



Painful Diabetic Neuropathy: Why Treatment Response Stays Poor and What Patients Actually Report

Andrin Bucher^{1*}, Ana Rozman² and Fergal O'Rourke³

¹Department of Neurology, Ticino Metabolic Centre, Lugano, Switzerland

²Department of Pain Medicine, Julian Institute of Endocrinology, Kranj, Slovenia

³Department of Clinical Pharmacology, Barrow Institute of Diabetes Care, Kilkenny, Ireland

*Correspondence to: Andrin Bucher, Department of Neurology, Ticino Metabolic Centre, Lugano, Switzerland

Received: 7 February 2024; Accepted: 23 July 2024; Published: 30 October 2024

Copyright: © 2024 Bucher A. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Roughly a quarter of people with diabetes experience painful neuropathy, and the drugs recommended for it have not changed materially in twenty years. A multicentre randomised crossover trial compared three first-line pathways in 130 patients across 13 centres and found them equivalent: mean pain fell from 6.6 to 3.3 on an eleven-point scale in all three, with a difference between pathways of -0.1 (98.3% CI -0.5 to 0.3). Pooled analyses put the number needed to treat for meaningful pain relief at about 5 for both duloxetine and pregabalin, against a number needed to harm of 15 for withdrawal due to adverse effects. The trial team stated the ceiling plainly: the best achievable with any monotherapy is 50 per cent pain relief in 50 per cent of patients, with side effects in 10 to 20 per cent depending on dose. This review sets out why the choice between first-line drugs matters less than it is usually made to, and what the trial data say about what patients experience.

Keywords: Painful diabetic neuropathy; Neuropathic pain; Duloxetine; Pregabalin; Number needed to treat

Introduction

Distal symmetrical polyneuropathy is the commonest complication of diabetes, and about a quarter of people with diabetes experience the painful form of it [1,2]. The pain is typically burning, worse at night, and associated with sleep disturbance, emotional distress and reduced quality of life [31,32,33], together with reduced function and low mood [3,4].

National guidance recommends amitriptyline, duloxetine, pregabalin or gabapentin as initial treatment, all licensed for the indication except amitriptyline, which has been used off-licence for more than 25 years [5,6]. Cochrane reviews and meta-analyses support moderate efficacy for each [7,8,9]. European and international guidance reaches similar conclusions [26,34], and network meta-analysis has compared the options indirectly [27].

Until recently there was little direct comparison between them, and the choice was made on side-effect profile and prescriber habit [5,10,20]. The individual placebo-controlled trials that established each drug date from the preceding two decades [28,29,30]. This review examines what the comparative

evidence now shows and why response remains poor.

Material and Methods

Search strategy: PubMed and the archives of the major diabetes, neurology and pain journals were searched for studies of pharmacological treatment of painful diabetic neuropathy. Search terms combined diabetic peripheral neuropathic pain with duloxetine, pregabalin, amitriptyline, gabapentin, number needed to treat and randomised trial. Reference lists of the principal comparative trial [11] and its technology assessment [12] were screened by hand for primary sources.

Eligibility: Studies were included if they reported analgesic outcomes in defined populations with painful diabetic neuropathy, or synthesised such studies. Guidance documents are cited for the recommendations they contain and are identified as such.

Data extraction and handling: Design, population, comparator, the responder definition used and the reported estimate were extracted as published. The responder threshold is stated alongside every figure, because 30 per cent and 50 per

cent pain reduction produce materially different numbers from the same data. This review reports trial findings; doses are given as used in the trials and this article does not constitute prescribing guidance. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The comparative trial: A multicentre, double-blind, randomised crossover trial recruited from 13 UK centres between November 2017 and July 2019. Eligible patients had a mean daily pain score of 4 or above on an eleven-point numerical rating scale. Participants received three treatment pathways in randomised order, each lasting 16 weeks: amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin. Monotherapy ran for six weeks and the second drug was added if pain relief remained suboptimal, defined as a score above 3. Doses were titrated to maximum tolerated, being 75 mg daily for amitriptyline, 120 mg for duloxetine and 600 mg for pregabalin [11,12].

