

Gabapentin documents raise concerns about off-label promotion and prescribing

Melissa Sweet, Health and Medical Writer, Sweet Communication, Sydney

SYNOPSIS

Anticonvulsant medications have been widely used for off-label indications. Court documents recently released in the USA suggest that some of the off-label use of the anticonvulsant gabapentin was driven by deceptive and illegal marketing practices. Reliable evidence is not available to support many of the off-label uses of gabapentin. Off-label use of medications can be beneficial, but clinicians and patients should be aware of the quality of evidence available to support such usage.

Index words: pharmaceutical industry, advertising.

(*Aust Prescr* 2003;26:18–9)

Since its approval in the USA in late 1993 as an add-on treatment for partial seizures, gabapentin (Neurontin) has become the world's top-selling anticonvulsant, according to the web site of its manufacturer, Pfizer. The company also says that gabapentin has one of the fastest-growing markets of any drug and that it is one of the key products expected to drive its manufacturer's future profits.

In Australia, gabapentin is approved as add-on therapy for partial epilepsy and for neuropathic pain, but only subsidised by the Pharmaceutical Benefits Scheme (PBS) for patients with epilepsy whose seizures are not controlled by other drugs. Health Insurance Commission data show that scripts dispensed for gabapentin under the Pharmaceutical Benefits Scheme increased by 320% between 1996–97 and 2001–02 (from 15 340 to 64 686). By comparison, PBS scripts for a comparable anticonvulsant, lamotrigine, increased by 81% over the same period, while vigabatrin scripts dropped by 58%.

Anticonvulsants have a long history of off-label use; carbamazepine and valproate were widely used, for example, as alternative and adjunctive treatments to lithium for mood disorders, before they received regulatory approval. Literature searches show that there has also been widespread interest in off-label use of gabapentin, including for mood disorders, aggressive behaviour associated with dementia, treatment of drug and alcohol addiction, low back pain, postoperative pain, muscle cramps, and hot flushes associated with tamoxifen therapy. Some of these indications are being studied in clinical trials.¹

Evidence has recently emerged suggesting that at least some of the off-label use of gabapentin in the USA was driven by

deceptive and illegal marketing practices.^{2,3} Court documents allege that Parke-Davis, a subsidiary of Warner-Lambert which merged with Pfizer in 2000, systematically promoted gabapentin for off-label uses for which there was not good evidence.

Dr David Franklin, a former employee of Warner-Lambert, has filed a lawsuit in the District Court for the District of Massachusetts against the company. It alleges that the company's sales representatives encouraged doctors to prescribe gabapentin for unapproved indications, including bipolar disorder, attention deficit disorder, restless leg syndrome, migraine, and drug and alcohol withdrawal seizures. Strategies for influencing prescribers included:

- funding dinners, conferences and medical education seminars where presentations were made on off-label uses
- providing educational grants to gabapentin advocates
- paying doctors honoraria for use of their names on ghost-written scientific articles
- establishing a Speakers Bureau to make payments to doctors who promoted gabapentin.

It has been described as 'the most complete and well documented case of off-label promotion to ever come into public view'.³

Meanwhile, Pfizer was reprimanded by the Association of the British Pharmaceutical Industry earlier this year, after being found in breach of the industry's code of conduct. The Prescription Medicines Code of Practice Authority found that Pfizer had been promoting off-licence indications for products, including gabapentin.⁴

Pfizer stresses that promotion of off-label indications is against company policy and that it is unaware of any such promotion of gabapentin having occurred in Australia. The industry body Medicines Australia has not received any complaints alleging off-label promotion of gabapentin.

However, there is some anecdotal evidence of off-label promotion of gabapentin in Australia. An Australian psychiatrist says he attended a conference in Sydney, organised by Parke-Davis, where an American speaker gave a presentation endorsing gabapentin's use in bipolar disorder and other psychiatric conditions, despite a lack of evidence from randomised trials.^{5,6}

Off-label prescribing can be a double-edged sword for clinicians and patients. It may be clinically appropriate, for example, if

there is reliable evidence of benefit. It is also important to distinguish between lack of evidence of benefit and evidence of lack of benefit; sometimes no studies may have been done in a population, such as the elderly or children, who might benefit from off-label prescribing. Sometimes there may be little financial incentive for companies to conduct trials for an indication which is widely accepted but not approved by drug regulatory authorities.

