.12 to 1.15), but the number of events was low despite long follow-up periods, and differences were not statistically significant.
Monotherapy or combination medications Overall strength of evidence: Insufficient	0 RCTs in people with Type 1 diabetes n=0 1 cohort study in people with Type 2 diabetes n=23,395	High[b]	Direct	Inconsistent	Imprecise	None	None	Not enough studies to draw any conclusions.

Table 66. KQ1a - Pharmacologic treatment for the prevention of diabetic foot ulcers and lower extremity amputations: Strength of evidence domains (continued)

Key Outcomes Strength of evidence	Study Design: No. Studies (N)[a]	Study limitation	Directness	Consistency	Precision	Reporting Bias	Other issues	Key Findings
Lower extremity amputations								
Intensive vs. standard glycemic control Overall strength of evidence:Moderate	1 RCT in people with Type 1 diabetes n=1,257 6 RCTs in people with Type 2 diabetes n=9,441	Low	Direct	Consistent	Imprecise	None	None	One RCT did not show a statistically significant differences between lower extremity amputations in the intensive vs. standard glycemic control arms in people with Type 1 diabetes. Six RCTs with reported a decreased risk of lower extremity amputations in the intensive vs. standard glycemic control arms (pooled OR 0.61, 95%CI 0.41 to 0.92) in people with Type 2 diabetes
Monotherapy or combination medications Overall strength of evidence: insufficient	0 RCTs in people with Type 1 diabetes 1 RCT in people with Type 2 diabetes n=5,238	Low	Direct	Inconsistent	Imprecise	None	None	Not enough studies to draw any conclusions.

a. Moderate because of studies' lack of clarity about how outcomes assessed and ascertained for foot ulcers
b. High limitations because of study design as single observational study. Non-randomized design contributes significant risk of bias and limitations.

CI=Confidence Interval; DM=Diabetes Mellitus; N=sample size; OR=odds ratio; RCT=Randomized Controlled Trial

Table 67. KQ1b – Non-Pharmacologic treatment for the prevention of diabetic foot ulcers and lower extremity amputations: Strength of evidence domains

Key Outcomes Strength of evidence	Study Design: No. Studies (N)[a]	Study limitation	Directness	Consistency	Precision	Reporting Bias	Other issues	Key Findings
Diabetic foot ulcers								
Integrated foot care Overall strength of evidence: Low	3 RCTs and 1 cohort (n=350)	Medium	Direct	Consistent	Precise	None	None	The Netten review reported a of reduction in foot ulcer incidence or recurrence using integrated care. The reduction was ~20% across studies
Self-management: Self-monitoring of foot temperature Overall strength of evidence: moderate	4 RCTs (n=943)	low	Direct	Consistent	Precise	None	None	Reduction in incident foot ulcers in patients using self-monitoring of foot temperature compared with standard of care.
Self-management: Topical treatment on foot Overall strength of evidence: low	1 RCT and 1 cohort	high	Direct	Inconsistent	Imprecise	None	None	Inconsistent findings in 2 studies
Patient Education Overall strength of evidence: low	3 RCTs and 1 cohort (n=16943)	Medium	Direct	Inconsistent	Imprecise	None	None	Findings were inconsistent regarding the effect of a single session of patient education on the incidence of foot ulcers

Table 67. KQ1b – Non-Pharmacologic treatment for the prevention of diabetic foot ulcers and lower extremity amputations: Strength of evidence domains (continued)

Key Outcomes Strength of evidence	Study Design: No. Studies (N)[a]	Study limitation	Directness	Consistency	Precision	Reporting Bias	Other issues	Key Findings
Diabetic foot ulcers (continued)								
Therapeutic footwear Overall SOE: moderate	7 RCTs and 3 cohorts	Medium	Direct	Inconsistent	Imprecise	None	None	Specific modalities of therapeutic footwear can be effective in the prevention of a recurrent plantar foot ulcer compared with more standard-of-care therapeutic footwear. The risk reduction ranged from 4% to 45% across studies.
Surgical Intervention Overall: low	3 RCTs and 6 cohort	high	Direct	Inconsistent	Imprecise	None	None	Achilles tendon lengthening, single or pan-metatarsal head resection, and metatarsophalangeal joint arthroplasty) appear to reduce ulcer recurrence risk ranged 24% to 43% in some patients with initially non-healing ulcers when compared with non-surgical treatment

Table 67. KQ1b – Non-Pharmacologic treatment for the prevention of diabetic foot ulcers and lower extremity amputations: Strength of evidence domains (continued)

