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# Long-Term Outcome of the Management of Chronic Neuropathic Pain: A Prospective Observational Study

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**Abstract:** **This prospective observational cohort study addressed the long-term clinical effectiveness of the management of chronic neuropathic noncancer pain at 7 Canadian tertiary pain centers. Patients were treated according to standard guidelines and were followed at 3, 6, 12, 18, and 24 months. Standard outcome measures for pain, mood, quality of life, and overall treatment satisfaction were administered, with the primary outcome measure designated as the composite of 30% reduction in average pain intensity and 1-point decrease in the mean Interference Scale Score (0–10) of the Brief Pain Inventory at 12 months relative to baseline. Of 789 patients recruited, mean age was 53.5 ± 14.2 years (55% female) and mean duration of pain was 4.88 ± 5.82 years. Mean average pain intensity (0–10) at baseline was 6.1 ± 1.9. All standard outcome measures showed statistically significant improvement at 12 months relative to baseline ($P < .001$). However, only 23.7% attained clinically significant improvement in pain and function at 12 months as the primary outcome measure. Univariable analyses showed poorer outcomes at 12-month follow-up with longer duration of pain ($P = .002$), greater cigarette use ($P = .01$), more disability compensation ($P = .001$), and higher opioid doses at baseline and at 12 months ($P < .02$). Our present treatment modalities provide significant long-term benefit in only about a quarter of patients with neuropathic pain managed at tertiary care pain clinics. Opioid therapy may not be beneficial for the long term.**

***Perspective:*** ***Evidence-based treatment of chronic neuropathic pain provides long-term benefit in only about one-quarter of patients seen in tertiary care centers. Opioid therapy may not be beneficial.***



***Key words:*** *Prospective cohort study, chronic neuropathic pain, long-term outcome, opioid treatment.*

Neuropathic pain (NeP) arising as a result of a lesion or disease affecting the somatosensory system[43] is often a challenging clinical problem because of severe and disabling pain.[24] Prevalence studies indicate that NeP affects as much as 7 to 8% of the general population.[5,41] In the United States, health care costs

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associated with chronic pain have been estimated at more than $150 billion annually, and almost a third of this is attributable to NeP.[44] Effective pharmacological treatments for NeP are therefore imperative. The efficacy of certain antidepressants, anticonvulsants, opioid analgesics, and miscellaneous agents has been established in many short-term randomized controlled trials (RCTs) and systematic reviews,[11,12,18] and several evidence-based guidelines for the management of NeP have been developed.[1,31,32] Many of these guidelines are based on number-needed-to-treat (NNT) to obtain 50% pain relief in 1 patient as an estimate of treatment efficacy. This approach yields NNT in the range of 2 to 5 for most of these agents in a wide variety of NeP conditions.[1,18,31] However, NNT methodology has significant limitations, including variability in study design, exclusion of non–placebo-controlled studies, and lack of consideration of other important outcomes such as disability and quality of life. There are major limitations in determining the effects of treatment in RCTs. High-quality RCTs generally have very good internal validity, but their external validity or generalizability is questionable, raising the question of whether the results apply to clinical practice.[35] Limitations of RCTs include short durations, relatively small sample size, confinements to specific conditions such as painful diabetic neuropathy and postherpetic neuralgia, the use of highly selected inclusion and exclusion criteria, and a tendency to publish only those trials with positive outcomes.[35,45]

The Canadian Neuropathic Pain Database was established in 2008 to provide a registry for patients with NeP seen in academic tertiary care pain centers in Canada. We used the database to carry out a long-term observational prospective study of a large cohort of patients to determine the real-world clinical effectiveness of the management of chronic NeP in tertiary care centers.

# Methods

## Study Design and Patient Population

This longitudinal, prospective, multicenter, observational study was conducted in 7 academic pain centers across Canada (affiliated with University of Calgary, Alberta; Western University, McMaster University, University of Toronto, and University of Ottawa, Ontario; McGill University, Quebec; Dalhousie University, Nova Scotia). The study was managed by a multidisciplinary scientific advisory board (SAB), with representation from each center and also from industry (Pfizer Canada). Each site had 1 vote on the SAB, and all decisions were made by majority opinion. The SAB met face to face in preparation for the study and at least biannually during the trial for study monitoring purposes. A patient advocate with chronic NeP was included on the SAB to provide input on study design and selection of primary and secondary outcome measures. Ethical approval was obtained by independent review boards representing each institution, and all patients provided written informed consent before enrollment.

