EVIDENCE, REGULATION AND “RATIONAL” PRESCRIBING: THE CASE OF GABAPENTIN FOR NEUROPATHIC PAIN

Authors:

*Narcyz Ghinea, BSc(Hon), National Health and Medical Research Council Doctoral Scholar, Australian Institute for Health Innovation. Level 1, AGSM Building (G27). University of New South Wales, NSW 2052 Australia.

Dr Wendy Lipworth, MBBS, MSc, PhD, Senior Research Fellow, Centre for Values, Ethics and the Law in Medicine. Medical Foundation Building (K25), University of Sydney, NSW 2006 Australia.

Associate Professor Ian Kerridge, BA, BMed(Hons), MPhil(Cantab), FRACP, FRCPA, Director, Centre for Values, Ethics and the Law in Medicine, Medical Foundation Building (K25), University of Sydney, NSW 2006 Australia.

*Narcyz is the corresponding author and can be contacted via email at n.ghinea@student.unsw.edu.au.

ABSTRACT

Rationale, aims and objectives: In 2004, the pharmaceutical company Warner-Lambert paid US$430million to resolve criminal and civil legal liability for aggressive off-label marketing of gabapentin. Perhaps surprisingly, however, regulatory and legal concerns regarding the marketing of gabapentin has not significantly impacted upon the attitude of physicians towards using gabapentin for neuropathic pain. In this paper we attempt to understand the reasons for this discrepancy between clinical practice and regulatory/legal concerns through an analysis of published discussions about gabapentin prescribing.

Methods: We performed a qualitative empirical analysis of the published clinical debate surrounding the use of gabapentin for the management of neuropathic pain.

Results: The ongoing use of gabapentin for neuropathic pain use was primarily driven by the perception that it was a safe, non-addictive drug with few drug interactions, by possible similarities between the physiology of chronic pain and other neurological conditions, by the well-established
clinical precedent of using antiepileptic drugs in pain management, and by the lack of alternative options available in the market. Emerging evidence of lack of effectiveness and controversies about the integrity of the scientific record appeared to be of relatively little importance to practicing clinicians.

Conclusions: Those who want to promote “rational” prescribing need to recognise that prescribing is driven by many factors other than epidemiological data and regulatory indications and that even intensely negative publicity about medicines may not penetrate clinical reasoning. This suggests that a range of measures may be needed to ‘incentivise’ rational prescribing and to promote research integrity. Regulators must be more sensitive to the contextual issues that are relevant to clinical practice when evaluating drugs for approval and developing guidelines.

KEYWORDS: Chronic Pain; Neuralgia; Pain Management; Off-Label Use; Drug Industry; Physician’s Practice Patterns.

INTRODUCTION

The idea of “evidence-based medicine” (EBM) is now over 20 years old [1]. Over this time, the concept has evolved significantly. Whereas early versions of EBM emphasised principally epidemiological data, it is now broadly accepted that factors other than epidemiological evidence have a place in clinical decision-making [2]. This shift has occurred, in part, as a result of concerns that EBM in its original form was biased towards interventions and diseases that were reducible to quantifiable measures [3] and as a result that EBM inadvertently promoted ‘epistemic injustice’ by undervaluing physicians’ and patients’ roles as ‘knowers’ capable of making judgements outside of the confines of epidemiological evidence [4]. At the same time, physicians became more concerned about the formulaic nature of evidence-based practice [5], its focus on standardised rather than individualised clinical practices [6], and the fear it caused among clinicians about the legal consequences of practicing outside of clinical practice guidelines [7]. As a result of these criticisms, evidence based medicine has gradually been broadened to take account of patient values, physiological reasoning, and contextual considerations when making clinical judgements [8]. It is often not clear, however, exactly how the patient-centred, value-laden or contextual features of decision making are to be integrated with epidemiological evidence, and models of EBM are generally silent on this matter. In this article we will examine the ways in which clinicians have justified using gabapentin – a drug that is widely prescribed “off-label”—that is, prescribed outside the indications for which it has been formally approved by regulatory agencies [9]. By definition, prescribing outside of regulatory indications occurs when there is either not enough evidence to support registration for a particular indication, or there is evidence that has either not been presented to the regulator, or is contested. Off-label prescribing of gabapentin for neuropathic pain thus provides a useful means for examining the complex and value-laden nature of clinical decision-making.

