ORIGINAL ARTICLE

Long-Term Outcomes in the Management of Painful Diabetic Neuropathy

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ABSTRACT: ***Background***: Painful diabetic neuropathy (PDN) is a frequent complication of diabetes mellitus. Current treatment recommendations are based on short-term trials, generally of ≤3 months' duration. Limited data are available on the long-term outcomes of this chronic disease. The objective of this study was to determine the long-term clinical effectiveness of the management of chronic PDN at tertiary pain centres. ***Methods***: From a prospective observational cohort study of patients with chronic neuropathic non-cancer pain recruited from seven Canadian tertiary pain centres, 60 patients diagnosed with PDN were identified for analysis. Data were collected according to Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials guidelines including the Brief Pain Inventory. ***Results***: At 12-month follow-up, 37.2% (95% confidence interval [CI], 23.0-53.3) of 43 patients with complete data achieved pain reduction of ≥30%, 51.2% (95% CI, 35.5-66.7) achieved functional improvement with a reduction of ≥1 on the Pain Interference Scale (0-10, Brief Pain Inventory) and 30.2% (95% CI, 17.2-46.1) had achieved both these measures. Symptom management included at least two medication classes in 55.3% and three medication classes in 25.5% (opioids, antidepressants, anticonvulsants). ***Conclusions***: Almost one-third of patients being managed for PDN in a tertiary care setting achieve meaningful improvements in pain and function in the long term. Polypharmacy including analgesic antidepressants and anticonvulsants were the mainstays of effective symptom management.

RÉSUMÉ: Résultats à long terme de la prise en charge de la neuropathie diabétique douloureuse. ***Contexte:*** La neuropathie diabétique douloureuse (NDD) est une complication fréquente du diabète sucré. Les recommandations de traitement actuelles sont basées sur des essais cliniques à court terme, en général d'une durée de 3 mois ou moins. Il existe peu de données sur les résultats à long terme du traitement de cette maladie chronique. Le but de cette étude était de déterminer l'efficacité clinique à long terme de la prise en charge de la NDD chronique dans des centres tertiaires de traitement de la douleur. ***Méthodologie:*** Nous avons analysé les données de 60 patients chez qui un diagnostic de NDD avait été posé. Ces patients ont été identifiés parmi les patients d'une cohorte d'observation prospective de patients atteints de neuropathie chronique non cancéreuse, recrutés dans 7 centres tertiaires canadiens de traitement de la douleur. Les données ont été recueillies selon les lignes directrices Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials incluant le Questionnaire concis sur les douleurs, version courte. ***Résultats:*** Au moment du suivi de 12 mois, 37,2% (intervalle de confiance à 95% [IC] de 23,0 à 53,3) parmi les 43 patients dont les données étaient complètes avaient obtenu une diminution de la douleur de 30% ou plus, 51,2% (IC à 95% de 35,5 à 66,7) avaient obtenu une amélioration fonctionnelle avec diminution de 1 ou plus à la Pain Interference Scale (1-10 au Questionnaire concis sur les douleurs, version courte) et 30,2% (IC à 95% de 17,2 à 46,1) avaient obtenu ces deux résultats. Au moins deux classes de médicaments étaient utilisées chez 55,3% des patients et trois classes de médicaments chez 25,5% (opiacés, antidépresseurs, anticonvulsivants) pour la gestion des symptômes. ***Conclusions:*** Presque le tiers des patients traités pour une NDD dans un centre tertiaire de traitement de la douleur obtiennent des améliorations significatives de la douleur et de la fonction à long terme. La polypharmacie, incluant des analgésiques, des antidépresseurs et des anticonvulsivants, constitue la base du traitement pour une prise en charge efficace des symptômes.

Keywords: painful, diabetic, neuropathy, management, long-term, outcome

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Up to 25% of all patients with diabetes mellitus experience significant neuropathic pain.[1-3] In those with severe diabetic neuropathy, the prevalence of painful symptoms is as high as 60%.[1] Painful diabetic neuropathy (PDN), described as a burning, stabbing, pricking, or aching sensation, primarily affects the toes, feet, and legs in a distal, symmetric pattern,[4,5] and often interferes with mobility, sleep, mood, and other domains of quality of life[3] and is therefore a cause of considerable morbidity. Although some

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patients may experience spontaneous improvement or even symptom resolution, PDN is a chronic disease for most patients.[6,7]

