South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Endocrinology/Pain

MEDICINE REVIEW:

1. Executive Summary

Date: 2 May 2018
Medicine (INN): Serotonin-noradrenaline reuptake inhibitors (SNRI) i.e. Duloxetine, Venlafaxine
Medicine (ATC): N06AX21, N06AX16
Indication (ICD10 code): Diabetic neuropathy (E11.40)
Patient population: Type 1 and 2 diabetic patients diagnosed with painful diabetic neuropathy and not responding to standard of care.
Prevalence of condition: Based on the most recent 2017 International Diabetes Federation (IDF) estimates for South Africa, there were 1.8 million adults (20-79 years) with diabetes; the national prevalence was 5.5%. Of the 2.3 million people with diabetes, 1.5 million (84.8%) were undiagnosed.(1) Estimated prevalence of diabetic neuropathy in South Africa reported to be 30.3% (95% CI 27.4% to 33.2%) (18).
Level of Care: Hospital level
Prescriber Level: Medical Officer
Current standard of Care: Amitriptyline and/or paracetamol
Efficacy estimates: (preferably NNT) Duloxetine 60mg versus placebo for a ≥50% improvement in pain at 12 weeks: NNT 5 (95% CI 4 to 7) (8)
Motivator/reviewer name(s): Dr R Griesel/Dr H Gunter/Mr A Gray; with assistance from Ms TD Leong
PTC affiliation: Groote Schuur Hospital PTC, KwaZulu-Natal Provincial PTC

2. Name of author(s)/motivator(s)

Primary reviewer: Dr R Griesel
Secondary reviewers: Dr H Gunter; Mr A Gray
(Ms TD Leong assisted with the estimated budget impact analysis)

3. Author affiliation and conflict of interest details

Primary reviewer:

- Dr R Griesel: Groote Schuur Hospital, Adult Hospital Level Committee member; no conflicts of interest declared.

Secondary reviewers:

- Dr H Gunter: Groote Schuur Hospital, Adult Hospital Level Committee member; no conflicts of interest declared.
- Mr A Gray: National Essential Medicines List Committee member; no conflicts of interest declared.

Other:

- Ms TD Leong: National Department of Health, Essential Drugs Programme, Secretariat to the Adult Hospital Level Committee; no conflicts of interest declared.

4. Introduction/ Background

Chronic pain has been classified as pain exceeding three months in duration. Chronic neuropathic pain is pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Neuropathy is prevalent among diabetics, with up to 50% in the UK developing a variation of the disease.(2) The pain of painful peripheral neuropathy can be diverse and distressing. Descriptions include burning, cold, electric shocks, lancinating, tight or aching. Other spontaneous and evoked positive sensory symptoms include painful numbness, tingling or paraesthesiae. In people with neuropathy and/or peripheral artery disease (PAD), minor trauma to the foot leads

to skin ulceration, infection and ultimately gangrene, resulting in amputation.(3,4) Chronic pain can have serious and complex adverse psychological and social effects.

The current standard of care for diabetic neuropathy according to the adult hospital level essential medicines list and standard treatment guidelines (section 8.7.1), includes amitriptyline, and if ineffective consideration of either added carbamazepine or replacement of this agent. A comment made by the Division of Endocrinology at the University of KwaZulu-Natal, queried the use of carbamazepine as second line therapy for diabetic neuropathy, stating that it is predominantly used for trigeminal neuropathic pain and advised that duloxetine be considered.
Duloxetine is one of a newer type of antidepressant drugs. It is a relatively balanced dual reuptake inhibitor of serotonin and noradrenaline (serotonin–noradrenaline reuptake inhibitors [SNRIs]). Serotonin modulates both pro-nociceptive and anti-nociceptive descending effects on central pain pathways from the brainstem. Noradrenaline has a predominantly anti-nociceptive effect. Balance between the facilitation and depression of pain pathways is important for normal function. Drugs that inhibit the reuptake of serotonin and noradrenaline potentiate monoamine neurotransmission in the descending inhibitory spinal pathways and so reduce nociceptive afferent transmission in the ascending spinal pain pathways. Onset of benefit occurs within days, earlier and at lower doses than in depression. Common side effects include nausea, headache, dry mouth, insomnia, constipation, dizziness, fatigue, somnolence, hyperhydrosis and diarrhoea.

The antidepressant agent venlafaxine is also a serotonin reuptake inhibitor with weak noradrenaline reuptake capabilities. It is used in the treatment and prevention of major depressive disorder, as well as in the treatment of generalized anxiety disorder, social anxiety disorder, panic disorder, and agoraphobia. Although not frequently licensed for the treatment of chronic or neuropathic pain, it is commonly used for these indications. Common adverse effects include nausea, dizziness, drowsiness, and dry mouth.

A medicines review was done to assess the efficacy and safety for the use of SNRIs (duloxetine and venlafaxine) in the management of painful diabetic neuropathy.

5. Purpose/Objective i.e. PICO

Are duloxetine or venlafaxine effective, safe and cost-effective alternatives to amitriptyline and/or paracetamol or carbamazepine in the management of pain associated with diabetic neuropathy?
-P Type 1 and 2 diabetic patients diagnosed with neuropathy
-I Duloxetine, venlafaxine (SNRIs)
-C Amitriptyline (tricyclic antidepressant [TCA]) or carbamazepine)
-O Improvement of pain

6. Methods:

a. Data sources

Pubmed, Medline, Cochrane library

b. Search strategy

((("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields]) OR ("peripheral nervous system diseases"[MeSH Terms] OR ("peripheral"[All Fields] AND "nervous"[All Fields] AND "system"[All Fields] AND "diseases"[All Fields]) OR "peripheral nervous system diseases"[All Fields] OR ("peripheral"[All Fields] AND "neuropathy"[All Fields]) OR "peripheral neuropathy"[All Fields])) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes insipidus"[MeSH Terms] OR ("diabetes"[All Fields] AND "insipidus"[All Fields]) OR "diabetes insipidus"[All Fields])) AND (("venlafaxine hydrochloride"[MeSH Terms] OR ("venlafaxine"[All Fields] AND "hydrochloride"[All Fields]) OR "venlafaxine hydrochloride"[All Fields] OR "venlafaxine"[All Fields]) OR ("duloxetine hydrochloride"[MeSH Terms] OR

("duloxetine"[All Fields] AND "hydrochloride"[All Fields]) OR "duloxetine hydrochloride"[All Fields] OR "duloxetine"[All Fields])) AND (Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb])

From this search strategy, there were 4 recently published systematic reviews relevant to the topic. The systematic review by Griebeler et al. (5) included trial data up to April 2014 for the management of diabetic neuropathy. The systematic review and meta-analysis by Waldfogel et al. (6) included recently published clinical trials until May 2016. Two Cochrane systematic reviews by Gallagher et al. (7) (2015) and Lunn et al. (8) (2014), which looked at the use of venlafaxine and duloxetine in neuropathic pain, respectively, were included.

