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Moisset X, **Pagé MG**, Pereira B, Choinière M. (2021). Pharmacological treatments of neuropathic pain: real-life comparisons using propensity score matching. *PAIN.* Sous presse. Doi : 10.1097/j.pain.0000000000002461

Pharmacological treatments of neuropathic pain: real-life comparisons using propensity score matching

Xavier Moisset[1], M. Gabrielle Pagé[2,3,4], Bruno Pereira[1], and Manon Choinière[2,3]

1- Université Clermont Auvergne, CHU de Clermont-Ferrand, Inserm, Neuro-Dol, F-63000 Clermont-Ferrand, France ;
2- Centre de Recherche du Centre hospitalier de l'Université de Montréal (CRCHUM), Montreal, Quebec, Canada;
3- Department of Anesthesiology and Pain Medicine, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada;
4- Department of Psychology, Faculty of Arts and Science, Université de Montréal, Montreal, Quebec, Canada.

Number of text pages (including Figures and Tables): 30

Number of Figures: 2

Number of Tables: 7

Supplemental files: 1 (Table S1)

Corresponding author:

Professeur Manon Choinière

Département d'anesthésiologie et de médecine de la douleur

Faculté de médecine, Université de Montréal

Centre de recherche du Centre hospitalier de l'Université de Montréal

Tour Saint-Antoine

850, rue Saint-Denis

Bureau S01-126

Montréal, Québec, H2X 0A9

Tel: 514-890-8000 poste 14082

Email: manon.choiniere@umontreal.ca

1. Introduction

Neuropathic pain (NP) is present in 7 to 10% of the general population [30]. It is often difficult to treat and it has a major impact on patients' quality of life along with important direct and indirect health care costs [1,13,16]. Several epidemiological studies have shown that many patients with NP do not receive recommended treatments [1,17,45]. Nonetheless, pharmacological and non-pharmacological therapies, although imperfect, are available [15,23,37]. Current international guidelines for pharmacological management of NP recommend tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors (SNRI) and gabapentinoids (pregabalin and gabapentin) as first-line treatment; tramadol as second-line; and strong opioids as third-line [23]. To date, the number of studies comparing different recommended drug regimens for NP is very limited [3,22,23,26,31,37,48], although comparative efficacy of different drugs could be informed, to some degree, by meta-analyses of placebo-controlled drug trials that allow for the estimation of number-needed-to-treat for each agent allowing, with some recognized limitations, for a quantitative comparison across different drugs [23,40]. However, knowing the comparative clinical effectiveness of these treatments in real-world settings would be of major importance.

The Quebec Pain Registry (QPR) has been implemented in 2008 in three university-affiliated multidisciplinary pain treatment centres in Quebec (Canada) and two other centres joined in 2012. Close to 9,000 patients have been included and have provided consent for their data to be used for research purposes. Among these patients, around 20% were presenting chronic NP. As pain was systematically and comprehensively assessed both at baseline (prior to first appointment at the pain clinic) and 6 months later, it is possible to use such data to compare treatment effectiveness in this selected population of patients. Indication bias is frequent in observational studies because the choice of treatment is generally influenced by the patients' characteristics (e.g. age, sex, presence of depression or sleep problems) [2] and

contraindications (e.g. cardiac conduction block or postural hypotension for tricyclic antidepressants; substance use disorder for opioids), cost/health care provider coverage, and patient preference. However, a propensity score (PS) can be determined to adjust for several of these differences [2].

The aim of the present study was to examine the clinical evolution of patients with chronic NP treated in tertiary care centres and compare in real-life clinical settings the effectiveness of recommended medication for NP using a PS analysis.

2. Materials and methods

2.1. Participants

Study participants were selected from patients enrolled in the Quebec Pain Registry (QPR) [10] (http://www.quebecpainregistry.com) who provided written consent for their QPR data to be used for research purposes (91.4% of patients). The QPR was developed and implemented to monitor the condition of patients suffering from various types of pain syndromes who were referred to large university-affiliated multidisciplinary pain treatment clinics (MPTCs) in the province of Quebec (Canada) using common demographics, identical clinical descriptors, and uniform outcome measures [10]. Patients were enrolled in the QPR if they were (1) scheduled for a first visit at the pain clinic for multidisciplinary treatment considerations, (2) aged 18 years or older, (3) fluent in spoken and written French and/or English, and (4) physically and cognitively able to complete questionnaires. Patients were excluded if they were eligible for recruitment in the pre-existing Fibromyalgia Registry at one of the participating sites. Patients seen at the MPTCs were offered different treatment options based on their clinical profile. Treatment was thus individualized to patient needs. Treatments could include one or a combination of the following treatments: pharmacotherapy, physiotherapy, psychotherapy, and interventions (e.g., blocks).

In the present study, patients suffering from chronic (≥3 months) NP were selected. Current recommended grading system for NP definition [25] was not applicable in the present database. Thus, we decided to keep only patients with highly probable NP--i.e., patients with a diagnosis of NP made by the pain physician at the MPTC and presenting a score on the DN-4 screening questionnaire of at least 3 out of 7 [8]. As the sensitivity of this score is 82%, several patients with NP have possibly been excluded but it is highly probable that retained patients do have a neuropathic type of pain. We excluded patients with complex regional pain syndrome (CRPS) as CRPS type was not specified. Moreover, we excluded patients with a trigeminal neuralgia diagnosis as this neuropathic type of pain responds to specific treatments [6].

2.2. Procedure

The QPR project was approved by the institutional research ethics boards (REBs) of the *Centre hospitalier de l'Université de Montréal*, the McGill University Health Center, the *Centre hospitalier universitaire de Sherbrooke*, the *Centre hospitalier Universitaire de Québec,* and the *Hôtel-Dieu de Lévis*. Successive patients who came for a first appointment at one of the participating pain clinics were enrolled in the QPR. They were informed that the information collected as part of the QPR had both clinical purposes (production of a summary report of their clinical condition for the clinician with whom they had an appointment) and administrative endeavours (e.g., generation of annual statistical reports). Patients were invited to sign the REB-approved consent form if they agreed to the use of their QPR data for research purposes.

