ORIGINAL RESEARCH

PEER-REVIEWED

# Prescribing gabapentin off label: Perspectives from psychiatry, pain and neurology specialists

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The lead author was interested in exploring the common practice of off-label use of medications as part of her Master's of Science degree. Optimizing off-label prescribing practices may enhance patient care, improve health outcomes and reduce costs.

*Dans le cadre de ses études de maîtrise en science, l'auteure principale désirait explorer l'utilisation non indiquée des médicaments. L'optimisation de cette pratique répandue pourrait améliorer les soins aux patients ainsi que les résultats pour la santé, et réduire les coûts.*

## ABSTRACT

**Objective:** The objective of the study was to explore the experiences of physicians prescribing gabapentin off label.

**Methods:** We used a case study approach to explore the experiences of physicians prescribing gabapentin for off-label indications. Semi-structured interviews were conducted with 10 physicians (psychiatry, pain and neurology specialists) in the Greater Toronto Area. Data were collected to the point of saturation of key themes and analyzed using interpretive content analysis.

**Key findings:** Key informants appeared to rely primarily on informal information from colleagues and meetings, putting into question the accuracy of their information about the potential off-label uses of gabapentin. Our findings suggest the need for more evidence-based information on off-label drug use.

**Conclusion:** There is a need for greater understanding of off-label prescribing practices as an important step toward improving rational prescribing and ultimately toward improving patient safety and health outcomes. *Can Pharm J* 2012;145:280–284.

## Introduction

Off-label use, as defined by Health Canada, is the use of a marketed health product outside of indications included in the approved product labelling. Off-label use of medications is a common practice in medicine; it is neither restricted to highly specific clinical situations nor to single countries.[1] Challenged by diseases without effective treatments or the failure of standard therapies, physicians may try new drug approaches that have some theoretical basis.[2] Off-label drug use does not imply improper or illegal use,[3] and it can provide opportunities to capitalize on a drug's potential effectiveness. However, there are also potentially negative effects of off-label use, which include adverse reactions, liability for pharmaceutical manufacturers and health care practitioners, lack of patient reimbursement for medications purchased for off-label uses and concerns with respect to the illegal promotion, advertising and marketing of off-label uses by the manufacturer.[3-5] As Haw and Stubbs state, "The use of a medication off label represents an area of potentially increased risk, since the national body that licenses drugs for medicinal use… has not examined the risks or benefits of using the drug in these circumstances" (p. 402).[6] Off-label prescribing and use also have the potential to be ineffective, resulting in wasteful medication use and possibly putting patients at risk.

Despite considerable debate around the extent and consequences of off-label prescribing, limited literature is available,[7-9] especially in the Canadian context, to explain how and why physicians prescribe medications off label. Optimizing off-label prescribing practices may enhance patient care, improve health outcomes and reduce costs.[10]

## Gabapentin as a case study

We conducted a case study to investigate and understand the practice of off-label prescribing. We selected gabapentin (Neurontin), a medication reported to be widely used off label, as a specific example to explore specialist physicians' experiences with off-label prescribing. This paper describes one component of this exploratory study, focusing on the knowledge and experiences of physicians with emphasis on resources and information sources for off-label use of gabapentin.

Radley et al. indicated that gabapentin was among the medications with the highest proportion of off-label use, with 83% of its use being off label.[9] Gabapentin was initially approved in Canada in April 1994 as adjunctive therapy for the management of epilepsy among patients over 18 years of age who are not controlled by conventional therapy.[11] Several generic forms of gabapentin have been approved in Canada since 2001.[12] The Food and Drug Administration (FDA) in the United States approved gabapentin in December 1993 as an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age with epilepsy.[13] The FDA subsequently approved gabapentin in October 2000 as adjunctive therapy for the treatment of partial seizures in pediatric patients 3 to 12 years of age,[14] as well as for the management of postherpetic neuralgia in adults (approved in May 2004).[13] In Europe, gabapentin is currently approved for similar indications.*