c. Excluded studies

The systematic review and meta-analysis by Finnerup et al. (9) assessed the evidence-based for the pharmacological treatment of neuropathic pain until 2015, however diabetic neuropathy was not separated out for this review. The 3 identified systematic reviews included all randomized controlled trials (RCTs) relevant to the research question and all of these will be discussed in detail.

d. Evidence synthesis

The systematic review and meta-analysis by Griebeler et al. (5) aimed to summarize and appraise the totality of evidence from RCTs regarding the efficacy of the most commonly used oral and topical analgesics for painful diabetic neuropathy. They adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and used an "umbrella" approach to identify relevant systematic reviews and RCTs. The search was performed on Ovid MEDLINE, Ovid EMBASE, and the Cochrane Database of Systematic Reviews. For a trial to be included, the intervention dose had to be at least the minimum effective dose. When more than 1 dose was evaluated in the same RCT, data for the highest dose tested within the drug's therapeutic range was extracted. Pairs of reviewers working independently identified randomized trials that enrolled adults with painful diabetic neuropathy without restrictions based on the language of publication, number of patients, or type of diabetes mellitus. Studies investigating combinations of medicines were excluded (except paracetamol and aspirin which were used as analgesic co-interventions and/or rescue agents in most RCTs) and disagreement between reviewers was solved by consensus or arbitrated by a third reviewer.

The main outcome was pain relief, which was assessed as a dichotomous (the proportion of patients whose pain decreased ≥30%) and continuous (the standardized mean difference [SMD] on a pain scale) variable. When both forms were reported, they were collected and analyzed separately. Only data on lower extremity pain was evaluated. If pain was reported at multiple time points, efficacy was assessed at the furthest time point within 3 months (short-term effect), longer than 3 months (long-term effect), or both.

Data extraction occurred on patient demographic characteristics, diabetes baseline characteristics, study design, sample size, type of intervention and pain scale, and adverse effects of the medications. The Cochrane Collaboration's risk-of-bias tool was used to evaluate the methodological quality of the RCTs. Two reviewers working independently assessed the risk of bias for random-sequence generation; allocation concealment; blinding of patients, caregivers, or outcome assessors; incomplete outcome data; selective reporting; and other biases. The risk of bias was summarized for all domains to produce an overall risk of bias for every trial. Risk of bias was considered to be high if there was concern for bias in any key domains (allocation concealment or blinding of patients), low if risk of bias was low for all key domains, and unclear in all other cases.

A network meta-analysis was done to combine direct and indirect evidence of class and agent comparisons using the Bayesian Markov-chain Monte Carlo method. A random-effects model was fitted because of the potential for heterogeneity among included trials. Authors used the I^2 statistic and the Cochran Q test to assess heterogeneity for direct comparisons.

Sixty-five RCTs that included 12 632 patients and compared 27 medications were included. Of these 9 were head-to-head trials, including 8 RCTs comparing medications of different pharmacologic classes. In general, trials were brief (mean follow-up, 14 weeks) and enrolled mostly middle-aged men who had type 1 or 2 diabetes for more than 5 years. Thirty of the 65 included RCTs were considered to have a low risk of bias. Risk of bias in the remaining studies was considered to be high or unclear because of concerns about random-sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.

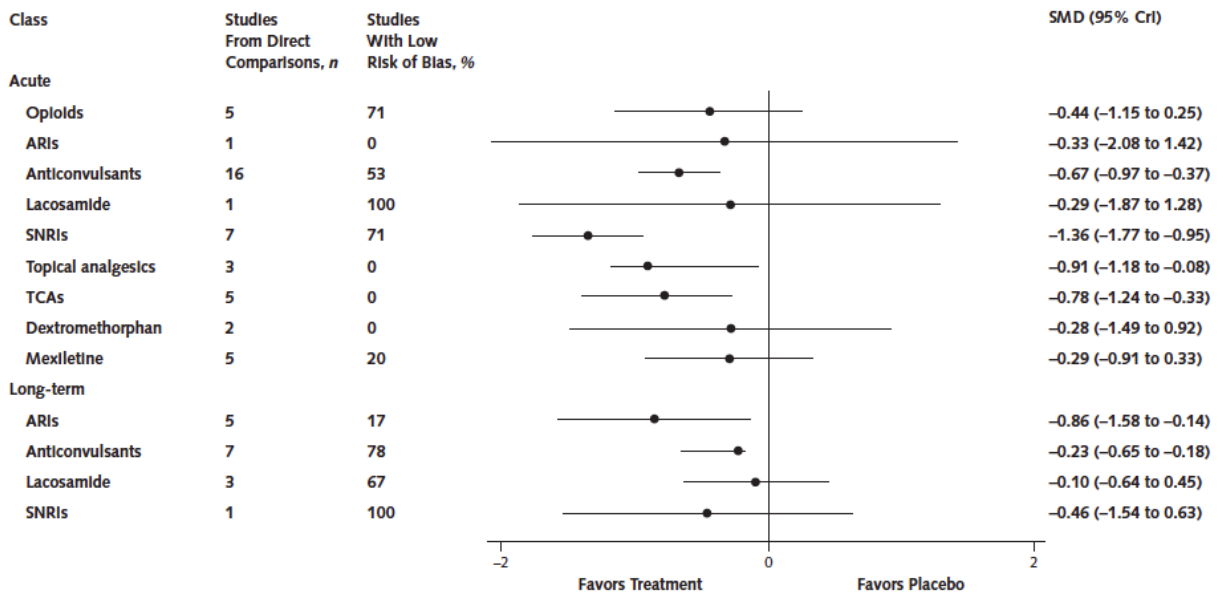
Network meta-analysis of drugs by class that combined estimates from direct and indirect comparisons showed that, within 3 months of treatment, SNRIs (SMD, -1.36 [95% credible interval (CrI), -1.77 to -0.95]) (Table 1), TCAs (SMD, -0.78 [CrI, -1.24 to -0.33]), and anticonvulsants (pregabalin, gabapentin and carbamazepine) (SMD, -0.67 [CrI, -0.97 to -0.37]) all resulted in larger and statistically significant reductions in pain compared with placebo. All trials of TCAs had unclear or high risk of bias and anticonvulsants had a similar effect size when only trials with low risk of bias were assessed (SMD, -0.663 [CrI, -0.914, -0.412]). In the network meta-analysis SNRIs as a group reduced pain more than anticonvulsants (SMD, -0.69 [CrI, -1.17 to -0.21]) (Table 1). Head-to-head trials also showed that SNRIs reduce pain more than anticonvulsants (SMD, -0.34 [CrI, -0.63 to -0.05]) (Table 1). The analysis of the long-term (>3 months) analgesic effect was limited by the scarcity of data. Compared with placebo anticonvulsants (SMD, -0.23 [CrI, -0.65 to -0.18]) had beneficial long-term analgesic effects that were statistically significant.

