Review Article

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The Gabapentoids Conundrum: "Mind the Gabs"

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Abstract

Concerns about two Gabapentoids namely Gabapentin and Pregabalin have been raised for years. Both were introduced as anti-epileptic agents before finding a myriad of indications, not without controversy. Experts are divided about their safety; one camp defends their use the other flagging incidents of diversion, reports of abuse cases of overdosing and even mortality. This article presents alarming Middle Eastern example of a wave of Gabapentoids abuse, mostly Pregabalin, among patients seeking treatment at the National Rehabilitation Center, Abu Dhabiand UAE. It also provides an overview of indications, side effects, evidence for and against abuse and misuse potential, laboratory tests, all within the context of a substance use disorder rehabilitation service.

Introduction

Gabapentoids are a class of drugs that include *Gabapentin*, *Pregabalin*, *Mirogabalin*, gabapentin prodrug *gabapentin enacarbil* and *phenibut*.

Gabapentin (street names "Johnnies" or "Gabbies) is a prescription drug misused for its euphoric effect. The clinical indications for Gabapentin (Neurontin®) use include: adjunctive treatment of focal seizures with or without secondary generalization, monotherapy for focal seizures with or without secondary generalization, migraine prophylaxis, peripheral neuropathic pain and menopausal symptoms, (particularly hot flushes, in women with breast cancer) [1].

Common adverse effects on the (CNS) include: anxiety, behaviour abnormalities, confusion, depression, emotional lability, headache, insomnia, malaise, movement disorders, muscle complaints, nystagmus, oedema, sexual dysfunction, abnormal thought, tremor and vertigo [2].

Gabapentin has been associated with a rare risk of severe respiratory depression even without concomitant opioid medicines. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of (CNS) depressants, and elderly people might be at higher risk of experiencing severe respiratory depression and dose adjustments may be necessary in these patients [2].

Pregabalin, on the other hand, is a gamma-aminobutyric acid (GABA) analogue that was initially synthesized as an anticonvulsant medication and a successor to Gabapentin by the pharmaceutical company Parke-Davis, which was later acquired by Pfizer. It is marketed under the brand name Lyrica in the United States where it is still on patent. Generic versions are available in Canada, the United Kingdom, Australia and Germany. Pregabalin has been described as the "New Valium" and is sometimes associated with the street name "pregabs".

Pregabalin is indicated for use in peripheral and central neuropathic pain conditions resulting from diabetes, multiple sclerosis and fibromyalgia, and adjunctive treatment of focal seizures with or without secondary generalization, generalized anxiety disorder [1]. Common adverse effects on the central nervous system (CNS), include: confusion, drowsiness, memory loss, mood alteration and movement disorders, sleep disorders, vertigo. Other side effects include sexual dysfunction, muscle complaints, weight changes and oedema with swelling affecting mainly the arms and legs. Withdrawal symptoms include trouble falling asleep or staying asleep, or seizures [1].

The NRC Data Set

The National Rehabilitation Centre in Abu Dhabi is the main drug & alcohol demand reduction response center in United Arab Emirates. It is now a World Health Organization collaborative center and has partnered with McLean Hospital in Boston, USA, is a certified Matrix Model training center and a Colombo plan-training site. As part of its mandates, it keeps a rigorous data set since its launch in 2002 to provide the decision makers with vital statistics about the trends of substance use and the changes and patterns of misuse. This includes patients' demographics, surveillance tools results and a thorough lab test results record. Recently this record was analyzed for the results of all substances used by the cohort of patients who attended the NRC services between 2013 and 2017. This exercise is being submitted for publication together with other authors and we will share a summary of these results here (Table 1).

Table 1: NRC data set (5-year positive lab test results) 2013-2018

	2013	2014	2015	2016	2017	2018
Opioids including Tramadol	1148	839	1209	1722	1180	1145
Antihistamines & Methorphan	190	459	857	1326	406	532
BDZ	293	238	361	553	691	999
Cannabinoids	113	236	374	380	359	562
Amphetamines & Methamphetamine	68	91	154	460	1330	2379
Pregabalin	6	3	589	644	644	731
Gabapentin	18	3	17	111	24	19

The years 2015 to 2017 show a considerable rise of positive results for Gabapentoids, mainly Pregabalin and even worse an exponential rise of Amphetamine and Methamphetamine positive test results. Pregabalin became the second most abused drug after opioids in 2015 climbing 4 places from 6th, then third spot in 2016 and finally 4th in 2017. Gabapentin use seems to have peaked in 2016 only to subside in the following year. It is noteworthy that crystal methamphetamine and amphetamines overtook opioids for the first time since records began at the NRC in 2002 becoming the drug of choice for the patients seeing treatment in 2017, a serious issue for the services. These results represent only a snap shot but we do not make the claim that they are representative of the drug scene neither prevalence of the drugs in the community. They only represent the results gathered from the cohort of patients who sought treatment and were picked up by the laboratory at the NRC.