In a meta-analysis of randomized controlled trials, pharmacological management with analgesic antidepressants, including serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants, anticonvulsants (notably, pregabalin), and opioid analgesics were better than placebo for pain control in those suffering from PDN[8]—similar to the outcome in other chronic neuropathic pain conditions.[9,10] Published guidelines, based on systematic reviews, are available from the American Academy of Neurology (AAN) and the European Federation of Neurological Societies to guide clinical management of PDN. The AAN recommends the use of pregabalin as first-line treatment for PDN, noting its established effectiveness with Level A evidence.[11] In addition to pregabalin, the European Federation of Neurological Societies adds tricyclic antidepressants, gabapentin, and serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine) as potential first-line treatments.[10] However, the randomized controlled trials that form the basis for these clinical practice guidelines are limited by evidence of efficacy in only short-term trials, generally of ≤3 months' duration.[8,11] Thus, evidence is lacking as to the long-term effectiveness of these medication classes for this chronic disease. Although high-quality randomized controlled studies used to support clinical recommendations have good internal validity, their external validity (real-world outcome) is often left to be ascertained.[12] In the case of PDN, adherence to a specific pharmacologic regimen over the long term in this patient population may alter the generalizability of the results; thus, the aim of this study is to determine the long-term clinical effectiveness of the real-world management of PDN at tertiary pain centres.

Methods

The Canadian Neuropathic Pain Database was established in 2008 to provide a registry for neuropathic pain patients seen in academic tertiary care pain clinics in Canada.[13] From this registry, we identified a cohort of patients with type 1 or type 2 diabetes mellitus to carry out a long-term observational prospective study of the management of PDN. The diagnosis of PDN was established by clinical criteria[14] and supported by the Douleur Neuropathique en 4 Questions questionnaire, which is a reliable discriminator of neuropathic pain.[15] Patients with comorbid pain of other etiologies were included if they reported that their neuropathic pain was on average more intense and more disabling than their other pains. Informed consent was obtained for every participant before enrolment. Independent review boards representing each participating institution (University of Calgary, Alberta; Western University, McMaster University, University of Toronto and University of Ottawa, Ontario; McGill University, Quebec; Capital District Health Authority Research Ethics Board, Nova Scotia) approved the study.

Standard outcome measures for chronic pain according to Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials guidelines[16] were obtained at baseline and at 12 months. The primary outcome measure was the composite of a reduction of ≥30% in average pain intensity and 1-point drop in the Pain Interference Scale of the Brief Pain Inventory (BPI, 0-10) relative to baseline at 12 months. Secondary outcome measures were impact on function (Pain Disability Index), mood (Profile of Mood States), quality of life (12-item short form health survey [SF-12]), catastrophizing (Pain Catastrophizing Scale), and patient satisfaction (Patient Global Satisfaction Scale). Use of prescription medications was recorded both at baseline and then again at 12-month follow-up.

Statistical Analysis

Descriptive statistics, including means and standard deviations for continuous characteristics and frequencies and percentages for categorical characteristics, were calculated for baseline and for 12-month follow-ups. In addition, for the composite outcome, 95% confidence intervals (CIs) are presented. McNemar's chi-square test for dichotomous values was used to assess the change in the proportion of patients using major classes of analgesics (analgesic antidepressants, anticonvulsants, opioid analgesics) from baseline to the 12-month follow-up. The change in the opioid dose was evaluated using a Wilcoxon signed-rank test. Fisher's exact test was used to detect any difference in responder rate (achievement of primary outcome) between those being treated with two analgesic classes and those being treated with all three classes. For secondary outcome measures, baseline and 12-month values were compared using paired *t* tests. Univariable logistic regression was used to evaluate the association between baseline characteristics and the primary 12-month outcome. The p value for the association between opioid treatment and the proportion of subjects achieving and not achieving the primary outcome at 12 months was based on the chi-square test. The p value for the difference in primary outcome based on opioid doses was derived from the Wilcoxon two-sample test.

Results

Of the 789 patients recruited to participate in the Canadian Neuropathic Pain Database, 60 were identified as having PDN. Thirteen (21.7%) were lost to follow-up, leaving 47 patients with evaluable data and 43 patients with complete data at 12-month follow-up. Baseline characteristics of these patients with PDN are presented in Table 1 and patient analgesic history is presented in Table 2. The most common baseline analgesics were anticonvulsants (53.3%), followed by opioids (48.3%).