Who completed it: Of 252 patients screened, 140 were randomised, 130 started a pathway and 84 completed at least two pathways and contributed to the primary analysis (Figure 5) [11].

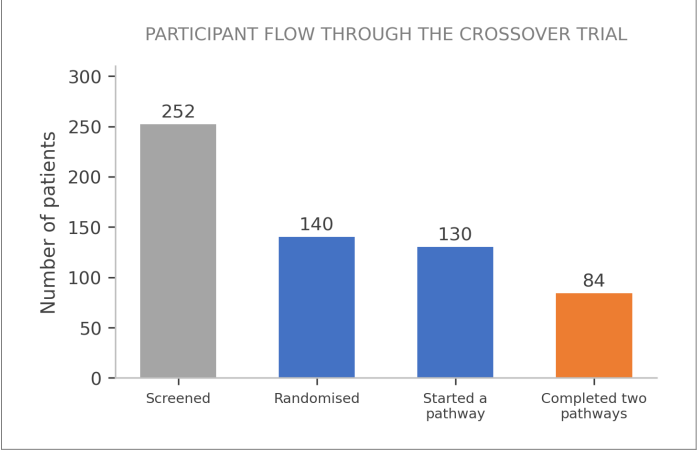


Figure 5: Participant flow through the crossover trial [11]

The three pathways performed identically: Seven-day average pain scores fell from a mean of 6.6 (SD 1.5) at baseline to 3.3 (1.8) at week 16 in all three pathways (Figure 1). The mean difference between pathways was -0.1 (98.3% CI -0.5 to 0.3) (Figure 2) [11]. Combination therapy improved pain further regardless of which drug was started first [11,13].

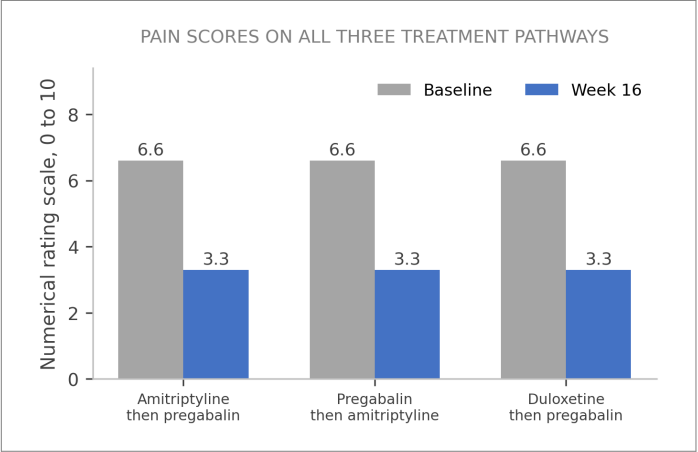


Figure 1: Pain scores at baseline and week 16 on all three pathways [11]

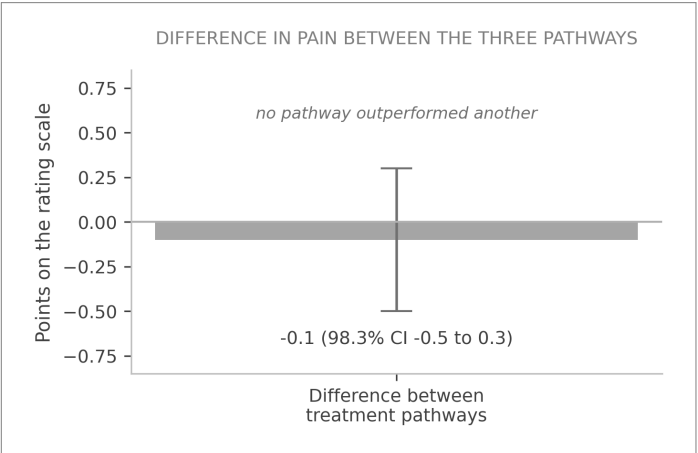


Figure 2: Difference in pain between the three treatment pathways [11]

Pathway	Monotherapy	Supplement	Result
A-P	Amitriptyline 75 mg	Pregabalin	6.6 to 3.3
P-A	Pregabalin 600 mg	Amitriptyline	6.6 to 3.3
D-P	Duloxetine 120 mg	Pregabalin	6.6 to 3.3
Difference	—	—	-0.1 (98.3% CI -0.5 to 0.3)