Biopsychosocial data including (pain intensity (Numerical Pain Intensity Scale [18]), pain interference (Interference items of the Brief Pain Inventory [11,46]), sleep quality (Sleep

Problem Index [34]), tendency to catastrophize in the face of pain (Pain Catastrophizing Scale [44]), depression (Beck Depression Inventory [4]), and physical and mental health-related quality of life (SF-12: 12-item Short Form Survey [47]) were collected with a self-report questionnaire (patient self-administered questionnaire) while medical/clinical data (e.g., pain duration, pain diagnosis, neuropathic pain questionnaire (DN4) [7], pharmacological/non-pharmacological treatments, etc.) gathered by the QPR nurses using a structured interview protocol (nurse-administered questionnaire) prior to the patient's first appointment at the pain clinic (baseline). The same questionnaires were administered six months later (M6). Only participants with NP who answered the patient and the nurse questionnaires at baseline and M6 were included in the present study. A pain reduction at M6 compared to baseline was noted with a negative score.

In order to evaluate the impact of drugs on the evolution of pain intensity and interference from baseline to M6, we compared these outcomes at these two time points. We focused on four drug regimens: antidepressants (i.e. tricyclic antidepressants and serotonine-norepinephrine reuptake inhibitors), antiepileptics (i.e. gabapentin and pregabalin), weak opioids (i.e. tramadol, codeine, dextropropoxyphene), and strong opioids (e.g. morphine, fentanyl, oxycodone, hydromorphone, tapentadol, buprenorphine, methadone). Thus, it was possible to define treatments taken at baseline only, at M6 only, or at both time points. To evaluate the role of drugs on pain evolution between baseline and M6, we took into account all the drug regimens taken at M6 evaluation. Indeed, these treatments were either initiated by the pain physician or at least evaluated and validated by the pain physician. Thus, even for a patient receiving a drug from the same treatment group both at baseline and M6, pain improvement can be expected as the treatment could have been modified in terms of the molecule used (e.g., tricyclic antidepressant replaced by serotonine-norepinephrine reuptake

inhibitor or pregabalin replaced by gabapentine), the posology, or the associated pharmacological treatments.

2.3. Statistical analysis

Continuous data are presented as the means ± standard-deviation (SD) or medians and interquartile range (IQR), depending on their distribution. The assumption of normality was evaluated using the Shapiro-Wilk test. Categorial data are presented as numbers and associated percentages.

In order to assess if participants with missing questionnaires at M6 qualified as "missing at random", differences between patients who completed questionnaires (n = 944) and those who did not (n = 696) were compared using independent Student t-tests for continuous variables and Chi-squared tests for categorical variables. However, such significant testing in studies involving large sample sizes like the present one can be misleading because even small differences can reach statistical significance while they can be viewed as trivial and not meaningful clinically. Therefore, effect sizes of differences between patients who completed and did not complete M6 assessments were calculated with Cohen's d [12]. For categorical variables, effect sizes were calculated using the Phi (φ) [42] and Cramér's V [14] statistics. Only differences reaching a Cohen's d ±0.5 or a φ or Cramér's V ±0.3 were judged as being clinically important.

Comparisons of patients' clinical evolution over time on quantitative variables (e.g., pain intensity scores) were performed using paired t-tests or Wilkoxon signed rank test. Chi^2 tests were used for categorial variables. A two-sided p value <0.05 was considered statistically significant and no correction for familywise error was performed [5]. Based on the IMMPACT recommendations, a decrease of 30% or more in pain intensity and interference was considered

as clinically meaningful and the proportions of patients showing such a reduction were calculated [19]. Because reductions in pain intensity of ≥50% appear to reflect substantial improvements [19], proportion of patients responding with this degree of improvement was reported as a sensitivity analysis.

As mentioned before, indication bias is frequent in observational studies because the choice of treatment is generally influenced by the patients' characteristics [2]. A propensity score (PS) can be calculated to adjust for these differences [2]. For PS analysis, two methods were used. First, a PS analysis was performed for each of the four treatment groups (antidepressants, antiepileptics, weak opioids, strong opioids) taking into account co-medications (treatments from the three other treatment categories). Inverse probability of treatment weighting (IPTW) was carried out by assigning to each participant an inverse weighting of the probability of receiving or not one of the NP treatments of interest, estimated by the PS [2]. The PS corresponds to the probability of a patient receiving the treatment according to their characteristics. Thus, the weight of patients who were highly likely to receive one treatment based on their observable characteristics was reduced and that of patients who were unlikely to receive was increased. The different treatment groups were thus rendered comparable because they would have had the same chance of being treated. Considering the characteristics of the participants at baseline, the PS model included the following variables: age, sex, pain duration, baseline pain intensity (pain intensity on the average in the past seven days), pain interference in the past seven days (Brief Pain Inventory [46]), non-pharmacological treatments (psychological and physical techniques), education level, employment, catastrophizing, mental health (SF-12 mental component sub-score) and co-medications (antidepressants, antiepileptics, weak and strong opioids; one drug class being analyzed and the three others being used as covariables for each analysis). The validity of the matching was then tested by analyzing the standardized differences ($|d|$), with $|d| > 0.2$

considered to be an imbalance. Second, a multiple treatment PS analysis was performed, as sensitivity analysis, for patients receiving only one of the four treatment categories. This analysis was performed using R software (version 4.0.2, R foundation) with *mnps* package, suitable for multinomial propensity scores for multiple treatments. Another sensitivity analysis was carried out by conducting PS analysis only in patients having a new treatment type initiated after the first appointment at the pain clinic.

A two-sided p value <0.05 was considered statistically significant. Apart from the multiple treatment PS analysis, all other analyses were performed using Stata (version 15, StataCorp, College Station, USA) software.

3. Results

3.1. Sample characteristics

Among the 12,079 patients who were referred to the participating pain clinics, 9,418 (78.0%) qualified for enrolment in the QPR and only 8.5% refused to do so (**Figure 1**). A final sample of 1640 participants was retained at baseline for this study; 944 of them (57.5%) had complete data at both baseline and M6 and were included in PS analysis (**Figure 1**). Demographic and biopsychosocial characteristics of these patients are presented in **Table 1**.

