

Evidence Tables

Neu1a: Are tricyclic drugs effective for the treatment of painful neuropathy in people with type 2 diabetes?

Neu1b: Is duloxetine effective for the treatment of painful neuropathy in people with type 2 diabetes?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Goldstein DJ, Lu Y, Detke MJ et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. <i>Pain</i> . 2005; 116(1-2):109-118. Ref ID: 3230	RCT 1++ double-blind multicentre	N=457 (randomised and safety analysis) (Efficacy ITT analysis)	Patients with type 1 (n=53 (11.6%)) or type 2 diabetes (n=404 (88.4%)) Inclusion criteria: > 18 yrs, diabetic polyneuropathy for 6 mths minimum, MNSI ≥ 3 Patient population (mean): age 60.1 yrs, 61.5% male, weight 96 kg, duration of diabetes 9.6 yrs, duration of diabetic	Duloxetine: 20 mg/d (20 mg QD) (N= 115) 60 mg/d (60 mg QD) (N=114) 120 mg/d (60mg BID) (N=113)	Placebo (N=115)	12 weeks	24hr Average Pain Score (0-10) Brief Pain Inventory (BPI) Clinical Global Impression of Severity Scale Patients Global Impression of Improvement (PGI-Improvement) Scale Short Form McGill Pain Questionnaire (SF-MPA) Euro Quality	Efficacy 24-hr Average Pain Score There were no significant differences between the treatment groups and placebo. NOTE: Analysis comparing each individual treatment with placebo for each time point revealed a significant difference in favour of duloxetine 60 mg/d and 120 mg/d. The mean difference between 60 mg/d and placebo at endpoint was -1.17 (95% CI: -1.84 to -0.50) (p≤0.001) and that between duloxetine 120 mg/d and placebo was -1.45 (95% CI-2.13 to -0.78) (p≤0.001) BPI average pain severity There was a significantly greater reduction in BPI average pain severity compared to placebo (mean change (SE) -2.40 (0.21) with duloxetine 60mg/d (-2.81 (0.21); p≤0.01) and 120 mg/d (-3.07 (0.22); p≤0.001) CGI-Severity There was a significant difference in favour of duloxetine 20mg/d (mean change (SE) -1.28 (0.11); p≤0.05), 60mg/d (-1.42(0.12);	Eli Lilly

			neuropathy 3.7 yrs and MNSI 5.2				<p>of Life (EQ-5D) Beck Depression Inventory (BDI) Beck Anxiety Inventory (BAI) Safety Assessment s</p> <p>p≤0.001) and 120 mg/d (-1.70(0.012);p≤0.001) compared with placebo (-0.83 (0.12))</p> <p>PGI-Improvement There was a significant difference in favour of duloxetine 60mg/d (mean change (SE) 2.21 (0.12);p≤0.001) and 120 mg/d (2.24 (0.12); p≤0.01) compared with placebo (2.91 (0.12))</p> <p>SF-McGill total score There was a significant difference in favour of duloxetine 20mg/d (mean change (SE)-8.25 (0.65); p≤0.05), 60mg/d (-8.25(0.65); p≤0.001) and 120 mg/d (-9.18 (0.64); p≤0.001) compared with placebo (-5.39 (0.66))</p> <p>SF36 There was a significant difference in favour of duloxetine 60mg/d compared to placebo on the sub-scales for bodily pain (mean change (SE) 18.00 (1.89) vs 10.32 (1.89); p≤0.01) and mental health (2.99 (1.65) vs -2.63 (1.69); p≤0.05).</p> <p>There was a significant difference in favour of duloxetine 120 mg/d compared to placebo on the sub-scales for mental (mean change (SE) 1.84 (0.75) vs -1.09 (0.75); p≤0.01), bodily pain (18.32 (0.88) vs 10.32 (1.89); p≤0.01), general health perceptions (9.56 (1.62) vs 2.03 (1.61); p≤0.001) and mental health (5.14 (1.62) vs -2.63 (1.69); p≤0.001).</p> <p>Euro quality of life</p>