The network meta-analysis, by combining results from direct and indirect comparisons of individual drugs, revealed significantly better pain control than placebo within 3 months of treatment for carbamazepine (SMD, -1.57 [CrI, -2.83 to -0.31]), duloxetine (SMD, -1.33 [CrI, -1.82 to -0.86]), venlafaxine (SMD, -1.53 [CrI, -2.41 to -0.65]) and amitriptyline (SMD, -0.72 [CrI, -1.35 to -0.08]) (Supplementary table 1). However, the findings for carbamazepine are based on only one crossover trial of 40 participants (Supplementary table 2). Duloxetine at varying doses was compared to placebo in 5 different trials and amitriptyline only in one (Supplementary table 2). Venlafaxine was compared to placebo in 2 trials (Supplementary table 3). No trials did a head-to-head comparison between amitriptyline, carbamazepine and duloxetine. Data from the studies that evaluated long-term efficacy of analgesics for painful diabetic neuropathy suggest that duloxetine (SMD, -0.46 [CrI, -0.81 to -0.10]) is more effective than placebo.

Table 1 Comparative analgesic effect by class

Class and Comparator	SMD From Direct Comparisons (95% CrI)	SMD From Network Meta-analyses (95% CrI)†
SNRIs		
Placebo	**−2.10 (−3.41 to −0.79)**	**−1.36 (−1.77 to −0.95)**
Opioids		**−0.92 (−1.72 to −0.09)**
ARIs		−1.02 (−2.85 to 0.75)
Anticonvulsants	**−0.34 (−0.63 to −0.05)**	−0.69 (−1.17 to −0.21)
Lacosamide		−1.06 (−2.71 to 0.53)
Topical capsaicin		−0.45 (−1.36 to 0.49)
TCAs	−0.25 (−0.78 to 0.28)	−0.58 (−1.16 to 0.01)
Dextromethorphan		−1.08 (−2.36 to 0.19)
Mexiletine		**−1.07 (−1.81 to −0.33)**

Figure 1 Treatment of diabetic peripheral neuropathy compared to placebo, by class



Combined direct and indirect estimates. ARI = aldose reductase inhibitor; CrI = credible interval; SMD = standardized mean difference; SNRI = serotonin–norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

Xerostomia was the most commonly reported anticholinergic symptom of the TCAs reported in trials (present in up to 89% of patients). Central nervous system symptoms associated with these drugs included somnolence (up to 69% of patients) and dizziness (5% to 16%). Fatigue (11% to 34%), insomnia (35%), and headache (11% to 21%) were also commonly described. SNRIs were associated mainly with central nervous system and gastrointestinal adverse effects. Somnolence and dizziness were present in 8% to 28% and 6% to 25% of patients in the SNRI trials, respectively. Nausea (10% to 32%), constipation (7% to 19%), and dyspepsia (9% to 18%) were also common. Xerostomia, anorexia, headache, diaphoresis, fatigue, and decreased libido were also frequently mentioned. Patients using carbamazepine most frequently complained of dizziness (10%–53%), somnolence (14%), vomiting (10%), headache, ataxia, nausea, and constipation.

The systematic review by Waldfogel et al. (6) included findings from the systematic review by Griebeler et al. (5) as well as patient-reported outcomes on health-related quality of life (QoL) and results from previously unpublished studies. They used the search strategy by Griebeler et al. (5) to search PubMed, Embase, and the Cochrane Central Register of Controlled Trials from January 1, 2013 to May 24, 2016. They supplemented the results of the search by reviewing the references of 3 other recent and relevant systematic reviews, as well as ClinicalTrials.gov for relevant studies. The authors only included relevant RCTs and abstracted data on study characteristics and the outcomes of pain intensity (continuous and categorical findings), health-related QoL, adverse effects, and dropouts due to adverse effects. Risk of bias of relevant systematic reviews were assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool. For the additional RCTs, risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk. For QoL, the most relevant subscale using the following hierarchy was used: Short Form-36 (SF-36) physical function, then Visual Analogue Scale QOL, then Euro Qol–5D overall, then other QOL score, then SF-36 bodily pain.

Results were summarized qualitatively and quantitatively. As in the prior review's methods, they used calculated SMD, which they classified into small (Cohen d < 0.5), moderate (>0.5 to <0.8), and large (>0.8) effect sizes. When there were at least 3 sufficiently clinically homogenous new studies and SMD could be calculated, a new meta-analyses was conducted. A sensitivity analysis was performed using the profile likelihood estimate when there

was high statistical heterogeneity. The strength of evidence was graded as recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews.

One hundred and six RCTs were included: 57 from the existing systematic review, with 24 additional published RCTs, and 25 studies from ClinicalTrials.gov. The systematic review by Griebeler et al. (5) was classified as high quality (according to the ROBIS tool). The 57 RCTs from Griebeler et al.'s (5) review compared 21 medications in 10,639 patients, with few of the studies extended beyond 3 months. The 24 additional RCTs published had 25 head-to-head comparisons. Follow-up duration ranged from 3 to 18 weeks (studies were not separated by length of follow-up), with a mean of 10.5 weeks of duration. All trials were placebo-controlled except for one comparing duloxetine, pregabalin, and combination therapy. The additional 25 trials in ClinicalTrials.gov, 18 were identified as completed. Seven of the 18 reported results in ClinicalTrials.gov and were included in the results.

For the outcome of pain reduction, the authors found that carbamazepine had only one additional study and they could not draw conclusions from this due to insufficient strength of evidence (SoE). Regarding SNRIs as class two additional RCTs identified in the updated search were consistent with the previous findings from Griebeler et al. (5) (SMD -0.33; 95% CI -0.54 to -0.12 and -0.11; 95% CI -0.42 to 0.21). They concluded that the SNRI drug class is effective (moderate SoE) for pain treatment in diabetic neuropathy. For specific SNRIs the previous meta-analysis of duloxetine versus placebo included 5 RCTs and the pooled SMD was -1.33 (95% CrI -1.82 to -0.86). The updated systematic review identified 2 additional RCTs that compared duloxetine versus placebo. One RCT reported a SMD of -0.33 (95% CI -0.54 to -0.12) and the other RCT also found that duloxetine was significantly more effective than placebo, although an SMD could not be calculated (Supplementary table 4). The conclusion was that duloxetine was more effective than placebo at reducing pain (moderate SoE). No additional studies assessing venlafaxine were identified. It was more effective than placebo (SMD -1.53; 95% CrI -2.41 to -0.65) in reducing diabetic neuropathy associated pain (large effect size, moderate SoE), as per Griebeler et al.