Key Outcomes Strength of evidence	Study Design: No. Studies (N)[a]	Study limitation	Directness	Consistency	Precision	Reporting Bias	Other issues	Key Findings
Lower extremity amputations								
Integrated Foot Care Overall strength of evidence: Low	2 RCTs and 2 cohorts (n=27840)	medium	Direct	inconsistent	Imprecise	None	None	Findings were inconsistent regarding the effect of integrated foot care on the amputation
Self-management Overall strength of evidence: insufficient	1 RCT (n=85)	high	Direct	unknown	Imprecise	None	None	Not enough studies to draw any conclusions.
Patient Education: Overall strength of evidence: low	2 RCTs and 1 cohort (n=16812)	medium	Direct	Consistent	Precise	None	None	No difference in amputation occurrence.
Therapeutic Footwear Overall strength of evidence: low	1 RCT and 1 cohort (n=46)	high	Direct	Consistent	Precise	Non	None	no difference in amputation in patients accepted a prescription of orthopedic footwear and wore the footwear while being active, vs. patients who did not ask for such a prescription
Surgical Intervention Overall strength of evidence: low	2 cohorts (n=168)	high	Direct	inconsistent	imprecise	None	None	Inconsistent findings from a limited number of studies

CI=Confidence Interval; DM=Diabetes Mellitus; N=sample size; OR=odds ratio; RCT=Randomized Controlled Trial

Table 68. KQ1b - Balance training intervention on outcomes of falls, foot ulcer and quality of life: Strength of evidence domains

Key Outcomes Strength of evidence	Study Design: No. Studies (N)[a]	Study limitation	Directness	Consistency	Precision	Reporting Bias	Other issues	Key Findings	SOE
Falls									
Balance training vs. control*	1 RCT (reported in 2 studies) N= 79	Low	Direct	Unknown	Imprecise	None	None	One RCT reported no statistically significant difference in falls between the balance training group and the control group (2.06 versus 2.02 falls/1000 person-days, respectively) and differences were not statistically significant.	Insufficient
Exercise training vs. control*	1 RCT (reported in 2 studies) N= 79	Low	Direct	Unknown	Imprecise	None	None	One RCT reported no statistically significant difference in falls between the balance training group and the control group (2.06 versus 2.02 falls/1000 person-days, respectively) and differences were not statistically significant.	Insufficient
Foot ulcer									
Exercise training vs. control*	1 RCTs (reported in 2 studies) 1 prospective cohort study (n=469)	Moderate	Direct	Consistent	Imprecise	None	None	Rate Ratio of all foot ulcers is 1.24; 95% CI, 0.70 to 2.19 reported in 1 RCT Another prospective study showed incidence of re-ulceration 16.5% in the least active group, 13.4% in the moderately active group, and 13% in the most active group	Insufficient
Physical therapy vs. control	1 RCT (n=29)	Low	Direct	Unknown	Imprecise	None	None	Reported number of ulcers in weight bearing versus non-weight bearing groups: 1 vs 3	Insufficient
Quality of life									
Balance training vs. control	1 RCT N= 39	Low	Direct	Unknown	Imprecise	None	None	The difference between the study arms in the mean difference from baseline was 0.29, in the direction favoring the intervention group, not statistically significantly different	Insufficient
Exercise training vs. control*	1 RCT (n=87)	Low	Direct	Unknown	Imprecise	None	None	% change from baseline for intervention and control was 28.40 in the direction favoring the intervention group, p<0.001).	Insufficient

High limitations because of study design as single observational study. Non-randomized design contributes significant risk of bias and limitations.
*Same study included under both interventions

Table 69. KQ2a -Strength of evidence for the key outcomes

Key Outcomes Strength of Evidence	Study Design: Number of Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Anticonvulsants vs. Placebo								
Pain Low	RCT: 27 (28 comparisons)	Unclear	Direct	Inconsistent	Precise	Suspected	Studies were short-term; newest studies did not find evidence of effectiveness	Anticonvulsants reduced pain moderately more than placebo in older studies, but newer studies were inconsistent (did not find evidence of effectiveness), and risk of bias was unclear
Quality of Life Low	RCT: 14 (15 comparisons)	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected	Studies were short-term	Results for quality of life were inconsistent
Serotonin-noradrenaline reuptake inhibitors vs. Placebo								
Pain Moderate	RCT: 9	Unclear	Direct	Consistent	Precise	Unsuspected	Studies were short-term	SNRIs reduced pain more than placebo
Quality of Life Low	RCT: 6	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected	Studies were short-term	Results for quality of life were inconsistent
Tricyclic antidepressants vs. Placebo								
Pain Low	RCT: 6	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Studies were short-term	
Capsaicin vs. Placebo								
Pain Low	RCT: 4	Unclear	Direct	Consistent	Imprecise	Unsuspected	Studies were short-term	Capsaicin reduced pain more than placebo with a large effect size, but results were imprecise and studies had unclear risk of bias

Table 69. KQ2a -Strength of evidence for the key outcomes (continued)