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							<p>There was a significant difference in favour of duloxetine 60mg/d (mean change (SE) 0.13 (0.02); $p \leq 0.05$) and 120 mg/d (0.13 (0.02); $p \leq 0.05$) compared with placebo (0.08 (0.02))</p> <p>BDI There was a significant difference in favour of duloxetine 120 mg/d (mean change (SE) - 3.11 (0.50); $p \leq 0.01$) compared with placebo (-1.74 (0.48))</p> <p>BAI There were no significant differences</p> <p>*Adverse events A total of 49 (10.7%) patients discontinued due to adverse events. There were fewest for the 20mg/d (4.3%) and most in the 120 mg/d group (19.5%). The following adverse events occurred significantly more in the 120 mg/d than placebo (%): Nausea (27.4 vs 9.6; $p \leq 0.001$) Somnolence (28.3 vs 7.8; $p \leq 0.001$) Dizziness (23 vs 7.0; $p < 0.001$) Constipation (12 vs 4; $p \leq 0.05$) Dry mouth (17 vs 7; $p \leq 0.05$) Sweating (10 vs 3; $p \leq 0.05$) Increased appetite (14 vs 0; $p \leq 0.001$) Anorexia (9 vs 1; $p \leq 0.01$) Weakness (8 vs 0; $p \leq 0.01$)</p> <p>Most adverse events were mild or moderate, except severe somnolence, which was reported significantly more frequently in the duloxetine 120 mg/d group than the other treatment groups.</p>	
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								There were no significant treatment group differences in the number of serious adverse events experienced.	
Raskin J, Pritchett YL, Wang F et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. <i>Pain Medicine</i> . 2005; 6(5):346-356. Ref ID: 3229	RCT 1++ double blind, multicentre Worldwide	N=348 (randomised) (ITT safety and efficacy)	Patients with type 1 (15.5%) and type 2 (84.5%) diabetes Inclusion criteria: ≥ 18 yrs, duration of ≥ 6 months, ≥ MNSI, ≥ when assessed for 24-hour average pain severity on the 11-point Likert scale Patient population (means): Age 58.8 yrs, 53% female, weight 85.9 kg, duration of diabetes 13.8 yrs, MNSI 5.0. The groups were well-matched	Duloxetine (N=116) 60 mg QD (type 2 n= 93, 80.2%) Duloxetine (N=116) 60 mg BID (type 2 n=99, 85.3%)	Placebo (N=116) (type 2 n=102, 87.9%)	12 weeks	Pain Treatment emergent adverse events (TEAE)	*Pain 24-hr average pain score There was a significant in favour of duloxetine 60 mg BID (mean change (SE) – 2.45 (0.18); p<0.001) and duloxetine 60 mg QD (-2.50 (0.18); p<0.001) compared to placebo (-1.60 (0.18)) BPI severity (average pain) There was a significant in favour of duloxetine 60 mg BID (mean change (SE) – 2.62 (0.19); p<0.01) and duloxetine 60 mg QD (-2.65 (0.19); p<0.01) compared to placebo (-1.82 (0.19)) CGI severity There was a significant in favour of duloxetine 60 mg BID (mean change (SE) - 1.40 (0.10); p<0.001) and duloxetine 60 mg QD (-1.42 (0.09); p<0.001) compared to placebo (-0.3 (0.09)) SF-MPQ total score There was a significant in favour of duloxetine 60 mg BID (mean change (SE) - 7.82 (0.61); p<0.001) and duloxetine 60 mg QD (-7.47 (0.61); p<0.01) compared to placebo (-4.96 (0.60)) PGI Improvement There was a significant in favour of duloxetine 60 mg BID (mean change (SE) 2.54 (0.10); p<0.001) and duloxetine 60 mg QD (2.50 (0.10); p<0.001) compared to placebo (3.04 (0.10))	Eli Lilly

			<p>apart from placebo patients having a significantly higher MNSI score (p=0.036) compared to the treatment groups</p>				<p>Hamilton Depression rating scale There were no significant differences between either treatment group and placebo</p> <p>BPI Interference (average score) There was a significant in favour of duloxetine 60 mg BID (mean change (SE) - 2.54 (0.18); p<0.001) and duloxetine 60 mg QD (-2.43 (0.18); p<0.001) compared to placebo (-1.56 (0.18))</p> <p>*Safety Reporting at least one TEAE n (%): placebo 57 (49.1) duloxetine 60mg QD 71 (61.2) (NS vs placebo), and 73 (62.9) duloxetine 60mg BID (p=0.047 vs placebo). Patients in both duloxetine groups reported treatment-emergent nausea, somnolence, hyperhidrosis, and anorexia significantly more frequently than placebo-treated patients. Additionally, vomiting and constipation were reported by duloxetine 60 mg BID-treated patients significantly more frequently than placebo-treated patients. Significantly more patients discontinued during therapy due to adverse events in the duloxetine 60mg BID group than placebo (14 (12.1% vs 3 (2.6%); p=0.010). Ten (2.9%) patients experienced serious adverse events with no significant treatment-group differences.</p> <p>There were no significant treatment-group differences in the overall incidence of taper-emergent adverse events or any single adverse event</p> <p>*Weight gain There was a slight but significant mean</p>	
