

Gabapentinoids: The Next Opioid Epidemic?

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Physical pain is a key aspect of the human condition. Although there is an evolutionary imperative to feel pain in response to certain stimuli, it has caused immeasurable suffering and misery throughout history. Chronic pain is defined as pain persisting for more than three months, associated with significant emotional distress and functional disability.[1] In 2017, the Global Burden of Disease Study identified lower back pain as the leading cause of disability and disease burden in the world.[2] Despite recently receiving ICD-11 disease status, our current ability to manage chronic pain is limited.

The opioid epidemic in the United States has highlighted the need for new treatments, resulting in many clinicians turning to gabapentinoids. These drugs, including gabapentin and pregabalin, have serious side effects, potential for abuse, and limited evidence surrounding their efficacy. We must therefore ask ourselves whether we are heading for a 'gabapentinoid epidemic'.

Chronic pain and the opioid epidemic

Chronic pain is a highly heterogeneous and complex condition, broadly falling into neuropathic, musculoskeletal, inflammatory or mechanical aetiologies. Chronic pain affects 44% of people in the United Kingdom (UK), with 14% of the population suffering from moderate to severely debilitating pain.[3] Numerous biological, psychological and social factors contribute to the development and protraction of chronic pain. These include increasing age, co-morbid medical conditions, previous surgery, obesity, psychiatric illness, low socio-economic background, substance abuse, and negative beliefs regarding the prognosis of pain.[4] These complex patients are very difficult to treat, and hence many healthcare providers turn to opioids to relieve their suffering. Interestingly, a large meta-analysis recently demonstrated that opioids have minimal efficacy compared to placebo in reducing chronic pain (-0.69 cm on a 10 cm scale), with longer follow-up times associated with lower pain relief.[5] Despite their relative ineffectiveness, we have found ourselves over-prescribing this addictive and harmful class of drug.

Numerous factors have contributed to opioid epidemic. The widespread uptake of the World Health Organisation's (WHO) pain ladder, pain as the "fifth vital sign" campaign, and aggressive pharmaceutical marketing techniques have all played major roles in increasing the volume of opioid prescriptions.

In 1986, the WHO presented the analgesic ladder as a solution to improve the management of cancer-related pain.[6,7] This stepwise system utilised relatively inexpensive medications (such as morphine), and legitimised the use of opioids for the treatment of cancer pain. Early reports demonstrated adequate pain relief in 70-90% of patients, however the methodology of these studies is contested nowadays.[8] The success of this model for cancer-related pain resulted in many evocative yet ill-informed commentaries questioning why opioids were reserved solely for cancer pain.[9] This, paired with a poor understanding of the aetiology of non-cancer pain,[10] resulted in opioids eventually becoming the mainstay treatment for chronic non-cancer pain.[11]

In 1996, the American Pain Society launched the “fifth vital sign” campaign based on quality improvement guidelines published the previous year.[12,13] This campaign was supported by numerous medical societies and regulatory organisations, and was subsequently adopted in the UK.[12] It stated that pain should be documented in a numerical manner, thereby facilitating regular reviews and promoting analgesic intervention.[12] Pain control has subsequently become a measure of patient satisfaction, which in some countries directly impacts physician rating scores, and is linked to reimbursement.[14] Although the “fifth vital sign” campaign increases recognition of pain, the strategy has been shown to not improve the quality of pain management.[15]

Pharmaceutical companies such as Purdue Pharma (owned by the infamous Sackler family) have also significantly contributed to the opioid epidemic. In the late 1990’s, Purdue initiated an aggressive marketing campaign to promote their slow-release version of oxycodone sold as *OxyContin*. Thousands of physicians, nurses and pharmacists attended all-expenses-paid symposia on the benefits of *OxyContin*, where Purdue consistently downplayed the risk of addiction to the drug.[16] The risk of addiction to *OxyContin* was consistently advised as “less than one percent,” however subsequent studies have demonstrated that up to 45% of chronic pain patients treated with long-term opioids develop addiction.[16] In 2007, Purdue Pharma pled guilty to criminal charges of misbranding, and was ordered to pay US\$634 million in fines for claiming it was less addictive and less subject to abuse than other opioids.[17] In August 2019, Purdue offered US\$10-12 billion US to settle numerous litigation cases linked to their fraudulent marketing of *OxyContin*. [18] Unfortunately, these fines will have little impact on the lavish lifestyles of the executives responsible for drastically increasing the number of patients embroiled in the opioid epidemic.