For TCAs, Griebeler et al. (5) concluded the drug class was effective based on a network meta-analysis of 4 RCTs (SMD-0.78; 95% CrI -1.24 to -0.33). No additional studies addressing TCAs were found and it was concluded that TCAs were more effective than placebo at reducing pain (moderate effect size, low SoE). For individual TCAs, only imipramine had 2 studies and the authors concluded that it was effective (low SoE). They were unable to draw conclusions for desipramine or amitriptyline (insufficient SoE). No individual drug–drug comparisons had more than one study with analyzable results, therefore no conclusions on drug–drug comparisons could be drawn (insufficient SoE).

For QoL assessment: sorted by drug class, anticonvulsants had 7 of 18 studies with statistically significant results, and SNRIs had 1 of 4 studies. Given incomplete reporting, conclusions could not be drawn for QoL (insufficient SoE for all comparisons).

Studies of SNRIs and anticonvulsants most commonly reported dizziness, nausea, and somnolence, while studies of TCAs reported xerostomia, somnolence, and insomnia. Dropout rates due to adverse effects varied widely from 2.5% up to 70% for oral agents.

A Cochrane systematic review by Gallagher et al. (7) found 6 eligible randomised, double-blind trials of ≥2 weeks duration (up until 14 August 2014). A total of 460 participants with neuropathic pain (mostly with painful diabetic neuropathy, but also with other causes of neuropathic pain such as polyneuropathy from non-diabetic etiology, neuralgia post chemotherapy, and atypical facial pain) were assessed. Four studies were of crossover design and two were parallel trials. Comparators included placebo, imipramine, and carbamazepine and duration of treatment ranged from 2 to 8 weeks. The risk of bias was considerable overall in the review, especially due to the small size of most studies and due to attrition bias. No first or second tier evidence of

efficacy could be extracted from the available studies.

In the largest study being by Rowbotham et al. (10) with 245 adults with diabetic neuropathy, 56% of participants receiving 150 to 225mg venlafaxine achieved at least a 50% reduction in pain intensity versus 34% of participants in the placebo group. Participants were randomized to placebo, venlafaxine 75mg, or venlafaxine 150 to 225mg; their pain intensity and pain relief was measured using the VAS scales at week six. Only the higher dose of venlafaxine differed significantly from placebo with the number needed to treat for additional benefit (NNTB) being 4.5 for the higher dose of venlafaxine. However, this study was subject to significant selection bias and could only be classified as third-tier evidence of efficacy.

Jia et al. (11) compared venlafaxine and carbamazepine in a randomised, parallel trial of 132 participants with painful peripheral diabetic neuropathy. In this double-dummy design study, venlafaxine was dosed twice daily and the total daily dose was 50mg. Although there was a significant reduction in pain intensity in both groups at five, seven, 10, and 14 days compared with their baseline scores, venlafaxine was superior to carbamazepine at reducing pain intensity at all time points by per-protocol analysis, with an apparent reduction from 6.8 to 2.2 in mean pain intensity after 14 days of venlafaxine, measured on an 11-point scale. Venlafaxine was also superior to carbamazepine at improving quality of life, measured as improved sleep, routine work, and mood.

Rowbotham et al. (10) reported treatment-emergent adverse effects in 75% of participants on placebo, 88% of participants on venlafaxine 75mg, and 89% of participants on venlafaxine 150 to 225mg. Nausea, dyspepsia, sweating, and somnolence were the most commonly reported and all of these were significantly more frequent in at least one of the venlafaxine groups versus placebo. The same authors reported that 10% of placebo, 9% of venlafaxine 75mg and 12% of venlafaxine 150 to 225mg groups had a serious adverse effect, although their precise nature was unclear. They also reported that 7/162 participants who commenced venlafaxine had clinically important electrocardiograph (ECG) changes over the course of their treatment.

Jia et al. (11) reported 29 adverse effects in the venlafaxine group, with these affecting 43.9% of participants. Common adverse effects were reported as those occurring in more than 10% of participants and these included mild gastrointestinal discomfort, dizziness, and somnolence. However, as this trial was not placebo-controlled, it is difficult to draw a definitive conclusion. Severe gastrointestinal disturbance occurred in one participant on venlafaxine.

Venlafaxine 225 mg was compared with imipramine 150 mg in a placebo-controlled study conducted by Sindrup 2003 (13), in 40 participants with polyneuropathy (of whom fifteen had diabetes-related polyneuropathy). Venlafaxine and imipramine were both found to be effective in producing at least moderate pain relief compared to placebo (8/30 participants in the venlafaxine arm compared to 2/29 in the placebo arm reported at least moderate pain relief). There was however no statistically significant difference between the two drugs.

Forssel 2004 (14) conducted a placebo-controlled, cross-over study of venlafaxine (dose of up to 75 mg/day) in 30 participants with atypical facial pain. Despite a significant improvement in pain relief on the participant-reported verbal rating scale (VRS), venlafaxine did not show significant reduction in pain intensity.

Venlafaxine was compared with placebo in 15 women with neuropathic pain following breast cancer treatment in a randomised, double-blind cross-over trial conducted by Tasmuth 2002 (15). The dose of venlafaxine was escalated from 18.75 mg/day to a maximum of 37.5 mg (two participants) or 75 mg (11 participants). Primary outcome measures were current pain intensity during the last three days of the maximum tolerated dose (VAS-PI and verbal rating scale - pain intensity (VRS-PI)). There was found to be no

difference in pain intensity between treatment arms. A strong placebo effect was also noted.