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								<p>decrease in weight from baseline to endpoint for duloxetine 60mg BID (mean change (SD) -0.90 kg (2.39); p=0.006) treated patients compared with placebo treated patients.</p> <p>*Withdrawals N=52 (15%) withdrew:</p> <p>Duloxetine 60 mg QD N=15(13%) Duloxetine 60 mg BID N=21 (18%) Placebo N=16 (14%)</p> <p>Due to adverse event N=22 (6.3%):</p> <p>Duloxetine 60 mg QD N=5 (4.3%) Duloxetine 60 mg BID N=14 (12.1%) Placebo N=3 (2.6%) Significantly more patients withdrew due to adverse events in the duloxetine 60 mg BID than placebo (p=0.01)</p>
<p>Max MB, Lynch SA, Muir J et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy.[see comment]. <i>New England Journal of Medicine</i>. 1992; 326(19):1250-1256. Ref ID: 3274</p>	<p>RCT 1+ double-blind, cross-over, single site</p>	<p>N=54 (randomised)</p>	<p>Patients with diabetes with stable glycemic control. Inclusion criteria: signs of neuropathy for at least three months or more.</p> <p>Exclusion criteria: Severe depression,</p>	<p>Amitriptyline Weeks 1-4 titration period: range 12.5 to 150 mg/day (mean 105 mg)</p> <p>Weeks 5-6 maintenance period</p> <p>Desipramine Weeks 1-4 titration period: range 12.5 to 150 mg/day (mean 111 mg)</p>	<p>Active placebo 0.125 to 1.5 benztropine mg/day (to mimic dry mouth)</p> <p>Note: The results of two studies are combined by the authors, one comparing amitriptyline with desipramine and one comparing</p>	<p>12 weeks (6 weeks per intervention)</p>	<p>Pain diary Global pain relief</p>	<p>*Pain Amitriptyline vs desipramine There were no statically significant differences in pain scores between desipramine and amitriptyline (mean difference 0.07 (95% CI -0.04 to 0.18; NS) in pain diary scores.</p> <p>On global descriptors of pain, there were no statistically significant differences between the proportion of patients reporting moderate or greater pain relief during treatment with amitriptyline compared to desipramine (74% vs. 64%; NS).</p> <p>Amitriptyline and desipramine vs placebo</p>

			<p>postural hypotension, symptomatic coronary artery or peripheral vascular disease and nephropathy</p> <p>Patient population (median): 61% male,</p>		<p>fluoxetine with placebo (fluoxetine results not reported here)</p>		<p>Mean pain-diary scores (\pmSE) for the patients receiving amitriptyline (0.47 ± 0.12) and desipramine (0.35 ± 0.11) decreased more than placebo-treatment (0.15 ± 0.07; $p < 0.05$ for both).</p> <p>Amitriptyline and desipramine were associated with a statistically significant reduction in pain intensity compared with placebo (-0.48 and -0.48 vs -0.15^2; $p < 0.05$, one-tailed Dunnett's test)</p> <p>¹ Amitriptyline (N=12), desipramine (N=13) and placebo (N=15) – patients for who a direct comparison with placebo was possible ² Figures are approximate (extracted from graphic representation)</p> <p>*Adverse effects The proportion of patients experiencing 'any side' effects associated with amitriptyline, desipramine or placebo –treatments was 81%, 76% and 68% respectively.</p> <table border="1"> <thead> <tr> <th></th> <th>Amitrip-tyline</th> <th>Desip-ramine</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>Dry Mouth</td> <td>63%</td> <td>32%</td> <td>35%</td> </tr> <tr> <td>Tired-Ness</td> <td>34%</td> <td>34%</td> <td>17%</td> </tr> <tr> <td>Head-Ache</td> <td>21%</td> <td>11%</td> <td>9%</td> </tr> <tr> <td>Consti-Pation</td> <td>8%</td> <td>21%</td> <td>7%</td> </tr> <tr> <td>Insom-Nia</td> <td>-</td> <td>13%</td> <td>-</td> </tr> <tr> <td>Palpi-Tations</td> <td>13%</td> <td>3%</td> <td>-</td> </tr> <tr> <td>Sweat-</td> <td>11%</td> <td>13%</td> <td>2%</td> </tr> </tbody> </table>		Amitrip-tyline	Desip-ramine	Placebo	Dry Mouth	63%	32%	35%	Tired-Ness	34%	34%	17%	Head-Ache	21%	11%	9%	Consti-Pation	8%	21%	7%	Insom-Nia	-	13%	-	Palpi-Tations	13%	3%	-	Sweat-	11%	13%	2%