The study was conducted between April 2008 and December 2011. Each center screened all newly seen patients for presence of NeP for at least 2 days per week. NeP was diagnosed if there was clinical evidence of a lesion or disease affecting the somatosensory system.[43] The DN4 (Douleur Neuropathique en 4) questionnaire was administered at baseline as a valid and reliable discriminator of NeP[3] in support of this diagnosis. Four centers recruited patients for 2 years and 3 centers for 1 year. All patients were provided with a minimum of 1 year follow-up. Inclusion criteria were the presence of NeP of at least 3 months' duration and an estimated life expectancy of at least 2 years. Patients with multiple pain syndromes were eligible for inclusion if they reported that their NeP was on average more intense and more disabling than their other pains. Patients were excluded if they declined participation, did not have primarily NeP (mostly patients with chronic musculoskeletal and visceral pain), were deemed unreliable because of personality disorder, cognitive impairment or history of substance abuse, had a significant language barrier, or presented with active cancer or tumor infiltration of a nerve. Patients with fibromyalgia were also excluded from participation in the study because there remains uncertainty as to whether it represents a disorder of the somatosensory system.[43] All exclusions were documented according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[46]

To determine the generalizability of the findings across sites, among-site differences in terms of patient demographics, pain characteristics, and the primary outcome measure were evaluated.

## Assessment and Procedures

Initial assessment included documentation of previous and present analgesic and psychotropic medication trials, demographics, and standard clinical assessment. Analgesics were defined as nonsteroidal anti-inflammatory drugs, antidepressants with significant analgesic properties (tricyclic antidepressants and norepinephrine-serotonergic reuptake inhibitors), anticonvulsants, opioid analgesics, and miscellaneous agents such as cannabinoids and muscle relaxants. Psychotropic medications were defined as sedatives (eg, benzodiazepines) and antidepressants with weak or negligible analgesic properties (eg, serotonergic-specific reuptake inhibitors). Pharmacological management of NeP was based on standard evidence-based guidelines.[1,31,32] Study follow-up was arranged for 3, 6, and 12 months in all patients and at 18 and 24 months in those centers with prolonged follow-up. Most patients were seen more frequently for purely clinical reasons, including dose titration and monitoring of side effects, especially in the first 6 months. Outcome measures administered at baseline and at each follow-up visit were consistent with IMMPACT (Initiative on Methods Measurement and Pain Assessment in Clinical Trials) guidelines[13] and included measures of pain intensity (Brief Pain Inventory [BPI]), interference with function (Interference Scale

Score of the BPI, Pain Disability Index), quality of life (short-form 12-item general health survey [SF-12]), mood (Profile of Mood States–Short Form [POMS-SF]), Global Satisfaction, Global Impression of Change, and catastrophizing (Pain Catastrophizing Scale).[39] All analgesic and psychotropic medication changes were documented at each visit and expressed as milligrams per day. Opioid analgesics were converted to oral morphine equivalent doses according to standard equianalgesic tables.[27,38] Nonpharmacological treatments and injections were also documented at each visit. Adverse events were presented as a list of possible adverse effects and were tabulated by severity and frequency and graded using standard criteria.

Data entry at baseline was performed primarily using hard copy, but most patients learned to use a computer tablet with touch-screen data entry at follow-up, with data transfer to a secure central server (ORTECH Data Centre, London, Ontario).

### Outcome Measures

The primary outcome measure for this study was the proportion of patients who achieved 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. This composite outcome measure was selected to recognize clinically significant improvements in both pain and function.[14,15] The same composite outcome at 18 and 24 months was deemed to be a secondary outcome measure.

Secondary outcomes, measured at 3, 6, 12, 18, and 24 months, included average pain intensity of the BPI (0–10), Interference Scale Score of the BPI (0–10), Pain Disability Index (0–70) quality of life as measured by SF-12 (0–100), Profile of Mood States-SF (0–120), Pain Catastrophizing Scale (0–52), and Patient Global Satisfaction with Treatment Score (0–10). Patient Global Impression of Change, represented as a categorical scale (1–7), was also analyzed as a secondary outcome measure.

### Statistical Analyses

An independent clinical trials firm (Axon, Toronto, Ontario, Canada) conducted an interim audit over September to December 2009 to examine data quality and consistency across sites over time. Examination of a random sample of 10% of subject data at each site determined that the overall error rate in missing data and data transfer was 4.5%. This was deemed to be acceptable, and no further screening of data acquisition was carried out.

Baseline descriptive statistics, including means and standard deviations for continuous characteristics and frequencies and percentages for categorical characteristics, were calculated. Similarly, descriptive statistics for all primary and secondary outcome measures at all time points in the study were also calculated. Among-site differences were evaluated using $\chi^2$ tests for categorical characteristics and analysis of variance for continuous characteristics. For the composite outcome, 95% confidence intervals (CIs) were calculated at each time point. A mixed regression model was used to compare mean secondary outcome measures across time, with a Dunnett t-test being used to compare each follow-up time point against baseline.