In October 2017, Donald Trump declared the opioid epidemic a public health emergency.[7] The current rate of opioid-related deaths in the United States has increased five-fold since 1999, with 130 people dying every day due to an opioid overdose – surpassing the number of deaths attributable to road traffic accidents.[19] Although the increase in opioid prescribing in the UK has not been as dramatic, we still observed a 127% increase in dose-adjusted prescribing between 1998 and 2016.[20] Strategies have been utilised to prevent opioid-related deaths, such as access to opioid agonist therapies (e.g. methadone),[21] naloxone [22] and supervised injection facilities.[23] However, the opioid epidemic remains one of the most pressing public health issues facing modern society.

The rise of gabapentinoids

The opioid epidemic has forced clinicians to reconsider how they treat pain, and search for alternatives to opioids. Gabapentin and pregabalin act via inhibition of voltage-dependent calcium channels, reducing the release of excitatory neurotransmitters and decreasing neuronal

excitability.[24,25] Although the two gabapentinoids share similar mechanisms of action, pregabalin is characterised by a higher potency, faster absorption rates and greater bioavailability.[26] In the UK, gabapentin is licenced for peripheral neuropathic pain and focal seizures; while pregabalin is licenced for neuropathic pain, focal seizures and general anxiety disorder.[27] Despite this narrow set of indications, the OpenPrescribing database shows a recent 2.9-fold increase in the number of gabapentin and pregabalin prescriptions, from 74 prescriptions per 1,000 of the population in 2014 to 215 per 1,000 of the population in 2018.[28] Similarly, data from the Clinical Practice Research Datalink (CPRD) demonstrates that in the UK the number of new patients treated with gabapentinoids tripled between 2007 and 2017 (figure 1).[29] In the US, gabapentin was the tenth most commonly-prescribed medication in 2016.[30]

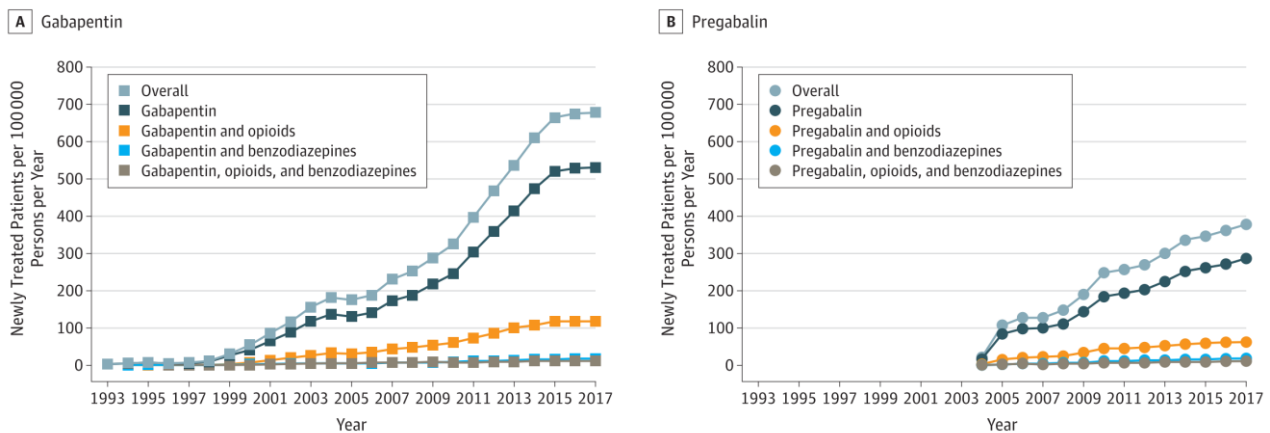


Figure 1: New users of Gabapentin and Pregabalin in the UK Primary Care System from 1993 to 2017. Rates of new users of gabapentin (A) and pregabalin (B) in the UK primary care system documented in the UK Clinical Practice Research Datalink from 1993 to 2017.[29]

Cochrane reviews have consistently demonstrated the benefits of gabapentinoids in the treatment of postherpetic neuralgia pain and painful diabetic neuropathy.[31,32] Although there is proven benefit for these applications, an alarming proportion of prescriptions are for off-label indications with poor evidence. In the UK, 52% of gabapentin and 55% of new pregabalin prescriptions were for off-label purposes (figure 2).[29] Given this statistic ignores patients where an indication could not be identified, it is likely that the true proportion of off-label prescriptions is far higher. The majority of off-label prescriptions were for non-neuropathic pain, with some clinicians stating that they see gabapentinoids being used for almost any kind of pain.[29,33] Other common off-label uses include trigeminal neuralgia, bipolar disorder, attention-deficit disorder, restless leg syndrome and substance withdrawal.[26] This widespread use of gabapentinoids to treat pain without evidence of effectiveness is concerning. Meta-analyses have demonstrated that gabapentinoids produce minimal improvements in chronic low back pain, poorer response than other analgesic medications, and no efficacy as an adjunct to opioids; all with very low quality evidence.[34]

