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Original article
Pregabalin for chronic pain: does one medication fit all?

Hili Giladi
The Alan Edwards Pain Management Unit (AEPMU), McGill University Health Centre, Montreal, Quebec, Canada

Manon Choinière
Centre de recherche du Centre hospitalier de l’Université de Montréal (CRCHUM); Department of Anesthesiology, Faculty of Medicine, University of Montreal, Montréal, Québec, Canada

Mary-Ann Fitzcharles
Mark A. Ware
The Alan Edwards Pain Management Unit (AEPMU), McGill University Health Centre, Montreal, Quebec, Canada

Xianming Tan
Biostatistics Core Facility, McGill University Health Centre, Montreal, Quebec, Canada

Yoram Shir
The Alan Edwards Pain Management Unit (AEPMU), McGill University Health Centre, Montreal, Quebec, Canada

Address for correspondence:
Dr. Hili Giladi MD, PO Box 390, 8499000 Midreshet Ben Gurion, Israel.
Tel: +972 50 212 9465; Fax: +972 8 9579642; gladih@post.bgu.ac.il

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Chronic pain — Health Canada — Off-label — Pharmacotherapy — Pregabalin

Abstract

Background:
Pregabalin is frequently prescribed for chronic non-cancer pain. No previous study has examined its off-label use.

Objectives:
Our primary aim was to assess the proportion of patients taking pregabalin for conditions approved by Health Canada (‘on-label’) and compare their perspectives on its use to those who use pregabalin for other conditions (‘off-label’).

Methods:
Patients who have used pregabalin within the past year were recruited from two registries of chronic non-cancer pain patients treated in tertiary care clinics: the Quebec Pain Registry and the Fibromyalgia Patients Registry. Data on the use of pregabalin and its perceived benefits were collected from the registries and from completed questionnaires.

Results:
Out of 4339 screened chronic non-cancer pain patients, 355 (8.18%) met the study selection criteria. Three-quarters of them (268/355) used pregabalin for pain conditions not approved by Health Canada and were therefore regarded as off-label users. The most prevalent condition for pregabalin use was lumbar back pain (103/357; 28.85%). There were no significant differences between on- and off-label users in their perceived satisfaction from pregabalin therapy and its effect on function and quality of life. Among former users, the most prevalent reason for discontinuation was adverse effects, mainly dry mouth and weight gain.

Conclusions:
We conclude that despite specific indications for pregabalin prescription, it is mainly used off-label, notably for low back pain. Nevertheless, off-label users were equally satisfied with its clinical effects. Although formal exploration of the broader analgesic properties of pregabalin is warranted, treating heterogeneous chronic pain conditions with pregabalin may be legitimate.

Limitations:
The main limitations of the study are patients’ low response rate, the recruitment of participants solely from a tertiary pain center and not from the general patient population and a possible recall bias that may have arisen from the retrospective nature of the study.

Introduction

Pregabalin was initially compounded in the late 1980s as an anticonvulsant. It was introduced in the 1990s and was first approved by regulatory authorities for use in 2004 in Europe and in North America. Since its introduction, it has been approved for use in specific neuropathic pain conditions including diabetic...
of this mechanism in humans is unknown. In the nervous system tissues, thereby reducing release of excitatory neurotransmitters. However, the clinical relevance of pregabalin is still a patented drug with relatively high costs both for patients and health insurers. In the province of Quebec (Canada), pregabalin was patented until May 2013 and was fully covered by the provincial drug plan, and physicians of any specialty could prescribe it to their patients without the need to provide the rationale for its use or to specify the diagnosis for which it is prescribed.

For individuals experiencing neuropathic pain or FM, pregabalin offers a potentially effective treatment option. Prior to its introduction, the mainstay of therapy for these conditions was confined to tricyclic antidepressants (TCAs) and later to gabapentin. The use of TCAs is frequently associated with orthostatic hypotension, greater risk of adverse cardiovascular effects and greater relative risk of overall mortality. Gabapentin therapy improved therapeutic outcome in patients with neuropathic pain, but was limited by its wide therapeutic dosing range, the need for high and frequent dosing, its non-linear absorption properties and its variable bioavailability. Currently, in Quebec, tricyclic antidepressants and gabapentin are covered by the provincial drug plan. Duloxetine (Cymbalta*), indicated for treatment of neuropathic pain and fibromyalgia, necessitates special approval for coverage by the provincial drug plan.