Patients with 6-month follow-up were slightly older (53.4 ± 13.3 compared to 50.1 ± 13.8 for patients evaluated at baseline only; d = 0.24 [0.14 – 0.34]). There was no clinically meaningful difference concerning pain duration, presence of allodynia or hypoesthesia, pain intensity or pain interference (see **Table S1** in supplemental file for a comprehensive comparison of the two sub-groups). Thus, there was no obvious selection bias for patients with 6-month follow-up compared to the whole NP cohort.

3.2. Type of drug regimens

Previously and currently used treatments at baseline are presented in **Table 2**. Before their first appointment in a pain clinic, 585/944 patients (62.0%) had taken or were currently taking at least one first-line drug therapy (recommended antiepileptics and recommended antidepressants or both). Only 21.5% (203/944) had ever taken both. Among the 741 individuals that had not tried the two types of first-line drugs, 351 (47.4% of the subgroup or 37.2% of the whole sample) had already tried strong opioids whereas it is a third-line treatment.

Over the first six months after initiating treatment at the pain clinic, pharmacological pain treatments were modified for many patients. Several treatments received at baseline were discontinued whereas other drug treatments were initiated (**Table 3**). Overall, strong opioids were more likely to be discontinued (20% vs 11 to 17% for the three other treatment categories, Sidak-adjusted p-values < 0.001 in all cases). Concerning the reasons for discontinuation, strong opioids were stopped more often because they were "not needed" (36% vs 18 to 23%; Sidak-adjusted p-values < 0.001 compared to antidepressants and antiepileptics, p = 0.04 compared to weak opioids) but less frequently due to side effects (Sidak-adjusted p-values < 0.001 compared to antidepressants, not significant compared to the other treatment categories). There was no significant difference concerning discontinuation due to a lack of benefit. Six months after the first appointment in a pain clinic, 752/944 patients (79.7%) had taken at least one first line drug and 327/944 (34.6%) had tried both antidepressants and antiepileptics. Among the 617 that had not tried two types of first line drugs, 348 (56.4% of the subgroup or 36.9% of the whole sample) had already tried strong opioids.

3.3. Patients' clinical evolution from baseline to 6-month follow-up

Patients' clinical evolution in terms of pain intensity and interference, sleep, tendency to catastrophize in the face of pain, physical and mental health-related quality of life, and depression from baseline to 6-month follow-up is presented in **Table 4**. There was a statistically significant improvement on all the parameters. According to Cohen [12], an effect size between 0.2 and 0.5 is a small one in terms of clinical significance. Nonetheless, such small effects are of interest for neuropathic pain treatment. In the present case, the overall effect size for pain evolution between baseline and 6-month follow-up was 0.37 for pain intensity and 0.42 for interference, i.e. corresponding to number needed to treat (NNT) of 8.4

and 7.3, respectively [35]. Such NNTs are in the range of expected values for SNRIs or gabapentinoids [24]. Further examination of the proportion of patients who showed at least a 30% decrease in their pain intensity scores at M6 revealed that it was the case for 23.0% of the sample (217/944) while 30.6% showed at least a 30% decrease in their pain interference scores.

When focusing on the type of drugs the patients were taking to explain this positive evolution, comparisons of their median scores showed no impact of the medication taken at baseline on pain intensity six months later (**Table 5**). Thus, this parameter was not considered as a covariate when looking for factors influencing the patients' evolution during the six-month follow-up.

When focusing on the type of medications the patients were taking at M6, group comparisons on the evolution of pain intensity from baseline to M6 showed a significantly less favourable outcome for those taking strong opioids compared to those who were not on this type of medication (**Table 6**). Accordingly, there was a less favourable outcome in the extent to which pain interfered with various aspects of daily life (Brief Pain Inventory interference score) for patients on strong opioids compared to those who were not (-6 [-18 – 5] versus -8 [-22 – 3]; p = 0.006; Difference = 2 [0.94 – 4.94]). There were no significant differences for the other types of medication (**Figure 2**). As patients receiving or not three drug classes (antiepileptics, antidepressants and weak opioids) were not presenting a significantly different pain evolution, while the fourth one (strong opioids) showed a significantly smaller number of responders, we decided to investigate this difference further.

Among patients taking strong opioids, 13.9% had at least 30% improvement in pain intensity at M6 versus 27.0% of those not receiving strong opioids (**Table 7**). These results were confirmed using a propensity score (PS) analysis which adjusted for age, sex, pain duration, pain intensity at baseline, and co-prescriptions. These results revealed that the 30%

responders' proportion was significantly lower among patients on strong opioids (14.2% versus 26.0%; p<0.001) (**Table 7**). These results were also corroborated using multi-treatment PS analysis among patients (n = 263) taking only one type of drug. Again, the 30% responders' proportion was the lowest among the patients taking strong opioids. The absolute difference in terms of responders was 0.8% (p = 0.925) when compared to weak opioids, 14.9% (p = 0.155) when compared to anti-neuropathic antidepressants, and 15.8% (p = 0.011) when compared to gabapentinoids.

As a sensitivity analysis, we used a 50% pain intensity reduction rather than a 30% one and the results were similar with 13.6% of the whole sample achieving a 50% reduction (128/944) and only 5.6% among patients taking strong opioids versus 17.1% among those who were not on this type of medication. Again, PS analysis confirmed these results with 6.1% of responders among those taking strong opioids and 16.8% among those who did not (p<0.001). For this particular outcome (50% pain intensity reduction), the proportion of responders was also significantly lower in patients who were taking weak opioids (7.0%) than in those who were not on this type of medication (14.5%) (p=0.006). Proportion of 30% and 50% responders before and after IPTW for each treatment class are presented in **Figure 2**.

A second sensitivity analysis was conducted using only the 271 patients for whom a new treatment type was initiated following the first appointment at the pain clinic (136 were put on anti-epileptics, 88 on antidepressants, 46 on weak opioids, and 90 on strong opioids, several patients taking more than one new drug type). Although the sample size was limited in this sub-group, the same pattern of results emerged for the patients taking strong opioids. The PS analysis revealed that the percentage of 30% responders was significantly lower in patients taking strong opioids than those who did not (14.7% vs 23.5%; p = 0.021).