Off-label prescribing of gabapentin

Originally approved in 1993 as an adjunct therapy for partial seizures, gabapentin quickly became a popular drug for the treatment of neuropathic pain. The first clinical trial that assessed gabapentin’s
efficacy for neuropathic pain was published in 1996 and concluded that gabapentin provided pain relief and had the advantage of a low side-effect profile and low toxicity [10]. Studies published in subsequent years generally concluded in favour of gabapentin for neuropathic pain, the most important of which were two double blind, placebo controlled, randomised trials that investigated gabapentin for the treatment of diabetic neuropathy and postherpetic neuralgia [11, 12]. These trials reported that gabapentin was effective in the treatment of pain and sleep interference associated with pain, and also improved quality of life. A few years later a Cochrane review concluded that while gabapentin was being increasingly used for neuropathic pain, it did not seem to be superior to other treatments, and the evidence base for the use of anticonvulsants in pain was generally lacking [13]. Other studies, however, were subsequently published that supported gabapentin’s use, and in 2005 a revised Cochrane review was published that was favourable of gabapentin [14].

While it appeared that the evidence for gabapentin’s effectiveness for the treatment of neuropathic pain was growing, it simultaneously became apparent that a strategic off-label marketing strategy was being used to increase sales. In 2004, the pharmaceutical company Warner-Lambert paid US$430million to resolve criminal and civil legal liability for aggressive marketing of gabapentin to treat ‘a wide array of ailments for which the drug was not approved’ [15]. It also became apparent that clinical trial data about gabapentin had likely been manipulated. In 2009, a paper, co-authored by the Director of the US Cochrane Centre, was published that looked at bias in the reporting of industry sponsored gabapentin trials [16]. The authors concluded that the studies did ‘not meet the ethical standards for clinical research’, and that ‘reporting biases ... increase[d] the likelihood that interventions will appear to be effective when they are not’. In response, the positive Cochrane review was rescinded, and revaluated data suggested that gabapentin was not as effective as it had previously been made out to be [17-20].

Regulatory agencies internationally have responded variably to this shifting data landscape. The FDA approved gabapentin for the treatment of postherpetic neuralgia, while Australia’s Therapeutic Goods Administration (TGA) and the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) approved gabapentin for neuropathic pain more generally. The TGA’s approval of gabapentin for neuropathic pain was based on studies demonstrating efficacy for postherpetic neuropathy and diabetic neuralgia [21]. The FDA, in contrast, were more reluctant to approve an indication as broad in scope as ‘neuropathic pain’, and set out their requirements for proof as follows [22]:

“In order for a general neuropathic indication to be granted, the sponsor must provide evidence that the underlying disease process is similar for DPN [diabetic peripheral neuropathy], PHN [postherpetic neuralgia], and the pain of other neuropathic disorders and/or that the drug is effective for the neuropathic pain of all (or at least most) etiologies”.

Given the (at best) equivocal evidence of benefit for the treatment of neuropathic pain, and the US regulator’s unwillingness to extend its label, one might expect that doctors would have felt “duped” and stop prescribing gabapentin for neuropathic pain (particularly in regions where regulators have not approved it for these indications). But in fact the contrary seemed to be true, and the use of gabapentin for neuropathic pain has continued largely with, for example 3.5 million gabapentin prescriptions being written annually in the England - an increase of 150% over 5 years [23, 24], and with authoritative clinical guidelines still recommending it as a first-line treatment for the
pharmacological management of neuropathic pain [25]. Further evidence of clinicians' commitment to ongoing prescribing are evident in the criticism that has been levelled at payers for subsidising pregablin, but not the cheaper gabapentin, which is now off-patent. As an Australian clinical pharmacologist commented [26]:

“Many patients with neuropathic pain have been paying very high prices for their gabapentin... the recent decision [to add pregablin to the Pharmaceutical Benefits Scheme] has created the illogical situation in which long-standing users of gabapentin... will be paying more than patients being started on a much newer drug with less well established efficacy and safety”.

This suggests that there are many drivers of prescription of gabapentin for neuropathic pain beyond data regarding its clinical effectiveness, and that it is a rich case study for understanding how the patient-centred, value-laden or contextual features of clinical decision-making are integrated with epidemiological evidence. In order to explore the clinical reasoning underpinning the ongoing prescribing of gabapentin for neuropathic pain, we performed a qualitative empirical analysis of the published clinical debate surrounding the use of gabapentin for the management of neuropathic pain.