In the past three years, we observed that a growing number of patients treated in tertiary pain management clinics reported using pregabalin for their chronic pain condition. A preliminary data analysis, performed in 2011 on 3096 patients enrolled in the Quebec Pain Registry (QPR, see below), indicated that 1034/3096 (33%) were either current or past-year users of pregabalin (unpublished data). For comparison, 1228/3096 (39%) of patients reported using acetaminophen during that time period (unpublished data). This suggested that pregabalin was being used off-label, i.e., outside its Health Canada regulatory approved indications, for multiple chronic pain conditions. The primary aim of the current study was to determine, for the first time, the prevalence of the off-label use of pregabalin in a heterogeneous group of patients with chronic non-cancer pain (CNCP). In addition, we aimed to compare the perceived effectiveness of pregabalin and the patterns of its use in on-label vs. off-label users, including average doses, time to clinical effect and adverse-effect profile. The results of this study could indicate whether the use of pregabalin in chronic pain diagnoses beyond those officially endorsed by health regulators is warranted.

Patients and methods

This was a descriptive cross-sectional study, focusing on CNCP patients who have been referred to large university-affiliated tertiary care facilities offering multidisciplinary pain treatment in the province of Quebec (Canada) and who were current or past-year users of pregabalin. The study was approved by the Institutional Ethics Boards and conducted in accordance with Good Clinical Practice (GCP) and applicable Canadian regulatory requirements. Written informed consent was obtained from all participants.

Eligibility and recruitment

Eligible participants were adult patients with CNCP with pain duration of more than 3 months, who were either current users of pregabalin or who had been treated with pregabalin in the previous 12 months. To avoid recall bias, former users of pregabalin, who discontinued its use more than a year prior to enrollment in the study, were excluded. Patients were recruited from two datasets of chronic pain patients: the Quebec Pain Registry and the Fibromyalgia Patients Registry (FMPR).

The Quebec Pain Registry is a province-wide database containing clinical and demographic information on patients with CNCP, who are referred for a first consultation at one of the three Pain Centers of Expertise in the province of Quebec (McGill University Health Centre, Centre hospitalier de l’Université de Montréal, Centre hospitalier de l’Université de Sherbrooke). The QPR prospectively collects data at four time points: prior to the first visit to the pain clinic, and 6, 12, and 24 months following their initial appointment. The Registry documents patients’ demographic data, medical and pain history, pain diagnosis, consumption habits, and past-year/current pharmacological and non-pharmacological treatments for pain. Patient diagnoses are established by the pain clinicians of the participating clinics using a comprehensive list of 112 different pain diagnostic codes. In accordance with the IMMPACT recommendations (Initiative on Methods, Measurement and Pain assessment in Clinical Trials), validated questionnaires and standardized scales are also used to collect information on peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), spinal cord injury (SCI) and central neuropathic pain. It is also approved for the treatment of fibromyalgia (FM). In Europe only, it is approved for general anxiety disorders. Pregabalin is not approved for nociceptive pain conditions such as low back pain or for other, non-central neuropathic pain conditions like cervical, thoracic or lumbar radiculopathy. Pregabalin acts by binding to the α2-δ subunit of voltage-gated calcium channels in central nervous system tissues, thereby reducing release of excitatory neurotransmitters.
verified that the participant was indeed a present or past-year user of pregabalin. The rest of the questionnaire was divided into three parts: the first part was intended for both present and past-year users, and included questions about the reasons for pregabalin prescription, the first prescriber’s specialty, time until clinical effect was achieved and adverse effects. The second part was intended for present users only, where patients were asked to specify concomitant use of pain medications, duration of pregabalin treatment, and total daily dose and frequency of its use. The third part was intended for past-year users only, and included questions about the reasons for discontinuation of pregabalin. Present and past-year pregabalin users were not presented with the same questions in order to avoid recall bias by past users. The questions covered the following topics and were all specific to pregabalin:

