Gabapentinoids: GabaWhys and GabaDont's

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Faculty/Presenter Disclosure

Faculty: Emily McDonald

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- **Other:** Scientific Director of **MedSafer Corp** (deprescribing software)

Overview

- History of gabapentinoids
- Understanding overuse
- The potential harms
- The evidence for and against
- How to deprescribe

History

Antiepileptics

Gabapentin first marketed in 1993 and then generic since 2004

Pregabalin since 2004

Since 2000: use for *neuropathy* (diabetic, post-herpetic, spinal cord injury (PG), fibromyalgia (PG))

History

- In the past 15 years prescriptions have tripled
- Gabapentin 10th most prescribed medication in the US in 2017
- Pregabalin 6th most prescribed medication in 2017
- Along with rising prescriptions, increase in off-label use

Gabapentin

A potential drug for epilepsy developed in 1974; approved to treat partial seizures in 1993

A pharmaceutical company called Parke-Davis, now owned by a division of Pfizer

Pfizer was found guilty of illegally marketing gabapentin for unapproved uses in 2004

Pfizer was heavily fined by the Department of Justice for defrauding public healthcare programs

Second largest fine in the US history (for healthcare cases)

Understanding overuse

Need for safer medications for pain control

Acetaminophen can be ineffective

NSAIDS can be problematic or medically contraindicated in heart failure, hypertension, chronic kidney disease

Opioid crisis

Off-label use implies safety and efficacy have not been proven to the FDA

Pfizer pleads guilty, but drug sales continue to soar

Jeanne Lenzer *New York*

Pfizer, the world's largest drug maker, pleaded guilty on 13 May to numerous civil and criminal charges for illegally promoting the off-label use of gabapentin (Neurontin). It has agreed to pay a $240m (£136m; €200m) criminal fine and $152m to state and federal healthcare programmes. The fine is the second largest given in the industry.

Meanwhile, off-label sales of gabapentin continue to soar, despite evidence that the drug is not effective for some of the problems it is used to treat.

David Franklin, 42, a microbiologist and former Harvard research fellow who worked as a "medical liaison" expert for Warner-Lambert before it was bought by Pfizer in 2002, filed a whistleblower suit under the False Claims Act in 1996, charging the company with using "fraudulent scientific evidence" to promote off-label uses of gabapentin.

Dr Franklin's suit detailed how the company suppressed study results, planted people in medical audiences to ask questions intended to put gabapentin in a good light, lavished perks on doctors, used ghostwriters, gave generous "consultation fees" to "thought leaders," and used psychological profiling of doctors in its successful bid to move gabapentin to so called blockbuster status (annual sales in excess of $1bn) (*BMJ* 2003;326:620). Dr Franklin said that off-label uses accounted for more than 90% of the drug's $2.7bn sales worldwide last year.

Gabapentin is approved for use as adjunctive therapy only for partial seizures and for postherpetic neuralgia. But the company trained staff to promote it for at least 11 off-label uses, including as monotherapy for seizures, restless leg syndrome, bipolar disorder, migraines, and alcohol withdrawal seizures.

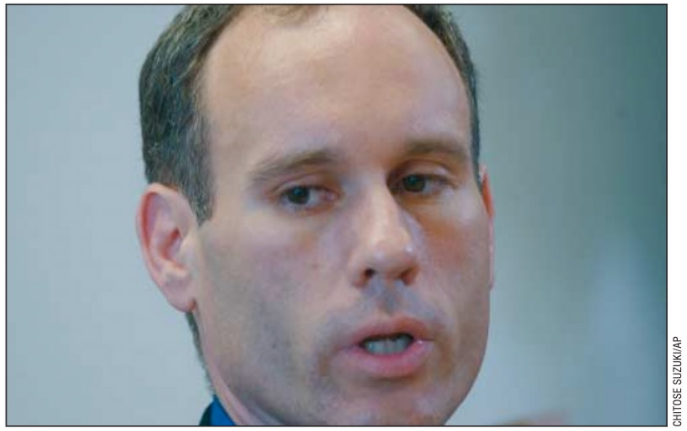
"A lot of people say it's a benign drug," said Dr Franklin. "But it's dangerous when patients are [taken off other] drugs that are effective."

Dr Matthew Keats, assistant professor of clinical psychiatry at Eastern Virginia Medical School, agrees, citing the case of a 16 year old man who committed suicide in May 2002 while taking gabapentin. "The shocking aspect of the story is that the manufacturer funded a study and knew as early as 1998 that Neurontin didn't work in bipolar disorder. But they didn't publish the results until two years later. Yet we still see it prescribed for bipolar disorder."