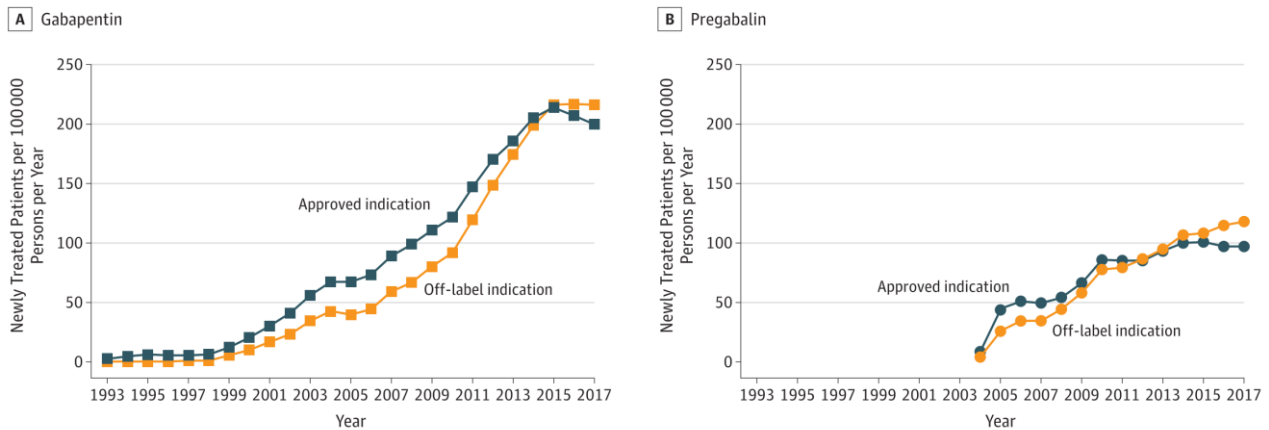


Figure 2: New Users with a Gabapentin and Pregabalin Indication in the UK Primary Care System From 1993 to 2017. Rates of new users with an identified gabapentin (A) and pregabalin (B) indication documented in the UK Clinical Practice Research Datalink from 1993 to 2017. Patients for whom a prescription indication could not be identified were not included.[29]

Aggressive marketing has also played a central role in the popularity of gabapentinoids since the original branded gabapentin, also known as *Neurontin*, was approved to treat seizures in 1993. Following this, the manufacturer Parke-Davis engaged in an extensive marketing campaign to increase the off-label use of *Neurontin* for pain, which it admitted to in 2004 and paid a penalty.[33,35] Pfizer, the original manufacturers of pregabalin, branded as *Lyrica*, were embroiled in claims that they ran marketing campaigns with the aim of increasing prescriptions for unlicensed indications. In 2009 they were accused of bribing healthcare workers and offering lavish compensation to encourage off-label prescriptions, resulting in what was the largest settlement ever of £1.4 billion.[36]

To reduce the reliance on opioids, clinicians have taken to increasing the prescribing of gabapentinoids. Recent guidelines from the Center for Disease Control and Prevention (CDC) recommend that clinicians consider several other medication classes before turning to opioids for patients with chronic noncancer pain.[37] Despite the availability and safety of non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, they are frequently contraindicated, or many patients state that they have previously not provided relief.[33] Physicians are desperate for alternatives to opioids, and thus are lowering their threshold for prescribing gabapentinoids to treat various types of pain.[33] CPRD data shows that between 2007 and 2017, the proportion of patients being co-prescribed gabapentinoids and opioids (and/or benzodiazepines) in UK primary care has approximately tripled.[38] In 2017, 20-25% of patients in the UK that started a gabapentinoid received a concomitant prescription, primarily for opioids.[29] In Canada, approximately 50% of patients taking gabapentin also received a prescription for opioids.[39] Research has shown that gabapentinoid administration can reduce post-surgical opioid consumption, however this obviously occurs with the trade-off of increased gabapentinoid side effects.[40] Although opioid consumption has decreased in the UK in recent years,[20] it is not yet clear whether transitioning patients to gabapentinoids will decrease morbidity and mortality.

Gabapentinoids have numerous adverse effects. Common side effects include visual disturbances, difficulty with mentation, dizziness, and fatigue.[34] Gabapentinoids also produce severe side effects in rare cases, with 190 deaths in the UK associated with pregabalin or gabapentin in 2017.[41] It is likely that this figure underestimates the number of deaths involving gabapentinoids, as post-mortem toxicology screening is only performed if these drugs are mentioned in the case notes. In a recent study conducted in the UK, 3,750 Coroner's cases were all screened for gabapentinoids regardless of the cause of death. It was subsequently found that the presence of pregabalin and gabapentin was underreported by 54% and 58% respectively, indicating that a large proportion of deaths attributable to gabapentinoids likely go unreported.[42] In light of the increase in gabapentinoid-related deaths, authorities have recently classified pregabalin and gabapentin as class C drugs to reduce their inappropriate consumption.[43]