Gabapentin has gained widespread use since its entry to the market and a significant portion of this use has been reported as off label, including use for bipolar disorder, neuropathic pain, diabetic neuropathy, complex regional pain syndrome, attention deficit disorder, restless leg syndrome, trigeminal neuralgia, periodic limb movement disorder of sleep, migraine and drug and alcohol withdrawal seizures.[14] Gabapentin may have become a "catch-all" medication due to the uncertainty around its exact mechanism of action.[15] Still, despite the common practice, off-label prescribing presents potentially large legal and ethical issues. In Canada and the United States, it is illegal to promote or advertise any medication for any indication other than that for which it was approved. This legal restriction was the basis for a 1996 landmark lawsuit. Dr. David Franklin, a former medical liaison for Parke-Davis, initiated a lawsuit in the United States pursuant to the False Claims Act that argued that the pharmaceutical company Warner-Lambert promoted the drug Neurontin (gabapentin) for a variety of off-label indications, including pain management, headaches, anxiety, depression, bipolar disorder and other psychiatric illnesses.[16,17] The case resulted in a large settlement, as well as new standards of marketing practices for the pharmaceutical industry.

## KNOWLEDGE INTO PRACTICE

- More widespread education of pharmacists, physicians and other health care professionals on off-label issues such as the common use of nontraditional sources of information, including informal professional networks, is needed.
- Better dissemination of evidence for off-label indications among prescribers is needed, particularly when clinical practice guidelines exist.
- There is often a mismatch between scientific knowledge and practice and pharmaceutical product label claims, suggesting the importance of greater consistency.

## Methods

A case study approach allowed the opportunity to intensely study a particular case (i.e., gabapentin) to gain the best possible explanations of a phenomenon.[18]

Open-ended, semi-structured, 1-on-1 interviews were conducted with 10 specialists in the areas of psychiatry, neurology and pain in the Greater Toronto Area (GTA) from January 2007 to January 2008. A list of physicians (psychiatrists, neurologists and pain management specialists) practising in the GTA was retrieved from the College of Physicians and Surgeons of Ontario (CPSO) website database. The physicians were selected from the CPSO database based on their area of specialization, proximity to the interviewer/researcher and recommendations of the research team regarding who might be most likely to frequently prescribe gabapentin off label.

An interview guide with open-ended questions and probes was developed to help guide each interview. Participants were asked how often they prescribed gabapentin off label and to describe a case in which they prescribed gabapentin off label for a particular patient, detailing how they came to decide on gabapentin for that patient and what resources they consulted during their decision-making. The interview guide was modified once

* As an adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children 6 years of age and above, as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents 12 years of age and above and treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

## MISE EN PRATIQUE DES CONNAISSANCES

- Il est nécessaire de mieux informer les pharmaciens, les médecins et les autres professionnels de la santé quant aux enjeux liés à l'utilisation non indiquée des médicaments, telle que l'utilisation répandue de sources d'information non traditionnelles, y compris les réseaux informels de professionnels.
- Une meilleure diffusion des données probantes concernant les indications non homologuées auprès des médecins prescripteurs est nécessaire, particulièrement lorsqu'il existe des lignes directrices en matière de pratiques cliniques.
- Il y a souvent une incohérence entre les connaissances scientifiques et la pratique, et ce que prétendent les étiquettes de produits, ce qui illustre l'importance d'améliorer la cohérence.

during data collection to include additional probes to elicit further discussion on issues that appeared to be of importance based on early interviews. These included additional questions to inquire about the following: 1) how most of their knowledge of gabapentin was acquired, 2) whether the way in which they prescribed gabapentin differed depending on the symptom or condition being treated, 3) if and how they explain off-label use to their patients and 4) how important off-label vs on-label status is in decisions to prescribe a drug. Interpretive content analysis was used to analyze the interview data.[19] Interviewing and data collection continued until saturation of the key emerging themes was reached.[20] This research received ethics approval by the University of Toronto Research Ethics Board.

## Results

The key informants are described in Table 1. A total of 10 specialists (7 males, 3 females) with expertise in psychiatry, neurology or pain participated in the study. Most key informants had been prescribing gabapentin for more than 5 years.

*Knowledge regarding off-label use of medications*

Most key informants knew the general meaning of prescribing off label, although one informant described off-label prescribing to be "using medications for which there is no official indication based on lack of evidence-based research" (Key informant 2007-008, psychiatry). Many viewed off-label use as of little concern in the context of practising medicine since they described official approved indications as driven by company decisions rather than by science. They underscored that studies are often conducted to assess the safety and efficacy of medications in other indications that never received formal regulatory approval and hence do not make it onto the official approved product label.