As part of the settlement agreement, Dr Franklin will receive $24.6m under whistleblowing legislation.

The settlement is not a major setback for Pfizer, whose worldwide sales of gabapentin rose from $1.3bn in 2000 to $2.7bn in 2003.

The company's promotional efforts, Dr Franklin said, were "profoundly effective." He added, "A huge majority of people taking [gabapentin] now are taking it for the wrong reasons." □



CHITOSE SUZUKI/AP

Whistleblower David Franklin said that Pfizer's efforts to promote gabapentin were "profoundly effective"

Whistleblower David Franklin

Detailed that the company suppressed study results

Planted people in medical audiences to ask questions that positively framed gabapentin

Lavished "perks" on doctors

Used ghostwriters for trial results

Used psychological profiling of physicians to move gabapentin to blockbuster sales (annual sales in excess of 1billion$)

Gabapentin- a new wonder drug???

- Neuropathic pain
- Restless legs
- Migraine
- Bipolar disorder
- Drug and alcohol dependance
- Attention deficit disorder
- Premenstrual syndrome…

Use continued to escalate

Despite the fines there was little negative impact on prescribing

Around 2010 the EU listed pregabalin as a new recreational psychoactive substance

Both drugs were noted to cause feelings of euphoria, relaxation and calmness particularly when used in rapidly escalating doses without time for tolerance to develop

In 2014 the NHS called for a “balanced and rational use” among fears that pregabalin was being sold on the black market

In 2015, 3.9% of US adults were prescribed a gabapentinoid (Rhee et al., JAMA internal medicine)

Overuse in Canada

Journal of Hospital Medicine

BRIEF REPORTS

Retrospective Cohort Study of the Prevalence of Off-label Gabapentinoid Prescriptions in Hospitalized Medical Patients

Published online first May 10, 2019. doi: 10.12788/jhm.3203

By: Marc-Alexandre Gingras, MD, MSc, Anthony Lieu, MD, Louise Papillon-Ferland, BPharm, MSc, Todd C Lee, MD, MPH, Emily G McDonald, MD, MSc, FRCPC

Overuse in Canadian Hospitals

- Retrospective study at the McGill University Health Centre over a four-year period
- From 2013-2017 we studied a total of 4103 admissions
- 1 in 8 admissions (13%) was prescribed a gabapentinoid
- Only ~15-20% had an indication
- Commonly prescribed for musculoskeletal pain (15%)
- Almost all prescriptions were low doses (found to be ineffective in trials)

