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Gabapentinoids: The rise of a new misuse epidemics?

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ABSTRACT

Gabapentinoids and opioids have in common that they are used in medicine in the treatment of pain, and by addicts in recreational use. In recent years, in the context of the "opioid epidemics", gabapentinoids, which had a reputation for low risk of abuse, have been increasingly prescribed. This was accompanied by increasingly frequent abuses, the patients most at risk being those suffering from opiate addiction. However, gabapentinoids increase the risks associated with opioids or other sedatives, due to a synergy of central depressant effects. This leads to reconsider the framework of their prescription and the management of chronic pain.

In recent years, the terms « opioid crisis » or « opioid epidemics » have been used to name the health situation in the United States, resulting from the increase in opiates abuse and the related mortality, which are estimated to have led to 33,000 deaths in 2015. New modes of consumption were observed in this epidemic, such as the massive arising of abuse of medical opioids (which would have concerned more than 4% of the American population in 2015), and a hitherto unheard of relationship between consumptions of non-medical opioids and synthetic medical opioids (fentanyl, in particular), which are now intertwined. A clear majority of opioid users now abuse medical opioids before resorting to illegal opioids, with heroin appearing like a more readily available and cheaper substance (Skolnick, 2018; Suter and Allaz, 2017). This opioid crisis comes after years of encouraging the destigmatization of opioid prescription in painful syndromes, and renews the distrust of these treatments. In this context, worrying signals are also arising concerning gabapentinoids, whose prescription is widely promoted in the treatment of chronic pain as an alternative to opioids. Indeed, while the prescription of gabapentinoids is increasing significantly in several countries, mainly as an alternative to opioid analgesics (Goodman and Brett, 2019; Morrison et al., 2017), recent data highlight on the one hand a drift in off-label prescribing, and on the other hand an increasingly well-documented potential for abuse and dangerousness.

The gabapentinoid group consists of gabapentin and pregabalin. Structurally similar to the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), gabapentinoids bind to a subunit (protein α2-δ) of a voltage-dependent calcium channel in the central nervous system, decreasing the intracellular calcium influx induced by cell depolarization, and the release of exciting neurotransmitters. It consequently decreases neurotransmission in pain signaling pathways, continuously activated in a variety of chronic pain syndromes, or in fear circuits, over-activated in anxiety disorders (Baldwin et al., 2013; Cross et al., 2021; Stahl, 2004a, b, c). In addition to the treatment of epilepsy (for which they were developed), the indications for gabapentinoids include the treatment of central and peripheral neuropathic pain as well as fibromyalgia (in the United States only) and they are recommended by international guidelines in these indications; by extension, they are widely prescribed in cases of pain syndromes involving central sensitization, though most evidence comes from studies performed in post-herpetic and diabetic neuropathy, with no evidence existing for radiculopathy (Mathieson et al., 2017) or visceral pain (pelvic pain in Horne et al., 2020), for example. Pregabalin is also indicated for the treatment of generalized anxiety disorder. While the main adverse effects described are somnolence, dizziness, weight gain, visual disturbance and lower limb edema, gabapentinoids are associated with a risk of respiratory depression (Food and Drug Administration (FDA), 2020), and pregabalin has the potential to generate a withdrawal syndrome (Barrett et al., 2015; Gahr et al., 2013; Grosshans et al., 2010; Naveed et al., 2018; Yargic and Ozdemiroglu, 2011).

Epidemiological data show an increase in recent years in the prescription of gabapentin and pregabalin in several Western countries (e.g.

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respectively +350% and +150%, in the United Kingdom, from 2012 to 2017) (Morrison et al., 2017; Spence, 2013). This increase is probably multifactorial, drawing its source on the one hand from a change in the attitude of society and the medical profession towards pain, resulting in more intensive management of pain syndromes, and on the other hand from a reputation for low risk of abuse, contrasting with the context of the health crisis linked to opioid abuse (Goodman and Brett, 2019; Morrison et al., 2017; Skolnick, 2018). In this context of increasing prescribing and therefore greater availability, there was an increase in the number of reports of gabapentinoid-related adverse events and abuse worldwide (Advisory Council for the Misuse of Drugs, 2016; Cairns et al., 2019; Evoy et al., 2017; Gahr et al., 2013; Lyndon et al., 2017; Schifano, 2014; Schjerning et al., 2016). Because of its rapid absorption and shorter onset of action, pregabalin is thought to have a higher risk of abuse than gabapentin, which epidemiological data seem to confirm (Driot et al., 2019; Hakkinen et al., 2014). Consumers take high doses of gabapentinoids for their euphoric effects (Bonnet and Scherbaum, 2017; Chiappini and Schifano, 2016; Evoy et al., 2017; Schifano et al., 2011) or in self-aggressive behaviours (Daly et al., 2018); anxiolytic and sedative effects can also be sought. Cases of dependence have been described, concerning a proportion of about 10% of patients with abuse, in a recent study of the French population (Driot et al., 2019; Pfizer, 2020). Pregabalin is reportedly regularly prescribed to people with risk factors for abuse – concerning about 14% of pregabalin prescriptions in Australia (Cairns et al., 2019), and there is a growing black market in populations at high risk of misuse, such as in prisons (Bicknell, 2013; Morrison et al., 2017; Royal College of General Practitioners, 2019; Spence, 2013).