**METHODS**

A Pubmed search was performed using the search terms ‘gabapentin & pain’, and ‘Neurontin & pain’. In order to elicit professional commentary, the search was limited to ‘comments’, ‘editorials’ and ‘letters’ in the English language. No time limitations were placed on the search which was performed on 4 August 2013. In total 116 articles were found from 61 different journals. The journals with the most articles identified were the *Journal of Pain Symptom Management*, *Pain*, and *Anaesthesia & Analgesia* respectively.

To analyse the data, we drew both on Morse’s outline of the cognitive basis of qualitative research [27] and on Charmaz’s outline of data analysis in grounded theory [28]. This procedure involved immersion in the data to identify common themes. Throughout the data analysis, a process of constant comparison was employed to refine, enrich, and reorganise the emergent themes. Thematic saturation was reached after approximately 30 articles (that is, no new themes emerged after 30 articles had been analysed).

**RESULTS**

**Scientific considerations**

Discussions among clinicians about prescribing gabapentin for neuropathic pain were striking in their lack of reference to the evidentiary concerns discussed above. Instead, discussions about the scientific merit of using gabapentin to treat neuropathic pain centred primarily on the physiology of chronic pain. The argument was consistently advanced by clinicians that, because both epilepsy and neuropathic pain originate from an ‘over-excitation’ in the nervous system, what worked for one of these diseases should also work for the other [29]. A similar justification was given for using other central nervous system drug classes such as antidepressants, and antipsychotics for the...
management of neuropathic pain. Other clinicians focused on the fact that the mechanism of action of gabapentin remains officially unknown, and of the hypothesis, confirmed by studies, that neuropathic pain is not caused by one disease mechanism, but many, and therefore might be best managed by targeting multiple disease mechanisms at once. However since most pain medicines are rather ‘blunt’ tools that act as general anti-hyperalgesics, it was argued that they couldn’t be used with any great accuracy [30]. This, in turn, seems to have contributed to heterogeneity in pain management practices—including the use of gabapentin—that Markus Klass and Marie Csete describe in the following terms [31]:

“Practitioners choose from a bewildering array of ingredients to create their own menus, based on local taste and local experience, with little literature serving up a gold-standard, prize-winning combination”.

To the extent that physicians were cognisant of epidemiological evidence, they focused on the ways in which researchers measure pain, on inconsistency of doses used in studies, and on the need to identify those patients who are most likely to benefit from gabapentin.

Pain scores used to evaluate gabapentin’s effectiveness were considered by some to be too opaque, with stakeholders arguing for measures that have a self-evident clinical significance. Gehling and Tryba, in particular, argued that measures should be chosen so that statistically and clinically significant differences were one and the same [32]. When Serpell and colleagues published an RCT that claimed to provide ‘further evidence of the clinical utility of gabapentin, with significant beneficial effects on overall pain scores’ [33], McCleane contested the conclusion, noting that the overall pain score was only reduced by 0.5 on an 11 point scale, that this result was only just statistically significant, and that therefore the trial showed that gabapentin had ‘at best, a very modest analgesic effect’ [34].

With respect to doses, Clendenen and Harrison noted inconsistencies in the evidence base as ‘doses as small as 300mg have demonstrated efficacy, while in one study doses greater than 600mg did not demonstrate efficacy, and finally in the literature doses of up to 1200mg have demonstrated efficacy’ [35]. In another case, differences in observed results were resolved by arguing that in spite of discrepancies ‘both observations concur that there are patients for whom gabapentin can change the outcome’ [36], and further details about the effectiveness of gabapentin could only be acquired through controlled studies.

**Clinical considerations**

Clinical precedent was commonly cited as a justification for prescribing gabapentin. Henry McQuay and colleagues, for example, noted in their early review about the topic that anticonvulsants have been used for this indication since the 1960s [37]. The Cochrane review, likewise, which was co-authored by several of the same authors, referenced this fact in its background information, as well as the clinical impression that anticonvulsants were useful for neuropathic pain [13]. Gabapentin was therefore not seen as a novel treatment, but rather as another treatment within a class of drugs that were already being used by clinicians in this way.