ACTUALITÉ SANTÉ

Trop d'antidouleurs inefficaces prescrits

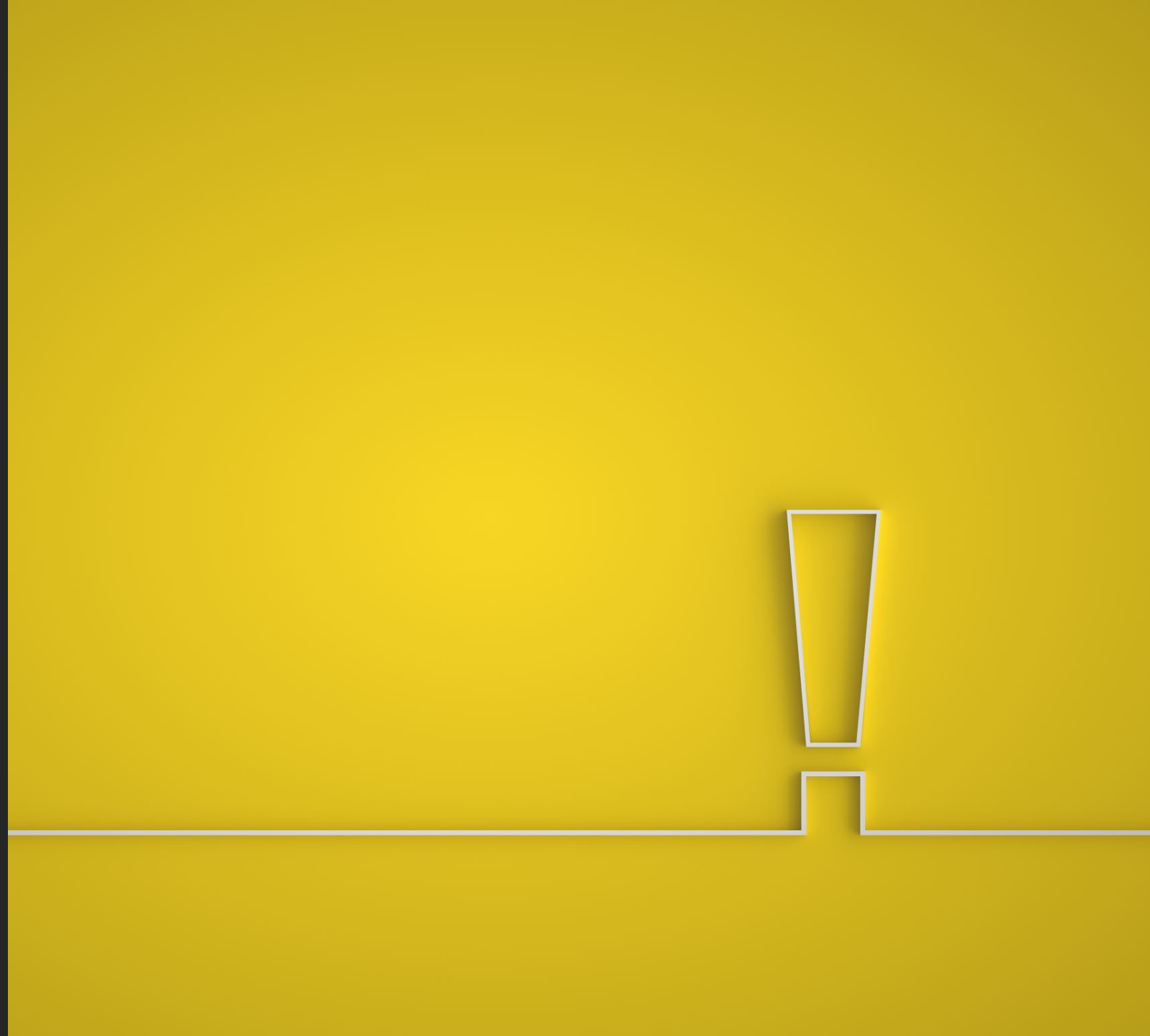
Une étude montréalaise met en garde les médecins

HUGO DUCHAINE

Jeudi, 9 mai 2019 22:36
MISE À JOUR Jeudi, 9 mai 2019 22:36

Des chercheurs montréalais tirent la sonnette d'alarme contre un médicament antidouleur fréquemment prescrit par les médecins, même s'il augmente le risque de chutes, de fractures, de troubles de la mémoire et que son efficacité reste à prouver.

The potential harms



Side effects from gabapentinoids

- Dizziness
- Somnolence (dose response)
- Urinary retention
- Dry mouth
- Ataxia
- Tremors
- Falls and fractures

Dangerous side effects

- Co-prescription with opioids doubles the risk of fatal overdose (Gomes, Juurlink et al., PLoS Med)
- Potential for dependency and risk of abuse (euphoric sensation)
- Reclassified in England to a Class C medication (illegal to possess without a prescription)

Evidence (For) and Against

General considerations

- Small trials (often < 100 participants) with short follow-up (4-12 weeks)
- For painful diabetic neuropathy evidence for GP is poor (2 trials- no benefit & 2 trials- no clinically significant difference)
- PG is approved for fibromyalgia, but GP isn't. Neither of them results in a clinically significant difference in studies (<1 point improvement on the 10-point scale)
- PG and GP are both approved for postherpetic neuralgia (pain>3 months after zoster) however 2 placebo controlled RCTs were both negative for acute zoster pain

GP:gabapentin; PG:pregabalin

Goodman and Brett; JAMA internal medicine, 2019

Take-home points from Goodman and Brett

"Gabapentinoids are sometimes prescribed to treat generalized pain that is multifactorial and nonspecific. Their effectiveness in such cases is unproven, and their **use may be especially problematic as a component of polypharmacy** in elderly patients."

"Because evidence for the efficacy of gabapentin in diabetic neuropathy is mixed in placebo-controlled trials, the balance of benefit and harm must be weighed carefully. **Underappreciation of common adverse effects**, such as dizziness, may result in overall harms outweighing benefits."

