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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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# Gabapentin for pain
## New evidence from hidden data

### Background

Gabapentin (Neurontin) was licensed in Canada in 1993 for adjunctive treatment of epilepsy. In 1998 two double blind randomized controlled trials (DBRCT) suggested mild analgesic effects of gabapentin in painful diabetic peripheral neuropathy (PDPN)[1] and post-herpetic neuralgia (PHN)[2]. Subsequently, unapproved use of gabapentin exploded for pain, migraine, and even as a "mood stabilizer".[3]

Therapeutics Letter #33 (Jan-Feb 2000) reviewed gabapentin for pain. It noted that gabapentin is eliminated by kidney filtration (half-life 6 hours with normal renal function) and that it reduced pain by a mean of 1-2 points on a pain score of 0-10, over 2 weeks, NNT=4 for "moderate or marked" benefit. The Letter concluded: *"Gabapentin benefits at best a minority of patients with painful diabetic or post-herpetic neuropathy. Toxicity, but not analgesia, is dose-dependent."*[4] A 2005 Cochrane Systematic Review similarly reported an NNT of 4.3, suggesting that 23% of patients improve.[5]

**Subsequently, U.S. litigation has revealed that Neurontin's off-label promotion was assisted by selective publication and citation of studies with favorable outcomes.[6]** Court-ordered access to unpublished studies now allows us to present a more accurate estimate of gabapentin's clinical effects.[7]

### How Neurontin became a blockbuster

Gabapentin never achieved major commercial success as an anticonvulsant. In 1995 Parke-Davis marketing staff proposed an experimental program to test anecdotal claims of efficacy for "neuropathic" pain and other syndromes. Research results were to be published, *"if positive"*.[8] Immediately after the 1998 JAMA publications, Parke-Davis launched a program of selective publication and intensive marketing, assisted by "Key Opinion Leaders" (KOL).[9] Sworn testimony indicated that Parke-Davis used its "clinical liaison" sales representatives and KOL to market Neurontin *"for everything"*.[10] By 2003 annual U.S. sales of gabapentin had expanded from $98 million to $2.7 billion/year.

A gradually broadened category of "neuropathic pain" became gabapentin's most durable market, reinforced by guidelines that refer to gabapentin as "first line treatment".[11] **In B.C. consumption is still rising, at a cost exceeding $30 million during 2009, 63% from public funds (see Figure).**

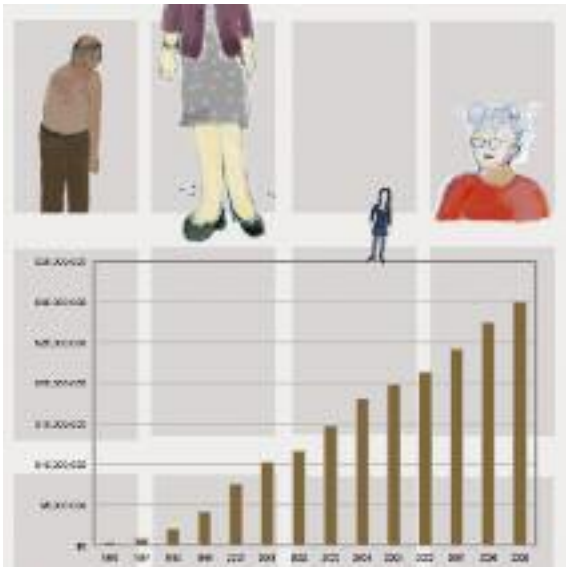

**Figure: Outpatient costs of gabapentin in B.C. from 1996-2009, based on PharmaNet data**

In February 2010 a U.S. court in Boston is scheduled to hear detailed evidence from published and unpublished DBRCT of gabapentin for pain and other unapproved uses in a civil trial of alleged fraud for the off-label marketing of Neurontin prior to 2004.[12]

### Re-evaluation including unpublished trials

Evidence before the Boston jury will include a 2008 critical appraisal and meta-analysis of all known RCTs of gabapentin for chronic neuropathic and acute pain, including detailed study reports that became public only through the U.S. litigation. Details are available in the Drug Industry Documents Database at UCSF.[13] DBRCT were typically from 2-8 weeks duration, in patients screened to eliminate many co-morbidities, such as kidney disease. Studies used either varying fixed doses of gabapentin or forced titration, with typical maximum doses of 1800-2400 mg/day.