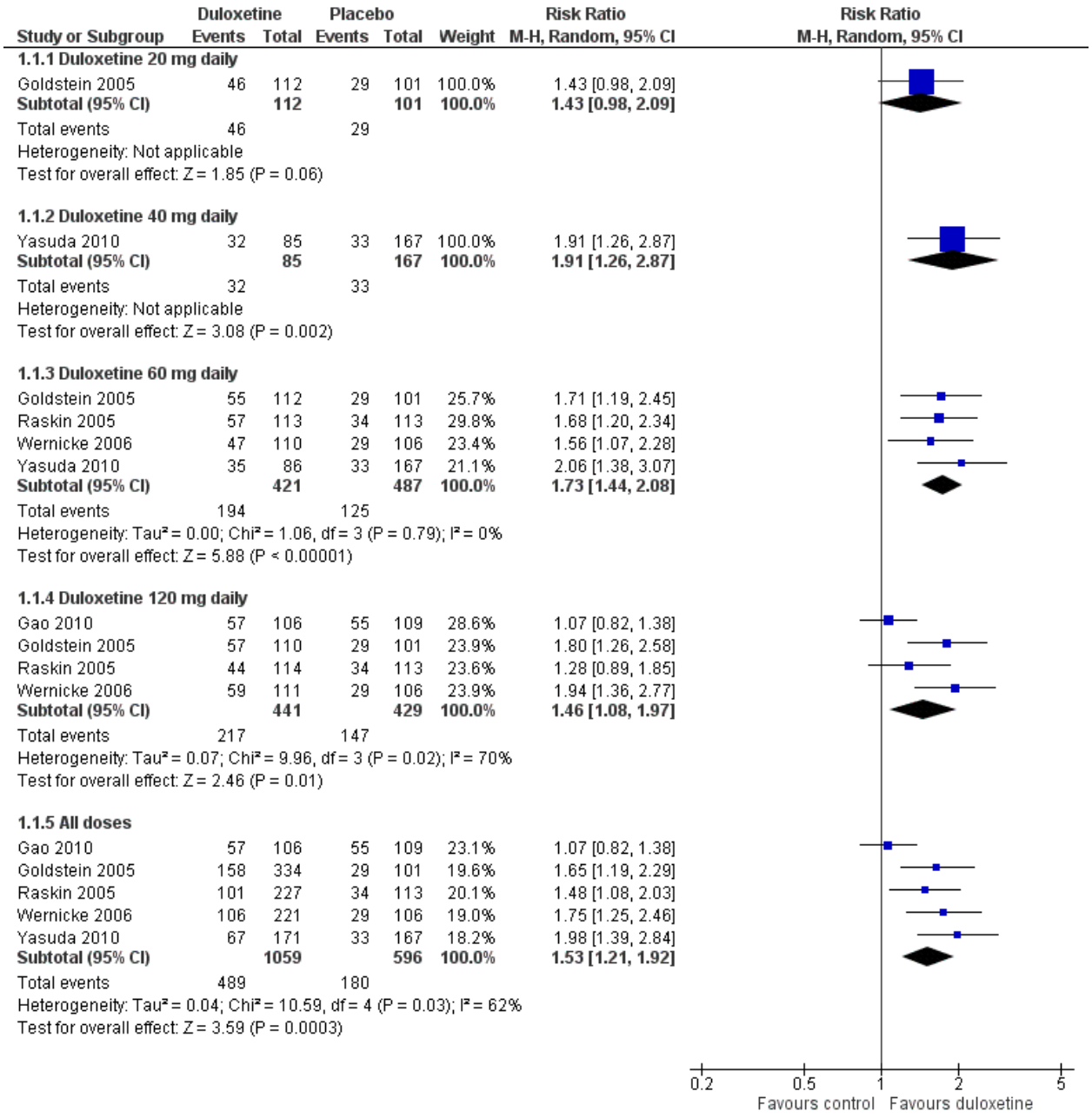
The authors of the Cochrane systematic review concluded that there is little compelling evidence to support the use of venlafaxine in neuropathic pain. While there was some third-tier evidence of benefit, this arose from studies that had methodological limitations and considerable risk of bias. Placebo effects were notably strong in several studies. (7)

Finally, a Cochrane systematic review by Lunn et al. (8), looked at the use of duloxetine for treating painful neuropathy and different types of chronic pain. Databases were searched in November 2013, with ClinicalTrials.gov searched up to April 2013. Six of 8 studies in diabetic neuropathy compared duloxetine with placebo in parallel groups for two to three months. One study compared duloxetine to amitriptyline in a crossover design with only six weeks' treatment in each arm with a short two-week washout (12), but because it was the only comparative trial of its type it was excluded from the meta-analysis. One study compared duloxetine to pregabalin in the randomised parallel group first arm of an enrichment trial design. Doses in the trials varied from 40mg to 60mg with an increase up to 120mg daily. Treatment was for 12 weeks with a one-week taper in four trials.

Only one small, high quality trial conducted by Vranken 2011 (16), examined the effect of duloxetine compared to placebo in participants with central neuropathic pain. Eligible participants had more than six months' severe neuropathic pain of spinal cord or cerebrovascular origin. Participants had a score of more than six on a 10-point VAS. The starting dose of duloxetine was initially 60 mg, which increased if participants did not improve by more than 1.8 points on VAS. This single investigator-led study had a low risk of bias but only included 48 participants. Duloxetine showed to have no therapeutic effect on the neuropathic pain of these participants. The trial authors recommended that larger studies are required to assess the role of duloxetine in central neuropathic pain.

Trials in painful diabetic neuropathy reported data on the primary outcome measure of ≥50% improvement of pain compared with baseline at less than 12 weeks, using the 11-point Likert score. Combining data from all doses of five trials comparative trials (1655 participants), the risk ratio (RR) of ≥50% improvement with any dose was 1.53 (95% confidence interval (CI), 1.21 to 1.92) compared with placebo (Figure 2). At 60mg daily dose the RR was 1.73 (95% CI 1.44 to 2.08) with a NNTB of 5 (95% CI 4 to 7).

Figure 2 Duloxetine versus placebo in the treatment of painful neuropathy: Number of patients with >50% improvement of pain at <12 weeks (Lunn et al)

