

Dispensing Patterns of Drugs used for neuropathic pain in Lebanon: An observational study from community pharmacies

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Abstract

Background: Neuropathic pain is a common chronic ailment that can be challenging to treat, because of the heterogeneity of its etiologies, symptoms, and underlying mechanisms. Drugs to treat neuropathic pain are highly prescribed; however, limited data exist on the rates and patterns of dispensing in Lebanon. **Aim:** This study was conducted to assess the patterns of dispensing neuropathic pain drugs in the Lebanese adult population. **Methods:** An observational study was conducted at 30 community pharmacies over a period of 10 months. Adults presenting to the community pharmacy diagnosed with a neuropathic pain disorder, and taking at least one pain medication were interviewed using a questionnaire that included socio-demographic characteristics of patients, comorbidities, neuropathic pain disorder type, physicians' specialty, class, and number of medications prescribed. **Results:** A total of 360 patients diagnosed with painful neuropathy were enrolled in our study. The mean patients' age was 50.2 years. Guideline-recommended first-line agents (serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and gabapentinoids) were prescribed to 278 patients (77.2%) with pregabalin being the most used drug (60.5%), nonsteroidal anti-inflammatory drugs (46.8%), opioids (15.8%), and topical agents (5.5%). Combination treatment for neuropathic pain was prescribed to 78.3% of patients. **Conclusion:** Our study revealed that the Lebanese community is following international guidelines in treating neuropathic pain disorders.

Title page

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Dispensing Patterns of Drugs used for neuropathic pain in Lebanon: An observational study from community pharmacies

Running title:

Neuropathic pain treatment

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Keywords: Neuropathic pain, medication use, community pharmacy, pregabalin, Lebanon

What's already known about this topic?

Neuropathic pain is difficult to treat effectively, with merely a minority of individuals experiencing a benefit from a single drug.

Gabapentinoids are the most commonly used first-line agents to treat neuropathic pain.

What does this article add?

- Despite the good adherence to standard treatment guidelines by prescribers in Lebanon, high rates of nonsteroidal anti-inflammatory drugs (NSAIDs) use was noted.
- The high rates of combination therapy should be brought to the attention of prescribers again to remind them of good prescribing practice and to improve patient safety.
- Pharmacists can play a key role in the dissemination of treatment guidelines and promoting awareness about the irrational use of NSAIDs to limit its dispensing in neuropathic pain disorders.

Introduction

Pain is an unpleasant sensation that affects person's physiological and emotional health, socio-economic well-being, and quality of life [1]. According to the International Association for the Study of Pain, neuropathic pain is defined as 'pain caused by a lesion or a disease of the somatosensory nervous system' that can be central or peripheral [1]. A systematic review of epidemiologic studies of neuropathic pain showed that the population prevalence of pain with neuropathic characteristics is likely to lie between 6.9% and 10% [2]. Neuropathic pain is very challenging to manage because of the heterogeneity of its etiologies, symptoms, and underlying mechanisms, therefore management focuses on pain medications rather than disease-modifying treatments [3]. Recommended first-line treatments for neuropathic pain syndromes by the Canadian Pain Society (CPS), European Federation of Neurological Sciences (EFNS), the International Association for the Study of Pain (IASP)/ Neuropathic Pain Special Interest Group (NeuroPSIG) and the American academy of neurology (AAN) include serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and gabapentinoids (pregabalin and gabapentin) [4]. Although opioid medications have also demonstrated short-term benefits in the treatment of neuropathic pain, the evidence that they are beneficial is very limited and the risks of using opioids chronically to control pain tend to outweigh their benefits due to overdose, dependency, addiction, and death [5]. Moreover, nonsteroidal anti-inflammatory drugs (NSAIDs) use is widespread however, there is insufficient evidence to support or refute the suggestion that oral NSAIDs have any efficacy in neuropathic pain conditions [6]. Topical agents such as lidocaine plaster and capsaicin patch are recommended as alternative pharmacological treatments exclusively in peripheral neuropathic pain [4].

