

Painful Diabetic Neuropathy (PDN): An Update for Clinicians



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Neuropathy is one of the most common complications in both type I and type II diabetes mellitus. It can present in various forms, either focal or symmetrical.¹ The most common form is a chronic, symmetrical, length dependent axonal sensorimotor polyneuropathy. This disease can also affect the autonomic nervous system and plays an important role in other subsequent complications. Some patients are asymptomatic, but many patients have sensory symptoms, either negative or positive ones. These symptoms may fluctuate over time. Some of them also have pain associated with neuropathy, so called painful diabetic neuropathy (PDN).² As Jambart et al noted about Middle Eastern patients: “*The odds of painful DPN were highest among patients with peripheral vascular disease, diabetic retinopathy and diabetic nephropathy.*”³

Diabetes mellitus is also the most common cause of distal symmetric polyneuropathy.⁴ Therefore, it is the most common cause of neuropathic pain.⁵ The prevalence of neuropathic pain in the diabetic population varies enormously according to different studies which estimate a range between 3% and 50% of patients.^{3,6} A recent survey in the United Kingdom revealed the prevalence of 26.4% and 80% of patients reporting moderate to severe pain.⁷ Having PDN has a significant negative effect on the quality of life, especially the physical aspect, and a significantly worse trajectory of quality of life outcomes over time and long-term increased total costs.^{7,8}

PDN pain syndrome

The diagnosis of PDN is a clinical one, which relies on the patient’s description of pain. The symptoms are distal, symmetrical, often associated with nocturnal exacerbations, and commonly described as prickling, deep aching, sharp, like an electric shock, and burning with hyperalgesia and frequently allodynia upon examination.^{1,9} The symptoms are usually associated with the clinical signs of peripheral neuropathy, although occasionally in acute painful diabetic peripheral neuropathy (DPN), the symptoms may occur in the absence of signs.

Common painful symptoms also include sharp or lancinating pain attacks, allodynia, cramping and gnawing.^{10,11} These symptoms are commonly used in rating scales and standard pain questionnaires to assess frequency and severity of painful symptoms, and treatment response. Moreover, since each type of pain is believed to be caused by a different pathophysiological mechanism, therefore, each neuropathic pain medication might have a different effect on sensory symptoms.¹²

Despite the advances in neurophysiologic studies, diagnosis cannot be made without taking a full history and giving a physical examination. Incorporating standard pain questionnaires in clinical evaluation will also aid earlier diagnosis and better management in these patients.¹¹ In our study,¹³ we used the DN4 questionnaire, which has been validated as a reliable screening tool for neuropathic pain in diabetic patients.¹⁴ The questionnaires can be used to screen and differentiate between neuropathic and non-neuropathic pain.¹⁵ Almost all patients had more than one type of pain which adds more complexity to the clinical evaluation.¹³ This may imply that the mechanism of pain is most likely due to small nerve fibers, rather than large fiber dysfunction. Previous clinical and electrophysiological studies also confirmed that the neuropathic pain in diabetic polyneuropathy is not associated with the degree of involvement of large diameter sensory fibers or the severity of the diabetes.^{16,17} Interestingly, when looking at sharp pain, the duration of diabetes was not associated with painful symptoms.¹³ This was due to the natural history of small fiber neuropathy which can occur in the pre-diabetes stage.¹⁸ Although the pain of PDN may resolve completely over time in some patients, in those in whom painful neuropathic symptoms had persisted over 5 years, no significant improvement in pain intensity was observed.¹⁹

Impact of PDN upon quality of life

The presence of PDN significantly affected patients' quality of life, especially physical function. Moreover, it was associated with a significantly worse trajectory of quality of life outcomes over time and long-term increased total costs, when comparing to patients with non-painful diabetic polyneuropathy. The presence and severity of neuropathic pain were associated with greater impairments in a number of important Health Related Quality of Life (HRQoL) domains.^{8,16,20,21} Regarding the SF-36 subcategories, pain symptoms had more effect on physical function and role-physical, than social function and emotional well-being.¹³ This data was in line with previous reports in diabetic patients whether they had PDN or not.²²⁻²⁴ When comparing to other diabetic populations and other diseases, PDN patients had a poorer physical function than those with other chronic neurological illnesses or the general diabetic population.²⁵ Their QOL was similar to that of diabetic foot ulcer patients, which indicated severe disability.