Clinicians also made reference to what was believed to be a low side effect profile of gabapentin. This was seen to be particularly important given that the exact cause of pain is often not clear, so pain is generally managed empirically, with physicians trying various drug combinations at different
doses to find a successful treatment regimen [38-40]. It was also argued that because people with pain often suffer from underlying diseases, such as cancer, and are therefore often on other medications, this feature of gabapentin made it even more attractive [41] as it permitted co-administration of other medicines, including other analgesics [42]. Dubey, for example, stated his reasons for choosing gabapentin as follows [43]:

“...we elected to use gabapentin in this case despite it being a costly agent because of its favorable safety profile and lack of drug interactions.”

In further support of gabapentin’s clinical utility was its lower sedative effect which made it useful for treating patients who were at risk of being over-sedated [41], and the fact it was not considered to be an addictive drug, which can be a limiting factor to the use of opioid pain medicines. Finally, it was argued that pain was itself an obstacle to life-saving treatment and therefore had to be managed by whatever means were available [44, 45].

DISCUSSION

The ongoing use of gabapentin for neuropathic pain use was primarily driven by physiological reasoning, by the perception that it was a safe drug with few drug interactions, by the well-established precedent of using antiepileptic drugs in pain management, and by the lack of alternative options available in the market. Other factors that appeared to influence the use of gabapentin were the fact it is used for a chronic illness and therefore treatment could be reversed if necessary, the fact that it was not considered to be as addictive as opioids, and the view that because the cause of pain was not always clear, different treatments had to be tried to find a drug (or drug combination) that works.

Taken together, our results demonstrate that at the coalface of health care, where physicians are confronted with the immediate clinical and moral dilemma of treating patients in severe and unresponsive pain in the absence of any single obviously effective treatment, there is seen to be a strong scientific and clinical case for prescribing gabapentin even in the absence of compelling epidemiological support.

Although this did not emerge in debates about gabapentin, it is also likely that clinicians felt compelled to use gabapentin for neuropathic pain because chronic pain is a neglected disease of great significance. It has been noted, for example, that chronic pain affects a significant proportion of the population [46]; that it has enormous psychological, social and economic costs to individuals, families, health systems and society [46-50]; that it disproportionately affects those who are already disadvantaged [48]; and that a significant proportion of those who suffer from chronic pain do not receive appropriate pain relief with current medications [51].

There are, therefore, a number of possible scientific, clinical, moral and socio-political explanations for ongoing prescribing of gabapentin for neuropathic pain despite accumulating scientific evidence that such prescribing might not be appropriate.

Nevertheless, despite these explanations, one might have expected at least some evidence of a scientific or clinical ‘counter-narrative’, focused on emerging evidence of ineffectiveness, and a moral or political ‘counter-narrative’, focused on the influence of commercial interests on the
popularity of gabapentin. These lacunae are particularly surprising given the intensity of the legal controversy about off-label promotion of gabapentin, the US Department of Justice’s conviction of the manufacturer, and the coverage in the media of claims of scientific and publishing misconduct on the part of gabapentin’s manufacturers. It seems unlikely, therefore, that doctors were unaware they were prescribing gabapentin off-label, or that companies had engaged in unethical promotion and manipulation of published data, and some other explanation is required.

One possible explanation for this lack of critical reflection on emerging evidence and on industry misbehaviour is that off-label promotion of gabapentin for neuropathic pain has been highly successful—so successful in fact that even major lawsuits and claims of data manipulation have not been able to shake clinicians’ conviction that gabapentin should be used to treat neuropathic pain. This, combined with the belief that chronic neuropathic pain is a serious unmet need—a belief that may itself be partly constructed by industry promotion—might render clinicians essentially blind to both contrary evidence about both efficacy and safety, and alternative ways of treating neuropathic pain. Given that clinicians are currently free to prescribe as they see fit, with regulatory labels being at most a guide, it might not be at all surprising that clinicians would be successfully influenced by industry in this way.

Practical implications

This analysis supports the notion that the promotion of rational prescribing cannot rely on regulatory standards, and associated “labels” to guide practice. The gabapentin case also shows the extent to which the clinical discourse can be removed from scientific and legal discourses—even when the latter call into question the very integrity of those who have generated the evidence for or against prescribing. There are four practical implications that arise from close examination of the case of gabapentin.