Neuropathic pain is difficult to treat effectively, with merely a minority of individuals experiencing a clinically relevant benefit from any single intervention. Thus, it constitutes a significant burden on healthcare systems and community at large, as well as being distressing for individual patients. Therefore, examining the dispensing pattern of medication for neuropathic pain disorders is needed to optimize treatment in Lebanon.

The main objective of this study was to assess the patterns of medications dispensed to adult patients diagnosed with neuropathic pain disorders presenting to the community pharmacy.

Ethics Approval

This study was approved by the Lebanese International University Institutional Review Board (2018/10) and performed in accordance with the Declaration of Helsinki. As the study did not include any active intervention, we obtained only oral consent from the patients.

Methods

Study population

This is an observational study that was conducted at 30 community pharmacies in Lebanon over a period of 10 months, from January till October 2019. To ensure a representative sample of subjects, a list of pharmacies was provided by the order of Lebanese pharmacists and a random sample was drawn from all the Lebanese governorates using the online research randomizer software.

Patients presenting to the community pharmacy were required to be (1) 18 years and older, (2) clinically diagnosed with a neuropathic pain disorder (cervical or lumbar radiculopathy, diabetic neuropathy, spinal cord injury, post-herpetic neuralgia, neuropathic postoperative pain, post-traumatic neuralgia, trigeminal neuralgia, atypical facial pain, multiple sclerosis, stroke leading to central post-stroke pain) by an orthopedist, neurologist, or neurosurgeon, (3) taking at least one pain medication at home, and (4) willing to participate in our study. Patients were not eligible for the survey if they (1) were not able to provide the name and contact information of their physician to only obtain a confirmation of diagnosis or (2) had a concomitant chronic pain unrelated to the study-defined condition that would interfere with the assessment of neuropathic pain. A sample of 360 patients was targeted to allow for adequate power for multivariable analysis to be carried out according to the Epi info software version 7.2.2.2 (Centers for Disease Control and Prevention, USA) sample size calculations.

Procedures

Each community pharmacy was observed for one week based on a predetermined schedule. Data were filled by the researcher after informing the pharmacists in charge that this research aimed to evaluate the patterns of neuropathic pain medication dispensing. After acquiring consent, the enrolled patients were face-to-face interviewed by the author based on a structured questionnaire that was translated into Arabic language and consisted of 25-items considering; socio-demographic characteristics of patients, comorbidities, neuropathic pain disorder type, and physicians' specialty and contact information. We requested permission to obtain confirmatory information about the diagnosis from the physician by telephone. Patients were also asked to report pain medications currently used, class, number, and duration of treatment. The questionnaire was piloted on a sample of 20 patients to ensure the appropriateness of questions.

Outcomes

The primary outcome was to study the patterns of drug dispensing in the management of neuropathic pain disorders, including medications commonly prescribed and analysis of prescriptions. To describe the current practice patterns of using pain medications, we determined the following three prescription states: first-line guideline-recommended drugs (TCAs, SNRIs, gabapentinoids), opioids, and NSAIDs. The secondary outcome was the association between patient-factors and first-line guideline-recommended medication, opioids, and NSAIDs use.

Statistical analysis

Data collected from questionnaires were recorded and analyzed using SPSS version v23 (IBM SPSS Statistics for Mac, Version 23.0. Armonk, NY: IBM Corp). Descriptive statistics were calculated for all study variables, including means and standard deviations (SD) for continuous measures, counts, and percentages for categorical variables. Separate multivariable logistic regression models were used to evaluate the association

between patient-level variables and the dependent variables of opioid medication use, first-line guideline-recommended medication use, and NSAIDs use. Statistical significance was set at a p-value of less than 0.05.

Results

A total of 360 patients clinically diagnosed with painful neuropathy were enrolled in our study. The mean patients' age was 50.2 years with a range of 23-88 years and 55% were females. Of the 360 patients, 110 (30.6%) had diabetes mellitus, 108 (30%) had anxiety, and 24 (9.4%) had depression (Table 1). Level of education and socioeconomic level were not associated with a specific prescribing pattern.

