dtbn
DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN
YEAR 2021
VOL 29, Issue 2
www.dtb.navarra.es
@DTB_Navarre.es

RISKS AND UNCERTAINTIES ABOUT GABAPENTINOIDS

INTRODUCTION The use of gabapentinoids has increased in the recent years. Approved indications include epilepsy, peripheral neuropathic pain, diabetic neuropathy, postherpetic neuralgia and anxiety disorder. However, these drugs are widely prescribed off-label for indications such as low back pain, fibromyalgia, migraine or restless legs syndrome. Side effects associated with these drugs are common, highlighting the risk of respiratory depression when combined with other drugs that depress the central nervous system, suicidal ideation, abuse and addiction. OBJETIVE To review the evidence available on the uses of gabapentinoids (epilepsy excluded) and its associated risks. METHODS A search in Tripdatabase and Dynamed was conducted for clinical practice guidelines. In addition, a PubMed search was performed including systematic reviews, clinical trials and observational studies in order to analyze the evidence available on these drugs for their different indications. Data about the use of gabapentinoids in Navarre were obtained from the electronic prescription database of the public health system of Navarre -Osasunbidea (SNS-O). CONCLUSIONS Off-label use of gabapentinoids is not recommended due to the lack of consistent evidence available and its potential risks (sedation, dizziness or respiratory depression). Some recommendations are provided for a safe prescription of gabapentinoids.

NATALIA ALZUETA[1] | PATRICIA GARCÍA[1] | IRATI IRIGOYEN[2]
(1) Medicines Advice and Information Service
(2) Pharmacy Service of Complejo Hospitalario de Navarra
Navarre Health Service

Bol Inf Farmacoter Navar. 2021;29(2):1-14
https://doi.org/10.54095/BITN20212902EN

index

Introduction

Approved indications of gabapentin and pregabalin, the gabapentinoids marketed in Spain, include epilepsy, peripheral neuropathic pain in adults, diabetic neuropathy and post-herpetic neuralgia.[1,2] Pregabalin has also been approved for generalized anxiety disorder in adults.[2] The prodrug of gabapentin, gabapentin enacarbil, is approved in USA and Japan. The role of these drugs as adjuvant treatment for epilepsy will not be discussed in this bulletin.

These drugs are widely prescribed also for off-label indications such as low back pain, fibromyalgia, migraine, or restless legs syndrome, among others. Off-label use has been extensively promoted by the pharmaceutical industry and is included in strategies for preventing the use of opioids for chronic pain or reducing the use of benzodiazepines.[3]

Pfizer was found guilty in two lawsuits (in 2004 and 2014) because Parke-Davis (parent company of Warner-Lambert, which they acquired in 2000) massively promoted the use of gabapentin for the treatment of pain in the '90s, when such indication had not yet been approved, and other off-label uses such as mental diseases or migraine.[4,5] The same occurred in relation to pregabalin in 2009.[6]

Although numerous warnings have been notified in the last years and awareness about the risk of abuse associated with gabapentinoids is growing, the consumption of these drugs surprisingly continues increasing.

The purpose of this bulletin is to review the evidence available on the different uses of gabapentinoids (epilepsy excluded) and its associated risks. We searched for clinical practice guidelines in Tripdatabase and Dynamed databases and for systematic reviews, clinical trials and observational studies in Pubmed database, in order to analyze the evidence available on these drugs for their different indications.

The consumption of gabapentinoids has increased in the last years

Gabapentinoids for neuropathic pain

The NICE guidelines for the treatment of neuropathic pain (2020) recommend the use of amitriptyline, gabapentin or duloxetine, as first line.[7]

However, pharmacological treatments for neuropathic pain are not effective enough, since only a low proportion of patients experience a meaningful relief of pain (defined as a ≥ 50% reduction of pain intensity). Considering the placebo effect (11-30%), pain only improved in 9-25% of patients with a pharmacological alternative, with a rate of failure of 52-70%.[8]

A Cochrane's review on the use of pregabalin for neuropathic pain revealed that this drug increased significantly the number of patients who achieved a good pain control that was considered clinically relevant, versus placebo, as shown in table 1 and figure 1.[9] In addition, gabapentin also reduced pain in patients with postherpetic pain and diabetic neuropathy, as shown in table 2 and figure 2.[10]

Neuropathic pain (postherpetic or diabetic neuropathy) decreased by 50% in four out of ten patients who were in treatment with pregabalin (600 mg/day) and three out of ten patients who took gabapentin (≥ 1800 mg/day) for eight weeks or more.[11]

Table 1. Comparison between the efficacy of pregabalin vs. placebo using different doses in postherpetic neuralgia and diabetic neuropathy.