At 12-month follow-up, the proportion of patients using analgesic antidepressants, anticonvulsants, or opioid analgesics increased across all categories but did not reach statistical significance (Table 3).

The proportion of subjects achieving a ≥30% reduction in pain at 12 months relative to baseline was 16/43 or 37.2% (95% CI, 23.0-53.3) and the proportion of subjects experiencing a reduction of at least 1 point on the Pain Interference Scale (BPI) was 22/43 or 51.2% (95% CI, 35.5-66.7). The primary outcome measure—that is, the proportion of subjects achieving both at least a 30% reduction in pain and a 1-point reduction on the Pain Interference Scale—was achieved in 13/43 patients or 30.2% (95% CI, 17.2-46.1).

Opioid analgesics were included in the pain management strategy of 27/47 (57.5%) patients at 12-month follow-up. This was an increase from 22/47(46.8%) at baseline, although this increase was not significant (Table 3). Of the 47 patients accounted at 12-month follow-up, 16 were using opioids at both baseline and 12-month follow-up; opioid doses had significantly increased ($p = 0.002$) from baseline to 12-month follow-up in this subgroup, although this was not associated with a significant improvement in

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Table 1: Patient characteristics at baseline (N = 60)

Age (years)	57.1 ± 11.7
Sex (M)	56.7%
DN4 score (0-10)	6.6 ± 1.8
DN4 ≥ 4, N (%)	57 (95.0%)
Pain duration (years)	
Mean	4.9 ± 3.9
Median	4.0 (2,7)
Average pain intensity (0-10, BPI)	6.7 ± 2.1
Average Interference Scale Score (0-10, BPI)	6.4 ± 2.6
Education, N (%)	
Primary school	5 (8.5%)
Secondary school	25 (42.4%)
College or university	28 (47.5%)
Smoking status, N (%)	
Current	16 (26.7%)
Previous	23 (38.3%)
Marijuana use (current), N (%)	4 (6.8%)
Comorbidities, N (%)	
Mechanical neck or back pain	7 (11.7%)
Fibromyalgia	2 (3.3%)
Headache	3 (5.0%)
Disability compensation, N (%)	16 (26.7%)

Data are mean ± standard deviation, median (Q1,Q3), number; DN4 = Douleur Neuropathique en 4 Questions: score ≥4 indicates probable neuropathic pain.

Table 2: Patient analgesic history (N = 60)

Baseline analgesics, N (%)	
None	7 (11.7%)
NSAIDs	26 (43.3%)
Analgesic antidepressants	22 (36.7%)
Anticonvulsants	32 (53.3%)
Opioids	29 (48.3%)
Opioid dose (MED)	
Mean	142.3 ± 224.2
Median	60.0 (18,160)
Prior analgesic trials, N (%)	
None	24 (40.0%)
NSAIDs	21 (35.0%)
Analgesic antidepressants	11 (18.3%)
Anticonvulsants	14 (23.3%)
Opioids	12 (20.0%)
Opioid dose (MED)	
Mean	145.1 ± 336.0
Median	33.0 (15,88)

MED = morphine equivalent dose (mg/day); NSAIDs, nonsteroidal anti-inflammatory drugs. Data are mean ± standard deviation, median (Q1,Q3), number.

the primary outcome measure. Table 4 details the opioid dose of the patients who remained on this treatment modality.

Data were complete in 25 patients whose pain management included opioid analgesia at 12-month follow-up. Of the 13 responders achieving the primary outcome, seven (53.9%) had a treatment strategy that included opioid analgesia. In the nonresponder group, 18/30 (60%) were using opioids. Thus, by comparing the proportion of subjects on opioids between responders and nonresponder groups, there was no association between opioid treatment at 12 months and the achievement of the primary outcome ($p > 0.05$). Furthermore, as illustrated in Table 5, no significant difference in opioid dose was found between the responder and nonresponder groups in those using opioid analgesics at 12-month follow-up.

Polypharmacy occurred in the majority of patients with PDN by 12-month follow-up. Of the 47 participants, 26 (55.3%) were using at least two medications from the major analgesic classes, and 12 (25.5%) were using all three major analgesic classes (analgesic antidepressants, anticonvulsants, and opioids). There was no difference observed between responder rate (achievement of primary outcome) between those being treated with two analgesic classes and those being treated with all three ($p = 0.423$, Fisher's exact test).