Table 1: The three treatment pathways and their outcomes, as reported by the original investigators [11]

How many benefit: Pooled analysis estimated the number needed to treat for improvement in pain at 5 for duloxetine (95% CI 3 to 7) and 5 for pregabalin (95% CI 4 to 8) [14]. A separate pooled analysis of six placebo-controlled trials with 1,696 patients reported a number needed to treat of 5.8 (95% CI 4.5 to 8.4) for duloxetine 60 mg and 5.7 (4.5 to 5.7) for 120 mg, using a threshold of at least 50 per cent pain relief at 12 to 13 weeks (Figure 3) [15]. What counts as a clinically important change on this scale has been defined both empirically and by consensus [21,22].

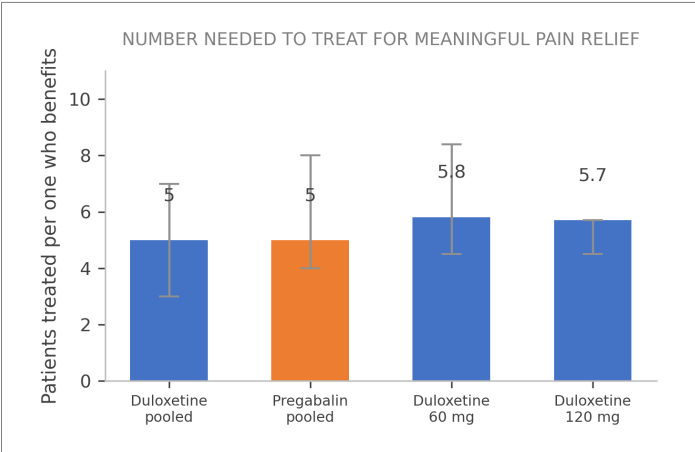


Figure 3: Number needed to treat for meaningful pain relief [14,15]

Benefit against harm: In the same pooled analysis, combining all doses of duloxetine gave fewer withdrawals for lack of efficacy than placebo, with a number needed to treat of 20 (13 to 42) to prevent one such withdrawal, but more withdrawals for adverse events, with a number needed to harm of 15 (11 to 25) (Figure 4) [15]. Adverse effects reported across this drug class include dry mouth, constipation, sedation, dizziness, falls, nausea and oedema, occurring in roughly 10 to 20 per cent of patients depending on dose [5,12].

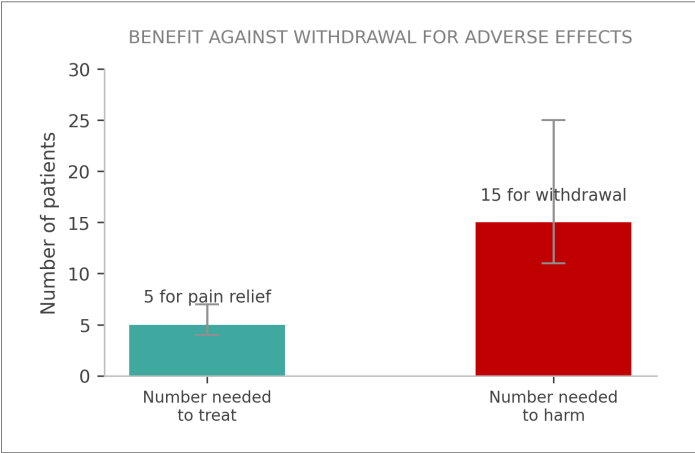


Figure 4: Number needed to treat against number needed to harm for duloxetine [15]

The ceiling, stated by the trialists: The investigators behind the comparative trial set out the position directly in their technology assessment: the best that can be expected from any monotherapy is 50 per cent pain relief in 50 per cent of patients, frequently accompanied by side effects (Figure 6) [12]. Individual placebo-controlled trials are consistent with this. Pregabalin at 600 mg daily in 82 patients against 85 on placebo produced a mean difference in pain score of -1.28 ($p < 0.001$) on an eleven-point scale, with no significant change in nerve conduction [16].