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								Ing Lighth- 8% 11% - headedness	
								*Study withdrawals due to adverse events Amitriptyline N=7 Desipramine N=7 Placebo N=2	
C. M. Morello, S. G. Leckband, C. P. Stoner, D. F. Moorhouse, and G. A. Sahagian. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. <i>Arch Intern Med</i> 159 (16):1931-1937, 1999.	RCT 1+ double blinded, crossover, single centre	N=25 (N=22 T2D), USA	Inclusion criteria: >18yrs, stable glycaemic control defined as HbA1c between 4.3% and 7.9% within 3 mths, chronic daily pain >3mths consistent with diabetic neuropathic pain Exclusion criteria: non-neuropathic pain, severe depression, other serious conditions	Amitriptyline, titrated for 2 days and dosage adjusted based on clinical response and adverse events. Doses for amitriptyline were: 54% 75 mg/day, 29% 50 mg/day and 17% 25 mg/day	Gabapentin, titrated for 2 days and dosage adjusted based on clinical response and adverse events. Doses for gabapentin were; 65% 1800mg/day, 26% 1200 mg/day and 9% 900 mg/day.	15 weeks 2 week wash out of any medications being used to treat neuropathic pain, 6 week treatment periods with 1 week washout, followed by 6 week crossover	Pain Scale Rating System, Global Rating Scale	* Pain intensity score There were significant reductions in the end of treatment pain scores for both gabapentin (p<0.001) and amitriptyline (p<0.001). However, there was no statistically significant difference in pain scores between gabapentin and amitriptyline at the end of treatment. * Global pain score There was no statistical difference in pain relief between the groups. * Adverse events With the exception of weight gain with amitriptyline (p<0.03) there was no significant difference in occurrence of adverse vents between the drugs. Adverse effects included sedation, dry mouth, dizziness, postural hypotension, weight gain, ataxia and lethargy. *Discontinuation 19 (76%) participants completed 6 weeks of treatment with both study arms, 2 (one from each group) crossed over early due to adverse events and completed the study	None stated
Raskin J, Smith TR, Wong K et al. Duloxetine versus	RCT 1+ open-label multicentre USA	N=179 (randomised) (ITT analysis)	Patients with type 1 (n=15 (9.3%)) or	Duloxetine 60 mg QD for three days and then 60mg BID (or QD	Routine care (N=76) Medications	52 weeks NB Patients	Treatment emergent adverse events	*Adverse events N=221 (93.2%) patients reported at least one TEAE. The following TEAEs occurred significantly more in routine care than	Eli Lilly

<p>routine care in the long-term management of diabetic peripheral neuropathic pain. <i>Journal of Palliative Medicine</i>. 2006; 9(1):29-40. Ref ID: 15</p>	<p>and Puerto Rico</p>		<p>type 2 diabetes (n= 146 (90.7%))</p> <p>Inclusion criteria: > 18yrs, daily pain for ≥ 6 months, HbA1c>12%</p> <p>Patient population (means): age 60 yrs, Michigan Neuropathy Screening Instrument 5.7, duration of diabetes 9.9 yrs, mean duration of diabetic neuropathy 3.5 yrs, mean weight 103 kg, male 61%</p>	<p>if they could not tolerate the dose) (N=116) Week 52-65 60mg QD. Patients were permitted to supplement their analgesia with acetaminophen, NSAIDs or opioid analgesics. Patients received most therapies, including nonmedical therapy offered to the routine care group, with the exception of antidepressants, anticonvulsants and antipsychotics</p>	<p>included n (%): neurontin 44 (57.9), Elavil 11 (14.5), amitriptyline 6 (7.9), Effexor-XR 9 (11.8), Tylenol 8 (10.5), Carbamazepine 