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Published in:
Pain Management

DOI:
10.2217/pmt-2021-0121

Publication date:
2022

Document Version
Peer reviewed version

Pain Management

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Journal:	*Pain Management*
Manuscript ID	PMT-2021-0121.R1
Manuscript Type:	Editorial
Keywords:	Opioids, Gabapentinoids, Prescribing rates, Drug-related deaths, Epidemiology

Colvin, L, Smith, BH & Hebert, H 2022, 'The impact of gabapentinoid and opioid prescribing practices on drug deaths: an epidemiological perspective', Pain Management. https://doi.org/10.2217/pmt-2021-0121

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Short running title: Gabapentinoid and opioid prescribing and drug deaths

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Introduction

In 2020, the number of drug-related deaths (DRDs) in Scotland reached a record high of 1,339 [1]. This is the seventh year in a row that deaths from drug misuse have reached record levels and represents a near 5½ fold increase since records began in 1996. Record levels were also registered in England and Wales in 2020, (for the 7th year running) and in Northern Ireland for 2019 [2,3]. When compared to other countries in Europe using the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) definition, Scotland had the highest number of drug deaths per capita in people aged 15-64 years, with 318 deaths per million in 2019 [1]. The next highest in Europe were Sweden and Norway each with 77 deaths per million. However, there is no internationally agreed definition of DRD and, in some countries, cases are under-reported. Consequently, comparisons between countries should be treated with caution, especially when some countries lack up-to-date data. The UK itself has one of the highest rates in Europe (76 deaths per million in 2017 using the EMCDDA definition) [1]. Together this has led to suggestions that the UK, and Scotland in particular, is in the middle of a “drug-death crisis”, with calls for greater intervention at the governmental and clinical level [4].

Opioids

The biggest contributor to DRDs are opioids, which are mainly used to treat people with pain, although those used for opioid replacement therapy (methadone, buprenorphine) feature disproportionately in ORDs. Opioids were implicated in 89% of all DRDs in Scotland, 49.6% in England and Wales (both 2020) and 67% in Northern Ireland in 2019 [1–3]. Opioid-related deaths (ORDs) have been rising steadily throughout the UK, with a 4-fold increase occurring in England and Wales between 1993 and 2020, and a similar level of increase in Scotland between 2000 and 2020 and in Northern Ireland between 2009 and 2019. Understanding the factors that contribute to ORDs is a key step in trying to tackle this issue.

One of the possible drivers for this increase in ORDs is the corresponding increase in prescribing rates of opioids. Studies conducted in the UK show that opioid prescribing and dose are associated with ORDs [5]. In Scotland, strong opioid prescriptions more than doubled from 2003 to 2015 and weak opioid prescriptions increased by more than 50% in the same time period [6]. In England, opioid prescriptions increased by 34% between 1998 and 2016 [7]. In Wales, there was a

4-fold increase in prescribing of strong opioids and 27% increase in prescribing of weak opioids in non-cancer patients between 2005 and 2015 [8].

There are a number of possible explanations for the rise in prescribing rates. One might be the increased demand from an aging population at greater risk of developing painful conditions. Another could be the increased use in treating pain conditions for which data on the long-term effectiveness of opioids is not available. Lack of adequate pain relief in people with these conditions can lead to escalation in dosage or switching to alternative opioids of increasing potency. This can in turn lead to tolerance and opioid-induced hyperalgesia initiating a cyclical relationship with duration of use [9]. The rising concern about patient safety when using opioids has prompted updated guidelines and regulatory action. Tramadol was classified as a Schedule 3 controlled substance by the UK government in 2014, which placed greater legal restrictions on its supply by pharmacists [10]. In Scotland, clinical guidelines on the management of chronic pain, originally published in 2013 in response to a lack of guidance, were updated in 2019 specifically for the section on opioids [9]. These included key recommendations for regular review and specialist referral if more than 90mg/day morphine equivalent dose is required (decreased from 180mg/day in the 2013 edition). This aligns with the 2016 Centers for Disease Control and Prevention (CDC) guidelines for prescribing opioids for chronic pain in the USA [11]. Additionally, opioid prescribing has become a key National Therapeutic Indicator (NTI) in Scotland, England and Wales. The NTIs are a set of prescribing indicators, in specific therapeutic areas (such as analgesics, which includes gabapentinoids), based on national administrative data. This can be used to compare prescribing behaviours in individual Health Boards, Health and Social Care Partnerships or General Practitioner (GP) practices against established guidelines and used for quality improvement work. Recent data from the NTIs and published studies suggest that opioid prescribing rates are beginning to plateau or even decline in the UK [12,13] and evidence is beginning to emerge that the publication of these clinical guidelines and updated regulatory changes are successfully reducing opioid utilisation [10]. Worryingly however, this does not appear to have translated into a reduction of ORDs, perhaps reflecting the multiple factors involved in ORDs, including availability of illicit opioids and wider psychosocial factors [1–3].

Gabapentinoids

Another predictor of ORDs is the concomitant use of gabapentinoids, which are usually understood to refer to gabapentin and pregabalin [14]. Gabapentinoids were originally developed as anti-epileptic drugs, but are now recommended as first-line medications for the treatment of neuropathic pain, especially pain associated with peripheral diabetic neuropathy and postherpetic neuralgia [15].