A recent American Academy of Neurology evidence-based review has used Visual Analog Scale (VAS) as a primary measure and physical function and QOL, e.g. SF-36 as guidelines for efficacious assessment, in order to formulate recommendations for pharmacological treatment of painful diabetic polyneuropathy.²⁶ However, in clinical trial situations, Quantitative Sensory Testing (QST) is still necessary for a more objective measurement of outcome, as well as HRQoL.^{21,27}

Treatment of PDN

Regarding the symptomatic treatment of this condition, Thai and international guidelines recommend the use of tricyclic antidepressants (TCA) e.g. amitriptyline, nortriptyline and calcium channel ligands (e.g. gabapentin, pregabalin) as first line treatments.^{5,9,26,28} The second and third line medications are selective norepinephrine serotonin reuptake inhibitors (SNRIs) e.g. venlafaxine and duloxetine and opioids (e.g. tramadol, oxycodone and morphine). However, using strong opioids in this indication should be reserved for severe and refractory cases under pain specialist supervision. Capsaicin cream and percutaneous electrical nerve stimulation can also be used as adjunctive treatments, with less systemic side effects.^{5,26}

When comparing the efficacy of each medication according to number needed to treat (NNT) for 50% pain reduction, TCA and opioid are slightly more effective than other groups. They are followed by calcium channel ligands and SNRIs.²⁹ The medication selection should also consider other factors, such as type of pain, pharmacokinetics, co-existing symptoms or diseases, side effects and price. Recommended medications and dosage of neuropathic pain medication were summarized in Table 1.

Despite the improvement in treatment modalities for chronic pain in recent years, patients with PDN continue to be inadequately treated. The different profiles of pain quality and spatial characteristics suggest that assessing patterns of pain symptoms might contribute to the identification of distinct pathophysiologic mechanisms, subgroups of patients and the development of mechanism-based treatment approaches.^{31,32} This will eventually improve the outcome and qualities of life in these patients.

Conclusion

Neuropathy is one of the most common complications in both type I and type II diabetes patients. The most common form is the chronic, symmetrical, length dependent, axonal sensorimotor polyneuropathy which affects either large or small sensory nerve fibers, or autonomic nerve fibers. Many patients suffer from neuropathic pain due to this condition, so called painful diabetic neuropathy. Generally, various types of pain can occur in the same patient in moderate to severe degree. Symptomatic treatment and pain control are the main therapeutic strategies. Many national and international organizations have recommended tricyclic antidepressants and calcium channel ligands as first line treatment options. This will eventually prevent other related complications and should improve the patient's quality of life.

Table 1: Common neuropathic pain medications

Medication	Initial dose and titration	Recommended dose
Antidepressants		
<i>Tricyclic antidepressants</i>		
Amitriptyline	10 mg/d, increase 10 mg/wk	25 to 75 mg/d
Nortriptyline	10 mg/d, increase 10 mg/wk	25 to 75 mg/d
<i>Other antidepressants</i>		
Venlafaxine	37.5 mg/d, increase 37.5mg/wk	75-225 mg/d
Duloxetine	30 mg/d	60 mg/d
Anticonvulsants		
Carbamazepine	200 mg/d, increase 200 mg/wk	600-1,200 mg/d
Oxcarbazepine	300 mg/d, increase 300 mg/wk	600-2,400 mg/d
Gabapentin	300 mg/d, increase 300 mg/wk	900-2,400 mg/d
Pregabalin	75 mg/d, increase 75 mg/wk	150-600 mg/d
Non-narcotic analgesics		
Tramadol	100 mg/d, increase 50 mg/wk	100-400 mg/d
Narcotic analgesics		
Morphine (oral)	15-30 mg/d in divided dose	30-120 mg/d
<i>Topical agents</i>		
0.075% capsaicin cream/gel	Apply locally	3-4 times/d

