

## Evidence Tables

### NEUR4: Is carbamazepine 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																		
Gomez PF, Choza R, Rios JM, Reza A, Huerta E, Aguilar CA et al. Nortriptyline-fluphenazine vs. carbamazepine in the symptomatic treatment of diabetic neuropathy. Archives of Medical Research 1996; 27(4):525-529. Ref ID: 3293	RCT Double blind, crossover  1+	16	Inclusion criteria: Diabetic patients with severe manifestations of symmetric, distal, mainly sensorial, peripheral neuropathy of at least 6 months duration and an abnormally prolonged motor nerve conduction velocity assessment.  Exclusion criteria: if patients did not fit the age	<b>Sequence A</b>  1. Nortriptyline-fluphenazine (10mg nortriptyline, 0.5mg fluphenazine per tablet)  2. Carbamazepine 200mg <sup>1</sup>	<b>Sequence B</b>  1. Carbamazepine 200mg <sup>2</sup>  2. Nortriptyline-fluphenazine (10mg nortriptyline, 0.5mg fluphenazine per tablet)	~10-12 weeks  4 weeks of therapy 2-4 washout period 4 weeks of therapy	VAS for the analysis of pain and paraesthesia	* VAS Both therapies produced significant reductions of paraesthesia and pain; however, no statistically significant differences were observed between both therapies for pain and paraesthesia.  No significant biochemical changes were observed with any of the two therapies  Adverse Events AEs were mild and more frequent in the NF treatment period. No patient was discharged from the study because of side effects.  <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">Symptoms</th> <th style="text-align: center;">NF</th> <th style="text-align: center;">CMZ</th> </tr> </thead> <tbody> <tr> <td>Dryness of mouth</td> <td style="text-align: center;">2</td> <td style="text-align: center;">0</td> </tr> <tr> <td>Dizziness</td> <td style="text-align: center;">3</td> <td style="text-align: center;">0</td> </tr> <tr> <td>Constipation</td> <td style="text-align: center;">2</td> <td style="text-align: center;">1</td> </tr> <tr> <td>Nausea</td> <td style="text-align: center;">1</td> <td style="text-align: center;">1</td> </tr> <tr> <td>Epigastric pain</td> <td style="text-align: center;">0</td> <td style="text-align: center;">1</td> </tr> </tbody> </table>	Symptoms	NF	CMZ	Dryness of mouth	2	0	Dizziness	3	0	Constipation	2	1	Nausea	1	1	Epigastric pain	0	1	Bristol-Myers-Squibb  Ciba-Geigy
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**Comment [JD1]:** Tricyclic antidepressants have been shown to block the norepinephrine reuptake at the first synapses level of the pain transmittin pathways, with this effect increasing the inhibitory action of norepinephrine on the spinal cord neurons involved in the nociceptive perception. Fluphenazine, like other phenothiazines, bind and blocks postsynaptic dopamine receptor site in the brain and some of them bind to opiate receptors.

With regard to CMZ, its mechanism of action as an analgesics has not been elucidated. Taking into consideration the available information, it could be postulated that this may result from a n increase in the rate of firing of noradrenergic neurons in the locus ceruleus induced by the drug

<sup>1</sup> Carbamazepine: ½ tablet TID for 2 weeks and 1 tablet TID for the next 2 weeks. NF: 1 tablet TID for 2 weeks and 2 tablets TID for the next 2 weeks. In sequence A, patients were started on NF and were crossed over to CMZ, while in sequence B patients received CMZ from the beginning