When gabapentinoids were first introduced in the UK (in 1993 for gabapentin and 2004 for pregabalin) little was known about their mechanisms of action and they were widely considered to be safe medications. Subsequently they have been used for a variety off-label indications, including as adjuncts for chronic non-neuropathic pain. In the UK it is estimated that approximately 50% of gabapentinoid prescriptions are for an off-label indication [16]. However, whereas there is good evidence for the effectiveness of gabapentinoids in neuropathic pain [17], in other forms of pain the evidence is limited.

Possibly as a result of this off-label use, increased awareness of neuropathic pain, and rising concerns around the use of opioids, gabapentinoid prescribing has been increasing. In Scotland, a recent study found that there was a more than 5-fold increase in the number of gabapentinoid prescription items overall (4-fold for gabapentin and 16-fold for pregabalin) from 2006 to 2016 [18]. In England, there was a 70% increase in the amount of defined daily doses per 1000 population for gabapentinoids from 2013/14 to 2018/19 [19]. In addition to this, the number of new patients treated with gabapentinoids increased 3-fold in the UK between 2007 and 2017 [16]. Whilst England, Scotland and Wales followed similar trajectories, Northern Ireland had a consistently higher rate of new pregabalin users, peaking at more than 5-fold higher than the other 3 nations in 2010 [20]. The reasons for this are not entirely clear and require further investigation.

In comparison to opioids, gabapentinoids have received relatively little attention, both from the media and in research. However, they have become desirable recreational drugs and can potentiate the effects of opioids [21]. A recent systematic review found that the prevalence of misuse amongst those with a prescription was 40-65%, compared to 1% in the general population [22].

In addition to increased reports of gabapentinoid abuse, figures suggest that the number of gabapentinoid-related deaths (GRDs) is also rising. Though lower than

opioids, the proportion of total DRDs in Scotland where gabapentinoids were implicated or potentially contributed rose from 4.3% in 2012 to 37.5% 2020, a near 9-fold increase [1]. In England and Wales, the proportion rose from 0.5% to 10.1% and in Northern Ireland the proportion rose from 1.7% to 48.2% from 2013 to 2019 [2,3]. This increase in GRDs is highly correlated with prescribing rates [21]. The number of GRDs increases by 5% for every 100,000 increase in gabapentinoid prescriptions, although it is still to be established whether prescribing is independently associated with GRDs.

As with Tramadol in 2014, the UK government's answer to this rise in deaths was to reclassify gabapentinoids as Class C drugs in April 2019, in an effort to reduce prescribing rates. It is not yet clear whether this intervention has been successful in reversing the upward trend of either outcomes; however, initial clinical views are sceptical. One of the reasons for this is that gabapentinoids are increasingly being obtained illicitly. In the Tayside region of Scotland, 77% of GRDs recorded in 2016 did not involve a gabapentinoid prescription [18]. Another reason is that, unlike when tramadol was reclassified, there are few safe alternatives for gabapentinoids in the treatment of chronic neuropathic pain. Indeed, it is possible that when tramadol was reclassified, there was a shift in prescribing to gabapentinoids. Guidance in Northern Ireland has gone even further and pregabalin has been removed from the country's formulary for neuropathic pain in August 2021. According to the country's Health and Social Care Board (HSCB), amitriptyline should be considered as a first-line treatment for new patients with neuropathic pain along with gabapentin, though GPs will still be able to prescribe pregabalin where deemed 'clinically appropriate'. The HSCB also advises that gabapentinoids should not be used to treat other off-label pain conditions such as fibromyalgia, low back pain and sciatica. This is in line with National Institute for Health and Care Excellence advice for chronic primary pain, though concerns have been raised regarding the validity of these guidelines. It will be interesting to see whether this change in policy simply shifts prescribing and abuse problems onto other neuropathic pain medications such as amitriptyline, or whether it succeeds in reversing GRD rates.

Co-Prescribing

Since opioids and gabapentinoids are both used to treat chronic pain, it is not unusual for them to be prescribed together. Across the UK, 15-20% of new gabapentinoid users were co-prescribed an opioid between 2007 and 2017 [20],

though the proportion was higher locally in the Tayside region of Scotland at 49.9% in 2016 [18]. Furthermore, the rate of patients co-prescribed an opioid (and/or a benzodiazepine) more than doubled for gabapentin and tripled for pregabalin in the UK between 2007 and 2017 [16]. At the same time as this increase in co-prescribing rates, the number of DRDs involving both an opioid and gabapentinoid in England and Wales increased 36-fold from 2009 to 2015. This was in line with the increase in GRDs [21]. However, despite this apparent positive correlation between opioid and gabapentinoid co-prescribing and DRDs, it is not yet clear whether co-prescribing of these drugs is associated with increased risk of DRDs involving both drugs, though concomitant gabapentinoid use has been associated with increased risk of ORD [14]. Currently, there is little guidance on the concomitant use of opioids and gabapentinoids and further work is required in this area so that it can be addressed in future clinical publications.

Conclusions

From the available data, action is needed in the UK, and Scotland in particular, to address the rising issue of DRDs. Opioids, along with gabapentinoids, are major contributors to these deaths and epidemiological studies have shown that increased rates of prescribing in both drug groups are linked to these outcomes. However, there are hints that changes in clinical guidelines can help to reverse some of these prescribing trends, particularly for opioids. These guidelines have themselves been informed and influenced by the available prescribing data. Studies identifying risk factors for ORDs and GRDs can help clinicians further, by identifying sections of the population most at risk of harm. Similar updates to clinical practice based on robust, clinically relevant research are also needed to address the rising concerns with gabapentinoids.

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