4. Discussion

This study assessed in "real life" clinical settings the impact of different pharmacological treatments on the evolution of NP intensity and interference in a large cohort of tertiary care patients. To the best of our knowledge, this is the first real-life, longitudinal multi-centered study that examined NP evolution using propensity score analysis to compare different drug regimens. Our results showed that the proportion of patients who showed improved pain intensity was significantly lower in those using strong opioids compared to patients who were not on this type of medication while taking into account potential confounders (age, sex, pain duration, pain intensity at baseline, co-prescriptions). The proportion of responders was equivalent among patients taking or not antidepressants and antiepileptics.

A recent meta-analysis of randomised controlled trials (RCTs) ranging between 4 and 12 weeks concluded that strong opioids can provide substantial pain relief in patients who suffer from postherpetic neuralgia and peripheral neuropathies of different aetiologies [43]. Despite this potential positive effect, strong opioids use for the treatment of chronic NP is usually restricted to tertiary care patients with a low risk of substance use disorder [23,37,39]. The current opioid crisis along with the limited evidence on the efficacy of long-term opioid treatment for chronic pain [39] encourage cautious prescribing. It has been shown in large databases that long-term opioid therapy for chronic non-cancer pain was associated with a higher all-cause mortality [21,28]. However, if strong opioids have a benefit and if there are no better alternatives, it makes sense to use them even if there is a risk of adverse side effects. But in the present observational study, when taking potential confounding factors into account, only one patient out of 10 receiving strong opioids had a clinically significant improvement over a 6-month period. The magnitude of effect is far smaller than that of the recent meta-analysis of RCTs, including studies lasting 12 weeks at the most [43]. Indeed, the

number needed to treat on the 12 week-period was around 5, whereas it is around 10 in the present cohort. Thus, we suggest using such treatment as third line and carefully reconsidering the prescription after 12 weeks. As recommended, both first- and second-line treatments should be proposed to all patients before trying third line treatments, which was not the case for many patients in this real-life study. In addition, non-pharmacological approaches such as spinal cord stimulation for selected patients or high frequency repetitive transcranial magnetic stimulation are of interest in patients with NP [15,37] and have been proposed as third line treatments before prescribing strong opioids [37].

A recent study failed to identify predictors of long term opioid therapy effectiveness, making it difficult to inform clinicians about which patients with chronic non-cancer pain are most likely to benefit from long-term opioid therapy [32]. In contrast, more information exist on the risk factors of opioid misuse/abuse [20,41]. Thus, if it is difficult to identify which patients with chronic NP would potentially benefit from opioids, we must assess properly the risks of using this type of medication. Moreover, it has been shown that pain intensity after discontinuation of long-term opioid therapy does not worsen for many patients [36], although opposite results have also been published, a significant sub-group of patients clearly presenting more pain when discontinuing strong opioids [27,33]. In addition, opioid dose escalation among patients with chronic pain is not necessarily associated with improvements in pain scores [29]. All these results, although not obtained specifically in NP patients, encourage clinicians to use long-term opioid therapy with parsimony.

It was surprising to note that 38% of our sample had never received any recommended first line drugs for chronic NP (i.e., gabapentinoids, tricyclic antidepressants or SNRIs antidepressants) before their first appointment at the pain clinic and nearly 80% had not tried both antiepileptics and antidepressants. The proportion of patients who tried appropriate treatments was close to what can be seen in the general population [1,9]. We do think that this

real-life pain patients' cohort analysis can guide prescribing consideration as it reinforces the proposed guidelines to use strong opioids as a third line option only. Nonetheless, the only way to clearly evaluate the relative efficacy of the various drugs would be to undergo a randomised controlled trial.

4.1. Strength and limitations

One of the strengths of the present study is that it involved a large group of well-defined NP patients with 6-month follow-up data (n = 944), without any obvious selection bias. The mean age was above 50 years which is similar to that found in population-based cohorts of patients with chronic NP [8,9]. Concerning the sex ratio, it was somewhat lower (51%) than the ones found in large epidemiological studies (60 to 64%) [8,9]. Considering health-related quality of life, the mean score on the mental subscale of the SF-12 was equivalent to that seen in the general population of NP patients [1]. Altogether, these comparisons suggest that the present results could be generalized to most NP patients. In addition, the propensity score took into account many factors to limit the risk of bias, including demographic characteristics, pain intensity and impact, psychological parameters (mental health, catastrophizing), non-pharmacological treatments, education level and employment.

However, several limitations should be considered when interpreting the present results. First, as it is a study carried out in "real-life" clinical settings, patients were not randomised to any of the four treatment groups so they were not perfectly comparable at baseline. Nonetheless, a propensity score analysis was used to reduce such a bias. Results of the two methods employed were concordant, showing a more limited proportion of responders in patients taking strong opioids. Of note, PS analysis reduces the risk of bias for included parameters, and many important known factors influencing the prescription were included, but some

potential confounders were not taken into account as they were not available (e.g. chemical coping, patients' preferences) or not known. Second, the follow-up duration was relatively short (6 months). However, most clinical studies have been performed with a follow up lasting 12 weeks at the most [43] and very few of those with more than 6-month follow-up [25,37]. Third, it was not possible to compare each drug treatment individually; they have rather been pooled into four classes, although treatment effectiveness can be different between drugs; for example, among gabapentinoids, gabapentine has been shown to be more effective than pregabalin [37,38]. Accordingly, all weak opioids have been pooled together whereas tramadol is the only one recommended for NP treatment [23,37]. However, tramadol was used by 73/94 patients (77.7%) in this group and it seemed important to be able to compare the impact of weak and strong opioids. In addition, baseline pain was taken into account even if the treatment evaluated at month 6 was initiated 3 months after baseline. For more specificity, pain should have been evaluated at the time of a significant prescription modification (new drug initiated or daily dose of an ongoing treatment modified). Fourth, several pain treatments have been used transiently and discontinued (**Table 3**). Unfortunately, there was no available information concerning potential pain exacerbation or intercurrent illnesses requiring analgesics treatments and such events cannot be taken into account in the analysis. Fifth, we can note that the population was heavily Caucasian, possibly reducing the applicability of the results in other populations. Finally, data were collected between 2008 and 2014. As a consequence of the opioid epidemic, the current practices are possibly different now and the proportion of patients receiving strong opioids is probably lower than during the data collection period although strong opioids prescriptions started decreasing in 2010 (Canadian Centre on Substance Use and Addiction, 2017).