Key Outcomes Strength of Evidence	Study Design: Number of Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Atypical Opioids vs. Placebo								
Pain Moderate	RCT: 6	Unclear	Direct	Consistent	Precise	Unsuspected	Studies were short-term	Atypical opioids reduced pain more than placebo
Quality of Life Low	RCT: 4	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected	Studies were short-term	Results for quality of life were inconsistent
Opioids vs. Placebo								
Pain Low	RCT: 4	Unclear	Direct	Consistent	Imprecise	Unsuspected	Studies were short-term	Opioids did not reduce pain more than placebo
Clonidine vs. Placebo								
Pain Low	RCT: 3	Unclear	Direct	Consistent	Imprecise	Unsuspected	Studies were short-term	Clonidine did not reduce pain more than placebo
Botulinum toxin vs. Placebo								
Pain Moderate	RCT: 2	Unclear	Direct	Consistent	Precise	Unsuspected	Studies were short-term	Botulinum toxin reduced pain more than placebo
Dextromethorphan vs. Placebo								
Pain Low	RCT: 3	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Studies were short-term	Dextromethorphan did not reduce pain more than placebo
Mexiletine vs. Placebo								
Pain Low	RCT: 5	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Studies were short-term	Mexiletine did not reduce pain more than placebo
Serotonin Norephinephrine Reuptake Inhibitors vs. Anticonvulsants								
Pain Moderate	RCT: 3	Unclear	Direct	Consistent	Precise	Unsuspected	Studies were short-term	SNRIs reduced pain more than anticonvulsants
Tricyclics vs. Anticonvulsants								
Pain Low	RCT: 3	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Studies were short-term	The confidence interval for the effect size for TCAs compared to anticonvulsants crossed zero

SNRI=serotonin-norepinephrine reuptake inhibitor; RCT=randomized controlled trial; TCA=tricyclic antidepressants

Table 69. KQ2a -Strength of evidence for the key outcomes (continued)

For pain, evidence was insufficient for nabilone given only one study. For quality of life, evidence was insufficient for opioids (oxycodone), nabilone, dextromethorphan or botulinum toxin compared to placebo, and for anticonvulsants compared with tricyclics. Where results are not reported above for quality of life, there were no studies that evaluated this outcome for the drug class or specific drug compared with placebo (e.g., tricyclic antidepressants).

Table 70. KQ2a –Additional strength of evidence for the key outcomes for individual drugs within drug classes

Key Outcomes Strength of Evidence	Study Design: Number of Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Gabapentin vs. Placebo (anticonvulsant)								
Pain Low	RCT: 8	Unclear	Direct	Inconsistent	Precise	Suspected	Studies were short-term; newest studies did not find evidence of effectiveness	Gabapentin did not improve pain more than placebo
Quality of Life Low	RCT: 3	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected	Studies were short-term	Anticonvulsants reduced pain moderately more than placebo in older studies, but newer studies were inconsistent (did not find evidence of effectiveness), and risk of bias was unclear
Pregabalin vs Placebo (anticonvulsant)								
Pain Low	RCT: 9	Unclear	Direct	Inconsistent	Precise	Suspected	Studies were short-term; newest studies did not find evidence of effectiveness	Pregabalin did not improve pain more than placebo
Quality of Life Low	RCT: 7	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected	Studies were short-term; newest studies did not find evidence of effectiveness	Pregabalin reduced pain moderately more than placebo in older studies, but newer studies were inconsistent (did not find evidence of effectiveness), and risk of bias was unclear

Table 70. KQ2a –Additional strength of evidence for the key outcomes for individual drugs within drug classes (continued)

Key Outcomes Strength of Evidence	Study Design: Number of Studies (N)	Study Limitation	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding
Duloxetine (serotonin-noradrenaline reuptake inhibitor) vs. Placebo								
Pain Moderate	RCT: 7	Unclear	Direct	Consistent	Precise	Unsuspected	Studies were short-term	Duloxetine reduced pain more than placebo, but studies were short-term
Quality of Life Low	RCT: 3	Unclear	Direct	Inconsistent	Could not be evaluated	Unsuspected	Studies were short-term	Results for quality of life were inconsistent
Venlafaxine (serotonin-noradrenaline reuptake inhibitor) vs. Placebo								
Pain Moderate	RCT: 2	Unclear	Direct	Consistent	Precise	Unsuspected	Studies were short-term	Venlafaxine reduced pain more than placebo, but studies were short-term
Dextromethorphan vs. Placebo								
Pain Low	RCT: 3	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Studies were short-term	Dextromethorphan did not reduce pain more than placebo
Mexiletine vs. Placebo								
Pain Low	RCT: 5	Unclear	Direct	Inconsistent	Imprecise	Unsuspected	Studies were short-term	Mexiletine did not reduce pain more than placebo
Botulinum toxin vs. Placebo								
Pain Moderate	RCT: 2	Unclear	Direct	Consistent	Precise	Unsuspected	Studies were short-term	Botulinum toxin reduced pain more than placebo, but studies were short-term

N=sample size; RCT=randomized clinical trial

In this table, key individual drugs are listed only when there were sufficient numbers of studies of different drugs to assess SOE and therefore individual drugs were described separately, or where the strength of evidence varied within drug classes: within the classes of anticonvulsants and serotonin-adrenaline reuptake inhibitors, compared to placebo. If not listed, SOE was insufficient (only one study – venlafaxine for quality of life)

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