For Global Impression of Change, the reported score at each time point was compared with a score of no change using a signed rank test. Comparison of adverse effects at 12-month follow-up relative to baseline was made using a McNemar $\chi^2$ test for dichotomous values and signed rank tests for the scores. The percentage of participants reporting any side effect and in particular adverse effects at baseline and month 12 were compared using a McNemar $\chi^2$ test. A signed rank test was used to compare the number of side effects, the number of severe adverse effects, and the severity of individual adverse effects at 12-month follow-up relative to baseline.

Univariable logistic regression was used to evaluate the association between baseline characteristics and the primary 12-month outcome. The association between opioid use at 12 months and primary outcome was evaluated using a $\chi^2$ test. For those taking opioids at 12 months, the dosage of those patients experiencing a positive response and not showing a positive response was compared using a Wilcoxon 2-sample test.

Data analysis was conducted using both observed cases and last observation carried forward methodology to account for missing data. The 2 approaches yielded similar results, and hence only observed data are reported. *P* values less than .05 were considered statistically significant. This study, including preplanned data analyses, is registered with clinicaltrials.gov (#NCT00669006). All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc, Cary, NC).

## Results

### Patient Population

Fig 1 shows patient flow through the study. The number of patients assessed for eligibility was 2,199. The total number of patients excluded was 1,410 (64%); most exclusions were caused by the absence of NeP as the primary pain complaint. The number of patients eligible and consenting to enrollment was 789. Two hundred patients had dropped out by 12-month follow-up, providing a dropout rate of 25.3%. Dropouts (n = 200) were compared with completers of 12-month follow-up (n = 589) according to baseline demographics and analgesic history. Completers were significantly more likely to be better educated ($P < .001$), to be on disability compensation ($P = .007$), and to have a lesser score on the Interference Scale Score of the BPI ($P = .04$). Complete data were available at 12 months on 515 patients, and this formed the basis for analysis of univariable associations between baseline characteristics and improvement in pain and function at 12 months.

Table 1 provides baseline characteristics and analgesic history of the patient population. The mean age (± standard deviation [SD]) was 53.5 ± 14.2 years. The study group comprised 54.8% women. Screening for NeP with the 10-item DN4 questionnaire found that 652 patients (82.6%) scored 4 or more on a scale of 1 to 10,

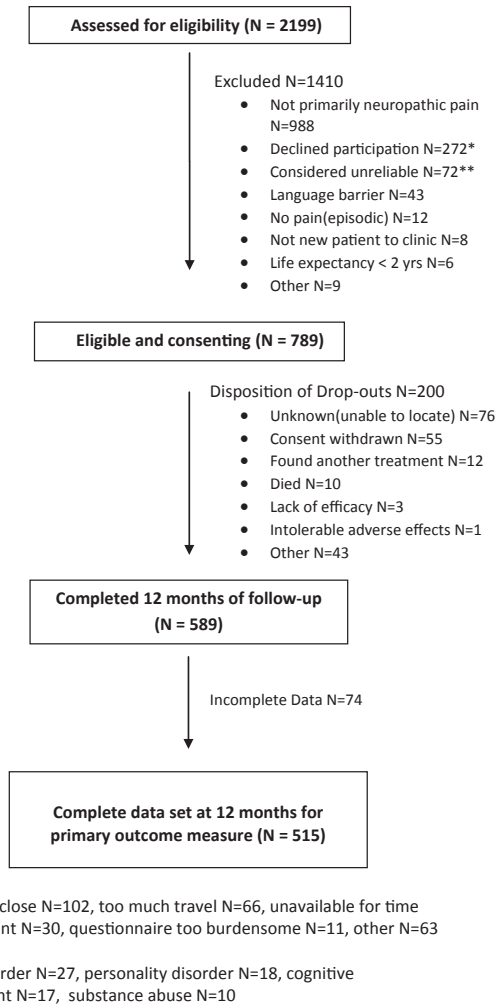


**Fig 1.** Flow of participants through the study.

suggesting that the DN4 was sensitive enough to detect NeP in most patients. Many of the patients who did not have a confirmatory DN4 score had trigeminal neuralgia, in which the pain is classically episodic and the neurological examination is normal. The mean (±SD) and median (Q1, Q3) pain duration were 4.88 (±5.82) and 3.0 (1.1, 6.0) years, respectively, and the average pain intensity (0–10, BPI) at baseline was 6.1 ± 1.9. There was no difference among sites regarding pain duration. However, there was a difference among sites for mean age, with the Calgary site having older patients than McGill and Ottawa ($P$ = .006). Sites were also different in terms of pain intensity, although no particular pairwise differences could be identified. The average Interference Scale Score (0–10, BPI) was 6.0 ± 2.5. At the time of the initial visit, 9.1% were not on any analgesic treatments for their NeP, 55.4% were receiving a nonsteroidal anti-inflammatory agent, 26.1% were being treated with an analgesic antidepressant, 46.6% were on an anticonvulsant, and 51.7% were being treated with an opioid analgesic. The mean daily opioid dose at study initiation was 103.2 ± 169.7 mg, expressed as oral morphine equivalent dose. The median dose was 45.0 mg (18.0, 120.0).

