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

Dwight E. Moulin,* A. John Clark,†,‡ Allan Gordon,§ Mary Lynch,†,‡ Patricia K. Morley-Forster,¶ Howard Nathan,‖ Cathy Smyth,‖ Cory Toth,** Elizabeth VanDenKerkhof,†† Ammar Gilani,‡‡ and Mark A. Ware§§

*Departments of *Clinical Neurological Sciences and ¶Anesthesia & Perioperative Medicine, Western University, London, Ontario.*
Departments of †Anesthesiology and ‡Psychiatry, Dalhousie University, Halifax, Nova Scotia.
§Wasser Pain Management Centre, University of Toronto, Toronto, Ontario.
‖Department of Anesthesiology, University of Ottawa, Ottawa, Ontario.
***Department of Clinical Neurological Sciences, University of Calgary, Calgary, Alberta.*
††School of Nursing & Department of Anesthesiology & Perioperative Medicine, Queens University, Kingston, Ontario.
‡‡Department of Internal Medicine, McMaster University, Hamilton, Ontario.
§§Department of Family Medicine, McGill University, Montreal, Quebec, Canada.

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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Address reprint requests to Dwight E. Moulin, MD, Department of Clinical Neurological Sciences, Victoria Hospital, 800 Commissioners Rd. E., London, Ontario N6A 5W9 Canada. E-mail: dwight.moulin@lhsc.on.ca

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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