<sup>2</sup> Carbamazepine: ½ tablet TID for 2 weeks and 1 tablet TID for the next 2 weeks. NF: 1 tablet TID for 2 weeks and 2 tablets TID for the next 2 weeks. In sequence A, patients were started on NF and were crossed over to CMZ, while in sequence B patients received CMZ from the beginning

			limits, demonstrated only mild manifestations of DPN, normal nerve conduction or any important disease.  No statistically significant differences were observed in baseline characteristics between patients on both sequences.						
Rull JA, Quibrera R, Gonzalez MH, Lozano CO. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. Diabetologia 1969; 5(4):215-218. Ref ID: 3292	RCT double blind, crossover  1-??	30 diabetic patients	Inclusion criteria: all cases were of more than one months' duration , and most were moderate or severe in intensity. Each patient was asked to describe his symptoms in his own words, and the terms employed were	Carbamazepin e <sup>3</sup> (A)  Sequence 1 A→B→A N=14	Placebo (B)  Sequence 2 B→A→B N= 16	6 weeks  3 periods of 2 weeks	Symptoms were graded from 0 (no change) to 5- (disappearance) or 5+ (maximal increase)	* There were no major changes in body weight or diabetic control during the trial.  * The group placed on the A→B→A sequenced (CBZ – placebo – CBZ) shows a definite decrease in intensity , extension and duration of symptoms after the first period of CBAZ administration. Improvement persisted on some patients when changed to placebo, whereas in others there was a relapse. In contrast, resumption of CBZ was followed by a new general decrease in complaints.  * Patients on the B→A→B sequence (placebo – CBZ – placebo) demonstrated a different pattern. At the end of the first B	Geigy

**Comment [JD2]:** This study is subject to the following limitations  
1)it was based on subjective evaluations made by each patient.  
2)The complete efficacy of the double blind system can be questioned, since the frequency of secondary effects may serve as an identifying clue to both the patient and the treating physician.  
3)The two week periods proven to be too short, and there was considerable residual action of the durg during the placebo administration.

<sup>3</sup> Carbamazepine tablets contained 200mg each, an in most instances the daily dose was 600mg.

			used throughout the study to assess the changes in intensity, extension and duration of complaints at each subsequent visit.					<p>period, few or no changes were reported. On beginning therapy with CBZ, a general decrease in the symptomatology was the distinctive feature. After the second placebo period most patients relapsed, although a certain degree of improvement persisted in some.</p> <p>* Overall, a marked decrease in complaints at the end of every CBZ period can be observed in both groups, with minor improvement, no change or exacerbation following placebo administration</p>
<p>Dogra, S. Beydoun, J. Mazzola, M. Hopwood, and Y. Wan. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. <i>European Journal of Pain: Ejp</i> 9 (5):543-554, 2005.</p>	<p>RCT doubleblind, multicentre USA and Canada</p>	<p>N=146 (randomised and ITT population ) N=119 (PP population )</p>	<p>Patients with type 1 and type 2 diabetes ≥ 18 years of age</p> <p>Inclusion criteria included stable diabetic control, history of neuropathic pain range 6 mths to 5 years, pain rating on VAS of ≥ 50 units and ≤ 25% variation in severity of pain in the 7 days prior to randomisation</p> <p>Exclusion criteria:</p>	<p>Pre-randomisation (2 weeks)</p> <p>Oxcarbazepine(N=69)</p> <p>Treatment (18 weeks) comprising:</p> <p>Titration phase (4 weeks)</p> <p>Titration phase: Initially 300 mg/day increased to 300mg twice-daily three days later. Then titrated to target dose of 900 mg twice-daily in increments of 300 mg every five days</p>	<p>Placebo (N=77)</p> <p>As for intervention</p>	<p>VAS (0-100 units)</p> <p>GATE</p> <p>Daily sleep questionnaire (3 items)</p> <p>SF-36</p> <p>POMS</p> <p>Adverse events</p>	<p>16 weeks</p>	<p>*VAS</p> <p>Patients treated with oxcarbazepine experienced a significantly larger decrease from baseline in average VAS scores compared with placebo (mean change -24.3 (SD 27.2) vs. -14.7 (26.4) respectively; p=0.0108) (mean endpoints 48 vs 60).</p> <p>At end-point, a significantly greater proportion of oxcarbazepine patients experienced a &gt;50% (35.2% vs 18.4%, respectively; p=0.0256) and 30% (45.6% vs 28.9%, respectively; p=0.0288) reduction from baseline in VAS score compared with placebo-treated patients.</p> <p>The number needed to treat (NNT) for a 50% and 30% reduction from baseline in VAS score was 6.0.</p> <p>*GATE</p> <p>At end-point, 73% of oxcarbazepine-treated patients compared with 40% placebo-treated had some improvement ('slight', 'much' or 'very much' improved) (p=0.0003). 48% of oxcarbazepine-patients compared to 22% placebo-treated patients were 'very much' or</p>