Table 2 shows the NeP diagnoses in the study population. Mononeuropathy, asymmetric polyneuropathy (including radiculopathy and plexopathy), and distal symmetric polyneuropathy represented 45.1%, 25.7%, and 19.1% of the study population, respectively, whereas 10.1% of patients had central pain as a result of injury to either the brain or spinal cord. The largest single cause of NeP was lumbosacral radiculopathy (111 patients or 14.0% of the entire study group), almost always associated with a lumbosacral disk syndrome and subsequent failed surgery. Postherpetic neuralgia and painful diabetic neuropathy, the most common conditions studied in RCTs of NeP, affected 95 patients (12.0% overall).

**Table 1. Baseline Characteristics and Analgesic History of Patients (N = 789)**

| | |
|---|---|
| Age, y | 53.5 ± 14.2 |
| Gender, male/female, % | 45.2/54.8 |
| DN4 score (0–10) | 5.8 ± 2.3 |
| DN4 ≥ 4, n (%) | 652 (82.6) |
| Pain duration, y | |
| Mean | 4.9 ± 5.8 |
| Median | 3.0 (1.1, 6.0) |
| Average pain intensity (0–10, BPI) | 6.1 ± 1.9 |
| Average Interference Scale Score (0–10, BPI) | 6.0 ± 2.4 |
| Education, n (%) | |
| Primary school | 42 (5.4) |
| Secondary school | 283 (36.1) |
| College or university | 454 (58.0) |
| Smoking status, n (%) | |
| Current | 215 (27.4) |
| Previous | 240 (30.5) |
| Marijuana use (current), n (%) | 87 (11.2) |
| Comorbidities, n (%) | |
| Mechanical neck or back pain | 115 (14.7) |
| Fibromyalgia | 22 (2.8) |
| Headache | 18 (2.3) |
| Disability compensation, n (%) | 219 (27.9) |
| Baseline analgesics, n (%) | |
| None | 72 (9.1) |
| NSAID | 436 (55.3) |
| Analgesic antidepressants | 205 (26.0) |
| Anticonvulsants | 368 (46.6) |
| Opioids | 408 (51.7) |
| Opioid dose (MED) | |
| Mean | 103.2 ± 169.7 |
| Median | 45.0 (18, 120) |
| Previous analgesic trials, n (%) | |
| None | 224 (28.4) |
| NSAID | 374 (47.4) |
| Analgesic antidepressants | 130 (16.5) |
| Anticonvulsants | 200 (25.4) |
| Opioids | 230 (29.2) |
| Opioid dose (MED) | |
| Mean | 65.7 ± 121.0 |
| Median | 30.0 (10, 60) |

Abbreviations: DN4, Douleur Neuropathique en 4 questions (score ≥ 4 indicates probable NeP); NSAID, nonsteroidal anti-inflammatory drug; MED, morphine equivalent dose (mg/day).
NOTE. Data are mean ± SD, median (Q1, Q3), or number (%).

## *Treatment Modalities*

Patients were treated according to standard guidelines for the management of NeP.[1,31,32] At 12-month

**Table 2. Neuropathic Pain Syndromes (N = 789)**

| | *N (%)* |
|---|---|
| Central pain | 80 (10.1) |
| Myelopathy | 47 |
| After stroke | 11 |
| Other | 22 |
| Mononeuropathy | 355 (45.1) |
| Lumbosacral radiculopathy | 68 |
| Trigeminal neuralgia | 52 |
| Sciatic neuropathy | 37 |
| Ilioinguinal neuralgia | 35 |
| Pudendal neuralgia | 26 |
| Cervical radiculopathy | 18 |
| Thoracic radiculopathy | 12 |
| Trigeminal neuropathy | 12 |
| Intercostal neuralgia | 11 |
| Dental neuralgia | 11 |
| Median neuropathy | 9 |
| Femoral neuropathy | 8 |
| Ulnar neuropathy | 6 |
| Lateral femoral cutaneous neuropathy | 6 |
| Other | 44 |
| Asymmetric polyneuropathy | 203 (25.7) |
| Complex regional pain Syndrome | 71 |
| Lumbosacral radiculopathy | 43 |
| Postherpetic neuralgia | 36 |
| Brachial plexopathy | 14 |
| Cervical radiculopathy | 11 |
| Other | 28 |
| Symmetric polyneuropathy | 151 (19.1) |
| Painful diabetic neuropathy | 59 |
| Idiopathic | 51 |
| Other | 41 |