Indication	Variable	Pregabalin 300 mg/day	Placebo	RR (95%CI) NNT (95%CI)	Pregabalin 600 mg/day	Placebo	RR (95%CI) NNT (95%CI)
Postherpetic neuralgia	≥30% reduction in pain intensity	50%	25%	2.1 (1.6-2.6) 4 (3-6)	62%	24%	2.5 (2.0-3.2) 3 (2-4)
	≥50% reduction in pain intensity	32%	13%	2.5 (1.9-3.4) 6 (4-8)	41%	15%	2.7 (2.0-3.5) 4 (3-6)
Diabetic peripheral neuropathy	≥30% reduction in pain intensity	47%	42%	1.1 (1.01-1.2) 22 (12-200)	63%	52%	1.2 (1.04-1.4) 10 (6-41)
	≥50% reduction in pain intensity	31%	24%	1.3 (1.2-1.5) 22 (12-200)	41%	28%	1.4 (1.2-1.7) 8 (5-14)

Figure 1. Fifty percent reduction in pain intensity with pregabalin in postherpetic neuralgia and diabetic neuropathy.

A
Pregabalin 600mg/day and placebo in postherpetic neuralgia

B
Pregabalin 600mg/day and placebo in diabetic peripheral neuropathy

Improvement with placebo

Additional improvement with pregabalin

No improvement

Table 2. Comparison between the efficacy of gabapentin (gabapentin ≥1800 mg/day or gabapentin enacarbil 1200 mg/day) vs. placebo in post-herpetic neuralgia and diabetic neuropathy.

Indication	Variable	Gabapentin	Placebo	RR (95%CI) NNT (95%CI)
Neuralgia post-herpetic	≥50% reduction in pain intensity	33%	19%	1.7 (1.4-2.0) 7 (6-9)
	Improvement perceived as remarkable or very remarkable by the patient	39%	29%	1.3 (1.2-1.5) 10 (7-16)
Diabetic peripheral neuropathy	≥50% reduction in pain intensity	38%	23%	1.7 (1.4-2.0) 7 (5-10)
	≥30% reduction or important pain improvement on the PGIC scale	52%	37%	1.4 (1.3-1.6) 7 (5-10)

PGIC: Patient Global Impression of Change.

Figure 2. Fifty percent reduction in pain intensity with gabapentin in post-herpetic neuralgia and diabetic neuropathy.

A
Gabapentin ≥1800 mg/day or gabapentin encarbil 1200 mg/day and placebo in postherpetic neuralgia.

B
Gabapentin ≥1800 mg/day or gabapentin encarbil 1200 mg/day and placebo in diabetic peripheral neuropathy

Improvement with placebo
Additional improvement with gabapentin
No improvement

Pregabalin for generalized anxiety disorder

It is estimated that in one out of four patients diagnosed of generalized anxiety, selective serotonin reuptake inhibitor (SSRIs) or selective serotonin and noradrenaline reuptake inhibitors (SNRIs) are not effective as first-line treatment.[12]

Pregabalin is approved for generalized anxiety disorder, but it is not considered as a first-line treatment.[13]

In the controlled clinical trials that led to the approval of this indication, 52% of patients treated with pregabalin and 38% who received placebo, improved the overall score on the Hammilton scale for anxiety (HAM-A) by at least 50% compared to the data from the baseline visit to the end of study at 4-6 weeks.[14]

In a systematic review conducted later, pregabalin was better than placebo in reducing symptoms according to the HAM-A scale (standard mean difference: 0.37; 95%CI: 0.30 to 0.44). However, no differences were observed when compared to benzodiazepines.[15]

In another systematic review comparing the effectiveness and acceptability (therapy withdrawn for any cause) of different therapeutic options did not reveal any statistically significant differences between pregabalin and other options in terms of efficacy and showed a better acceptability as compared to quetiapine or tiagabine, albeit similar to that of sertraline.[12]

Therefore, pregabalin is effective for the short-term treatment of symptoms of generalized anxiety disorder, although with a moderate effect size comparable to that of other first-line therapies. There is no data available about its efficacy in case of failure or intolerance to other treatments.