4 (5.3)</p>	<p>had already completed a 13-week acute phase trial)</p>	<p>(TEAE) Quality of life</p>	<p>duloxetine therapy: pain in extremity (15.8% versus 6.2%; p=0.029), peripheral edema (15.8% versus 5.0%; p=0.010); balance disorder (5.3% versus 0.6%; p=0.038), erythema, feeling abnormal, and localised infections (3.9% versus 0%; p=0.032). There were no TEAEs that occurred significantly more in the duloxetine group than in routine care. In duloxetine-treated patients the only TEAEs reported by 10% or more of patients were peripheral edema and pain in extremity (15.8%), somnolence (14.5%), and dizziness (13.2%). Most TEAEs were moderate or mild. There were no significant differences between the group on the number of severe TEAEs.</p> <p>*Quality of life There were no significant therapy-group differences in the SF-36 subscales or on the EQ-5D</p> <p>*Discontinuation A total of 179 (75.5%) patients completed the extension phase of the study (116 (72%) duloxetine and 63 (82.9%) routine-care). Reasons for discontinuation included (duloxetine vs routine care) (%): adverse event 9.3 vs 2.6%, death 1.2 vs 2.6% Deaths: Two patients in each group died during the study, none were thought to be related to the study drug.</p> <p>Serious adverse events (SAE): A significantly higher percentage of routine care patients experienced 1 or more SAE (28.9% routine care vs 16.8% duloxetine-treated; p=0.039). A significant therapy group difference was observed in congestive</p>	
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								heart failure, with a higher percentage of routine care-treated patients (5%) experiencing this event versus duloxetine-treated patients (0.6%).	
								Discontinuation because of adverse events: A total of 21 (8.9%) patients discontinued due to any adverse event (including death): 4 (5.3%) routine-care and 17 (10.6%) duloxetine-treated patients	
Sindrup SH TC. Lack of effect of mianserin on the symptoms of diabetic neuropathy. <i>European journal of clinical pharmacology</i> . 1992; 43(3):251-255. Ref ID: 213	RCT 1+ double-blind crossover, single centre	N=22 (randomised)	Patients with diabetes and symptoms typical of peripheral neuropathy. Twelve patients were on insulin. Patient population (means): age 56 yrs, duration of diabetes 9 yrs, duration of neuropathy 4 yrs and 50% male	Imipramine Median dose 150 mg/day Dose adjusted to a target of 400-600 mmol l ⁻¹ plasma drug concentration after either a 10-day fixed-dose treatment period (50 or 75 mg per day) or from concentrations measured in a previous trial Mianserin 60 mg per day	Placebo	6 weeks (2 week per intervention)	Neuropathy scale (6-item, median for last 10 days) (Observer (physician) and self-rated) Side effects	*Neuropathy There was a significant difference in favour of imipramine compared to placebo (p=0.03) and mianserin (p=0.033) on the observer-rated score but not the self-rated score. There was no significant difference between mianserin and placebo. *Side effects The total adverse effect scores were significantly higher during mianserin (median 2.03, p=0.0093) and imipramine (median 4.00; p=0.0001) than during placebo (median 0.98) but there were no significant differences between the two active treatments. The most common side effects were dry mouth, orthostatic dizziness and fatigue. *Withdrawals N=4 N=1 due to adverse events (Imipramine)	Danish Diabetes Association
Sindrup SH, Gram LF, Skjold T et al. Clomipramine vs desipramine vs placebo in the	RCT 1+ double-blind crossover, single centre	N=26 (randomised)	Patients with diabetes and peripheral neuropathy Patient	Clomipramine: 75 mg/day (high metabolisers) 50 mg/day (low	Placebo	6 weeks (2 weeks per intervention)	Neuropathy observer scale (6 items) *Side effects	*Neuropathy There was a significant reduction on the observer and the self rating neuropathy scale in favour of clomipramine (p < 0.05) and desipramine (p < 0.05 and p < 0.01) both compared to placebo (p<0.05). There were	Danish Diabetes Association