5. Conclusions

Our results showed that the proportion of patients who suffered from chronic neuropathic pain who exhibited a clinically significant pain reduction was the lowest among those taking strong opioids compared to other drug regimens. Because strong opioids have adverse side effects, we suggest trying recommended first- and second-line drug treatments before using strong opioids. We also suggest that strong opioids should be discontinued if not providing significant relief or after overcoming transient pain exacerbation. Thus, long-term prescription can be helpful but should be limited to selected and carefully monitored patients.

Acknowledgments.

The conducted research was approved by the local ethics committee but was not preregistered with an analysis plan in an independent, institutional registry.

Data from the Quebec Pain Registry are available on demand (https://quebecpainregistry.com/data-information-and-access). Program codes used in analysis will be available upon reasonable request sent to the authors.

Conflict of interest statement

Xavier Moisset has received financial support from Allergan, Biogen, Bristol Myers Squibb, Grunenthal, Lilly, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, TBWA, and Teva and non-financial support from SOS Oxygène, not related to the submitted work.

Gabrielle Pagé has no conflict of interest to declare. She is a Junior 1 research scholar from the *Fonds de recherche du Québec - Santé.*

Bruno Pereira has received financial support from Biogen and Grunenthal.

Manon Choinière has no conflict of interest to declare.

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Figure Legends

Figure 1. Flow diagram of patients included in the analysis. QPR: Quebec Pain Registry. M0: baseline evaluation. M6: 6-month follow-up evaluation.

Figure 2. Proportion of patients with at least 30% or 50% pain intensity decrease between baseline and 6-month follow-up according to treatment class taken, before and after inverse probability of treatment weighting (IPTW) procedure.

Variables	Values
Age, years (mean±SD)	53.4 ± 13.3
Female sex, % (n)	51.4 (485)
Pain duration, years (median [IQR])	3.0 [1.0 – 8.0]
Caucasian ethnicity, % (n)	93.0 (878)
Presence of allodynia, % (n)	22.1 (209)
Presence of hypoesthesia, % (n)	
To touch	39.8 (376)
To prick	39.6 (374)
At least one hypoesthesia	43.8 (413)
Average pain intensity in the last 7 days (mean±SD)	6.8 ± 1.9
Brief Pain Inventory pain interference score in the last 7 days (mean±SD)	5.9 ± 2.1
Beck depression Inventory-I, % (n)	
0–9: normal range	19.9 (188)
10–18: mild to moderate depression	35.5 (335)
19–29: moderate-severe depression	30.4 (287)
30–63: severe depression	14.1 (133)
Sleep Problem Index (score 0-30) (mean±SD)	18.3 ± 8.4
Pain catastrophizing scale (score 0-52) (mean±SD)	29.8 ± 12.7
Quality of life	
SF-12 Norm-Based Physical Summary Scale (mean±SD)	28.2 ± 8.0
SF-12 Norm-Based Mental Health Summary Scale (mean±SD)	41.0 ± 11.6
Non-pharmacological treatments, % (n)	
Psychological	63.1 (596)
Physical	64.0 (604)
Education level, % (n)	
Primary	8.5 (59)
Secondary	40.4 (281)
CEGEP or Technical school	32.1 (223)
University	18.1 (126)
Work type, % (n)	
Full-time job	19.7 (137)
Part time job	7.3 (51)
No job	73.0 (508)

Table 1: Baseline characteristics of the 944 patients with chronic neuropathic pain. IQR: Inter-quartile range. SD: standard deviation. SF-12: 12-item Short Form Survey. CEGEP: French acronym for "general and professional teaching college". Psychological treatments correspond to relaxation, meditation, hypnosis, visualisation, distraction, psychotherapy, group therapy, self-help support group, other. Physical treatments correspond to physiotherapy, occupational therapy, hydrotherapy, transcutaneous nerve stimulation, intramuscular stimulation, ultrasound, biofeedback, acupuncture, massage, chiropractic, ostheopathy, therapeutic touch, reflexology, Reiki, magnet therapy, exercices at home, other.

	Previously used pain treatments (N=944)	Pain treatments used at baseline (N=944)
Antidepressants	118 (12.5)	148 (15.7)
Stopped (%) due to - Side effects	56.3	
- Lack of benefit	36.1	
Antiepileptics	245 (26.0)	342 (36.2)
Stopped (%) due to - Side effects	58.6	
- Lack of benefit	39.1	
At least one first line anti-neuropathic drug, n (%)	**294 (31.1)**	**400 (42.4)**
Acetaminophen, n (%)	171 (18.1)	367 (38.9)
Stopped (%) due to - Side effects	32.7	
- Lack of benefit	53.4	
NSAIDS	245 (26.0)	271 (28.7)
Stopped (%) due to - Side effects	31.9	
- Lack of benefit	48.0	
Weak opioids	147 (15.6)	94 (10.0)
Stopped (%) due to - Side effects	44.9	
- Lack of benefit	43.6	
Strong opioids	285 (30.2)	292 (30.9)
Stopped (%) due to - Side effects	43.3	
- Lack of benefit	26.4	
Cannabinoids	25 (2.7)	50 (5.3)
Stopped (%) due to - Side effects	50.0	
- Lack of benefit	15.4	
Anti-spastic drugs	87 (9.2)	78 (8.3)
Stopped (%) due to - Side effects	34.1	
- Lack of benefit	45.5	
Ketamine	6 (0.6)	5 (0.5)
Topical capsaicin	2 (0.2)	2 (0.2)
Topical lidocaine	1 (0.1)	3 (0.3)

Table 2. Pharmacological pain treatments used before to the first visit at the pain clinic with reason for discontinuation (possibility to note more than one reason for discontinuation) and treatment used at baseline for the 944 patients with complete evaluation both at baseline and six-month follow-up. NSAIDs: Non-steroidal anti-inflammatory drugs.