Off-label practice was considered by all key informants to be a routine part of their specialty practice:

> *It's certainly an established practice that if a medication is available for one indication, physicians are sort of free at their discretion to prescribe it for other indications. It's a pretty well established practice. (Key informant 2007-003, psychiatry)*

The reasons cited for this practice were similar among the key informants and included the perception that clinical practice is often ahead of scientific research. Therefore, the number of approved medications that are available is insufficient to treat all diseases and all populations if these medications were prescribed only for on-label purposes.

> *I think clinicians are often many steps ahead of the research and do what they can to help patients and I think that the rationale for receiving indication for a drug overlaps it, but I don't think it's entirely the same reason that we want to use drugs. (Key informant 2007-001, psychiatry)*

The need to prescribe off label seemed also to be based on the perception that other treatments had failed or that there was a lack of available treatments. These beliefs appeared to inspire physicians to look for more options to treat their patients.

Most physicians in this study were not able to distinguish between on- and off-label indications for gabapentin because they could not identify the approved indication(s) for gabapentin. One key informant believed that it was approved to treat neuropathic pain and some were uncertain whether there were additional formally approved indications in Canada besides epilepsy.

*Information sources*

We found that awareness about an off-label use was a prerequisite to prescribing a medication for an off-label purpose. When the key informants were asked how they first learned about potential off-label uses for gabapentin, most cited conferences and colleagues as their initial source of information. Word of mouth was commonly used to share off-label uses, with respected colleagues identified as particularly reputable sources.

Some also mentioned the literature as an initial starting point. Some key informants discussed actively seeking literature on a potential off-label use in order to get more information or to determine what studies have been conducted for a par-

**TABLE 1** Demographic characteristics of key informants

| Key informant | Specialty | Sex | Academic affiliation (Y/N) | Experience in practice setting | Experience with gabapentin |
|---|---|---|---|---|---|
| 2007–001 | Psychiatry | M | Y | 8 years | ~8 years |
| 2007–002 | Neurology | M | N | 11 years | Not indicated |
| 2007–003 | Psychiatry | M | Y | ~26 years | 7–8 years |
| 2007–004 | Pain | M | N | 15 years in pain; 52 years overall in medicine (including 30 years in anesthesiology) | Not indicated |
| 2007–005 | Psychiatry | M | Y | 15 years in psychiatry; 22 years overall in medicine | 10 years |
| 2007–006 | Pain | F | Y | 25 years | Since its availability |
| 2007–007 | Pain | M | N | 15 years (4 years in pain, remainder as physician in emergency setting) | 5 years |
| 2007–008 | Psychiatry | F | Y | 15 years | Not indicated |
| 2007–009 | Neurology | M | Y | 10 years | Since its availability |
| 2008–010 | Neurology | F | N | 1.5 years | Not indicated |

ticular use. Some key informants also mentioned studies such as randomized controlled trials (RCTs) and discussed how the findings of these studies influenced their off-label prescribing decisions. In some cases, they reported that the studies showed negative results, but this did not seem to deter them from using gabapentin because their personal experience with the medication was positive. Although they acknowledged that RCTs would be the gold standard in terms of assessing positive efficacy of a drug, this level of evidence was often not available in off-label situations. They described searching for anything that identified alternatives that may help their patients, especially when there were limited options available.

Some informants viewed themselves as experts in their field and indicated that they directly contributed to knowledge sharing about the use of gabapentin from publications or by teaching. They described "trying it" on their own to treat their patients as a way of gaining experience with the medication:

> *And then you go out there and you're trying it yourself and eventually after a couple of years or a year of trying the drug, you come up with your own impression of whether or not it's doing anything. (Key informant 2007-002, neurology)*

Some of the more experienced key informants indicated that they were active promoters or innovators in the use of gabapentin for off-label indications.

These results seem to indicate that personal experience with gabapentin was directly related to confidence in prescribing it. A large component of their knowledge and perceptions about gabapentin and its potential usefulness in the off-label context seemed to be derived from individual experience.