<p>treatment of diabetic neuropathy symptoms. A double-blind crossover study. <i>British Journal of Clinical Pharmacology</i>. 1990; 30(5):683-691. Ref ID: 53</p>			<p>population (means: 55 yrs and duration of neuropathy 5 yrs)</p>	<p>metabolisers) Desipramine: 200 mg/day (high metabolisers) 50 mg/day (low metabolisers) Drug doses were adjusted according to the spartein phenotype as the metabolism of clomipramine and desipramine to some extent on the basis of the sparteine oxygenase</p>				<p>no statistically significant differences between the two treatments. The median reduction as compared with placebo was on clomipramine 39% (95% CI 27 to 79%). And desipramine 32% (0 to 46%).</p> <p>*Side effects The total side effect score was significantly higher for clomipramine (median 4.0) and desipramine (median 4.5) than during placebo (median 0.02; p < 0.05 for both).</p> <p>There were no statistically significant differences between clomipramine and desipramine.</p> <p>The most common side effects were dry mouth, sweating, orthostatic dizziness and fatigue.</p> <p>*Withdrawals N=6 (all due to side effects 3 each during clomipramine and desipramine)</p>	
<p>Kvinesdal B, Molin J, Froland A, Gram LF. Imipramine treatment of painful diabetic neuropathy. <i>JAMA</i> 1984; 251(13):1727-1730. Ref ID: 3271</p>	<p>RCT 1-fixed-dose double blind, crossover</p>	<p>15 patients recruited from a diabetic clinic</p>	<p>Inclusion criteria: T2D with several of the following neurological signs of neuropathy: impaired vibration, sense, impaired</p>	<p>Placebo</p>	<p>Imipramine</p>	<p>10 weeks crossover treatment (5 – 5) No washout period</p>	<p>PPG 6-item neuropathy scale, including pain, dysesthesia, paresthesia, numbness, nocturnal deterioration</p>	<p>* Global Assessment of improvement It showed notable improvement in the imipramine period in 7 patients and in no patients in the placebo period (p<0.02)</p> <p>* Neuropathy scale It showed a tendency toward a placebo response with 2 patients showing notable response and 2 partial response in the placebo period.</p> <p>* Clinical evaluation</p>	<p>Dumex Ltd</p>

¹ (0 no effect, + doubtful/some effect. ++ notable effect)

			<p>position sense, reduced reflexes, and reduced sensibility.</p> <p>Exclusion criteria: patients with foot ulcers, intermittent claudication, amputations, renal or cardiac dysfunction, or anemia.</p> <p>Characteristics: 12 patients who had diabetes for ten to 45 years and signs and symptoms of neuropathy for at least 2 years. Their insulin doses varied from 24 to 68 IU/day.</p>				<p>and sleep disturbances</p> <p>Global assessment of improvement¹</p>	<p>No changes in the neurological signs of neuropathy could be detected.</p> <p>*Adverse Events 2 patients complained of dizziness, and one of them dropped out for this reason. Dryness of the mouth was reported in 9 patients during imipramine treatment and in one patient during placebo therapy. Two patients complained of impaired micturition during imipramine treatment.</p> <p>Discontinuation rate 3 patient dropped out because of compliance problems (2) and side effects – dizziness and orthostatic hypotension (1).</p>	
Max MB, Kishore KR, Schafer SC et al. Efficacy of desipramine in	RCT 1-Double-blind, crossover, single	N=24 (randomised)	Patients with painful diabetic neuropathy.	4 week drug-free baseline 6-week treatment phase consisting	Protocol as for intervention Active placebo benzotropine	6 weeks (per intervention)	Pain diary Pain intensity	*Pain Within-group comparison showed that desipramine gave superior pain control compared with placebo (p < 0.01, 2-tailed paired t test).	