	Pain treatments discontinued within 6 months after initial appointment at the pain clinic (N = 944)	Pain treatments used at 6 months (N = 944)	Pain treatments - initiated after initial appointment at the pain clinic (N = 944)	Ongoing pain treatments before initial appointment that was continued until at least the 6-month follow-up (N = 944)
Anti-neuropathic antidepressants	107 (11.3)	189 (20.0)	88 (9.3)	101 (10.7)
Stopped (%) due to - Side effects	48.7			
- Lack of benefit	22.6			
- No more needed	18.3			
Anti-neuropathic antiepileptics	158 (16.7)	364 (38.6)	136 (14.4)	228 (24.2)
Stopped (%) due to - Side effects	46.1			
- Lack of benefit	19.4			
- No more needed	20.6			
At least one first line anti-neuropathic drug, n (%)	**236 (25.0)**	**433 (45.9)**	**197 (20.9)**	**236 (25.0)**
Acetaminophen, n (%)	146 (15.5)	343 (36.3)	98 (10.4)	245 (25.9)
Stopped (%) due to - Side effects	19.0			
- Lack of benefit	21.5			
- No more needed	33.9			
NSAIDS	147 (15.6)	224 (23.7)	136 (14.4)	88 (9.3)
Stopped (%) due to - Side effects	15.0			
- Lack of benefit	22.8			
- No more needed	37.1			
Weak opioids	115 (12.2)	94 (10.0)	46 (4.9)	48 (5.1)
Stopped (%) due to - Side effects	35.9			
- Lack of benefit	20.3			
- No more needed	23.4			
Strong opioids	190 (20.1)	288 (30.5)	90 (9.5)	198 (21.0)
Stopped (%) due to - Side effects	24.6			
- Lack of benefit	16.4			
- No more needed	35.9			

Table 3. Pharmacological pain treatments used during the 6 months after the first visit (M0) at the pain clinic, either discontinued (with reason for discontinuation, possibility to note more than one reason) or used 6 months after the first visit (M6). NSAIDs: Non-steroidal anti-inflammatory drugs.

	Baseline N = 944 Mean±SD	**M6 N = 944 Mean±SD**	**Effect size [95%CI] Cohen's *d***	**P**
Average pain intensity in the last 7 days	6.8 ± 1.9	5.9 ± 2.3	0.37 [0.31 – 0.43]	<0.001
Relative average pain intensity variation between M0 and M6, % (n)				
≥ 50% pain decrease	13.6 (128)			
≥ 30% pain decrease	23.0 (217)			
≥ 10% pain decrease	50.9 (480)			
Stable pain (variation < 10%)	23.9 (226)			
≥ 10% pain increase	25.2 (238)			
≥ 30% pain increase	9.5 (90)			
≥ 50% pain increase	5.0 (47)			
Brief Pain Inventory interference score in the last 7 days (global score)	5.9 ± 2.1	5.0 ± 2.5	0.42 [0.36 – 0.49]	<0.001
Relative pain interference variation between M0 and M6, % (n)				
≥ 50% pain decrease	16.2 (153)			
≥ 30% pain decrease	30.6 (289)			
≥ 10% pain decrease	51.3 (484)			
Stable pain (variation < 10%)	27.3 (258)			
≥ 10% pain increase	21.4 (202)			
≥ 30% pain increase	10.7 (101)			
≥ 50% pain increase	6.6 (62)			
Sleep problem index (score 0-30)	18.3 ± 8.4	15.5 ± 9.2	0.37 [0.30 – 0.43]	<0.001
Quality of life				
SF-12 Physical Summary Scale	28.2 ± 8.0	30.3 ± 9.1	0.28 [0.22 – 0.35]	<0.001
SF-12 Mental Health Summary Scale	41.0 ± 11.6	41.9 ± 11.8	0.08 [0.02 – 0.15]	0.010
	% (n)	% (n)	**Cramér's *V***	
Beck Depression Inventory, % (n)				
0–9: normal range	19.9 (188)	25.6 (241)		
10–18: mild to moderate depression	35.5 (335)	34.5 (325)	0.09 [0.05-0.12]	<0.001
19–29: moderate to severe depression	30.4 (287)	26.5 (249)		
30–63: severe depression	14.1 (133)	13.4 (126)		

Table 4. Evolution of pain intensity, pain interference, sleep, catastrophizing, health-related quality of life and depression from baseline to 6-month follow-up (M6). SD: standard deviation, CI: confidence interval

Treatment (number of patients taking the medication out of 944)	Taken at baseline Median [IQR]	Not taken at baseline Median [IQR]	Difference Median [IQR]	p
Weak opioids (n = 94 vs 850)	-1 [-3 – 0]	-1 [-2 – 1]	0 [-0.54 – 0.51]	0.111
Strong opioids (n = 292 vs 652)	0 [-2 – 1]	-1 [-2 – 0]	1 [0.65 – 1.35]	0.451
Antiepileptics (n = 342 vs 602)	-1 [-2 – 1]	0 [-2 – 1]	-1 [-1.33 – 0.66]	0.396
Antidepressants (n = 148 vs 796)	0 [-2 – 1]	-1 [-2 – 0]	1 [-0.56 – 1.44]	0.270