The most common painful neuropathic disorder encountered was cervical or lumbar radiculopathy 154 (42.8%) followed by diabetic neuropathy 94 (26.1%). Guideline-recommended first-line agents were prescribed in 278 (77.2%) of patients. NSAIDs were used by 169 (46.8%) and opioids by 57 (15.8%) of patients. The most common first-line agents used were pregabalin 218 (60.5%) and gabapentin 48 (13.3%). Monotherapy for neuropathic pain was prescribed to 78 patients (21.7%). Polypharmacy in pain was reported in 282 patients (78.3%) and the most common dual combination used was pregabalin plus NSAIDs (21.6%).

Physicians were involved in the medication plan of 300 patients (83.5%), of which 182 (50.5%) were followed up by an orthopedist, 96 (26.6%) by a neurologist, and 22 (6.1%) by neurosurgeon. Patients who received pain medication without a physician's recommendation accounted for 16.5%. Of the different neuropathic pain etiologies, post-herpetic neuralgia patients reported the lowest rate of physicians prescribed pain medication use 14/34 (41%).

Only 11% of patients used pain medication for less than one month and 36% reported less than 6 months treatment duration.

Table 2 summarizes the results of the multivariate analysis. Guideline-recommended first-line medication utilization was associated with physician visits whereas NSAIDs utilization was not. Older patients experienced significantly less initiation of first-line medications. Opioids were significantly less initiated in patients with diabetic neuropathy and cervical or lumbar radiculopathy. However, they were more significantly used in patients with positive alcohol intake and smoking history.

Discussion

Several studies conducted worldwide have focused on the epidemiology and treatment of neuropathic pain. However, none was performed in the Lebanese community. Our study was conducted across all Lebanese governorates to review the pattern of drug dispensing in patients with neuropathic pain in a community setting.

The majority of patients included in our study were taking guideline-recommended first-line agents prescribed by physicians. Post-herpetic neuralgia was the most common etiology treated without any prescription and this can be attributed to the fact that for the diagnosis and management of skin conditions including herpes zoster and its complications, a large number of people seek advice and treatment from the community pharmacy [7].

Gabapentinoids, mainly pregabalin, was the most commonly used class of drugs to treat neuropathic pain from different etiologies, while only a minority of patients used SNRIs and TCAs in the present study. The transition from TCAs to gabapentinoids can be attributed mainly to their low safety profile. Moreover, gabapentinoids monotherapy is as effective as amitriptyline and decrease pain with tolerable adverse effects [8]. Many studies supported the use of pregabalin as a first-line treatment in neuropathy and its efficacy in reducing pain, according to several types of pain assessment scores and improving sleep quality [9]. Furthermore, pregabalin has many advantages over gabapentin; two times daily dosing, less side effect profile, more rapid therapeutic effect, and has an adjunctive anxiolytic effect. The switch from gabapentin to pregabalin has decreased the overall cost of care [10]. This might explain the underuse of TCAs and SNRIs and the preference of pregabalin in the Lebanese community.

Our results illustrate two main problems with the current practice of treating neuropathic pain. First, the majority of patients were taking a combination of drugs, which is consistent with previous studies showing that at least 45% of patients with neuropathic pain are treated with two or more drugs [4]. The most common combinations encountered were gabapentinoid plus NSAID, gabapentinoid plus tramadol, and gabapentinoid plus NSAID plus tramadol and it is noteworthy that we didn't find any combination of two first-line drugs. However, combination therapy received an inconclusive recommendation due to conflicting findings, and due to safety concerns and the US Food and Drug Administration has expressed concern over the increasing use of gabapentinoids, mainly when prescribed concurrently with opioid analgesics or benzodiazepines [11]. Although opioids use is limited in our study, its use must be reserved for refractory patients who fail three first-line drugs for neuropathic pain.