2017 Cochrane Review Gabapentin

For painful diabetic neuropathy or postherpetic neuralgia doses of 1800 to 3600 mg daily are required for some effect

More than half of people treated will have no relief from the medication

2013 Cochrane Review Pregabalin

- Modest benefits for diabetic, postherpetic neuralgia, central neuropathic pain, fibromyalgia
- Significant risk of harm
- Commonly stopped due to adverse events and side effects

2017 Systematic Review Chronic low back pain; PLoS Med

Randomized controlled trials

Gabapentinoids

Chronic low back pain

Use for 3 months or longer

Compared to placebo: n=3 studies; minimal to no improvement in pain

Compared to other analgesia: n=3 studies; favoured the comparator

When used as an adjuvant: n=1 study; no benefit

From the same study: the harms

Dizziness RR of 1.99 (NNH 7)

Fatigue RR of 1.85 (NNH 8)

Difficulties with mentation RR of 3.34 (NNH 6)

Visual disturbances RR 5.72 (NNH 6)

All statistically significant

2017 NEJM RCT for Sciatica

- Pregabalin 150-600 mg daily vs placebo x 8 weeks
- No difference in pain scale between groups
- Significantly more adverse events in the treatment group (particularly dizziness)

Gabapentinoids and opioid-related adverse events in surgical patients

JAMA December 2020

Cohort study from 2007-2017 of 5,547,667 surgical admissions

Propensity score trimming

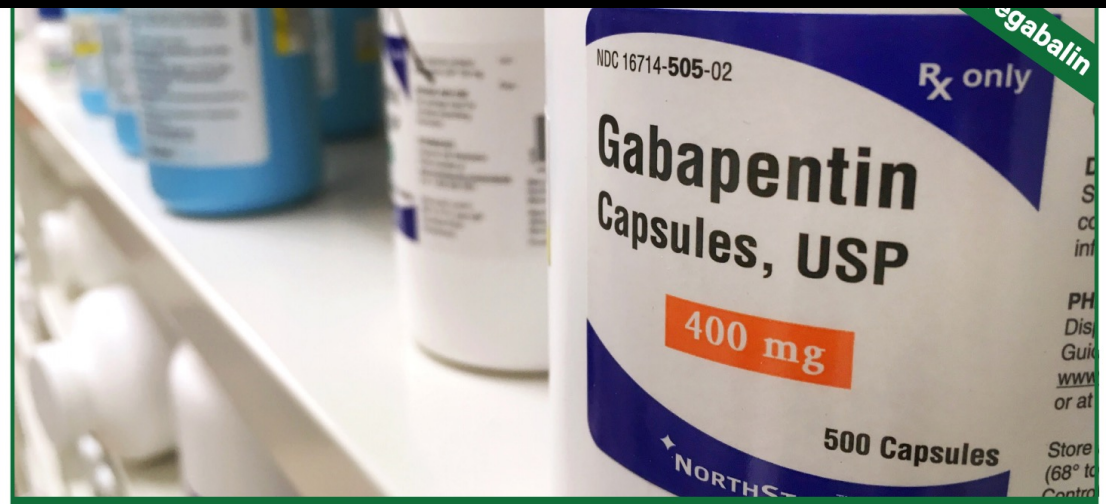
441 overdose events, with absolute risks of 1.4 per 10 000 patients with gabapentinoid exposure and 0.7 per 10 000 patients receiving opioids only (double the risk)

Concomitant use of gabapentinoids with opioids was associated with increased risk of opioid overdose and other opioid-related adverse events

Evidence-based Deprescribing

Risks from stopping suddenly

- Seizure
- Anxiety
- Insomnia
- Agitation
- Nausea
- Pain
- …taper suggested



You May Be at Risk

You are taking one of the following medications for pain:

- ○ Gabapentin (Neurontin®)
- ○ Pregabalin (Lyrica®)

https://static1.squarespace.com/static/5836f01fe6f2e1fa62c11f08/t/5f4f9501ca1e2c27719f7a77/1599051021132/Gabapentinoids_EN_Brochure.pdf

Evidence for deprescribing brochure efficacy

Sedative hypnotics in the community (Tannenbaum et al., JAMA int med) EMPOWER

Sedative hypnotics in the hospital (Wilson et al., JAGS)

Gabapentinoids controlled before-and-after trial enrolling now at the MUHC NCT04855578 GABA-WHY trial

Alternative ways to deal with pain

- Self-management program (therapist can help)
- Cognitive behavioural therapy
- Mindfulness based interventions
- Physiotherapy or massage therapy
- Yoga, tai chi, pilates, exercise
- Weight loss, quitting smoking, diet
- Reducing alcohol and drugs

Tapering regimens

Short Course	Short course taper (consider in the setting of a hospitalization with an adverse event or delirium) over 2-3 weeks
Longer Course	Longer course taper (prior to an adverse event or in the setting of symptoms) over 6 weeks
Start with am dose	Start by reducing the am dose to minimize cognitive and dizziness symptoms during the daytime
Week 4	By week 4: down to half the dose twice daily
Eliminate	By week 6: eliminate the am dose entirely and thereafter reduce the evening dose

Questions or comments?

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