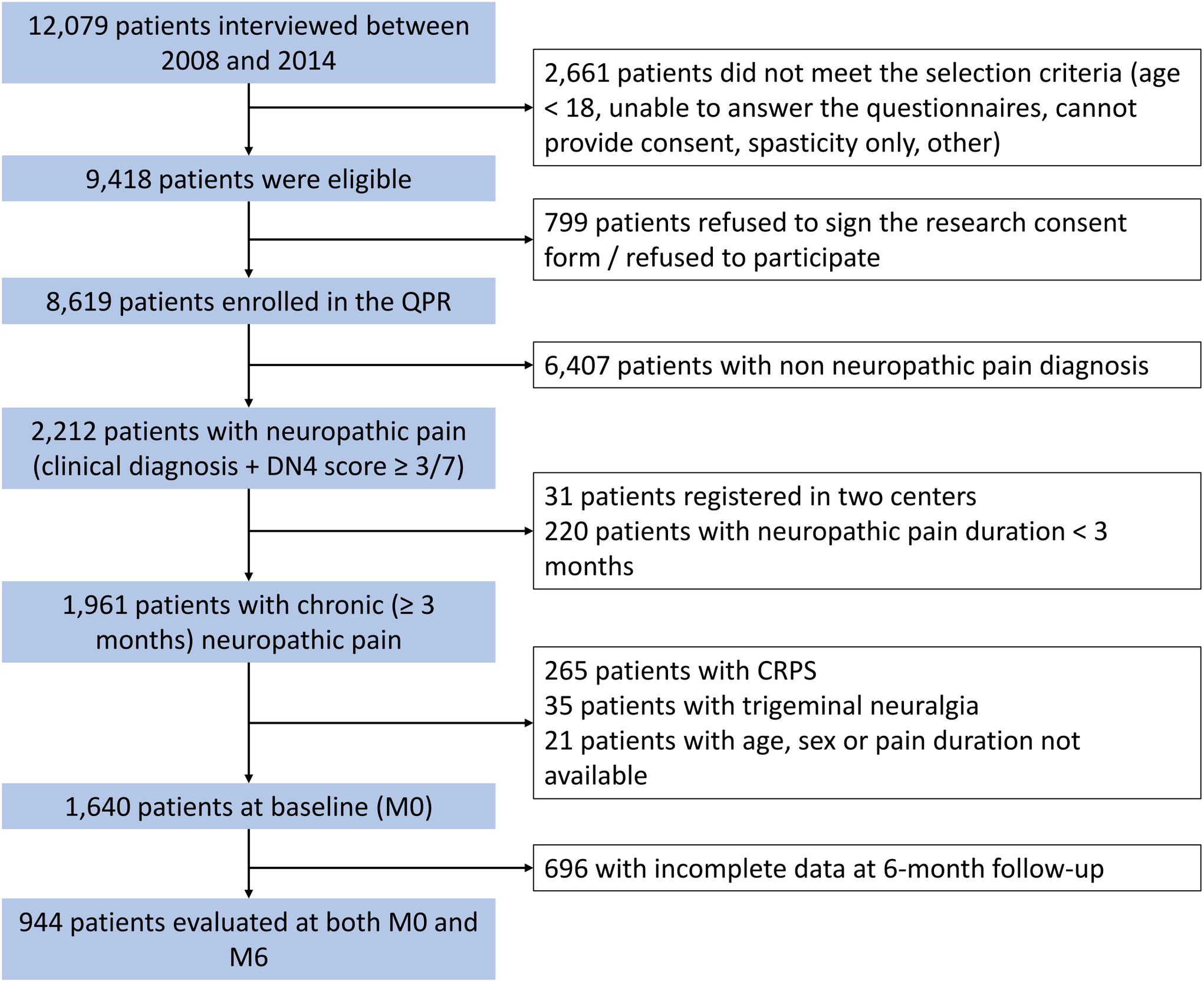
Table 5. Mean pain intensity variation from baseline to 6-month follow-up depending on the type of medications taken at baseline. A negative value for pain variation is in favor of a pain decrease between baseline and M6. SD: standard deviation

Treatment (number of patients taking the medication, out of 944)	Taken at M6 Median [IQR]	Not taken at M6 Median [IQR]	Difference Median [IQR]	P
Weak opioids (n = 94 vs 850)	0 [-2 – 0]	-1 [-2 – 1]	1 [-0.46 – 1.53]	0.853
Strong opioids (n = 288 vs 656)	0 [-1 – 1]	-1 [-2 – 0]	1 [0.65 – 1.35]	0.012
Antiepileptics (n = 364 vs 580)	-1 [-2 – 0]	0 [-2 – 1]	-1 [-1.33 – 0.67]	0.351
Antidepressants (n = 189 vs 755)	0 [-2 – 0]	-1 [-2 – 1]	1 [-0.60 – 1.40]	0.716

Table 6. Mean pain intensity variation from baseline to six-month follow-up (M6) depending on the type of medications taken at M6. A negative value for pain variation is in favour of a pain decrease between baseline and M6.

	Before propensity score			After inverse probability of treatment weighting			
	Opioids (n = 288)	**No opioids (n = 656)**	**p**	**Opioids (n = 288)**	**No opioids (n = 656)**	**|d|**	**p**
Age, years (mean± SD)	52.7 ± 12.5	53.7 ± 13.6	0.28	53.2 ± 12.8	53.2 ± 13.7	0.002	0.99
Female sex	137 (47.6%)	348 (53.1%)	0.12	51.3%	51.2%	0.002	0.98
Pain duration, years (median [IQR])	4.0 [1.5-9.5]	3.0 [1.0-7.0]	< 0.001	3.0 [1.3-8.0]	3.0 [1.3-8.0]	0.021	0.79
Average pain intensity in the last 7 days at baseline(mean±SD)	7.1 ± 1.8	6.6 ± 2.0	< 0.001	6.8 ± 1.8	6.8 ± 1.9	0.021	0.79
Percentage (%) of patients with at least 30% pain intensity decrease	**13.9**	**27.0**	**< 0.001**	**14.2**	**26.0**	**0.298**	**< 0.001**
Brief Pain Inventory pain interference score in the last 7 days (mean±SD)	6.4 ± 2.0	5.7 ± 2.1	< 0.001	6.0 ± 2.1	5.9 ± 2.1	0.051	0.58
Percentage (%) of patients with at least 30% pain interference decrease	23.3	33.9	< 0.001	22.5	32.6	0.228	0.003
Antiepileptics (Yes, n(%))	159 (55.2%)	205 (31.3%)	< 0.001	36.1	38.8	0.056	0.48
Antidepressants (Yes, n(%))	94 (32.6%)	95 (14.5%)	< 0.001	20.4	19.5	0.021	0.78
Weak opioids (Yes, n(%))	16 (5.6%)	78 (11.9%)	0.003	13.5	10.0	0.108	0.34
Non-pharmacological treatments (%)							
Psychological							
Never used	28.5	40.6	<0.001	34.3	38.3	Ref	0.04
Past use	67.7	54.0		62.8	54.8	0.120	
Current use	3.8	5.5		2.9	6.9	0.230	
Physical							
Never used	34.7	36.7	0.78	34.8	36.4	Ref	0.82
Past use	56.9	56.1		58.5	56.2	0.042	
Current use	8.3	7.3		6.6	7.4	0.024	
PCS (mean±SD)	31.9 ± 12.8	28.9 ± 12.6	<0.001	29.8 ± 12.5	29.0 ± 13.4	0.063	0.51
Education (%)							
Primary	9.8	7.4	0.004	7.6	8.2	Ref	0.92
Secondary	42.5	34.5		35.3	37.4	0.008	
CEGEP or Technical school	29.6	28.8		30.8	28.7	0.060	
University	18.1	28.8		26.2	25.7	0.041	
Work (Yes, n(%))							
Full-time job	13.5	23.5	<0.001	21.4	20.4	Ref	0.75
Part time job	4.5	8.7		6.3	8.2	0.078	
Other	81.9	67.8		72.3	71.4	0.014	
SF-12 Mental (mean±SD)	39.3 ± 11.3	41.8 ± 11.6	0.003	41.8 ± 11.5	41.1 ± 11.6	0.061	0.47