Gabapentinoids for off-label indications

Fibromyalgia

Symptoms of fibromyalgia include generalized chronic pain, sleep disorders, fatigue and depression. Patients with fibromyalgia frequently develop a high level of disability, with a poor quality of life and high drug consumption.[16,17]

Currently, there is no treatment approved for this indication in Spain. Pain management in these patients is a challenge. Therapies include SNRIs, amitriptyline, gabapentinoids or combinations of these drugs.[16]

The use of pregabalin for fibromyalgia is approved in USA.[18] However, in 2009 the EMA denied the indication of pregabalin for fibromyalgia for different reasons: it had not been proven to be effective because it did not provide any clinical benefit in reducing pain intensity or improving functionality, its efficacy was not maintained over time and, therefore, the benefit/risk balance was not favorable.[19]

A Cochrane's review concluded that pregabalin increased significantly the number of patients who experienced at least a 50% reduction in pain intensity as compared to placebo (RR:1.8; 95%CI: 1.4 to 2.1) and at least a 30% reduction in pain intensity (RR 1.5; 95%CI: 1.37 to 1.7), as shown in table 3 and figure 3.[20]

The last Cochrane's review on the use of gabapentin in fibromyalgia only included a 12-week study of very poor quality in 150 patients. The following results were obtained: 49% of patients on gabapentin achieved at least a 30% improvement in pain intensity as compared to baseline pain (31% of patients in the placebo group). Its effectiveness in reducing pain intensity by at least 50% could not be analyzed because the outcome was not reported at the end of the study. Twelve participants of the gabapentin group (16%) and seven of the placebo (9%) dropped out of the study due to adverse events.[21]

Migraine prophylaxis

In 2013, a Cochrane's review including five randomized clinical trials on gabapentin and gabapentin enacarbil concluded that none was effective in preventing episodic migraine in adults.[22] In addition, due to the adverse events associated with gabapentin (dizziness and somnolence) its use in routine practice is not recommended.

Recent studies have excluded the usefulness of gabapentin as a preventive treatment for episodic migraine. Hence, its use should be avoided.[23]

No studies have been published with pregabalin for the prevention of migraine.

Table 3. Comparison between the efficacy of pregabalin vs placebo in fibromyalgia.

Indication	Variable	Pregabalin	Placebo	RR (IC95%) NNT (IC95%)
Fibromyalgia	≥50% reduction in pain intensity	24%	14%	1.8 (1.4-2.1) 10 (7-15)
	≥30% reduction in pain intensity	43%	29%	1.5 (1.4-1.7) 7 (5-10)

Figure 3. Fifty percent reduction in pain intensity with pregabalin in fibromyalgia.

Low back pain

The use of gabapentinoids for low back pain has increased in the recent years. A meta-analysis of eight clinical trials including 687 patients assessed the use of gabapentinoids for the treatment of chronic low back pain.[24] Studies were divided into three groups:

- Three studies of gabapentin vs placebo
- Two studies of pregabalin vs an active comparator
- Three studies of pregabalin as co-adjuvant

The studies included had a low methodological quality. No studies of pregabalin compared to placebo were found.

Pain was assessed using the NRS scale (Numeric Pain Rating scale). It is a numeric 11-point scale (0-11), where a ≥ 2-point reduction is considered clinically relevant. In the case of gabapentin, pain did not improve as compared to placebo and caused a high rate of side effects such as dizziness (RR: 1.99; 95%CI: 1.17 to 3.37), fatigue (RR: 1.85; 95%CI: 1.12 to 3.05) or blurred vision (RR: 5.72; 95%CI: 1.94 to 16.91).

When compared pregabalin with other analgesics (amitriptyline, celecoxib, or tramadol/paracetamol), these showed greater improvement in pain control (SD: 0.42 units; 95%CI: 0.20 to 0.64).