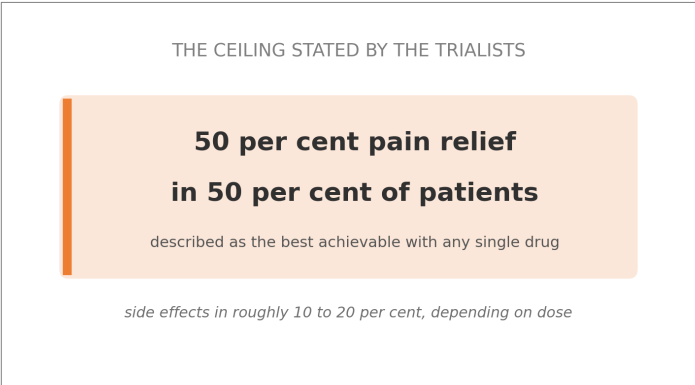


Figure 6: The treatment ceiling as stated by the trial investigators [12]

Measure	Reported value	Source
Number needed to treat, duloxetine	5 (95% CI 3 to 7)	Pooled analysis [14]
Number needed to treat, pregabalin	5 (95% CI 4 to 8)	Pooled analysis [14]
Number needed to harm, duloxetine	15 (11 to 25)	Six trials, 1,696 patients [15]
Difference between pathways	-0.1 points	Crossover trial [11]
Side effects	10% to 20% by dose	Guideline commentary [5,12]

Table 2: Key quantitative findings and their source

Question	What the evidence supports
Which first-line drug is best?	None outperformed another [11]
Does combining them help?	Yes, regardless of starting drug [11,13]
How many get meaningful relief?	About one in five treated [14,15]
How many withdraw for side effects?	About one in fifteen [15]
Does treatment alter the neuropathy?	No; nerve conduction unchanged [16]

Table 3: What this literature can and cannot answer

What counts as a response: The thresholds used in these trials are not arbitrary. A reduction of about 30 per cent, or two or more points on an eleven-point scale, corresponds to a patient-reported impression of meaningful improvement, and 50 per cent to substantial improvement [21,22]. Because numbers needed to treat are calculated against one threshold or the other, figures quoted without the threshold attached are uninterpretable, and the same dataset yields materially different values at 30 and 50 per cent [15,21].

Where the guidance came from: The four recommended agents were established by placebo-controlled trials conducted between the early 1990s and the mid 2000s, each showing superiority over placebo but none against the others [28,29,30]. Successive guidelines have restated that list, and network meta-analysis attempted indirect comparison in the absence of head-to-head data [26,27,34]. The crossover trial is the first adequately powered direct comparison of the pathways as they are actually used [11,12].

Discussion

The most useful result is a null one. Three first-line pathways, tested head to head in the same patients, produced identical outcomes, with a difference of a tenth of a point on a ten-point scale [11]. The question most often asked in clinic, which of these drugs to try, does not have an answer because it does not have a difference. That reframes the decision as one about tolerability, comorbidity and cost rather than efficacy.

The size of the fall in pain, from 6.6 to 3.3, looks impressive and should be read carefully. This was a crossover trial without a placebo arm, so the reduction encompasses drug effect together with regression to the mean, natural fluctuation and expectation, and the design cannot separate them [11,12]. The placebo-controlled evidence gives a more modest estimate of the drug-attributable component, with a mean difference against placebo of about 1.3 points for pregabalin at full dose [16].

The numbers needed to treat are the honest summary of what a patient can expect. At around 5, four in five people given the drug do not achieve the response threshold, and with a number needed to harm of 15 for withdrawal, roughly one in fifteen stops because of adverse effects [14,15]. Set against a condition affecting a quarter of people with diabetes, that is a treatment offer with a low probability of substantial benefit, and it should be described as such at the outset rather than after three failed trials of medication.

The trialists themselves put the ceiling at 50 per cent relief in 50 per cent of patients [12]. That statement deserves more prominence than it gets, because the sequential prescribing pattern common in practice implicitly assumes that the next drug may succeed where the last failed. The comparative trial suggests that assumption is weakly founded for the first-line agents, though it did find that adding a second drug helped irrespective of which came first [11,13].