References

1. Dyck PJ, Albers JW, Andersen H, et al. Diabetic Polyneuropathies: Update on Research Definition, Diagnostic Criteria and Estimation of Severity. *Diabetes Metab Res Rev* 2011 Jun 21. doi: 10.1002/dmrr.1226. [Epub ahead of print]
2. Tesfaye S, Vileikyte L, Rayman G, et al. Painful Diabetic Peripheral Neuropathy: Consensus Recommendations on Diagnosis, Assessment and Management. *Diabetes Metab Res Rev* 2011 Jun 21. doi: 10.1002/dmrr.1225. [Epub ahead of print]
3. Jambart S, Ammarche Z, Haddad F, et al. Prevalence of painful diabetic peripheral neuropathy among patients with diabetes mellitus in the Middle East region. *J Int Med Res* 2011;39:366-77.
4. England JD, Gronseth G, Franklin G, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review): Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 2009;72:185-92.
5. Attal N, Cruccu GG, Baron R, et al. European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010;17:1113-88.
6. Boulton AJ, Malik RA, Arezzo JC, et al. Diabetic somatic neuropathies. *Diabetes Care* 2004;27:1458-86.
7. Davies M, Brophy S, Williams R, et al. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care* 2006;29:1518-22.
8. daCosta DiBonaventura M, Cappelleri JC, Joshi AV. A longitudinal assessment of painful diabetic peripheral neuropathy on health status, productivity, and health care utilization and cost. *Pain Medicine* 2011;12:118-26.
9. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010;33:2285-93.
10. Baron R, Tolle TR, Gockel U, et al. A cross-sectional cohort survey in 2100 patients with painful diabetic neuropathy and postherpetic neuralgia: differences in demographic data and sensory symptoms. *Pain* 2009;146:34-40.
11. Petrikonis K, Sciupokas A, Samušytė G, et al. Importance of pain evaluation for more accurate diagnosis of painful diabetic polyneuropathy. *Medicina (Kaunas)* 2010;46:735-42.
12. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010;9:807-19.
13. Kulkantrakorn K, Lorsuwansiri J. Sensory profile and its impact on quality of life in patients with painful diabetic polyneuropathy. *Neurol Sci* 2012 (submitted).

14. Spallone V, Monganti R, D'Amato C, et al. Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. *Diabet Med* 2012;29:578-85.
15. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011; 152:14-27.
16. Erbas T, Ertas M, Yucel A, et al. Prevalence of peripheral neuropathy and painful peripheral neuropathy in Turkish diabetic patients. *J Clin Neurophysiol* 2011;28:51-5.
17. Mondelli M, Aretini A, Baldasseroni A. Distal symmetric polyneuropathy in diabetes: difference between patients with and without neuropathic pain. *Exp Clin Endocrinol Diabetes* 2012;120:45-50.
18. Tavee J, Zhou L. Small fiber neuropathy: A burning problem. *Cleve Clin J Med* 2009;76:297-305.
19. Daousi C, Benbow SJ, Woodward A, et al. The natural history of chronic painful peripheral neuropathy in a community diabetes population. *Diabet Med* 2006;23:1021-4.
20. Taylor RS. Epidemiology of refractory neuropathic pain. *Pain Pract* 2006;6:22-6.
21. Jensen MP, Chodroff MJ, Dworkin RH. The impact of neuropathic pain on health-related quality of life : review and implications. *Neurology* 2007;68:1178-82.
22. Beydoun A, Kobetz SA, Carrazana EJ. Efficacy of oxcarbazepine in the treatment of painful diabetic neuropathy. *Clin J Pain* 2004;20:174-8.
23. Rerkasem K, Kosachunhanun N, Tongprasert S, et al. A multidisciplinary diabetic foot protocol at Chiang Mai University Hospital: cost and quality of life. *Int J Low Extrem Wounds* 2009;8:153-6.
24. Swislocki A, Orth M, Bales M, et al. A randomized clinical trial of the effectiveness of photon stimulation on pain, sensation, and quality of life in patients with diabetic peripheral neuropathy. *Pain Symptom Manage* 2010;39: 88-99.
25. Hermann BP, Vickrey B, Hays RD, et al. A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. *Epilepsy Res* 1996;25: 113-8.
26. Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011;76:1758-65.
27. Backonja MM, Walk D, Edwards RR, et al. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. *Clin J Pain* 2009;25:641-7.
28. Thai Association for the Study of Pain. Clinical Practice Guideline for Neuropathic Pain 2008. Bangkok, Thailand, Beyond Enterprise Publishing, 2008.
29. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain* 2010;150:573-81.
30. Kulkantrakorn K. Diabetic neuropathy. *Clinic* 2012;28:15-21.
31. Dworkin RH, Jensen MP, Gammaitoni AR, et al. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *J Pain* 2007;8:118-26.
32. Koroschetz J, Rehm SE, Gockel U, et al. Fibromyalgia and neuropathic pain - differences and similarities. A comparison of 3057 patients with diabetic painful neuropathy and fibromyalgia. *BMC Neurology* 2011;11:55.