		<p>Currently or previously taken oxcarbazepine, history of renal insufficiency, hyponatraemia chronic infectious disease and medications (other than those specified) likely to affect neuropathic pain</p> <p>Patient population (means): Age 58 yrs, duration of diabetes 14.4 yrs, mean HbA1c 7.6%, duration of neuropathy 2.7 yrs and mean VAS score 72.9.</p> <p>The groups were well-matched at baseline</p>	<p>Maintenance phase (12 weeks) Dose maintained at that reached by day 28</p> <p>Follow-up (2 weeks safety monitoring)</p> <p>Note: Rescue medication of 4g acetaminophen daily. Benzodiazepines (excluding clonazepam) and SSRIs permitted</p>			<p>'much' improved (p=0.0025).</p> <p>The NNT for 'much' or 'very much' improved rating was 3.9</p> <p>*Sleep The mean proportion of days that patients were awakened during the night due to pain was lower in oxcarbazepine-treated patients compared with the placebo group (31% vs 49% of study days; p=0.02).</p> <p>*Quality of life There were no differences between the groups on the SF-36 scales except aggregate mental health where there was a significant difference in favour of oxcarbazepine (oxcarbazepine vs placebo, 47.2 vs 50.2, respectively; p=0.03).</p> <p>There were no significant differences on the POMS total mood score.</p> <p>*Adverse events Serious adverse events occurred in 10% (7/69) (3 treatment related) oxcarbazepine-treated patients and 4% (3/77) of placebo treated patients.</p> <p>The most frequently occurring adverse events (<math>\geq 10\%</math> titration period) (top 5 extracted):</p> <table border="1"> <thead> <tr> <th></th> <th>Oxcarbazepine (n=55)</th> <th>Placebo (n=70)</th> </tr> </thead> <tbody> <tr> <td>Dizziness</td> <td>31 (44.9)</td> <td>6 (7.8)</td> </tr> <tr> <td>Headache</td> <td>17 (24.6)</td> <td>6 (7.8)</td> </tr> <tr> <td>Nausea</td> <td>16 (23.2)</td> <td>7 (9.1)</td> </tr> <tr> <td>Somnolence</td> <td>8 (11.6)</td> <td>2 (2.6)</td> </tr> <tr> <td>Fatigue</td> <td>8 (11.6)</td> <td>5 (6.5)</td> </tr> </tbody> </table>		Oxcarbazepine (n=55)	Placebo (n=70)	Dizziness	31 (44.9)	6 (7.8)	Headache	17 (24.6)	6 (7.8)	Nausea	16 (23.2)	7 (9.1)	Somnolence	8 (11.6)	2 (2.6)	Fatigue	8 (11.6)	5 (6.5)	
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<p>Beydoun A, Shaibani A, Hopwood M et al. Oxcarbazepine in painful diabetic neuropathy: results of a dose-ranging study. <i>Acta Neurologica Scandinavica</i>. 2006; 113(6):395-404. Ref ID: 7</p>	<p>RCT double blind, multicentre USA</p>	<p>N=347 (ITT and completer population)</p>	<p>Patients with type 1 and type 2 diabetes</p> <p>Inclusion criteria: &gt; 18 yrs, pain attributed to diabetic neuropathy for 6 months to 5 yrs, score of 50 units on a 100 unit scale (VAS). Patients had to be tapered off and totally withdrawn from their current neuropathic</p>	<p>Oxcarbazepine :</p> <p>600 mg/day (n=83)</p> <p>1,200 mg/day (n=87)</p> <p>1,800 mg/day (n=88)</p> <p>Titration phase (4 weeks): At visit 2 one 300mg tablet for the next two days, Fourth day patients titrated to one</p>	<p>Placebo (n=89)</p> <p>Schedule as for intervention</p> <p>Plus rescue medication</p>	<p>16 weeks</p>	<p>VAS score GATE (Global Assessment of Therapeutic Effect) (-3 very much improved to 3 very much deteriorated) Quality of life Adverse events</p>	<p>*VAS score</p> <p>At week 12, there were no significant differences in mean VAS scores among the treatment groups<sup>4</sup>. The weekly average VAS scores were significantly different, favouring oxcarbazepine 1,200 (38.2% mean improvement from baseline) and 1,800 mg/day (37.2%) compared to placebo (vs 27.1%; <math>p &lt; 0.05</math>).</p> <p>For the completed patient population, there was a significant improvement in mean VAS scores (49.2 vs 33.7; <math>p=0.034</math>), during the last week of double-blind treatment, favouring oxcarbazepine 1,800 mg/day group compared to placebo<sup>2</sup>.</p> <p><sup>1</sup> Treatment groups were compared using analysis of covariance that adjusted for center and average VAS scores during the week prior to randomisation</p>																		