The risk factors for gabapentinoid abuse are broadly the same as for opiates and other substances: a history of abuse, comorbid psychiatric disorders, young age, multiple prescribers (Boden et al., 2014; Chiappini and Schifano, 2016; Driot et al., 2019; Evoy et al., 2017; Lyndon et al., 2017; Papazisis et al., 2013; Public Health England and NHS England, 2014). Contradicting the prejudice that gabapentinoids would be a less risky alternative to opioids, current data show a risky relationship between these two categories of molecules. Pregabalin is thought to enhance the effects of opiates and reduce withdrawal symptoms, which would be major motivations for its use in combination with opiates. It is estimated that about 10% of patients followed for opiate addiction would have consumed pregabalin, mostly without a medical prescription (Grosshans et al., 2013; McNamara et al., 2015). Association with high-dose pregabalin leads to an increased risk of respiratory depression related to opiates or other sedatives (alcohol, benzodiazepines) (Lyndon et al., 2017; Pfizer, 2020; Public Health England and NHS England, 2014), with a lethal risk (Hakkinen et al., 2014). The lethality of gabapentinoids, probably underestimated (Nahar et al., 2019), is linked in particular to the increase they cause in opiate-related mortality (Gomes et al., 2017). In this overall context, a framework limiting their prescription and administration has been implemented, or is under consideration, in several countries (United Kingdom, United States, Norway, Australia) (Crossin et al., 2019; Schifano and Chiappini, 2019).

Gabapentinoids and opioids have in common that they are used in medicine in the treatment of pain. The « opioids epidemic » and recent data on the abuse potential of gabapentinoids raise questions about how patients with chronic pain are managed by medicine. Ideally, this management should be multidisciplinary and holistic (Hayes et al., 2017), combining analgesic pharmacotherapy, mobilization of patient resources, physical exercise and even psychotherapy. Limiting this management to drug prescription and thinking that the risk of abuse of analgesics is linked only to opiates are errors which today show their limits. It appears that for a patient with risk factors for abuse and an indication for pregabalin, the prescription of pregabalin should be closely monitored.

Physicians, who were tempted to prescribe gabapentinoids as analgesics to avoid the risks of opioids, may now encounter in their practice a request for prescriptions from patients who are substance abusers. An example illustrating this phenomenon is encountered in prison medicine, where opiate-dependent inmates request gabapentinoid treatment to avoid withdrawal sensations. However, gabapentinoid use during incarceration may worsen the risk of overdose on release from prison for these prisoners (Nicholls et al., 2019). Gabapentinoid abuse in prison, which is now well documented, leads to a variety of attitudes in different penitentiaries, with some prisons refusing to prescribe pregabalin (Advisory Council for the Misuse of Drugs, 2016; HM Inspectorate of Prisons, 2015), or implementing specific medication decay management programs for prisoners with unclear drug use (opiates, benzodiazepines, gabapentinoids) (Nicholls et al., 2019).

Gabapentinoids, which are indicated for the treatment of certain types of pain and anxiety, have been increasingly prescribed, particularly due to the « opioids crisis », which has been accompanied by increasingly frequent abuse. Pregabalin is particularly concerned, as its pharmacological characteristics makes it more prone to abuse. The patients most at risk of abuse are those already suffering from opiate addiction, in which case gabapentinoids are used either to reinforce the effects of opiates or to reduce withdrawal sensations. However, the association of gabapentinoids with opiates or other sedatives is particularly dangerous, due in particular to a synergy of central depressant effects.

This situation raises questions about the management of chronic pain, highlighting the limits of a pharmacological treatment alone. Gabapentinoids should not be prescribed off their recognized indications, and in particular not in pain syndromes for which there is no evidence of efficiency (i.e. some neuropathic pain syndromes only), or as sedative or anxiolytic treatment in the absence of a generalized anxiety disorder. Like opiates, they should be avoided in patients with risk factors for abuse. In opioid-dependent patients, they increase the risks associated with opioids, and their dangerousness is currently being reassessed on the rise.

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CRediT authorship contribution statement

Michel Hofmann: Conceptualization, Writing – original draft. **Marie Besson:** Conceptualization, Writing – review & editing, Supervision.

Declarations of Competing Interest

None.

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