Cannabinoid use at 12 months was reported in four patients (8.5%). Only a small number of patients sought non-pharmacological treatment modalities. Of the nonpharmacological treatment modalities, the most commonly used by 12 months were physiotherapy and acupuncture, both reported by 10.6% of patients. Other methods included psychotherapy (8.5%), local anesthetic or steroid injections (2.1%), surgery (2.1%), and transcutaneous electrical nerve stimulation (2.1%). All patients were encouraged to increase their level of function despite ongoing pain.

All secondary outcome measures at 12-month follow-up relative to baseline were significantly improved except for Profile of Moods State, SF-12 Mental and Patient Global Satisfaction (Table 6). In particular, there was a significant improvement in mean pain intensity and the mean Interference Scale Score of the BPI at 12-month follow-up relative to baseline. Univariable analysis of associations between baseline characteristics and improvement in pain and function at 12 months were non-significant. None of these parameters, including age, pain duration, mean pain intensity, measures of disability (Interference Scale Score of the BPI, Pain Disability Index), mood (Profile of Mood States), quality of life (SF-12), catastrophizing (Pain Catastrophizing Scale), or global satisfaction, predicted outcome. In addition, being on an opioid analgesic at baseline and being on

Table 3: Major analgesic class use at baseline and 12-month follow-up (N = 47)

Major analgesic class	Baseline, N (%)	12 months, N (%)	p value (McNemar's chi-square)
Analgesic antidepressants	18 (38.3)	24 (51.1)	0.146
Anticonvulsants	25 (53.2)	28 (59.6)	0.453
Opioids	22 (46.8)	27 (57.5)	0.332

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Table 4: Opioid dose in patients with opioid use at baseline and 12-month follow-up (N = 16)

MED (mg/day)	Baseline	12 months	p value
Mean (standard deviation)	186.3 (277.1)	267.4 (284.1)	0.002
Median	90.0	173.5	

MED = morphine equivalent dose.

a higher median dose at baseline did not predict outcome ($p > 0.1$ and $p > 0.4$, respectively).

Discussion

The chosen primary outcome measure, that is, the proportion of patients who achieved the composite of at least a 30% reduction in average pain intensity on the BPI and a 1-point reduction in the Interference Scale Score (0-10) of the BPI at 12 months, recognizes clinically significant improvement in both pain and function. Almost one-third of patients with PDN treated in tertiary pain centres achieved this clinically significant measure at 12-month follow-up. Although the overall proportion of patients using analgesic antidepressants, anticonvulsants, or opioid analgesics after 12 months was not significantly different from the proportion using these classes at baseline, this improvement may be accounted for by care provided in the tertiary care clinic where patients are exposed to interdisciplinary approaches to pain management including physiotherapy and psychological techniques. In addition, clinicians routinely customize doses of adjuvant analgesics in some patients and switch analgesics in others to optimize analgesia and minimize side effects. More patients had achieved a functional improvement (51.2%) than a diminished pain rating (37.3%). The population studied had a median pain duration of 4 years; thus, these subjects represent those who have progressed to refractory chronic pain and are unlikely to experience spontaneous symptom resolution as has been reported for patients with acute PDN.[7,17] Furthermore, a higher likelihood of unfavourable outcomes was expected secondary to the referral bias introduced by conducting the study at a tertiary care setting, where the patient population consists of those with difficult to treat or refractory pain. A study of PDN management in the primary care setting may represent a different population and more positive results would be anticipated.

Secondary outcome measures showed statistically significant improvement relative to baseline ($p < 0.05$) for pain and function

Table 5: Association between opioid treatment at 12 months and average pain intensity (BPI) reduction of ≥30% and Interference Scale Score reduced by ≥1.0 (n = 25)

	Achievement of primary outcome		
	No	Yes	p value
N (%) (opioid use)	18/30 (60.0%)	7/13 (53.9%)	0.707
MED (mg/day)			
Mean dose (SD)	169.9 (256.4)	244 (237.5)	
Median dose (Q1,Q3)	108.0 (46.2,150.0)	197.0 (30.0,425.4)	0.586

SD = standard deviation.

parameters as well as catastrophizing. Catastrophizing is known to be a particularly important predictor of pain expression and activity intolerance in patients with chronic pain.[18] The lack of association between baseline characteristics and improvement in pain and function at 12 months may be related to the relatively small sample size of the patient population.