			<p>pain treatment for at least 2 weeks prior to randomisation</p> <p>Patient population (means): age 60.7 yrs, duration of diabetes 10.5 yrs, HbA1c 7.5%, duration of neuropathic pain 2.8 yrs, mean VAS 73.7 and 55% were male. There were no significant differences between the groups at baseline</p>	<p>tablet BD. Thereafter the dose was increased by one tablet until the target dose.</p> <p>12 week maintenance: Dose reductions were allowed if there were tolerability problems phase</p> <p>Rescue medication of acetaminophen to a maximum of 4g/day.</p>				<p><sup>2</sup> The results of the 'completer' analysis should be interpreted with caution due to the high withdrawal rate, especially in the oxcarbazepine 1200/1800 mg/day groups</p> <p>*GATE There were no significant difference between the oxcarbazepine groups and placebo on the GATE.</p> <p>The number need to treat and the number of patients needed to harm were oxcarbazepine 600 mg/d (NA and 24.4), 1,200 mg/d (7.9 and 6.2) and 1800 mg/d (8.3 and 2.9)</p> <p>Quality of life There were no significant differences between the oxcarbazepine groups and placebo on the SF-36 or POMS (Profile of Mood States)</p> <p>*Adverse events One patient in the oxcarbazepine group experienced a serious adverse event (dysarthria, nausea and vomiting) thought to be related to the study drug.</p> <p>The number of patients needed to harm (NNH) were 24.2, 6.2 and 2.9 in the oxcarbazepine 600-, 1,200 and 1,800 mg/day groups, respectively.</p> <p>Clinically notable decreases in serum sodium were (&lt;125 mmol/L) were observed in four patients in the 1,200 mg/day and two patients in the oxcarbazepine 1,800 mg/day. The most frequently occurring adverse events (experienced by ≥0% in any of the</p>	
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								<p>four groups) during titration and maintenance periods:</p> <p>600 1,200 1,800 Plac. Oxcarbazepine mg/day</p> <p>Dizziness 5(6.0) 16(18.8) 30(34.5) 2(2.2) Tremor 1 (1.2) 1(1.2) 11(12.6) 2(2.2) Headache 9(10.8) 9(10.6) 10(11.5) 7(7.9) Nausea 2(2.4) 13(15.3) 17(19.5) 5(5.6) Somnolence 2(2.4) 5(5.9) 9(10.3) 3(3.4) Fatigue 4(4.8) 11(12.9) 13(14.9) 6(6.7)</p> <p>*Study withdrawals Oxcarbazepine 600 mg/day 16/83 Oxcarbazepine 1200 mg/day 34/87 Oxcarbazepine 1800 mg/day 48/88 Placebo 17/72</p>	
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