The second problem is that physicians visit was not associated with NSAIDs use, which means that the overuse of NSAIDs in the Lebanese community is due to the over the counter dispensing of NSAIDs to relieve neuropathic pain, although their use is not recommended by existing evidence and are not thought to be effective in treating neuropathic pain by consensus guidelines. The continued widespread use of NSAIDs for neuropathic pain was also reported by McDermott et al. In this study, a total 602 patients with neuropathic pain were recruited from general practitioners in six European countries and the results showed that the mean age was 62.9 years, 50% were females, 35.7% of the patients were taking non-prescription ibuprofen and 26.5% were taking aspirin [12].

As these drugs are over-the-counter, several factors can contribute to adverse effects including duration of treatment, dose, coadministration with other drugs especially antimicrobials, antihypertensives, and anticoagulants. Moreover, irrational dispensing has furtherly exacerbated the adverse effects of NSAIDs. Pharmacists must ensure appropriate analgesic dosing and patient knowledge about the adverse effects of this class of drugs and the need for guidance and medical monitoring in the face of pain symptoms.

Thus, a strategy must be developed to implement effective community pharmacy-based interventions to raise patient and pharmacist awareness about the rational use of medications which includes continuing medical education regarding the potential risks of NSAIDs and the importance of their appropriate use.

Limitations

To our knowledge, this is the first study that describes the patterns of pain medication dispensing in neuropathic diseases in Lebanon. Nevertheless, it was subject to some limitations. First, it is an observational study in which outcomes were not evaluated. Second, not all Lebanese pharmacies were included in the sample studied. Third, data were reported by the patient and may be subject to recall bias.

Conclusion

Our study revealed that the Lebanese community is following international guidelines in treating neuropathic pain disorders. Pregabalin is the most commonly used drug and combination treatments are usually needed to alleviate neuropathic pain and improve patients' quality of life. Continuing education lectures, e-learning courses, or conferences should be designed to raise pharmacists awareness about the overuse of NSAIDs and to limit its dispensing for neuropathic pain.

Declarations

Conflicts of Interest The author declares no conflict of interest.

Funding No sources of funding were used in the preparation of this study.

Ethics Approval Ethical approval was obtained for the study (Ref:2018/10).

Consent to Participate Oral consent.

Consent to Publication Not applicable.

Availability of Data and Material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability SPSS version 23 institutional license.

Author Contributions All authors were involved in the conception or design of the analysis, interpretation of data, drafting the manuscript or revising it critically for important intellectual content, and final approval of the version to be published.

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Table 1: Demographic and clinical characteristics

Demographics and clinical variables (N, %) unless otherwise specified

Age (mean, SD)	50.22 (14.17)
Female	198 (55)
Marital status	Marital status
Single	64 (17.8)
Married	296 (82.2)
Current smoker	250 (69.4)
Alcohol consumption	Alcohol consumption
Abstainer	256 (71.1)