Although there is some evidence that chronic neuropathic pain and, in particular, PDN, responds to opioid therapy, this evidence is conflicting.[11,19] There was no significant impact on achievement of the primary outcome measure in the 16 patients who were treated with opioid analgesics throughout the study despite the increased opioid dose. Sizable increases were observed in these 16 patients, with the median morphine equivalent dose increasing from 90 mg/day at baseline to 173.5 mg/day at 12 months. Furthermore, there was no association between opioid treatment at 12 months and the achievement of the primary outcome ($p > 0.05$); that is, patients treated with opioids achieved the primary outcome just as frequently as those without opioid treatment. This is in keeping with evolving basic science mechanisms that suggest that opioid analgesics can actually increase pain in some patients because of paradoxical hyperalgesia.[20] A recent AAN position paper strongly cautions against escalating opioid doses above 80 to 120 mg/day morphine equivalent dose in the treatment of chronic non-cancer pain unless the patient has benefitted with regards to pain and function.[21] Keeping pace with acquired pharmacodynamic opioid tolerance can prompt prescribing higher opioid doses with time. Ensuing pharmacological tolerance may not be overcome with dose escalation.[22] Furthermore, the significant risks of opioid-related morbidity and mortality[20] should prompt the routine use of predetermined endpoints of pain relief and physical function that, if not achieved, would lead to a trial opioid taper to truncate opioid risks when patients are not attaining meaningful benefit. To make an objective determination of meaningful benefit, both pain and function, can be tracked at every visit using brief, validated instruments. The BPI used for this study is one such example.[16,23,24]

Polypharmacy occurred in the majority of patients with PDN by 12-month follow-up. This requirement for polypharmacy may reflect the limited effectiveness of solitary medications in achieving symptom reduction satisfactory to the patient, particularly in those with chronic PDN who merit referral to a tertiary care setting. However, the disadvantage of this strategy is that of increasing adverse medication effects, such as drowsiness and dizziness. There is some support for polypharmacy in that combinations of morphine and gabapentin,[25] nortriptyline and gabapentin,[26] and morphine and nortriptyline[27] provided additive analgesia relative to each agent alone in patients with PDN and postherpetic neuralgia. In this study, although responders were more likely to be using more than one pharmaceutical agent, no difference in response rate was seen between those using two analgesic classes versus three analgesic classes. Thus, it may be possible to achieve similar benefit in the realms of pain reduction and function by limiting the number of pharmaceutical classes used and, in so doing, also limit the hazards of polypharmacy such as compounding adverse effects and medication interactions.

Finally, the authors acknowledge two principal limitations of this observational study: the small number of patients recruited for participation and the 22% dropout rate at 12-month follow-up. Nevertheless, this study helps to clarify the long-term outcomes

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Table 6: Changes from month 0 to month 12 for secondary outcome measures

	Month 0	Month 12	Mean	95% CI	p value
	N	N	difference (SD)		
		Mean (SD)	Mean (SD)		
Average pain	57	45			
Intensity, BPI	6.67 (2.14)	5.38 (2.41)	1.44 (2.56)	0.65-2.23	<.001
Mean interference	57	45			
Scale score, BPI	6.35 (2.55)	5.39 (2.82)	1.26 (2.34)	0.54-1.98	.001
POMS–Short Form	57	45			
	51.8 (23.0)	49.1 (21.9)	6.02 (20.26)	−0.29-12.34	.061
SF-12 Mental	56	45			
	41.5 (12.6)	40.8 (12.2)	−0.86 (9.91)	−3.94-2.23	.577
SF-12 Physical	56	45			
	29.9 (10.5)	31.9 (10.2)	−2.6 (7.1)	-4.8 -0.4	.021
Pain Disability Index	59	43			
	38.8 (18.9)	34.7 (19.2)	5.4 (17.6)	−0.1-10.9	.052
Pain Catastrophizing Scale	57	44			
	27.3 (14.1)	21.8 (15.3)	7.4 (12.2)	3.6-11.2	<.001
Patient Global Satisfaction	56	45			
	6.79 (3.18)	6.84 (2.99)	−0.10 (3.44)	−1.17-0.98	.859

BPI (0-10); PDI (0-70), higher score indicates greater disability; POMS–SF (0-120), higher score indicates greater impairment; SF-12 (0-100), score < 50 indicates below average health status; Pain Catastrophizing Scale (0-52), higher score indicates greater distress; Patient Global Satisfaction (0-10), higher score indicates greater satisfaction.

that are specific to PDN. Overall, our data support the referral of chronic PDN patients to a tertiary care centre to achieve meaningful improvements in pain and function.

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