What the drugs do not do is worth stating. Pregabalin at full dose produced no significant change in nerve conduction velocity or amplitude across four nerves [16]. These are analgesics, not disease-modifying treatments, and the underlying neuropathy continues to progress on the trajectory set by glycaemic exposure and other risk factors [1,17,23,24,25]. Enhanced glycaemic control has itself been examined as a preventive measure, with limited effect in type 2 diabetes [17]. A patient told that treatment is available may reasonably infer more than that.

The burden of the condition gives these modest treatment effects their weight. Painful neuropathy is associated with sleep disturbance, emotional distress and reduced quality of life, and carries measurable economic costs across European health systems [31,32]. A treatment that helps one patient in five is not negligible against that background; the objection is to presenting it as more reliable than it is [33].

The absence of disease modification is the gap that matters most. Enhanced glycaemic control has been examined as a

preventive strategy and has limited effect on established neuropathy in type 2 diabetes [17,23]. Nothing in current practice slows the underlying nerve damage once pain has developed, which is why the analgesic ceiling described here is also, in effect, the ceiling of what can be offered [24,25].

Study limitations

The limitations belong to the underlying literature. The comparative trial randomised 140 patients and 84 completed at least two pathways, so the primary analysis rests on a modest sample [11]. It had no placebo arm, so the proportion of the observed benefit attributable to the drugs cannot be determined from it [11,12]. Crossover designs assume no carry-over between periods, and a two-week washout may be insufficient for drugs with prolonged central effects [12]. Numbers needed to treat are pooled across trials with differing responder thresholds, and a 30 per cent threshold yields a different figure from 50 per cent [14,15]. Most trials run 12 to 16 weeks against a condition lasting years, so durability is largely unknown [15,16]. Participants with significant depression or substance use are commonly excluded, though both are common in this population [4,12]. And the newer agents and non-pharmacological approaches were not compared in the same design, so their relative place is unresolved [18,19]. Spinal cord stimulation has been trialled in refractory cases and reported substantial benefit in a selected population [19].

2. Abbott CA, Malik RA, van Ross ERE, Kulkarni J, Boulton AJM. "Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the UK". *Diabetes Care* 34(2011):2220-2224.

Conclusion

Three recommended first-line drugs for painful diabetic neuropathy perform identically when compared directly, differing by a tenth of a point on a ten-point scale, so the choice between them is properly made on tolerability and comorbidity rather than expected efficacy. About one in five treated patients achieves the response threshold and about one in fifteen withdraws because of side effects. The investigators who ran the comparison stated the ceiling as 50 per cent relief in half of patients, and nothing in the subsequent literature has raised it. None of these drugs alters nerve conduction. Setting that expectation at the first consultation is more useful than discovering it after the third drug has failed.

Acknowledgements

The authors thank the investigators who conducted a direct comparison of first-line treatments, and the participants who completed three sequential treatment pathways over the better part of a year.

Funding

No dedicated funding from public, commercial or charitable sources supported the preparation of this review.

Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

- Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. "Diabetic neuropathy: a position statement by the American Diabetes Association". *Diabetes Care* 40(2017):136-154.
- Selvarajah D, Kar D, Khunti K, Davies MJ, Scott AR, Walker J, et al. "Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention". *Lancet Diabetes Endocrinol* 7(2019):938-948.
- Themistocleous AC, Ramirez JD, Shillo PR, Lees JG, Selvarajah D, Orengo C, et al. "The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy". *Pain* 157(2016):1132-1145.
- National Institute for Health and Care Excellence. "Neuropathic pain in adults: pharmacological management in non-specialist settings, clinical guideline CG173". NICE, London (2013, updated 2020).
- Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. "Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis". *Lancet Neurol* 14(2015):162-173.
- Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. "Pregabalin for acute and chronic pain in adults". *Cochrane Database Syst Rev* (2009):CD007076.
- Lunn MPT, Hughes RAC, Wiffen PJ. "Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia". *Cochrane Database Syst Rev* (2014):CD007115.
- Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. "Amitriptyline for neuropathic pain in adults". *Cochrane Database Syst Rev* (2015):CD008242.
- Waldfoegel JM, Nesbit SA, Dy SM, Sharma R, Zhang A, Wilson LM, et al. "Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life: a systematic review". *Neurology* 88(2017):1958-1967.
- Tesfaye S, Sloan G, Petrie J, White D, Bradburn M, Julious S, et al. "Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial". *Lancet* 400(2022):680-690.
- Tesfaye S, Sloan G, Petrie J, White D, Bradburn M, Young T, et al. "Optimal pharmacotherapy pathway in adults with diabetic peripheral neuropathic pain: the OPTION-DM RCT". *Health Technol Assess* 26(2022):1-100.
- Barry HC. "Amitriptyline, duloxetine, and pregabalin each effective in decreasing pain from diabetic peripheral neuropathy; combinations even better". *Am Fam Physician* 107(2023):319.
- Quilici S, Chancellor J, Lothgren M, Simon D, Said G, Le TK, et al. "Meta-analysis of duloxetine vs pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain". *BMC Neurol* 9(2009):6.
- Sultan A, Gaskell H, Derry S, Moore RA. "Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials". *BMC Neurol* 8(2008):29.
- Arezzo JC, Rosenstock J, LaMoreaux L, Pauer L. "Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial". *BMC Neurol* 8(2008):33.
- Callaghan BC, Little AA, Feldman EL, Hughes RAC. "Enhanced glucose control for preventing and treating diabetic neuropathy". *Cochrane Database Syst Rev* (2012):CD007543.
- BLOSSOM investigators. "Efficacy of pregabalin and duloxetine in patients with painful diabetic peripheral neuropathy: a multi-centre phase IV clinical trial". *Pharmaceuticals* 16(2023):1011.
- Petersen EA, Stauss TG, Scowcroft JA, Brooks ES, White JL, Sills SM, et al. "Effect of high-frequency spinal cord stimulation on painful diabetic neuropathy: a randomized clinical trial". *JAMA Neurol* 78(2021):687-698.
- Ziegler D, Fonseca V. "From guideline to patient: a review of recent recommendations for pharmacotherapy of painful diabetic neuropathy". *J Diabetes Complications* 29(2015):146-156.
- Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. "Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations". *J Pain* 9(2008):105-121.
- Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. "Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale". *Pain* 94(2001):149-158.
- Boulton AJM, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. "Diabetic neuropathies: a statement by the American Diabetes Association". *Diabetes Care* 28(2005):956-962.
- Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. "Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and

- treatments". *Diabetes Care* 33(2010):2285-2293.
25. Vinik AI, Nevoret ML, Casellini C, Parson H. "Diabetic neuropathy". *Endocrinol Metab Clin North Am* 42(2013):747-787.
 26. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. "EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision". *Eur J Neurol* 17(2010):1113-1123.
 27. Griebeler ML, Morey-Vargas OL, Brito JP, Tsapas A, Wang Z, Carranza Leon BG, et al. "Pharmacologic interventions for painful diabetic neuropathy: an umbrella systematic review and comparative effectiveness network meta-analysis". *Ann Intern Med* 161(2014):639-649.
 28. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. "Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial". *Pain* 110(2004):628-638.
 29. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. "Duloxetine vs placebo in patients with painful diabetic neuropathy". *Pain* 116(2005):109-118.
 30. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. "Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy". *N Engl J Med* 326(1992):1250-1256.
 31. Selvarajah D, Cash T, Sankar A, Thomas L, Davies J, Cachia E, et al. "The contributors of emotional distress in painful diabetic neuropathy". *Diab Vasc Dis Res* 11(2014):218-225.
 32. Alleman CJ, Westerhout KY, Hensen M, Chambers C, Stoker M, Long S, et al. "Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature". *Diabetes Res Clin Pract* 109(2015):215-225.
 33. Davies M, Brophy S, Williams R, Taylor A. "The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes". *Diabetes Care* 29(2006):1518-1522.
 34. Ziegler D, Papanas N, Schnell O, Nguyen BDT, Nguyen KT, Kulkantrakorn K, et al. "Current concepts in the management of diabetic polyneuropathy". *J Diabetes Investig* 12(2021):464-475.

Citation: Bucher A, Rozman A, O'Rourke F. "Painful Diabetic Neuropathy: Why Treatment Response Stays Poor and What Patients Actually Report". DOI: 10.5281/zenodo.22260618