<p>painful diabetic neuropathy: a placebo-controlled trial. <i>Pain</i>. 1991; 45(1):3-9. Ref ID: 3270</p>	<p>centre</p>		<p>Inclusion criteria: signs and symptoms of diffuse, predominantly sensory neuropathy or single or multiple mononeuropathy and daily pain for at least 3 months</p> <p>Exclusion criteria: Presence of another type of pain and severe depression</p> <p>Patient population: median duration of pain 24 months, median age 62 yrs and 63% male</p>	<p>of: 2 week titration phase: Desipramine 12.5 to 250 mg/day 2 week maintenance phase</p>	<p>0.5 to 1 mg/day</p>	<p>No washout period</p>		<p>11/20 patients categorised their pain relief as moderate or better compared to 2/20 on placebo.</p> <p>Steady burning pain was significantly reduced on desipramine, relative to placebo ($p < 0.05$, 2-tailed paired t test). There were no significant differences for steady aching pain, brief pain, intensity of mechanical and warm allodynia and cold hyperalgesia.</p> <p>*Study withdrawals N=4 N=2 due to adverse events whilst taking desipramine</p> <p>Side effects during 6 week treatment period %</p> <table border="1" data-bbox="1536 794 2033 1102"> <thead> <tr> <th></th> <th>Desipramine</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>Dry mouth</td> <td>40</td> <td>45</td> </tr> <tr> <td>Sedation</td> <td>40</td> <td>40</td> </tr> <tr> <td>Insomnia</td> <td>35</td> <td>15</td> </tr> <tr> <td>Constipation</td> <td>30</td> <td>20</td> </tr> <tr> <td>Orthostatic - hypertension</td> <td>30</td> <td>5</td> </tr> <tr> <td>Palpitations</td> <td>15</td> <td>5</td> </tr> <tr> <td>Increased sweating</td> <td>15</td> <td>5</td> </tr> <tr> <td>Any side effect</td> <td>90</td> <td>85</td> </tr> </tbody> </table>		Desipramine	Placebo	Dry mouth	40	45	Sedation	40	40	Insomnia	35	15	Constipation	30	20	Orthostatic - hypertension	30	5	Palpitations	15	5	Increased sweating	15	5	Any side effect	90	85	
	Desipramine	Placebo																																		
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Orthostatic - hypertension	30	5																																		
Palpitations	15	5																																		
Increased sweating	15	5																																		
Any side effect	90	85																																		
<p>Max MB CM. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed</p>	<p>RCT 1-double-blind cross-over, single</p>	<p>N=37 (randomised)</p>	<p>Inclusion criteria: Patients with diabetes (fasting blood</p>	<p>Amitriptyline (N=29) 2 week drug-free baseline 6 week treatment</p>	<p>Placebo (N=29) 2 week drug-free baseline 6 week</p>	<p>6 weeks</p>	<p>Pain diary Hamilton Depression Scale (21 items) POMS-D</p>	<p>*Pain relief 23/29 patients reported less pain during amitriptyline than placebo, 1 had less pain with placebo, and 5 reported similar levels of pain during the two phases ($p < 0.0001$, sign test). Amitriptyline significantly reduced pain</p>	<p>None stated</p>																											

<p>mood. <i>Neurology</i>. 1987; 37(4):589-596. Ref ID: 3272</p>	<p>centre</p>		<p>glucose over 180 mg/dl on at least one occasion) with diffuse, predominately sensory neuropathy or mononeuropathy and pain during some part of every day</p> <p>Exclusion criteria included: evidence on another etiology for neuropathy and contraindications to amitriptyline therapy (eg unstable cardiovascular disease, heart block)</p> <p>Patient population: 59% male, median duration of diabetes 11 yrs, median</p>	<p>period: One to six 25-mg tablets</p>	<p>treatment period: One capsule of 1mg benzotropine (to produce dry mouth) and Nought to Five lactose capsules at bedtime. During the first 18 days, 5 mg of diazepam was added to mimic initial sedative effects of amitriptyline.