- First prescriber (family physician, specialist, etc.) and side effects. Patients were entitled to select multiple adverse effects, and list others in free text.
- Pain diagnosis that prompted the prescribing physician to recommend pregabalin.
- Time elapsing from beginning of therapy until clinical effect was achieved. Patients could choose from one of five optional time frames: from the minute pregabalin was taken for the first time; one hour post initial use; one day to one week post initial use; one week to one month post initial use; more than one month post initial use. Two additional optional answers were ‘I do not remember’ and ‘I experienced no pain relief’.
- Dosage of pregabalin and the concomitant use of other types of analgesic medications. To prevent recall bias, this section was directed to current pregabalin users only.
- Patients’ satisfaction with pregabalin treatment, measured by a 6 point Likert scale (very unsatisfied – very satisfied).
- Patients’ global impression of change following pregabalin treatment using a 7 point Likert scale, focusing on impression of change in terms of pain (greatly increased – greatly decreased), level of function (greatly deteriorated – greatly improved) and quality of life (greatly deteriorated – greatly improved).
- Reasons for discontinuation of pregabalin. Past-year pregabalin users were entitled to select multiple reasons for discontinuation.

Data analysis

The primary analysis was to compare different subgroups of eligible patients (e.g., off-label users vs. on-label users) with respect to specific preselected variables of interest. Specifically, Fisher’s exact test was used for comparing nominal responses, the proper Cochran–Mantel–Haenszel test for ordinal responses, and the Wilcoxon
Rank Sum test for numerical responses. All analyses were carried out using a two-sided test at an alpha level of 5% unless otherwise specified. No formal adjustments were made for the multiplicity of testing due to multiple outcomes.

Results

A total of 355 patients were eligible for the study, 325 from the QPR and 30 from the FMPR. Eighty-two of the 325 eligible QPR patients (25.2%) and 27/30 (90%) eligible FMPR patients completed and returned the study questionnaire. Of the 109 participants, 91 were current users of pregabalin, 17 were past-year users and one patient did not respond to this question (Figure 1).

Clinical indications for pregabalin use are shown in Table 1. These data were obtained from all 355 eligible patients’ registry data, as well as the questionnaires. The most prevalent reason for prescribing pregabalin was lumbar pain with or without radiculopathy (103/355 patients; 29%), followed by FM (59/355 patients; 16.6%). Seventy-three percent (260/355, 95% confidence interval: 68.6%–77.8%) of patients received pregabalin for a pain problem not approved by Health Canada (off-label). Of the 95 patients taking the medication on-label, 59 were diagnosed as having FM, 25 with other peripheral neuropathy and the rest with PHN (n = 9) or spinal cord injury (n = 2).

Results obtained from the self-administered questionnaire used in the present study (N = 109) revealed that therapy with pregabalin was initiated by a pain specialist in 33% of the responders, by other specialists in 39% and by a family practitioner in 28%. Eighty patients (73%) reported a pain diagnosis that was consistent with the diagnosis made by the pain management specialist at the tertiary pain center. Seventeen patients (16%) reported a pain diagnosis that was different from the one given by the pain specialist. For nine patients (8%) the pain diagnosis report was missing and three patients (3%) reported that pregabalin was prescribed for reasons not related to pain. The time to attain a positive response after initiating pregabalin therapy varied between one day and more than a month and was not significantly different among the on-label users (1 week to 1 month) and off-label users (1 day to 1 week) (p = 0.16). One fifth of the patients (n = 18) indicated that pregabalin did not provide any pain relief. Of them, one third (n = 6) were using pregabalin on-label.