Drinker	102 (28.3)
Lebanese governorate	Lebanese governorate
Beirut	126 (35)
Bekaa	93 (25.8)
Mount Lebanon	85 (23.6)
North Lebanon	27 (7.5)
Nabatiye	13 (3.6)
South Lebanon	12 (3.3)
Others	4 (1.2)
Comorbidities	Comorbidities
Diabetes mellitus	110 (30.6)
Anxiety	108 (30)
Depression	24 (9.4)
Painful neuropathic disorder (N=384)*	Painful neuropathic disorder (N=384)*
Cervical or lumbar radiculopathy	154 (42.8)
Diabetic neuropathy	94 (26.1)
Spinal cord injury	50 (13.9)
Post-herpetic neuralgia	34 (9.4)
Neuropathic postoperative pain	24 (6.7)
Post-traumatic neuralgia	20 (5.6)
Trigeminal neuralgia/ atypical facial pain	4 (1.1)
Multiple sclerosis	2 (0.6)
Stroke leading to central post-stroke pain	2 (0.6)
Guideline-recommended medications as first-line for neuropathic pain	Guideline-recommended medications as first-line for neuropathic pain
Any	278 (77.2)
Pregabalin	218 (60.5)
Gabapentin	48 (13.3)
Tricyclic antidepressants	6 (1.7)
Duloxetine	4 (1.1)
Venlafaxine	2 (0.6)
NSAIDs	169 (46.8)
Opioids (Tramadol)	57 (15.8)
Other agents	
Topical agents (Capsaicin, Lidocaine)	20 (5.5)
Acetaminophen	12 (3.3)
Number of medications used to treat neuropathic pain per patient	Number of medications used to treat neuropathic pain per patient
One	78 (21.7)
Two	142 (39.4)
Three	108 (30)
Four	32 (8.9)
Most common drug combination used to treat neuropathic pain disorders	Most common drug combination used to treat neuropathic pain disorders
Dual: Gabapentinoids + NSAIDs	78 (21.6)
Gabapentinoids + Tramadol	32 (8.9)
Triple: Gabapentinoids + NSAIDs + Tramadol	22 (6.1)
Quadruple: Gabapentinoids + NSAIDs + Tramadol + topical agents	18 (5)
Medication dispensing	

Prescription (orthopedist, neurologist, neurosurgeon)	300 (83.5)
No prescription	60 (16.5)
Medication utilization duration	Medication utilization duration
<1 month	40 (11.1)
<6 months	132 (36.7)
6 months – 1 year	94 (26.1)
>1 year	94 (26.1)

*22/360 patients were diagnosed with more than 1 type of neuropathic pain disorder

Table 2: Demographic and clinical factors associated with the most commonly used drugs for neuropathic pain

Evaluated Factors	First-line agents OR (95% CI)	Opioids OR (95% CI)	NSAIDs OR (95% CI)
Age	0.96 (0.93-0.98) ⁺	0.98 (0.95-1.01)	1.03 (1.01-1.05) ⁺
Female (ref male)	0.46 (0.21-1.00)	1.36 (0.61-3.01)	0.45 (0.26-0.79) ⁺
Diabetes mellitus	0.75 (0.24-2.32)	3.38 (0.69-16.58)	0.75 (0.24-2.32)
Anxiety	0.34 (0.09- 1.27)	1.00 (0.29-3.38)	0.67 (0.26-1.69)
Depression	1.16 (0.47-2.89)	1.00 (0.41-2.44)	0.99 (0.53-1.82)
Alcohol intake	0.41 (0.19-0.90) ⁺	2.32 (1.01-5.35) ⁺	0.96 (0.52-1.77)
Smoking status	0.89 (0.42-1.86)	3.59 (1.46-8.81) ⁺	0.56 (0.32-1.00)
Diabetic neuropathy	6.27 (1.72-22.82) ⁺	0.05 (0.004-0.62) ⁺	1.09 (0.25-4.75)
Post-herpetic neuralgia	6.15 (0.78-47.99)	0.14 (0.01-1.57)	1.31 (0.33-5.20)
Cervical/lumbar radiculopathy	2.74 (0.46-16.16)	0.05 (0.008-0.34) ⁺	2.63 (0.97-7.12)
Spinal cord injury	3.00 (0.46-19.26)	0.99 (0.16-6.11)	2.33 (0.74-7.29)
Neuropathic post-operative pain	1.78 (0.24-12.86)	0.79 (0.12-5.14)	1.01 (0.28-3.61)
Trigeminal neuralgia	0.55 (0.05-7.50)	0.75 (0.04-11.60)	0.00 (0.00-.)
Post traumatic neuralgia	1.02 (0.99-5.57)	1.14 (0.15-8.27)	1.20 (0.30-4.79)
Prescribed by a physician	23.33 (9.36-58.11) ⁺	5.17 (1.02-25.95) ⁺	0.10 (0.03-0.26) ⁺

+ p<0.05