follow-up, the percentage of patients being treated with analgesic antidepressants, anticonvulsants, and opioid analgesics did not change significantly. However, the mean daily opioid dose expressed as oral morphine equivalents increased from a baseline of 103.2 mg to 152.4 mg (±401.8), and the median dose increased from 45.0 mg to 60.0 mg (22.5, 162.5) at 12-month follow-up ($P < .001$, signed rank test). Polypharmacy was common, with 27.8% of patients receiving 2 of the 3 major classes of analgesics for NeP (antidepressants, anticonvulsants, and opioid analgesics), and 16.5% were treated with all 3 classes of analgesics concurrently at 12-month follow-up. Cannabinoids were used in 81 patients (13.8%) at 12-month follow-up. Nonpharmacological treatments administered by 12-month follow-up were the following: physiotherapy (355 patients [45.0%]), local anesthetic or steroid injections (265 [33.6%]), acupuncture (247 [31.3%]), surgery (139 [17.6%]), transcutaneous electrical nerve stimulation (138 [17.5%]), psychotherapy (113 [14.3%]), and local anesthetic infusions (84 [10.7%]).

## *Outcomes*

The primary outcome measure, defined as the composite of at least a 30% reduction in average pain intensity and a 1-point reduction in the Interference Scale Score of the BPI at 12 months, was achieved by 122/515 (23.7%; 95% CI = 20.1–27.6%) of patients relative to baseline. This outcome measure at 18- and 24-month follow-up was 102/415 (24.6%; 95% CI = 20.5–29.0%) and 94/337 (27.9%; 95% CI = 23.2–33.0%), respectively. Responder analysis for pain only, defined as a 30% or greater reduction in average pain intensity at 12 months, was 167/515 (32.4%) and for disability only, defined as at least a 1-point reduction in the Interference Scale Score, it was 240/515 (46.4%). There were no site differences regarding the primary outcome measure. However, central NeP was significantly less likely to respond than peripheral NeP (6/53 [11.3%] vs 116/462 [25.1%], respectively) ($P = .025$, $\chi^2$ test).

All secondary outcome measures at each follow-up time point relative to baseline were significantly improved ($P < .001$). Table 3 shows all secondary outcome measures expressed as continuous variables specifically comparing month 12 with baseline. The average pain intensity of the BPI (0–10) improved by 1.10 (±2.21), and the mean Interference Scale Score of the BPI (0–10) improved by 1.12 (±2.33). Favorable changes in these outcome measures and all others involving mood (POMS), quality of life (SF-12), disability (Pain Disability Index), catastrophizing (Pain Catastrophizing Scale), and Global Satisfaction were all statistically significant ($P < .001$). Patient Global Impression of Change scores on average exceeded no change at all time points up to and including 24 months ($P < .001$).

At 12-month follow-up, 92.1% of patients reported 1 or more adverse effects and 43% reported severe adverse effects. The mean and median number of adverse effects per patient was 7.3 (±4.5) and 7,[4,11] and the mean and median number of severe adverse effects was 1.0 (±1.5) and .00. The following adverse effects were reported by a third or more of patients: lightheadedness/dizziness, drowsiness, confusion, impaired memory, dry mouth, constipation, urinary hesitancy, fatigue, insomnia, weight gain, visual blurring, and decreased sex drive. The only parameters that were significantly increased relative to baseline were urinary hesitancy ($P = .006$) and visual blurring ($P = .012$). The increased frequencies of these adverse effects at 12-month follow-up were 6.0 and 7.5%, respectively.

Table 4 shows univariable associations between baseline characteristics and improvement in pain and function at 12 months. A longer duration of pain, a higher DN4 total score, being on disability compensation, being a current smoker and being on an opioid analgesic with a higher mean opioid dose all decreased the odds of favorable outcomes. Gender, average pain intensity, measures of disability (Interference Scale Score of the BPI, Pain Disability Index), mood (POMS), quality of life (SF-12), catastrophizing (Pain Catastrophizing Scale), and Global Satisfaction were not associated with outcome.