*Individual physician experiences: Off-label uses of gabapentin*

When participants were asked to describe a case or situation in which they decided to use gabapentin off label, the responses were varied. There were no apparent patterns of use within or across specialty areas. Use of gabapentin seemed to be idiosyncratic and based primarily on personal experience. Several of the psychiatrists noted that gabapentin was clinically meaningful and effective in treating their patients. Their uses were reported to be in the areas of mood disorders, managing anxiety and insomnia/sleep disorders. Most referred to gabapentin as an augmentation agent as opposed to monotherapy. Interestingly, key informants within the same specialty had differing views about the perceived benefits of using gabapentin off label. Two of the psychiatry informants reported using it as a last resort after all available approved treatment options had been exhausted.

## Discussion

This study was conducted to obtain an in-depth look at the experiences of medical specialists in prescribing gabapentin off label, which we found was common. The key informants in this study did not seem to distinguish off-label prescribing practice from prescribing drugs according to their approved uses. Many of the participants who regularly prescribed gabapentin could not correctly identify its approved uses, highlighting the lack of importance this played in their prescribing decisions. This may in part be related to the reality that a pharmaceutical company may seek regulatory approval for uses not only because of

scientific evidence of efficacy but also as part of strategic corporate planning and other commercial reasons. Thus, indications approved by regulatory authorities may not reflect the scientific information available regarding a range of potential uses of the product.

Although the rational use of drugs is determined by the totality of medical evidence, not just by product labelling,[21] obtaining good quality information about off-label uses appears to be much more difficult than for approved indications. Results of this study indicate that the participants were required to consult a wide range of resources to obtain information related to potential off-label uses of gabapentin. These resources included colleagues, conferences, literature searches and even pharmaceutical representatives. Although information about off-label uses can be found in the published literature, controlled trials and critical analysis of aggregate data are often lacking. It is also time consuming for individual health care providers to locate, retrieve and analyze these data. This may make it difficult for pharmacists to assess the safety and efficacy of medications used off label. To understand the rationale for off-label uses, pharmacists may need to explore nontraditional sources of evidence (i.e., informal professional networks), to think mechanistically about the drugs and their actions to provide clues about how they may be used in off-label contexts and to ask questions of prescribers if they are concerned about the rationale for an off-label prescription. Pharmacists should keep in mind that off-label use is not necessarily "incorrect" but that it may require additional scrutiny to ensure patients are receiving safe and effective therapy.

Like other studies of physician decision-making,[22-24] we found that clinicians do not make decisions solely based on scientific evidence. They may be influenced by information that does not necessarily come from reputable sources and they use a lot of trial and error in their prescribing practices with patients. Our findings raise the question of whether clinicians should treat off-label prescribing decisions any differently than decisions to prescribe drugs for approved indications. Further research into the consequences of off-label prescribing practices for patients and the implications for pharmacists who dispense these prescriptions appears warranted.

We acknowledge the limitations of our study. First, we had a small number (10) of key informants who were limited to specialists in the areas of psychiatry, pain and neurology. Differences between physician types (i.e., generalists vs specialists) in terms of information sources that are used have been noted in the literature.[25,26] We do believe that further study should include the experiences of family physicians with off-label prescribing, since they are usually the initial point of contact with the health care system for patients. Their experiences and perceptions could differ from the specialists who participated in this study and any differences would be important to explore to determine the implications related to off-label prescribing practices in general. We focused on gabapentin because of its reported widespread off-label use, more than for its approved indication(s). However, its extensive length of time on the market (approximately 15 years) and its general low-risk safety profile do not make this case representative of other off-label prescribing situations with medications that have been marketed for a short period of time, as well as those with significantly greater risks for toxicity and side effects.

## Conclusion

Participants in this study did not differentiate between on- and off-label prescribing of gabapentin. We found an inconsistent, ad hoc model of knowledge translation regarding off-label use of medications and little attention to clinical practice guidelines by physicians. Based on these findings, we believe there are opportunities, through the more widespread education of pharmacists, physicians and other health care professionals on issues related to off-label use of drugs, to improve the current system, particularly when compelling scientific evidence for unapproved indications exists. For example, clinical practice guidelines may recommend evidence-based off-label use of medications (e.g., the Canadian Pain Society's guideline of management of neuropathic pain, which lists gabapentin as a first-line treatment[27]). Pharmacists also need to focus more on the influence of informal professional networks used by prescribers, as these are important for off-label decision-making, and to think more mechanistically about drugs and their actions, as this may help us better understand prescriber decision-making. Finally, we need to continue to probe prescribers about how and why they make their decisions in order to gain a clearer understanding of the reality of prescribing decisions. ■

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