The average daily dose of pregabalin among current users was 279 ± 176 mg. Of these, 21% used less than 150 mg/day, 40% were taking 150–300 mg/day and 39% were using 300–600 mg daily. The average daily dose of prescribed pregabalin did not differ significantly
among the on- and off-label users (300 ± 183 mg vs. 237 ± 155 mg, respectively; \( p = 0.11 \)). Of the current pregabalin users, 77 (85%) reported its use with at least one other type of analgesic medication. Users of pregabalin as a single agent did not differ from the multiple analgesic users in their global impression of change in their pain (\( p = 0.14 \)) and their overall satisfaction with the treatment (\( p = 0.17 \)). However, the group of patients using pregabalin as a single agent reported a significantly greater impression of change in terms of their level of function (\( p = 0.02 \)) and quality of life (\( p = 0.04 \)). Notably, these differences became insignificant when specifically comparing users of pregabalin (\( n = 14 \)) with patients using pregabalin concomitantly with opioids (\( n = 58; p > 0.05 \) for all parameters).

When questioned about adverse effects, 77/109 pregabalin users (70%) reported having adverse effects associated with its use. From the group of former pregabalin users, 12/17 patients (70%) reported that the reason for discontinuation of the medication was adverse effects. This was the most common reason for discontinuation, followed by lack of clinical effect (\( n = 9; 53 \% \)). The most common adverse effect reported among all patients was dry mouth (\( n = 57; 52 \% \)), followed by weight gain (\( n = 44; 40 \% \)), drowsiness (\( n = 42; 59 \% \)), confusion (\( n = 41; 38 \% \)) and gastrointestinal symptoms (\( n = 40; 37 \% \)). One patient discontinued the medication because of suicidal ideation.

Global satisfaction, as well as perceived overall improvement in pain, level of function and quality of life was not significantly different between the on- and off-label pregabalin users (Figure 2). Two thirds of patients (68%; \( n = 74 \)) were at least somewhat satisfied with their treatment with pregabalin; 74% (\( n = 80 \)) had at least some pain relief with it; 55% (\( n = 59 \)) reported at least slightly improved function; and 70% (\( n = 75 \)) experienced at least slight improvement in their quality of life. Additional comparisons of the four outcome measures were done between specific subpopulations treated with pregabalin. When comparing FM patients (\( n = 33 \); i.e., on-label indication) to patients with lumbar back pain (\( n = 24 \), i.e., off-label indication), no significant differences were found with respect to satisfaction, reported changes in pain, function, and quality of life (\( p > 0.34 \) for all). Similar results were found when comparing patients with cervical, thoracic and lumbar pain without radiculopathy (\( n = 17 \)) to patients with radicular cervical, thoracic and lumbar pain (\( n = 21; p > 0.28 \)). No significant difference was found when comparing patients with lumbar pain (\( n = 11 \)) to patients with radicular lumbar pain (\( n = 13; p > 0.13 \)). Finally, when comparing FM patients to patients with complex regional pain syndrome (CRPS; \( n = 10 \), i.e., off-label indication) no significant differences were found in terms of satisfaction, reported changes in pain, function, and quality of life (\( p > 0.18 \) for all).

**Discussion**

Since the introduction of pregabalin to the Canadian market in 2005, we observed that it has gained significant popularity among health providers and patients alike. In Quebec, pregabalin is being used almost as frequently as acetaminophen for patients with chronic pain (unpublished data). We have conducted for the first time an analysis of the actual use of pregabalin in tertiary care settings, exploring reasons for use, discontinuation, and overall impact on clinical outcomes of this medication. The main finding of the study was that pregabalin in our population is mostly used off-label, mainly for lumbar back pain. No significant differences were found in the self-reported outcomes between patients receiving pregabalin for its approved and non-approved indications for various chronic pain conditions. These findings suggest that pregabalin could be useful in treating chronic pain syndromes other than those for which the medication is