Table 5 shows the association between opioid treatment at 12 months and the management of chronic NeP. Both the presence of opioid treatment (44% improved vs 63% not improved; $P < .001$) and a higher median daily morphine equivalent dose (improved 39.0 mg vs not improved 61.8 mg; $P = .013$) reduced the

**Table 3. Changes From Month 0 to Month 12 for Secondary Outcome Measures**

| | Month 0 | | Month 12 | | Mean | | |
|---|---|---|---|---|---|---|---|
| | n | Mean (SD) | n | Mean (SD) | Difference (SD) | 95% CI | P Value |
| Average pain intensity, BPI | 763 | 6.06 (1.93) | 537 | 4.96 (2.36) | 1.10 (2.21) | .88–1.31 | <.001 |
| Mean Interference Scale Score, BPI | 764 | 5.89 (2.51) | 538 | 4.77 (2.88) | 1.12 (2.33) | .91–1.39 | <.001 |
| POMS-SF | 764 | 48.7 (22.3) | 525 | 43.9 (21.2) | 4.80 (18.28) | 3.25–6.95 | <.001 |
| SF-12 mental | 757 | 41.6 (12.1) | 535 | 43.1 (11.9) | −1.57 (10.73) | −2.74 to .51 | .001 |
| SF-12 physical | 757 | 32.8 (9.9) | 535 | 34.5 (10.6) | −1.77 (8.50) | −2.44 to .74 | <.001 |
| PDI | 779 | 37.6 (16.6) | 533 | 31.8 (18.6) | 5.81 (15.79) | 4.20–7.35 | <.001 |
| PCS | 776 | 23.66 (12.46) | 534 | 18.77 (13.32) | 4.90 (11.01) | 4.00–6.21 | <.001 |
| PGS | 743 | 6.16 (3.24) | 528 | 6.85 (2.88) | −.68 (3.71) | −1.02 to .33 | <.001 |

Abbreviations: BPI, Brief Pain Inventory (0–10); POMS-SF, Profile of Moods State–Short Form (0–120), higher score indicates greater impairment; SF-12, 12-item short form health survey (0–100), score < 50 indicates below average health status; PDI, Pain Disability Index (0–70), higher score indicates greater disability; PCS, Pain Catastrophizing Scale (0–52), higher score indicates greater distress; PGS, Patient Global Satisfaction (0–10), higher score indicates greater satisfaction.

odds of a significant reduction in pain intensity and improvement in function.

## Discussion

Large-scale long-term observational prospective studies are needed to determine effectiveness of treatment in routine clinical practice. There are few studies of this type that focus on NeP. Toth and Au[42] followed 182 patients with polyneuropathy-associated NeP for 6 months and reported an approximate NNT in the range of 2 to 3 for achievement of at least 30% pain relief. Watson et al[47] surveyed 84 patients with predominantly NeP for a median of 8.4 years. These were highly selected patients treated with opioid analgesics and most reported at least 50% pain relief and moderate improvement in disability. Our observational study is the largest to assess real-world effectiveness of the management of chronic NeP in a diverse population of patients using established current guidelines.[18,1] The major finding of this study is that only about one-quarter of patients (23.7%) attending academic tertiary care pain centers achieved the primary outcome of a significant reduction in pain intensity and disability over 1 year. Isolating the parameter of a clinically significant reduction in pain intensity, about a third of patients (32.4%) achieved this outcome. If we isolate the improvement in disability, 46.4% improved. This is in contrast to what would be predicted from earlier systematic reviews of RCTs for NeP, in which NNT for 50% pain relief ranged from 2 to 5 for individual agents.[1,18,31] Our findings are more consistent with a recent systematic review and meta-analysis[19] that found that the NNT for serotonin-noradrenaline reuptake inhibitors and gabapentinoids was in the range of 6.4 to 7.7. Recognizing that our primary outcome is not directly comparable with NNT methodology because our study does not include a control group receiving a placebo, a lower benchmark of 30% pain relief and the usefulness of drug combinations with additive analgesic effects[22,23] suggest a better outcome, at least for reduction in pain intensity.

The strengths of this observational cohort trial include a large sample of patients, less stringent inclusion and exclusion criteria, the use of real-world combinations of polypharmacy and nonpharmacological approaches, longer follow-up, and a primary outcome measure that recognizes the importance of both reduction in pain intensity and disability.[15] We also studied a more heterogeneous population of patients, because only 12% carried a diagnosis of painful diabetic neuropathy or postherpetic neuralgia, the most common conditions studied in RCTs of NeP.[18] The observation that the percentage of patients being treated with major classes of analgesics did not differ between baseline and 12-month follow-up is consistent with clinical practice. Clinicians routinely switch analgesics in some patients and customize doses to optimize analgesia and minimize adverse effects. This practice tends to cancel out drug changes in the overall study population.