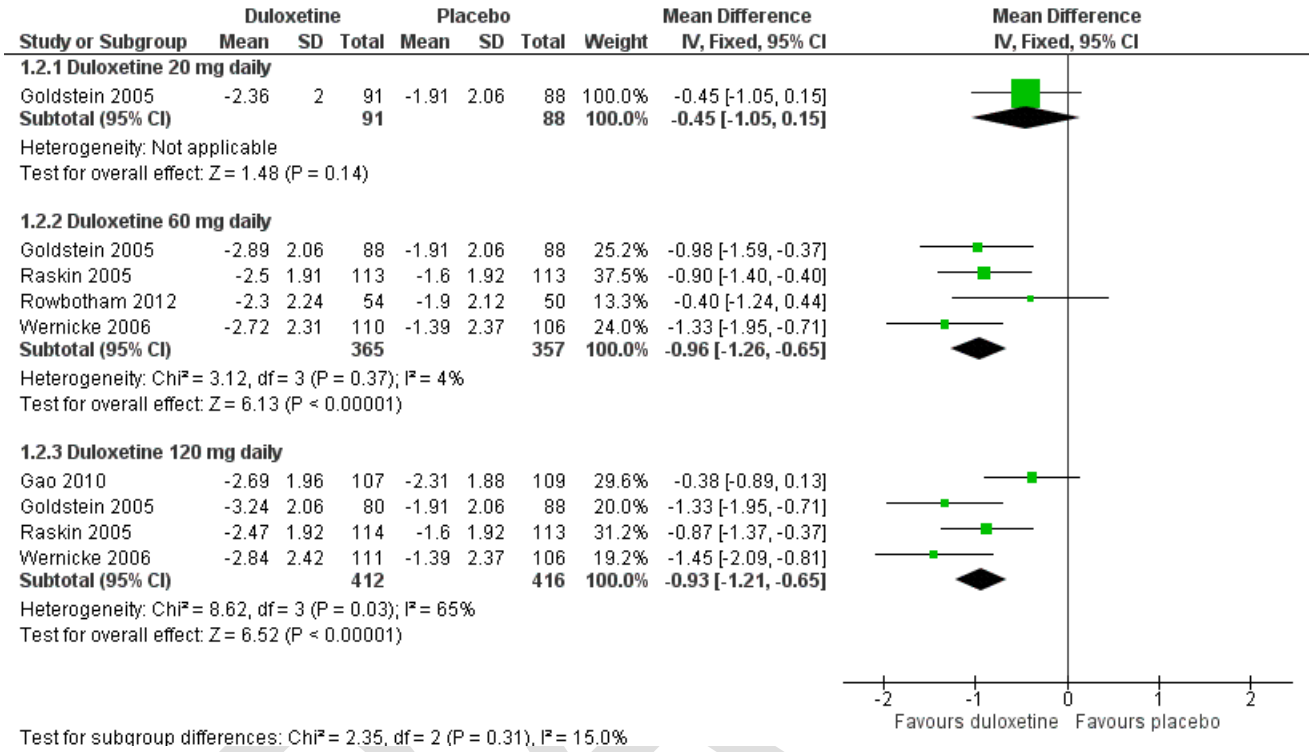


The RR of improvement was significantly greater than placebo for the 40 mg, 60 mg and 120 mg daily doses but not the 20 mg daily dose, for which it was 1.43 (95% CI 0.98 to 2.09; the CIs for 20mg were wide as only one study with few participants provided data). There was no significant difference or a dose effect in the RR of improvement with increasing doses of duloxetine from 40mg to 120mg.

The mean improvement in pain at 12 weeks or less on an 11-point Likert scale was significantly greater than placebo with the 60 mg dose of duloxetine (Mean difference (MD) -0.96, 95% CI -1.26 to -0.65; 4 trials, 722

participants) and the 120 mg dose (MD -0.93, 95% CI -1.21 to -0.65; 4 trials, 828 participants), but not with the 20 mg dose (Figure 3).

Figure 3 Duloxetine versus placebo in the treatment of pain: Mean improvement in pain at 12 weeks



The quality of the evidence available for this outcome remains moderate, mainly as a result of relatively high dropout rates.

Five trials included data on ≥ 30% improvement of pain at 12weeks or less. The results were similar to those for at least 50% improvement. Relative rates of improvement were significantly greater than placebo with duloxetine for the 40 mg dose (RR 1.57, 95% CI 1.18 to 2.07; 1 trial, 252 participants), the 60 mg dose (RR 1.53, 95%CI 1.33 to 1.75; 4 trials, 799 participants), the 120 mg dose (RR 1.38, 95% CI 1.21 to 1.58; 3 trials, 659 participants) and for all three doses combined (RR 1.45, 95% CI 1.30 to 1.63; 4 trials, 1220 participants).

Trials that included quality of life information used the SF-36. In painful diabetic neuropathy, the effect of 20 mg duloxetine was not significantly different from placebo on any of the selected SF-36 subscores at 12 weeks or less or the mental subscore at 60 mg daily doses. The MD of improvement in the physical summary component was significantly greater than placebo with the 60 mg dose (2.65, 95% CI 1.38 to 3.92; 3 trials, 514 participants) and 120 mg dose (2.80, 95% CI 1.04 to 4.55; 2 trials, 409 participants). The MD on the bodily pain subscale showed significantly more improvement than placebo with the 60mg dose (5.58, 95% CI 1.74 to 9.42; 2 trials, 421 participants) and even more with the 120mg dose (8.19, 95%CI 4.33 to 12.05; 2 trials, 420 participants) but not with the 20 mg dose (1 trial, 209 participants).

The only trial comparing duloxetine to amitriptyline by Kaur et al. (12), was a blinded cross-over study with 62 participants comparing six weeks' treatment with each active agent in escalating dose: duloxetine up to 60 mg and amitriptyline up to 50 mg. it is the only comparative trial of its type. Significant carryover effects were evident (VAS pain scores only returned to 75% of baseline during washout) and a number of predefined

outcome measures were not presented in the results, so there was an unclear risk of bias. Sixty-five per cent of participants achieved 60 mg of duloxetine per day and 48% of participants 50 mg amitriptyline. The majority of participants (59% duloxetine and 55% amitriptyline) were reported to have achieved a 'good' (> 50% improvement) response to the interventions.

Adverse events were analysed across all included studies (all indications). Serious adverse events were uncommon and were no more frequent with duloxetine than placebo at any dose or when combining all doses together (42 events in 2785 duloxetine-treated participants versus 39 events in 2191 placebo participants RR 0.81 (95% CI 0.53 to 1.25). Adverse events of any sort, however, were very common in all of the trials in both experimental and placebo groups. The rate of any adverse event was high in both the treatment and placebo arms of all studies, with 1530 adverse events being reported in 2462 control participants and 2033 adverse events occurring in 2796 participants in the combined treatment arms covering all doses (RR 1.15, 95% CI 1.11 to 1.20). Doses of 60 mg and 120 mg duloxetine were also associated with a significantly greater risk of cessation compared to placebo (number needed to treat for an additional harm (NNTH) outcome for duloxetine 60mg daily, all indications, and all adverse effects leading to cessation: 18 (95% CI 13 to 30)).

Withdrawal syndrome on SNRIs

Withdrawal symptoms after dose reduction and/or discontinuation of SNRIs have been widely reported. Symptomatology can vary in clinical presentation, onset, and duration. Of importance is early recognition in order to differentiate from relapse symptoms of the initial treating disease.

Fava et al. (17) conducted a systematic review to identify the occurrence, frequency, and features of withdrawal symptoms after SNRI discontinuation. PRISMA guidelines were followed and electronic databases included PubMed, the Cochrane Library, Web of Science, and MEDLINE from the inception of each database to June 2017. Titles, abstracts, and topics were searched using a combination of the following terms: "duloxetine" OR "venlafaxine" OR "desvenlafaxine" OR "milnacipran" OR "levomilnacipran" OR "SNRI" OR "second generation antidepressant" OR "serotonin norepinephrine reuptake inhibitor" AND "discontinuation" OR "withdrawal" OR "rebound."

The systematic review included 22 double blind randomized controlled trials, 6 studies where patients were treated in an open fashion and then randomized to a double-blind controlled phase, 8 open trials, 1 prospective naturalistic study, 1 retrospective study, and 23 case reports. Withdrawal symptoms occurred after discontinuation of any type of SNRI. The prevalence of withdrawal symptoms varied across reports and appeared to be higher with venlafaxine. The rates of withdrawal symptoms from both RCT and open trials ranged from 23 to 78% after discontinuation of venlafaxine, from 17.2 to 55% after desvenlafaxine, from 6 to 55% after duloxetine, from 13 to 30% after milnacipran, and from 9 to 10% after levomilnacipran. Symptoms were broad in presentation (involving multiple systems such cardiovascular, gastrointestinal, neuromuscular and neurocognitive), typically ensued within a few days from discontinuation and lasted a few weeks. Withdrawal symptoms appeared regardless of whether abrupt or gradual discontinuation of therapy was implemented. Late onset and/or a longer persistence of disturbances also occurred.