**Chronic "neuropathic" pain:**

**Benefits:** 9 trials (N=1917) assessed mean pain reduction from baseline. Gabapentin reduced weighted mean pain score by -0.78 (-0.99, -0.58) as compared with placebo on a 0-10 point scale. 7 trials (N=1971) assessed patient-reported "moderate or much improvement": gabapentin 37.7%, placebo 20.2%; difference 17.5%, NNT=6. 3 trials (N=1028) assessed percentage of patients achieving at least a 50% reduction in pain score: gabapentin 31.4%, placebo 18.4%; difference 13%, NNT=8. Efficacy was greater in PHN than for other pain syndromes.

**Harms:** In 12 trials (N=2362) gabapentin

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increased adverse events: gabapentin 67.6%, placebo 55.2%; difference 12.4%, NNH=8. Specific adverse events included dizziness (NNH=6), somnolence (NNH=7), confusion or ataxia (NNH=10) and edema (NNH=11).
Comparisons of gabapentin with tricyclic antidepressants did not favor either treatment, although adverse events differed qualitatively.

**Acute nociceptive pain:**
Four DBRCT (N=1371) compared gabapentin with placebo, acetaminophen, naproxen and hydrocodone, alone or in combinations for acute pain after dental extraction, orthopedic surgery or exacerbations of osteoarthritis. In contrast with conventional analgesics, gabapentin was not efficacious for acute pain. These studies were never published.

**Dose dependence:**
Multiple DBRCT provide no evidence that larger doses confer greater analgesia, whereas toxicity is clearly dose-dependent.[13,14]

**Additional DBRCTs since 1999:**
A DBRCT (N=87) in acute shingles found that gabapentin titrated from 300 to 1800 mg/d was not better than placebo over 4 weeks, whereas oxycodone CR, titrated from 20 to 120 mg/d, reduced mean pain score by 1.2 points vs. placebo on a scale of 0-10.[15]
One publicly funded crossover DBRCT (N=57) compared gabapentin and morphine alone or together for chronic neuropathic pain (PDPN and PHN).[16] The authors interpreted this very complex experiment as evidence that gabapentin may enhance the analgesic effect of morphine. An alternative interpretation is that gabapentin is ineffective for neuropathic pain vs. placebo.[17] The same authors compared gabapentin and nortriptyline alone or together in another complex 3-period crossover DBRCT (N=56) in a similar population.[18] Combined nortriptyline/gabapentin reduced mean daily pain score by 0.6 vs. nortriptyline alone, and by 0.9 vs. gabapentin alone (scale 0-10). Careful inspection of the original graphical data suggests that gabapentin effects do not increase with higher doses nor with time. DBRCT of delayed-release gabapentin for PDPN and PHN were completed by July 2007 and October 2009, but only one is partially reported.[19]

## How does pregabalin compare?

Pregabalin (Lyrica) has not been compared with gabapentin for chronic pain. A September 2009 Common Drug Review[20] recommended against provincial formulary listing of pregabalin because new studies raise additional questions about its efficacy for neuropathic pain. One unpublished DBRCT comparing pregabalin to an active comparator found that amitriptyline was better than placebo for PDPN, whereas pregabalin was not. Like gabapentin, drug effects are apparent almost immediately. In 2009 British Columbians spent about $10 million on pregabalin.

## Conclusions and recommendations

- Misleading promotion pushed gabapentin to blockbuster status; scientific evidence suggests gabapentin has a minor role in pain control.
- Gabapentin reduces neuropathic pain by < 1 point on a 0-10 point scale and benefits about 15% of carefully selected patients (NNT=6-8).
- A similar proportion of people suffer harm (NNH=8).
- A test of benefit/harm can be made after 1-2 days at a low dose (100-900 mg/day).
- Benefit is unlikely to increase with higher doses or longer treatment.
- Opioids afford greater relief in chronic neuropathic pain, with qualitatively different adverse effects.
- Use particular caution for people at risk of cognitive impairment, balance disturbance, falls, or when edema is undesirable (e.g. peripheral vascular disease in the elderly).
- Reassess patients already taking gabapentin at least every 2 months. The short elimination half-life allows reassessment of benefit vs. harm by stopping the drug for 1-2 days (longer if kidney function is impaired).
- Gabapentin has no role in acute nociceptive pain.
- Benefits and harms of pregabalin are similar to gabapentin, at higher cost.

NNH = number needed to treat to cause one harmful event
NNT = number needed to treat
RCT = randomized controlled trial
DBRCT = double blind randomized controlled trial
PDPN = painful diabetic peripheral neuropathy
PHN = post-herpetic neuralgia

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*For the complete list of references, including citations 8-20, go to: http://ti.ubc.ca/letter75#1*

The draft of this Therapeutics Letter was submitted for review to 55 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.