First, while off-label prescribing is not, in-and-of-itself, undesirable, the extent of off-label prescribing of gabapentin in the face of emerging evidence against its use suggests that rational prescribing may be immensely difficult without the use of incentives and counter-incentives to combat unwarranted commercial influence. These might include “sticks”, such as punishment for excessive prescribing of drugs off-label in the absence of compelling scientific or clinical reasons to do so; “carrots”, such as rewarding those who prescribe ‘appropriately’; more stringent controls of third party reimbursement systems; and stronger, more binding, regulation.

Second, it is important that the ‘right’ research is done, and that this research reflects clinical need rather than commercial interest. This would need to be followed by regulatory processes that assess evidence on the basis of clinical need rather than on the basis of commercial viability. This would require greater public funding and ownership of late-stage research, combined with more sophisticated methods of evaluating evidence, so that results can potentially be applied to a broad range of related diseases, not only the immediate disease being studied. Currently this type of analogical reasoning is exclusively applied by doctors, at their own risk.

Third, the gabapentin case illustrates the need for more sophisticated measures to ensure the integrity of science and of the scientific record, so that those who have the means to produce knowledge do not engineer the choices available to physicians according to their own private interests. Jerry Ravetz describes the corruption of scientific research as follows [52]:
‘At every phase of the process, science now becomes problematic and compromised. Priorities for research are set not by scientists but by the external interests that supply funds... Applications are directed to the furtherance of profit and power; issues of safety and ethics are seen as secondary. Regulation... comes after the event... and is therefore characteristically too little and too late.”

Steps are being taken to address some of these concerns. Clinical trial registries (such as ClinicalTrials.gov and EU Clinical Trials Register) have been set up to raise awareness of privately and publicly funded trials, not only those that industry chooses to publish. In support of this initiative, in 2005, the International Committee of Medical Journal Editors began to require that trials submitted for publication had to be registered, and in 2006 the World Health Organisation recommended that all clinical trials should be registered [53]. WHO also recommended a list of 20 data fields that all clinical trials should report on, and developed a search portal intended to be a single point of access for information about ongoing and completed clinical trials [53]. Efforts such as these clearly need to be institutionalised and perhaps extended (e.g. requiring all publications to include a data completeness clause so that we know when the data has been selectively chosen for publication; requiring more information about the context of the research; and promoting timely and robust post-publication review).

Finally, the gabapentin case demonstrates that ultimately there needs to be a change in medical culture so that doctors learn to ask the hard questions about “unmet needs” and all the possible ways of meeting them (versus the way drug companies construct unmet needs and their solutions). For instance, it may be true that neuropathic pain is an “orphan” disease in need of a pharmacological solution, but this is certainly not the entire story. While a drug that does not harm and is relatively inexpensive might provide an additional therapeutic option to physicians and an excellent business opportunity for industry, on the other hand it may also be a futile approach that uses up limited health care resources and precludes other, more effective approaches.

CONCLUSION

Clinicians prescribing gabapentin off-label do so for many reasons, but trustworthy clinical trial evidence—or lack thereof—does not appear to be one of these reasons. Rather, the decision to prescribe gabapentin is made primarily on physiological and clinical grounds, and is likely encouraged by the moral and socio-political imperative to treat chronic pain and by off-label promotion. This demonstrates the complexity of clinical decision-making. It also raises questions about whether clinicians need to be made more accountable for their decision-making and, if so, how. We believe that, while prescribing gabapentin for neuropathic pain may be relatively harmless, the practice reflects a worrying lack of cognisance among clinicians of the factors influencing their decision-making. What is needed, therefore, is a means to make these influences more transparent. At the same time, the socio-political and commercial factors that shape the evidence-base, especially in instances where decision stakes are high, need to be given as much emphasis as the data itself, and researchers and regulators need to be more sensitive to the questions that really concern clinicians, so that regulatory “labels”, and the guidelines that stem from them, are clinically meaningful.
ACKNOWLEDGEMENTS

Narcyz Ghinea and Wendy Lipworth declare that they receive financial support through National Health and Medical Research Council grants.

REFERENCES


15. Warner-Lambert to pay $430 million to resolve criminal & civil health care liability relating to off-label promotion. Department of Justice website.  