There were methodological limitations pertaining to findings from this systematic review. Methods of detection of symptoms relied mostly on spontaneous reporting which could have lead to an underestimation of withdrawal symptoms, as well as difficulties in identifying the presence of new withdrawal symptoms, rebound, and/or persistent postwithdrawal syndromes.

e. Evidence quality:

The quality of the network meta-analyses and systematic reviews performed to assess the pharmacological agents for treatment of diabetic neuropathy was high. However, the overall impression of the RCTs assessed was that they were high risk for bias and low SoE, except those assessing duloxetine, which were moderate SoE. The quality of evidence from the Cochrane systematic review on duloxetine remains moderate, mainly because of high dropout rates. Although all six studies included in the Cochrane Systematic Review on venlafaxine for neuropathic pain were double-blinded randomised controlled trials, the overall reporting quality was average to poor. Evidence arose from studies that had methodological limitations such as small sample sizes and short durations, which could lead to an overestimation of efficacy and a risk of bias. Placebo effects were notably strong in several studies.

7. **Alternative agents:**
   This medicines review will not be exploring pregabalin or gabapentin. A separate medicines review will explore the use of these agents in neuropathic pain syndromes.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [x] Uncertain: [ ]	Assessment of quality of evidence of individual RCTs were done by the Cochrane Collaboration's risk-of-bias tool, which evaluates the methodological quality of the RCTs. The quality and risk of bias of the systematic review by Griebeler et al was assessed by the Risk of Bias in Systematic Reviews (ROBIS) tool. For the individual drugs, carbamazepine had insufficient SoE, duloxetine moderate SoE, venlafaxine moderate SoE, and amitriptyline insufficient SoE. For the systematic review by Gallagher et al., the risk of bias was considerable overall, especially due to the small size of most studies and due to attrition bias. The systematic review by Lunn et al. reported moderate quality of evidence for the primary outcome of duloxetine versus placebo.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [X] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	Difficult to make a judgment on this, as the harms/adverse effects are not assessed in the same manner as benefits. However, it appears that the benefit of pain reduction in this condition is worth the non-serious adverse reactions mentioned in the 4 systematic reviews. Lunn et al. does clarify the risk of any adverse event among duloxetine treated participants as RR 1.15 (95% CI 1.11 to 1.20), but the risk of serious adverse events were equal. Participants also discontinued treatment at a higher rate in the duloxetine treatment group with a NNTH 18 (95% CI 13 to 30).
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [ ] No: [X] List specific exclusion from the group:	

<table>
<tr>
<td>VALUES & PREFERENCES / ACCEPTABILITY</td>
<td>
Is there important uncertainty or variability about how much people value the options?

Minor [ ] Major [ ] Uncertain [x]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [x]
</td>
<td></td>
</tr>
<tr>
<td>RESOURCE USE</td>
<td>
How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [x]
</td>
<td>
Cost of medicines/day:
<table>
<tr><th>Medicine</th><th>Cost (ZAR)</th></tr>
<tr><td>Duloxetine 30mg, oral</td><td>10.59*;60% SEP: 6.36**</td></tr>
<tr><td>Duloxetine 60mg, oral</td><td>12.14*; 60% SEP: 7.28**</td></tr>
</table>
* Weighted average of generic duloxetine (Drl Duloxetine®, Yelate®; Cymgen®). SEP database – Medicine price registry accessed 31 May 2019:
** 60% of average generic SEP: SEP database – Medicine price registry accessed 31 May 2019.

<u>Estimated budget impact analysis:</u>
Based on the following estimates:
1. StasSA 2018 midyear population statistics of 57.72 million (19).
2. Diabetes prevalence in South Africa of 5.5% (3.2% to 10.6%), as reported by the International Diabetes Federation (1)
3. Prevalence estimate of diabetic neuropathy: 30.3% (27.4% to 33.2%) (18).
4. Assumption that non-responders to amitryptiline & carbamazepine, requiring duloxetine is 40% (30% to 50%) of diabetics diagnosed with neuropathy.

A: Analysis based on SEP (weighted average as indicated above):
Estimated projected annual budget is as follows:
- Duloxetine 30mg daily: R1 488 mil (R587 mil to R3 927 mil))
- Duloxetine 60 mg daily: R1 705 mil (R673 mil to R4 500 mil)

B: Analysis based on 60% of SEP (weighted average as indicated above):
Estimated projected annual budget is as follows:
- Duloxetine 30mg daily: R893 mil (R352 mil to R2 356 mil)
- Duloxetine 60 mg daily: R1 023 mil (R404 mil to R2 700 mil)

Additional resources: n/a
</td>
</tr>
<tr>
<td>EQUITY</td>
<td>
Would there be an impact on health inequity?

Yes [ ] No [x] Uncertain [ ]
</td>
<td></td>
</tr>
<tr>
<td>FEASIBILITY</td>
<td>
Is the implementation of this recommendation feasible?
Yes [ ] No [ ] Uncertain [X]
</td>
<td></td>
</tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	X				

Recommendation

The Adult Hospital Level Committee acknowledges that duloxetine 30 – 60mg once daily may be considered as second line agent for diabetic neuropathy. However, this agent is currently cost-prohibitive. There is little compelling evidence to support the use of venlafaxine for neuropathic pain due to diabetic neuropathy or neuropathic pain related to etiology other than diabetes.

Rationale: A review of the available evidence shows that TCAs (amitriptyline) are a valid choice as first line therapy for the management of diabetic neuropathy. As a group they had an efficacy in pain relief as assessed by change in pain scale with SMD of -0.78 (CrI -1.24 to -0.33) and as individual agent amitriptyline had an SMD of -0.72 (CrI -1.35 to -0.08). The known side-effects of TCAs are quite frequent (present in up to 89% of patients as described by Griebeler et al. (5)), however these are seldom severe in nature and the low cost of the agent makes a strong recommendation for its use as first line treatment in diabetic neuropathy.