Table 3 shows the value of performing a responder analysis to determine a clinically meaningful difference between end point and baseline. The percentage of patients showing a clinically meaningful pain reduction (ie, ≥30% reduction from baseline) is often more informative than the mean reduction in pain intensity.[14] The mean difference in average pain intensity between 12-month follow-up and baseline was 1.10 (±2.21 SD). This provides a highly significant *P* value (<.001) but corresponds only to a minimally important improvement in pain intensity.[15] Knowing that a third of patients (32.4%) achieve this benchmark provides more valuable information. The mean difference of 1.12 (±2.33 SD) for mean Interference Scale Score is considered a minimally important improvement in function, whereas the mean differences for the other parameters (POMS, SF-12, Pain Disability Index, Pain Catastrophizing Scale) are either insignificant or of unknown relevance.[15,33,37]

Univariable analyses identified that a longer duration of pain and a higher DN4 total score at baseline were predictors of a poor outcome, whereas pain intensity was not predictive of outcome. Pain intensity at baseline is a well-known predictor of persistent NeP after surgery[26] and after herpes zoster virus infection.[4] It may be that the long duration of pain at baseline in this

**Table 4. Univariable Associations Between Baseline Characteristics and Improvement in Pain and Function at 12 Months (N = 515)**

| | Average Pain Intensity (BPI) Reduced by ≥30% and Interference Scale (BPI) Reduced by ≥1.0 | | | |
|---|---|---|---|---|
| | No (n = 393) | Yes (n = 122) | Odds Ratio (95% CI) | P Value |
| Age, mean (SD) | 53.7 (13.9) | 54.1 (13.1) | 1.00 (.99, 1.02) | .779 |
| Female gender | 226 (57.5) | 68 (55.7) | .93 (.62, 1.40) | .730 |
| DN4 Score (SD) | 6.01 (2.31) | 5.45 (2.09) | .90 (.82, .98) | .020 |
| Pain duration/mo, mean (SD) | 62.7 (72.0) | 49.3 (73.5) | 1.04 (1.00, 1.08) | .082 |
| <12 | 58 (14.9%) | 33 (27.7%) | 2.19 (1.34, 3.57) | .002 |
| <24 | 121 (31.1%) | 52 (43.7%) | 1.72 (1.13, 2.62) | .012 |
| <36 | 164 (42.2%) | 66 (55.5%) | 1.71 (1.13, 2.58) | .011 |
| <48 | 207 (53.2%) | 76 (63.9%) | 1.55 (1.02, 2.37) | .042 |
| <60 | 242 (62.2%) | 86 (72.3%) | 1.58 (1.01, 2.48) | .046 |
| Average pain intensity BPI, mean (SD) | 6.03 (1.92) | 6.19 (1.97) | 1.05 (.94, 1.16) | .415 |
| Average Interference Scale Score, mean (SD) | 5.84 (2.58) | 6.09 (2.27) | 1.04 (.96, 1.13) | .322 |
| Level of education | | | | .802 |
| None/primary school | 22 (5.6%) | 2 (1.6%) | Reference | |
| Secondary school | 130 (33.3%) | 44 (36.2%) | | |
| College or university | 238 (61.0%) | 76 (62.3%) | 1.06 (.69, 1.60) | |
| Disability compensation | 135 (34.6%) | 20 (16.4%) | .37 (.22, .63) | <.001 |
| Smoking status | | | | .013 |
| Current | 104 (26.7%) | 19 (15.6%) | Reference | |
| Previous | 175 (44.9%) | 54 (44.3%) | 2.42 (1.34, 4.37) | |
| Never | 111 (28.5%) | 49 (40.2%) | 1.69 (.95, 3.01) | |
| Diagnosis | | | | .145 |
| Central pain | 47 (12.0%) | 6 (4.9%) | Reference | |
| Mononeuropathy | 177 (45.0%) | 64 (52.5%) | 2.83 (1.16, 6.94) | |
| Symmetrical polyneuropathy | 75 (19.3%) | 25 (20.5%) | 2.58 (.98, 6.75) | |
| Asymmetrical polyneuropathy | 93 (23.7%) | 27 (22.1%) | 2.27 (.88, 5.89) | |
| Opioids | | | | |
| Any | 209 (53.2%) | 56 (45.9%) | .75 (.50, 1.12) | .161 |
| Median (Q1, Q3) | 45.0 (20.0, 120) | 27.6 (9.0, 60) | | .004 |
| POMS-SF, mean (SD) | 48.9 (23.0) | 48.7 (20.1) | 1.00 (.99, 1.01) | .920 |
| SF-12 mental, mean (SD) | 41.6 (12.3) | 41.5 (11.5) | 1.00 (.98, 1.02) | .933 |
| SF-12 physical, mean (SD) | 32.5 (9.8) | 33.5 (10.2) | 1.01 (.99, 1.03) | .316 |
| Pain Disability Index, mean (SD) | 37.8 (17.0) | 35.9 (15.7) | .99 (.98, 1.01) | .259 |
| Pain Catastrophizing Scale, mean (SD) | 23.6 (12.8) | 23.7 (12.2) | 1.00 (.98, 1.02) | .959 |
| Global Satisfaction, mean (SD) | 6.0 (3.3) | 6.5 (3.2) | 1.04 (.98, 1.11) | .206 |