The Gabapentoids Conundrum

Pregabalin and Gabapentin appeared as part of the Novel or New Psychoactive substances (NPS) culture due to their potential for abuse resulting from their high dosage/idiosyncratic methods of self-administration [3]. Concern about their diversion and abuse have been raised in many parts of the world since 2014. In the **United Kingdom** evidence of a black market trade, abuse by prisoners and violence towards staff, calls from (BMA) and other institutions lead to a consultation process by the (NHS). This culminated in the UK government's decision to reclassify both drugs as Class C controlled substances from April 2019 under the 1971 Misuse of Drugs Act [4-6]. In the ***United States*** Pregabalin is classified as a Schedule-V controlled substance (a substance that presents a low risk for abuse) (controlled substances Act CSA 1970), however, gabapentin (one of the top 10 most commonly prescribed medications in the United States by September 2017) is still not a scheduled substance [7]. There have been calls for international harmonization and scheduling of gabapentin as a controlled substance [8]. Bothdrugs have now become part of the drugs of abuse market, with around one of five opioid abusers also using gabapentin in USA [9]. ***In Australia*** health officials are also concerned about Pregabalin, estimate that one in seven Australians prescribed the drug are at risk of misusing it, with research revealing an increase in poisonings, and there have been 88-recorded deaths associated with Pregabalin in recent years [10]. In addition, up to two-thirds of people who intentionally misused Pregabalin had a prior documented substance abuse history [10]. ***In Canada*** a warning about use opioids and Pregabalin after a number of overdose deaths that involved, but not necessarily caused by Pregabalin. Researchers found that patients who were co-prescribed opioids and Pregabalin had a significantly higher risk of an overdose probably due to the cumulative effect. The risk of death was over two times higher for patients receiving opioids and a high dose of Pregabalin (over 300mg) compared to those who took opioids alone. Researchers found that Pregabalin has a sedative effect and may interact with opioids in ways that increase respiratory depression [11]. Gabapentinoids are thought to possess GABA-mimetic properties whilst possibly presenting with direct/indirect effects on the dopaminergic 'reward' system. Overall, Pregabalin is characterized by higher potency, quicker absorption rates and greater bioavailability levels than gabapentin [3].

Chiappini & Schifano conducted an analysis of the European Medicines Agency's (Eudra Vigilance) suspected Adverse Drug Reactions' Database in 2016. Their main findings were 6.6% adverse drug reaction reports of misuse/abuse/dependence, associated with Pregabalin and 4.8% associated with gabapentin, with an overall reporting frequency increasing over time. For both drugs, patients typically involved were female adults. A total of 27 and 86 fatalities were reported to be associated with Pregabalin and gabapentin respectively, and mostly in combination with opioids.

We can broadly group the reasons for the current concerns with Gabapentoids into the following categories:

a. Aggressive marketing and promotion. The manufacturers of these two agents were involved in an advertising and branding scheme, that was deemed misleading, and with intent to defraud. They were found guilty and fined US$ 2.3 Billion by the US government.
b. The opioid epidemic. Clinicians may be indirectly contributing to the rise in Gabapentoids prescriptions in their efforts to look for safer alternatives to opioid analgesics and conscious of the rise in the morbidity and mortality due to the opioid epidemic [12]. This practice is also promoted by some respectable guidelines like the American College of Physicians (who promote gabapentin as a non-opioid option and the Centers for Disease Control and Prevention recommendations for chronic pain management [13,14]. Some authorities challenge the guidance claiming that Gabapentoids are ineffective and overpriced with significant side effects and abuse potential. for example gabapentin fails to show benefit in neuropathy associated with chemotherapy or chronic low back pain [15,16].
c. Lack of awareness of the abuse potential.
d. The euphoriant and anxiolytic effects. Those individuals who tend to misuse Pregabalin are also likely to be misusing opioids such as heroin or morphine as the drug enhances the effects of other substances. Both gabapentin and Pregabalin are anxiolytic in therapeutic doses, stimulating in lower and sedating along with increasing doses.
e. Perceptions that Gabapentoids provide a good substitute for some common illicit drugs.