The true question raised by this review is whether the SNRIs (duloxetine or vanlafaxine) are more suitable drugs of choice for second line therapy of diabetic neuropathy, should TCAs be contra-indicated, patients have severe adverse effects, or not have adequate effect in reducing the pain. For this question the available evidence, points toward duloxetine as the preferred agent. The meta-analysis by Griebeler et al. identifies an SNRI SMD of -1.36 (CrI -1.77 to -0.95) compared to placebo, and a significant effect against anticonvulsants as well (SMD -0.69, CrI -1.17 to -0.21). Looking at individual drugs duloxetine and venlafaxine significantly reduce pain compared to placebo, SMD of-1.33 (CrI -1.82 to -0.86) and SMD of -1.53 (CrI -2.41 to -0.65), respectively. However, the level of evidence for venlafaxine is poor. Waldfogel et al. (6) could not add any significant evidence to the assessment of efficacy among these classes of drugs, except for two further RCTs strengthening the evidence in favour of duloxetine. The Cochrane systematic review by Gallagher et al. (7) stated that the overall evidence for venlafaxine was poor (third-tier evidence of efficacy) and the major trial looking at efficacy for pain reduction among patients with diabetic neuropathy calculated a NNTB of 4.5 at the higher dose of venlafaxine (150 -220mg) (10). Where venlafaxine was compared to carbamazepine it was declared superior for the reduction of pain intensity. (11) A systematic review conducted by Fava et al. to identify the occurrence, frequency, and features of withdrawal symptoms after SNRI discontinuation, found that withdrawal symptoms occurred after discontinuation of any type of SNRI. However, the prevalence of withdrawal symptoms varied across reports and appeared to be higher with venlafaxine. The rates of withdrawal symptoms from both RCT and open trials ranged from 23 to 78% after discontinuation of venlafaxine versus 6 to 55% after duloxetine. To be considered is that there were methodological limitations pertaining to findings from this systematic review. Methods of detection of symptoms relied mostly on spontaneous reporting which could have led to an underestimation of withdrawal symptoms, as well as difficulties in identifying the presence of new withdrawal symptoms, rebound, and/or persistent post-withdrawal syndromes. Finally the Cochrane systematic review by Lunn et al. (8) assessed the use of duloxetine in diabetic neuropathic pain and calculated a RR for ≥50% improvement of pain at 12 weeks with 60mg duloxetine versus placebo of 1.73 (95% CI 1.44 to 2.08), with a NNTB of 5 (95% CI 4 to 7). Serious adverse events were no more frequent with duloxetine than placebo at any dose, but adverse events of any sort were increased with duloxetine (RR 1.15, 95% CI 1.11 to 1.20). Doses of 60 mg and 120 mg duloxetine were also associated with a significantly greater risk of cessation compared to placebo (NNTH outcome for duloxetine 60mg daily causing adverse effects leading to cessation of therapy: 18 (95% CI 13 to 30)).

From this it is clear that both duloxetine and venlafaxine improve pain scores for diabetic neuropathy, however duloxetine has the higher level of evidence for this conclusion, has a lower prevalence of developing withdrawal symptoms than venlafaxine, and should be considered as second line therapy.

Level of Evidence: II Systematic review with disease oriented outcomes

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
		X

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Monitor usage of duloxetine for the correct indication via medicine use evaluations at institutional level – scope creep for depression is a concern.

Research priorities

None

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Supplementary table 1: Refer to attached Excel spreadsheet

Supplementary table 2

First author, year	Cross-over trial	Intervention vs comparison (highest daily doses)	Length of interven-tion (weeks)	No. Patients	Age (average among all participants)	Gender, ethnicity	Diabetes years (average among all participants)	Neuropathy years (average among all participants)	HbA1c (average among all participants)	Diabetes medications	Type of pain scale and scale measurement	Analgesic cointerventions and/or rescueagents
Wilton, 1974	Yes	Carbamazepine 600 mg vs. Placebo	1	40	56	25% male, 98% White	Not Available	>one and half year	Not Available	Insulin and oral agents	10-cm analogue, 0-10	No or not reported
Raskin, 2005	No	Duloxetine 60 mg vs. Duloxetine 120 mg vs. Placebo	12	348	58	46% male, 99% white	13.8	4.3	Not Available	Insulin and oral agents	11-point Likert scale and 0-10	Acetaminophen (up to 4 g/day) and Aspirin (up to 325 mg/day) were allowed
Goldstei, 2005	No	Duloxetine 20 mg vs. Duloxetine 60 mg vs. Duloxetine 120 mg vs. Placebo	12	457	60	61% male, 77% white, 8% black	11.3	3.7	Not Available	Insulin and oral agents	11-point Likert scale and 0-10	Acetaminophen (up to 4 g per day) was allowed
Wernicke, 2006	No	Duloxetine 60 mg vs. Duloxetine 120 mg vs. Placebo	12	334	60	61% male, 78% white, 16% Hispanic	10.2	3.8	Not Available	Unclear	11-point Likert scale 0-10	Acetaminophen (up to 4 g/day) and Aspirin (up to 325 mg/day)
Gao, 2010	No	Duloxetine 120 mg vs. Placebo	12	215	59	47% male, 100% Asian	9.6	3.2	Not Available	Insulin and oral agents	Brief Pain Inventory Form, 0-10	No or not reported

Yasuda, 2011	No	Duloxetine 40 mg vs. Duloxetine 60 mg vs. Placebo	12	338	60	75% male, 100% Asian	Not Available	Not Available	7.1%	Unclear	11-point numerical pain scale and 0-10	No or not reported
Max, 1987	Yes	Amitriptyline 150 mg vs. Placebo	6	29	Not Available	Not Available	Not Available	Median 2 years	Not Available	Unclear	Pain Scale Rating 13-word list of verbal descriptors of pain	No or not reported

Supplementary table 3

First author, year	**Cross-over trial**	**Intervention vs comparison (highest daily doses)**	**Length of interven-tion (weeks)**	**No. Patients**	**Age (average among all participants)**	**Gender, ethnicity**	**Diabetes years (average among all participants)**	**Neuropathy years (average among all participants)**	**HbA1c (average among all participants)**	**Diabetes medications**	**Type of pain scale and scale measurement**	**Analgesic cointerventions and/or rescue agents**
Rowbotham, 2004	No	Venlafaxine ER 75 mg vs. Venlafaxine ER 225 mg vs. Placebo	6	244	59	59% male	4.8	Not available	Not available	Not reported	11-point Likert scale 0-10	Acetaminophen (3 g/day)
Kadrirog lu, 2008	No	Venlafaxine 150 mg vs. Combination of vitamins B1 and B6	8	60	53	22% male	8	Not available	8.6%	Not reported	11-point Likert scale 0-10	Acetaminophen (3 g/day)

Supplementary table 4

First author, year	Cross-over trial	Intervention vs comparison (highest daily doses)	Length of interven-tion (weeks)	No. Patients	Age (average among all participants)	Gender, ethnicity	Diabetes years (average among all participants)	Neuropathy years (average among all participants)	HbA1c (average among all participants)	Diabetes medications	Type of pain scale and scale measurement	Analgesic cointerventions and/or rescue agents
Gao, 2015	No	Duloxetine 60mg vs. Placebo	12	405	61	45% male, Asian	11.5	3.3	< 12%	Insulin and oral agents	11-point Likert scale 0-10	Acetaminophen (3 g/day)
Rowbotham, 2012	No	ABT-894 1 mg, 2 mg and 4 mg vs. Duloxetine 60 mg vs. Placebo	8	280	59	55% male, 76% white	Unclear	4.7	< 9%	Insulin and oral agents	11-point Likert scale 0-10	Acetaminophen (3 g/day)