</p>	<p>Depression Adjective Checklist (DACL) Adverse events</p>	<p>compared to placebo at weeks 3 to 6 (p<0.05, week 3; p<0.01, weeks 4 to 6, unpaired t-test) but only in patients who received placebo and then amitriptyline.</p> <p>The mean dose of amitriptyline was 90mg nightly</p> <p>*Mood change There was no significant difference between the groups on the Hamilton and POMS-D scores. Depression scores on the DACL were significantly lower after amitriptyline than placebo (median scores: amitriptyline 7, placebo 8, p<0.01, Wilcoxon paired signed-rank test) but not with placebo.</p> <p>*Adverse events 28/29 patients reported side effects during amitriptyline treatment:</p> <table border="0"> <tr><td>Dry mouth</td><td>26</td></tr> <tr><td>Sedation</td><td>19</td></tr> <tr><td>Dizziness</td><td>8</td></tr> <tr><td>Constipation</td><td>4</td></tr> <tr><td>Depression</td><td>2</td></tr> <tr><td>Tinnitus</td><td>1</td></tr> <tr><td>Urinary frequency</td><td>1</td></tr> <tr><td>Jitteriness</td><td>1</td></tr> <tr><td>Leg weakness</td><td>1</td></tr> <tr><td>Muscle cramps</td><td>1</td></tr> <tr><td>Unsteadiness</td><td>1</td></tr> <tr><td>Itching</td><td>1</td></tr> </table> <p>There were no significant difference in the incidence of side effects on amitriptyline compared with placebo</p> <p>*Study withdrawals</p>	Dry mouth	26	Sedation	19	Dizziness	8	Constipation	4	Depression	2	Tinnitus	1	Urinary frequency	1	Jitteriness	1	Leg weakness	1	Muscle cramps	1	Unsteadiness	1	Itching	1	
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			duration of pain 2 yrs, 24 patients had polyneuropathy, 21 were being treated with insulin.					N=8 (5 due to side effects)	
Sindrup SH EB. Imipramine treatment in diabetic neuropathy: relief of subjective symptoms without changes in peripheral and autonomic nerve function. European journal of clinical pharmacology 1989; 37(2):151-153. Ref ID: 3273	RCT 1- Double blind – cross over	13	Diabetics with one or more symptoms and signs of peripheral neuropathy. None of the patients had an ankle/arm systolic blood pressure index below 0.8, or serum creatinine >130 uM, and none was suspected of alcohol abuse or current depression.	Imipramine The treatment sequence was imipramine-placebo in 6 patients and placebo-imipramine in 3.	Placebo	1 week dose ranging 6 weeks of crossover treatment (3-3). No washout period	6-item neuropathy scale, including pain, dysesthesia, paresthesia, numbness, nocturnal deterioration and sleep disturbances	*Neuropathy scale Eight patients had a lower score on the neuropathy scale during imipramine treatment, an one had the same score in the two periods. (p<0.01) Eight patients felt most relieved of symptoms during imipramine and on during placebo (p<0.01) The measurement during placebo and imipramine vibration threshold on the finger and toe, temperature sensation, motor nerve conduction in the ulnar and peroneal nerves, sensory nerve conduction in the ulnar and sural nerves and test of autonomic nerve function never changed significantly. *Adverse Events During imipramine, significantly higher side-effects scores were recorded than during placebo. Eight patients complained of a dry mouth during imipramine, whereas this symptom was also present in 4 patients on placebo. Discontinuation rate 3 patients withdrew because of dizziness (2 on placebo, 1 on imipramine)	Ciba-geigy

								1 patient was excluded after having had acute myocardial infarction in the preliminary phase.	
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