Table 7. Characteristics of patients receiving strong opioids at six-month follow-up or not, before application of the propensity score and after application of the inverse probability of treatment weighting method. Anti-neuropathic antiepileptics, antidepressants and weak opioids correspond to treatments received at M6. $|d|$: standardized difference (difference is not significant when $|d| < 0.20$). SD: standard deviation, IQR: interquartile range


12,079 patients interviewed between 2008 and 2014
2,661 patients did not meet the selection criteria (age < 18, unable to answer the questionnaires, cannot provide consent, spasticity only, other)
9,418 patients were eligible
799 patients refused to sign the research consent form / refused to participate
8,619 patients enrolled in the QPR
6,407 patients with non neuropathic pain diagnosis
2,212 patients with neuropathic pain (clinical diagnosis + DN4 score ≥ 3/7)
31 patients registered in two centers
220 patients with neuropathic pain duration < 3 months
1,961 patients with chronic (≥ 3 months) neuropathic pain
265 patients with CRPS
35 patients with trigeminal neuralgia
21 patients with age, sex or pain duration not available
1,640 patients at baseline (M0)
696 with incomplete data at 6-month follow-up
944 patients evaluated at both M0 and M6

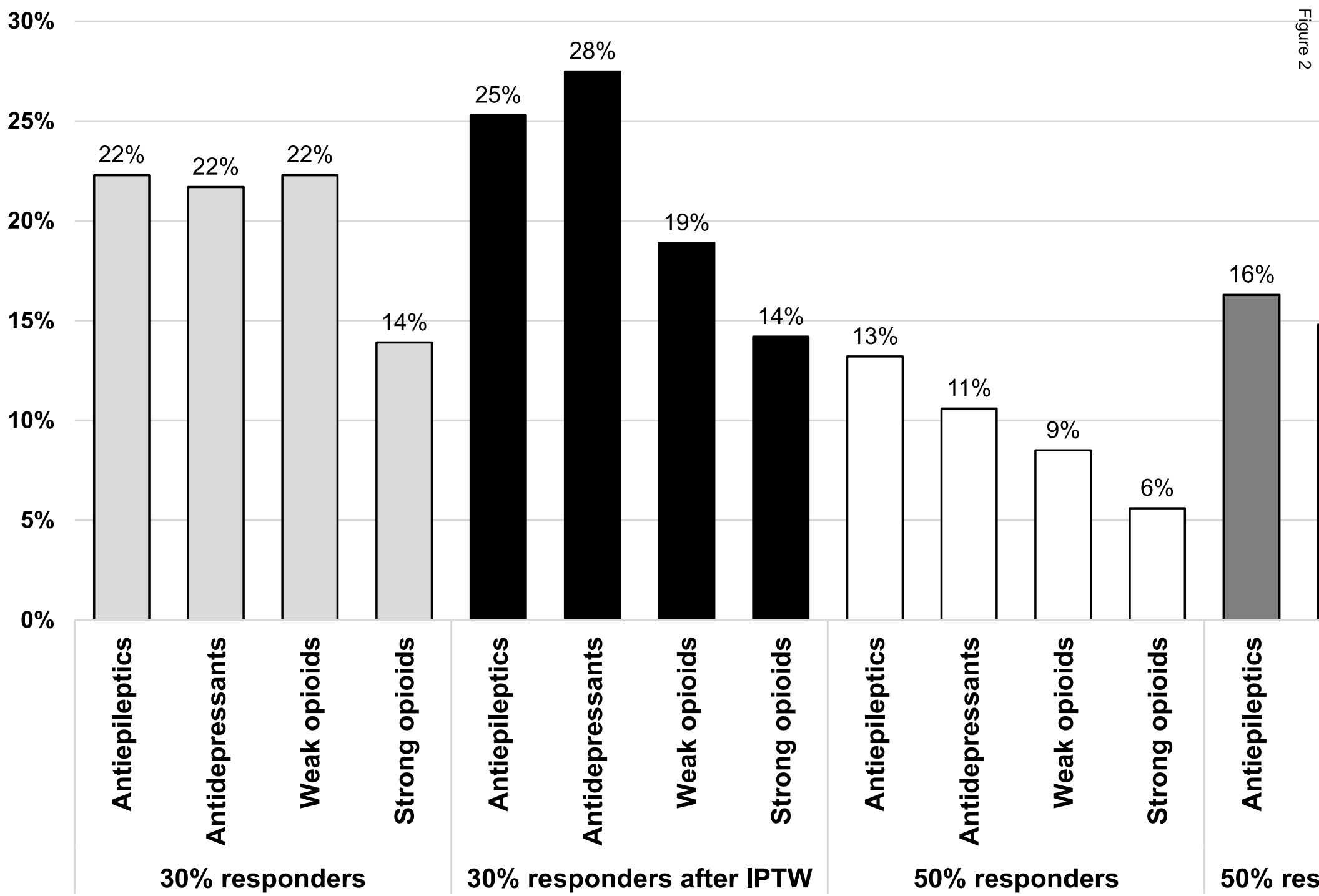

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Figure 2