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**Table 1.** Pain diagnoses of pregabalin users (\( N = 355 \)) and of patients who returned a full questionnaire (\( N = 109 \)).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>QPR and FMPR patients, ( n = 355 )</th>
<th>Patients who returned the questionnaire, ( n = 109 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients (( n ))</td>
<td>Percentage of patients (%)</td>
</tr>
<tr>
<td>Lumbar pain with or without radiculopathy</td>
<td>103</td>
<td>29.0</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>59</td>
<td>16.6</td>
</tr>
<tr>
<td>Cervical pain with or without radiculopathy</td>
<td>38</td>
<td>10.7</td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
<td>32</td>
<td>9.0</td>
</tr>
<tr>
<td>Peripheral neuropathies</td>
<td>25</td>
<td>7.0</td>
</tr>
<tr>
<td>Thoracic pain with or without radiculopathy</td>
<td>22</td>
<td>6.2</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>9</td>
<td>2.5</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>2</td>
<td>0.6</td>
</tr>
<tr>
<td>Other</td>
<td>65</td>
<td>18.4</td>
</tr>
</tbody>
</table>

QPR: Quebec Pain Registry; FMPR: Fibromyalgia Patients Registry.
indicated, similar to the indications of tramadol or acetaminophen. Off-label use of medications is common. For example, thalidomide was tragically marketed and prescribed in the late 1950s as a sedative and antiemetic. After causing severe deformities in over 8000 newborns, it was taken off the market, but several decades later it was found to be an effective treatment for leprosy and multiple myeloma and is currently used for these indications. Acetylsalicylic acid (aspirin) was initially advertised as a potent pain reliever and a remedy for rheumatism in 1899, but is currently used as a primary and secondary preventive agent of cardiovascular diseases. Pregabalin was initially developed as an anticonvulsant, but is mainly used as an analgesic medication, both in acute and in chronic pain conditions. Most of the trials examining the off-label analgesic use of pregabalin have been done in acute pain conditions, examining the role of perioperative pregabalin in decreasing postoperative pain and opioid consumption. These studies yielded conflicting results, some showing pregabalin to be beneficial whereas others did not find it to be effective or superior to placebo. Randomized, controlled trials (RCTs) testing the off-label role of pregabalin in CNCP yielded conflicting results as well. For example, pregabalin was found to be beneficial in patients with low back pain, chronic pancreatitis and in the prevention of chronic daily headache. However, pregabalin was not found to be advantageous for chronic prostatitis/chronic pelvic pain syndrome and its efficacy in neuropathic pain associated with chronic lumbosacral radiculopathy was questionable. Mixed results were also seen when pregabalin was prescribed for its approved indications. For example, an observational study on patients with peripheral neuropathy found pregabalin to be substantially beneficial, while other RCTs found that it brings only modest pain relief. Finally, while some studies found pregabalin to be favorable in FM patients other
studies demonstrated at most a moderate effect of this medication\textsuperscript{42}. One explanation for the different outcomes could be attributed to the known anxiolytic properties of pregabalin\textsuperscript{43,44}, prompting its approval for this indication in many European countries\textsuperscript{6}. Since anxiety is commonly associated with chronic pain\textsuperscript{45}, it is possible that the beneficial effect of pregabalin could be partially attributed to its anxiolytic properties.

Some of the clinical findings of this study merit further discussion. Firstly, two thirds of the participants have been prescribed pregabalin by either a primary care physician or a non-pain-management specialist. Since almost three quarters of the patients’ pain diagnoses reports were consistent with the diagnosis given by the pain management physician at the tertiary pain center it is clear that primary care physicians are competent and knowledgeable enough to diagnose chronic pain problems. Secondly, what could be the reason for the widespread off-label use of pregabalin? Although speculative, it could be attributed to the prescribing physician’s unawareness of the approved pregabalin indications, to lack of knowledge in differentiating between types of CNCP or perhaps the pressure to provide means of pain relief regardless of the type of pain. Thirdly, although the use of polypharmacy has been advocated in various CNCP conditions, we found that the use of pregabalin as a single agent, compared to its concomitant use with other analgesics, was associated with perceived improved function and quality of life. This result is supported by previous studies showing that the concomitant use of opioids with pregabalin did not result in additional pain reduction when compared to the use of pregabalin alone\textsuperscript{46}. It is possible that patients treated with multiple medications suffered from pain conditions that were more resistant to treatment. Fourthly, according to the manufacturer’s monograph, the expected length of time from the first pregabalin intake to the achievement of a clinical effect is one week in patients with DPN, SCI and PHN (no specific data exist relating to patients with FM\textsuperscript{3}). These recommendations do not mirror actual clinical practice, where dose escalation is frequently done gradually\textsuperscript{47}. Indeed, we found that a clinical effect could be attributed to the known anxiolytic properties of pregabalin\textsuperscript{43,44}, prompting its approval for this indication in many European countries\textsuperscript{6}. Since anxiety is commonly associated with chronic pain\textsuperscript{45}, it is possible that the beneficial effect of pregabalin could be partially attributed to its anxiolytic properties.