One of the most serious adverse effects of gabapentinoids is their ability to increase the risk of opioid-related death when these two drug classes are used in combination. Co-prescription of gabapentin or pregabalin with opioids was associated with a 50% and 68% increase in the risk of opioid-related death respectively, after adjusting for co-morbidities and other prescriptions.[39,44] This is likely due to the additive respiratory depression, as well as increased gabapentinoid bioavailability due to slowed gastrointestinal transit time. This effect is particularly concerning given how frequently these drugs are prescribed together. It is possible that clinicians are co-prescribing gabapentinoids to reduce opioid consumption, and are inadvertently increasing the number of patients suffering fatal opioid overdoses.

Gabapentinoids also have a social and economic burden to society and healthcare systems. A meta-analysis of 38 trials noted euphoria to be the second most common side effect produced pregabalin, making it a desirable recreational drug.[45] In 2015, 9.2% of patients receiving opioid substitution therapy in Ireland tested positive for pregabalin; with 73.6% of patients not having received a recent prescription.[46] A similar study conducted in Israel in 2017 demonstrated that 17.7% of patients enrolled in a methadone treatment program tested positive for pregabalin, with 85.5% not receiving a recent prescription.[47] The diversion of pregabalin has been well recognised, and some physicians advocate that pregabalin should only be prescribed to well-known patients.[48] As social factors play a strong role in chronic pain and contribute to the risk of overdose in patients taking opioids, unmonitored and illegal gabapentinoid consumption could spell disaster for people with chronic pain who turn to street drugs to treat their condition.

Do we face another epidemic?

There are concerning similarities between the opioid epidemic and the increase in gabapentinoid consumption. However, it is unlikely that gabapentinoids will produce devastating effects to the same degree as opioids. Both of these analgesics gained popularity in part due to necessity. For

opioids, this was the undertreatment of chronic non-cancer pain, while for gabapentinoids, the rise in popularity comes as clinicians desperately seek a safer alternative to opioids. Both classes of medications are frequently used outside their licenced indications, both utilise aberrant pharmaceutical marketing to influence patients, and both carry concerns regarding recreational abuse.

There are however two important caveats that we must consider. Firstly, we underestimated the harmful effects of opioids in the 1990's when they started gaining in popularity. We must be careful not to make the same mistakes, and further research into the adverse effects of gabapentinoids, particularly the incidence of serious adverse effects, is necessary. Secondly, we must be cognizant of the fact physicians are making a trade-off between the adverse effects of opioids and gabapentinoids, in the context of limited clinical efficacy. By switching chronic non-neuropathic pain patients from opioids to gabapentinoids, we are simply transferring the current issue of poorly managed pain from one class of drug to another.

The focus on pharmacological treatments for chronic pain demonstrates a behaviour that is pervasive throughout modern medicine. Doctors have been educated to believe that medications are a key part of their toolbox, and are often quick to prescribe for chronic pain despite limited evidence and significant harms.[34,49] Furthermore, people suffering with chronic pain may not take responsibility for their health, and be unwilling to engage in proven non-pharmacologic therapies (such as exercise therapy or cognitive behavioural therapy).[50] Studies have also shown that patients feel more satisfied with their visit if they leave with a prescription in hand, and more likely to receive one when they expect it.[50,51] As many people with chronic pain see their doctor with the expectation of receiving fast and complete pain relief, attempts to implement non-pharmacological strategies are challenging and time consuming, and contribute significantly to clinician burn-out.[52]

Patients and clinicians need to recognise the limitations of pharmacological treatments and increase the uptake of other management strategies. Opioids and gabapentinoids both have the ability to distance users from unpleasant thoughts and feelings which normally potentiate their symptoms; by limiting these factors, we can significantly reduce pain intensity.[53] Instead of prescribing dangerous drugs to high-risk patients, we must accept the complexity of these patients and adopt a biopsychosocial approach to meet their needs. This will likely require allocating more resources to non-pharmacological treatments for chronic pain.[54] For treatment to be effective, patients need to set realistic expectations, and acknowledge that chronic pain is a long-term condition without an instant cure.[55] By utilising these approaches, it may be possible to reduce the iatrogenic harms caused by over-prescription, and improve how people live with their pain.

Conclusion

Although gabapentinoids are effective for some indications, caution should be adopted when

prescribing them to treat chronic non-neuropathic pain. With the current evidence we have, it is unlikely that gabapentinoids will cause the same amount of suffering seen in the opioid epidemic. We must however be cognizant of our tendencies as healthcare professionals to over-utilise pharmacological intervention, and increase our uptake of effective non-pharmacological treatments. While history often repeats itself, I believe we can learn from our mistakes and avoid a gabapentinoid epidemic.

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