Laboratory Analysis of Gabapentinoids

Pregabalin and gabapentin are rarely included in routine toxicology testing regimes. This is largely due to the chemical nature of the drugs and need for specialist testing. Whilst generic non-selective extraction techniques can be used (e.g. direct urinary analysis following dilution or protein precipitation of blood), it is necessary to use gas chromatography with mass-spectrometry (GC-MS) or liquid chromatography with mass-spectrometry (LC-MS) for detection and quantification where required. However, in recent years, due to the increased prevalence of these drugs, some commercial immunoassay screening products are available that allow rapid and high throughput presumptive testing in urine, including point-of-care testing [17]. As monitoring of drug compliance as well as investigating potential misuse can be beneficial for patient care and safety, analytical testing for gabapentinoids in patients prescribed the drugs and in drug abuse populations, should be considered. An approach of initial drug screening for Pregabalin and gabapentin followed by GC-MS or LC-MS confirmation (Figures1, 2, 3 & 4) has been successfully applied at the National Rehabilitation Center (NRC) in Abu Dhabi in recent years for such a purpose [18,19].

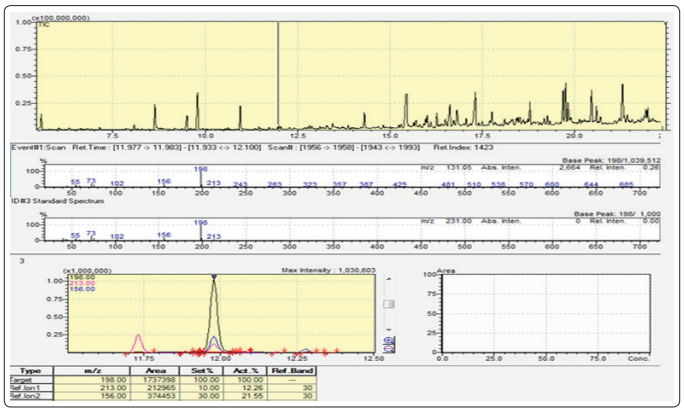

Figure 1: The chromatogram represents the spectra of positive result for Pregabalin by GC/MS at the National Rehabilitation Center, Abu Dhabi, UAE, 2017

Figure 2: The chromatogram represents the spectra of positive result for Gabapentin by GC/MS at the National Rehabilitation Center, Abu Dhabi, UAE, 2017

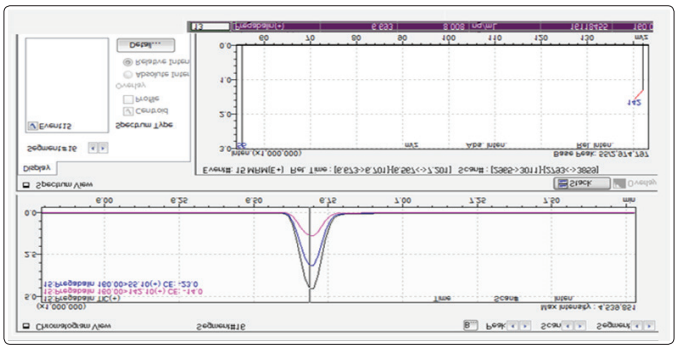

Figure 3: The chromatogram represents the MRM of positive result for Pregabalin by LC-MS/MS at the National Rehabilitation Center, Abu Dhabi, UAE, 2018

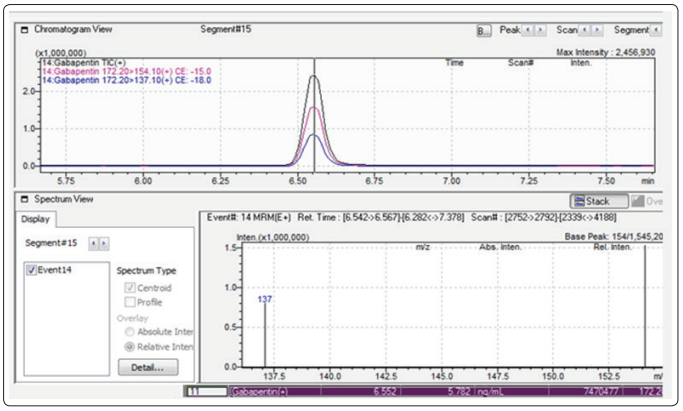

Figure 4: The chromatogram represents the MRM of positive result for Gabapentin by LC-MS/MS at the National Rehabilitation Center, Abu Dhabi, UAE, 2018

Conclusion

The dilemma faced by clinicians with regard to Gabapentoids is all too familiar, new products are approved for an indication, they are found to be useful for other disorders, off label prescriptions are promoted, they get included in guidelines before concerns are raised and then they are back to the initial licensed indications only. The UK government's decision to reclassify both drugs as Class C controlled substances from April 2019 under the 1971 Misuse of Drugs Act, mentioned above lends a hand to the camp that supported caution and raised concerns about the Gabapentoids abuse potential.

There is no doubt that these medicines are very useful and safe when indicated and when judiciously used. Clinicians need to be aware of the abuse potential especially in patients with a history of substance use disorders. It is prudent to monitor patients started on these medicines closely and intervene promptly if signs of abuse are flagged.

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