The current study has number of limitations. The response rate of eligible patients who returned the study questionnaire was low (30.7%). The reason for the low response rate from the QPR (25.2%) could be attributed to the fact that QPR patients could not be invited directly to participate in the study; they were informed about the study and were requested to initiate the first contact with the study coordinator if interested to join the study. Indeed, the response rate of patients from the FMR was much higher (90%), because they were approached directly. Still, the primary outcome data on the use of pregabalin in relation to pain diagnosis was independent of patients’ response rate, because it was extracted directly from the QPR and FMR (N = 355), including the pain diagnoses. A second limitation of the study is that all participants were treated in tertiary pain centers and may not represent the general chronic pain patient population; patients in our study are likely to be more refractory to treatment than patients with chronic pain in the general population. It is also important to point out that part of the data collected with our study questionnaire was based on patients’ retrospective recall (e.g., time to clinical effect of pregabalin, reasons for discontinuation). Although responders to these questions were only past-year former users and current users, these findings may be subject to some recall bias. Finally, the QPR diagnoses of chronic pain syndromes were determined by multiple physicians of heterogeneous background and expertise. This could potentially lead to certain bias, depending on the individual physician.

Conclusion

The current study indicates that the majority of patients with chronic pain, treated in tertiary pain units in the province of Quebec and using pregabalin for their pain, used it off-label. Seemingly, in their attempt to help in diminishing patients’ suffering, physicians of multiple disciplines, including pain management physicians, do not follow the official indications for pregabalin use, as approved by Health Canada. Still, the reported clinical benefits from pregabalin were similar in our study participants taking this medication on- and off-label, including patients with non-neuropathic or non-FM chronic pain conditions. Future prospective studies should, therefore, explore whether pregabalin is an acceptable non-specific analgesic medication, similar to acetaminophen or tramadol, in patients with CNCP.
Transparency

Declaration of funding
This study was supported by unrestricted education and research grants from the Louise and Alan Edwards Foundation, Montreal, Canada.

Declaration of financial/other relationships
This study was envisioned and conducted as a researcher-initiated project. H.G., M.-A.F., X.T. and Y.S. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article. M.A.W. and M.C. have no relevant relationships to disclose related to this study, but have disclosed that they have received speaker fees and grants from Pfizer Canada Inc.

CMRO peer reviewer 1 has no relevant financial or other relationships to disclose. Peer reviewer 2 has no relevant financial or other relationship pertaining to this study, but has disclosed that he has received honoraria and has participated in advisory boards on behalf of: Alkermes, AstraZeneca, Grunenthal, Johnson & Johnson, Lundbeck, Merck, Merz, M’s Science Corporation, Otsuka Pharmaceuticals, Pierre Fabre Pharmaceuticals, Pfizer, PharmaNeuroBoost, Richter, Roche, Servier, Synthesis, Takeda, Theracse, Transcept and Xytis. Peer reviewer 3 also has no relevant financial or other relationships related to this specific study, but maintains the following relationships: Consultant for Inspirion, Baxter, Purdue Pharma LLP, Grunenthal GmbH, Iroko, and Johnson and Johnson.

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