The gabapentin story is a reminder, however, of the need for caution, especially when the evidence is unreliable or being promoted by vested interests. Much of the enthusiasm for gabapentin's off-label uses appears to have been driven by case reports, uncontrolled studies and other unreliable forms of evidence. A recent review of prophylactic migraine treatments noted that gabapentin had been suggested to be effective despite a lack of rigorous, reliable data.⁷ A Cochrane review said anticonvulsants are used widely in chronic pain, although surprisingly few trials show analgesic effectiveness.⁸ It also raised questions about the increasing use of gabapentin in neuropathic pain.

Given the uncertainties that can surround off-label prescribing, there is an extra imperative to carefully weigh the potential benefits and harms involved, and to ensure these are openly canvassed, where possible and appropriate, with patients and their families.

E-mail: sweetcom@tig.com.au

REFERENCES

1. Oncology/Hematology Associates of Central Illinois. http://www.ohaci.com/palm/trials/misc_cancer_control_trials/N00CB_trials.htm
2. Neurontin (Gabapentin) – The illegal corporate creation of a blockbuster drug. *Worst Pills, Best Pills* 2002;8:36-8. <http://www.citizen.org/>
3. Update on the illegal promotion of Gabapentin (Neurontin). *Worst Pills, Best Pills* 2002;8:68-71. <http://www.citizen.org/>
4. Dinsdale P. Pfizer gets a public dressing down over promoting unlicensed drugs. *Br Med J* 2002;324:753.
5. Frye MA, Ketter TA, Kimbrell TA, Dunn RT, Speer AM, Osuch EA, et al. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. *J Clin Psychopharmacol* 2000;20:607-14.
6. Pande AC, Crockatt JG, Janney CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. *Gabapentin Bipolar Disorder Study Group. Bipolar Disord* 2000;2(3 Pt 2):249-55.
7. Krymchantowski AV, Bigal ME, Moreira PF. New and emerging prophylactic agents for migraine [review]. *CNS Drugs* 2002;16:611-34.
8. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2002. Oxford: Update Software.

Conflict of interest: none declared

Greed and gabapentin

Editorial comment

Some of the recent corporate collapses show that the relentless pursuit of profit can have disastrous consequences. Although the pharmaceutical industry aims to help patients it may not be immune from questionable corporate practices.

The New York Times has reported an accusation that rules were broken in the promotion of gabapentin.¹ 'Worst Pills, Best Pills', an American drug bulletin, has been keeping its readers and other members of the International Society of Drug Bulletins (including *Australian Prescriber*) informed of the case.²

Allegedly, the manufacturer concocted uses for gabapentin to boost profits. Despite a lack of independent supporting evidence, the company is said to have aggressively promoted these 'off-label' indications to doctors. The promotional strategy is alleged to have involved payments to opinion leaders and the placement of ghost-written articles in medical journals.

These strategies appear to have worked well as sales of gabapentin reached US\$1.3 billion in 2000. 'Worst Pills, Best Pills' reports that as much as 78% of these sales were for uses without evidence that gabapentin was safe and effective.²

Although these allegations are yet to be tested in court, and the manufacturer involved has now been taken over by

another company, the Editorial Executive Committee of *Australian Prescriber* believes readers will be interested in how big business might influence prescribing. As gabapentin is an extraordinary case, the Editorial Executive Committee has asked well-known medical journalist Melissa Sweet to provide more details.

Could it happen here? The code of conduct for the Australian pharmaceutical industry prohibits claims which are not consistent with the product information approved by the Therapeutic Goods Administration. Although the code offers some protection, similar rules in the USA did not prevent the gabapentin controversy. To strengthen the code it is important that health professionals contact Medicines Australia* if they have evidence of drugs being promoted for unapproved indications.

REFERENCES

1. Petersen M. Whistle-blower says marketers broke the rules to push a drug. *New York Times* 2002 March 14; Section C, Page 1 (col. 5).
2. Neurontin (Gabapentin) – The illegal corporate creation of a blockbuster drug. *Worst Pills, Best Pills* 2002;8:36-8.

* Medicines Australia
Level 1, 16 Napier Close DEAKIN ACT 2600
Phone (02) 6282 6888
Fax (02) 6282 6299
www.medicinesaustralia.com.au