NOTE. Pain Disability Index (0–70); Pain Catastrophizing Scale (0–52); Global Satisfaction (0–10).
Values are n (%) unless otherwise specified.

observational study (mean = 4.88 years) does not allow pain intensity to be predictive of outcome. On the other hand, the DN4 questionnaire includes brush-evoked allodynia and hyperalgesia to pinprick, and there is evidence that a higher DN4 score during zoster infection is predictive of postherpetic neuralgia.[4] There is also evidence that allodynia and hyperalgesia were strongly indicative of both moderate and severe pain in a large cohort of individuals with self-reported NeP.[8] It is surprising that negative affect and catastrophizing were not predictive of a poor outcome, because these are major risk factors for persistent pain after acute

**Table 5. Univariable Analyses to Identify Potential Role of Opioid Treatment at 12 Months in the Management of Chronic Neuropathic Pain**

| | Average Pain Intensity (BPI) Reduced by ≥30% and Interference Scale Reduced by ≥1.0 (N = 301) | | |
|---|---|---|---|
| | No | Yes | P Value |
| n (%) | 247 (62.8) | 54 (44.3) | <.001 |
| Mean dose (SD) | 170.6 (459.8) | 81.7 (123.0) | |
| Median dose (Q1, Q3) | 61.8 (23.0, 181.0) | 39.0 (19.0, 68.0) | .013 |

injury.[40,25] However, sensitivity to these parameters may also be blunted by the long duration of pain before study initiation. In addition, the scores on the Pain Catastrophizing Scale (range = 18.8–24.4) may not have been high enough to generate a differential response, because a score of 30 represents a clinically relevant level of catastrophizing.[39]

The role of opioid analgesia in the management of NeP remains controversial. Univariable analysis of opioid treatment and dose suggests that opioid dose at baseline has a negative impact on long-term outcome (Table 4). In addition, at 12-month follow-up, patients who had a favorable outcome were less likely to be on opioids, and when they were, the doses were significantly lower (Table 5). This is especially striking given that opioid treatment was fairly aggressive; the mean daily opioid dose increased by about a half and the median dose increased by about a third from baseline to 12-month follow-up. Most controlled trials of opioid therapy for NeP last 3 months or less, with doses up to 180 mg of morphine or morphine equivalent per day.[2] These studies show significant analgesic efficacy, although the evidence for improved functional outcome is mixed.[16] Evidence is lacking from controlled trials that opioid therapy is beneficial in the long term. However, opioid treatment in the long term can lead to analgesic tolerance and the development of opioid-induced hyperalgesia.[30] Recent evidence suggests that opioid-induced hyperalgesia is mediated in part by a microglial-neuronal network, which is distinct from analgesic tolerance.[17] A recent population-based pharmacoepidemiological study from Norway[20] supports the notion that most patients with chronic pain with persistent opioid use report strong or very strong pain despite opioid treatment. Although there is likely a subgroup of patients with NeP who benefit in the long term,[7] our outcome data cast doubt on overall benefit for most patients receiving opioid pharmacotherapies. In addition, opioid therapy is challenging because of the risk of opioid-related adverse effects, physiological and psychological dependence, and drug diversion.[6] Our finding that urinary hesitancy and visual blurring increase significantly relative to baseline may be related to opioid titration.

There are limitations with our observational study. This was a real-world study that did not permit comparison with an untreated control group, with the result that uncontrolled confounding factors may provide an alternative explanation for the treatment effect. These factors include the placebo response (based largely on expectation of benefit), regression to the mean, and the natural history of the underlying condition.[9,34] Some insight into natural history can be gleaned from the impact of wait lists in multidisciplinary pain treatment facilities. A systematic review[28] showed that patients with chronic pain who waited 6 months from the time of referral to treatment for chronic pain experience a reduction in health-related quality of life and psychological well-being. Another limitation was the great heterogeneity in patient presentation and treatment that simulated real-world management but prohibited specific analyses of individual interventions and individual conditions. Despite these confounding factors, systematic comparisons of RCTs and high-quality observational studies show similar treatment effects based on similar clinical issues.[10,21,29] High-quality observational studies can therefore complement RCTs in evidence-based guidance of treatment decisions. These studies tell us that only a few patients seen in tertiary care pain clinics realize significant benefit from the pharmacological and nonpharmacological treatments available. Nevertheless, these patients likely represent the most difficult-to-treat cohort of the population with chronic pain and almost a quarter met the stringent criteria of significant improvement in both pain and function. Outcomes in primary care may be better because family doctors see patients earlier in the course of their illness, but this has not been studied. Pragmatic trials that include alternative treatment groups rather than placebo may be more definitive in primary and tertiary care settings.[36]

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