The last group of studies compared pregabalin as adjuvant therapy in combination with buprenorphine, tapentadol, or celecoxib vs analgesic alone. It is a very heterogeneous group of studies (I_2=77%) with a small sample of patients so, it was not possible to draw conclusions.

In patients with chronic radiculopathy, pregabalin and gabapentin were not effective either in reducing pain or disability.[25]

Restless legs syndrome

Currently, the treatments authorized in Spain for restless legs syndrome (RLS) are dopaminergic agonists (pramipexole, ropinirole and rotigotine). In our country, no gabapentinoid has been approved for this indication. However, in USA, gabapentin enacarbil is approved for RLS.

In 2017, a network meta-analysis was published assessing the use of dopaminergic agonists (pramipexole, ropinirole and rotigotine) in patients with primary moderate-severe RLS.[26] To analyze variation on the International RLS (IRLS) Study Group Scale, 35 studies were included, with a total sample of 7,333 patients. Based on IRLS score, severity of symptoms is classified as mild (0-15 points), moderate (16-25 points) or severe (26-40 points). A difference greater than three points in IRLS score was considered clinically significant.[27] All treatments were superior to placebo, with a difference on the IRLS score for pregabalin of -5.20 (95%CI: -6.91 to -3.49), with very similar data for gabapentin enacarbil and rotigotin. There were no statistically significant differences when active treatments where compared among them.

To analyze the variable of Clinical Global Impression of Improvement scale (CGI-I), 24 studies were included, with a total of 5,137 patients. All treatments were higher than placebo, with better results for gabapentin enacarbil and rotigotin, (OR: 5.68; 95%CI: 4.14 to 7.21) and (OR: 4.68; 95%CI: 2.87 to 6.49), respectively. Gabapentin enacarbil was associated with a significant improvement in the variable CGI-I, as compared to ropinirole (OR: 3.21; 95%CI: 1.21 to 5.34) but without significant differences between other active treatments.[26]

The most common adverse events reported in studies on gabapentin enacarbil and pregabalin included dizziness and somnolence, whereas migraine and nausea were more frequent in studies on dopaminergic agonists.[26]

Gabapentinoids in the treatment of RLS emerge as a potential alternative to dopaminergic agonists when they fail or are poorly tolerated, especially in patients with other frequent comorbidities of RLS such as pain, anxiety or insomnia, considering the expected side effects associated with these drugs.[28]

Essential tremor

Essential tremor is one of the most prevalent movement disorders. Beta-blockers are the treatment of choice. However, it has been suggested that gabapentin and pregabalin could be an alternative, although their efficacy and safety are doubtful.

The studies available assessing the use of gabapentin or pregabalin in the treatment of essential tremor include a small sample of patients and, with such a low quality of evidence. Hence, conclusions cannot be drawn from these studies.[29]

There is no evidence supporting the use of gabapentinoids for essential tremor.

Off-label use of gabapentinoids is not recommended

Prevention of postoperative pain

Gabapentinoids are included in the WHO analgesic ladder as adjuvant therapy in the treatment of pain.

Their use has been proposed for postoperative analgesia with the purpose of reducing the dose of opioids. However, when administered together, their side effects on the central nervous system and respiratory depression can be potentiated.[30]

In a systematic review of 281 clinical trials including 24,682 surgical patients, gabapentin or pregabalin were not associated with clinically relevant differences in postoperative pain as compared to placebo.[31] The use of gabapentinoids was associated with a lower risk of postoperative nausea and vomiting, but with a higher risk of dizziness and visual disturbances.

Therefore, there is no evidence available at this moment supporting the use of gabapentinoids for prevention of postoperative pain.

Treatment of hot flushes in menopause

Vasomotor symptoms are common in menopausal women. Several studies have been conducted to assess the effects of gabapentin and pregabalin as a non-hormone treatment in postmenopausal women.

In a systematic review including 21 randomized clinical trials, 19 with gabapentin and two with pregabalin, analyzing outcomes in 3,519 postmenopausal women, several meta-analyses were performed to assess the different interventions. The studies revealed that gabapentin treatment administered for 4-12 weeks reduced the frequency of hot flashes vs placebo or vitamin E [(SD: -1.62; 95%CI: -1.98 to -1.26) at 4 weeks; (SD: -2.77; 95%CI: -4.29 to -1.24) at 12 weeks]. There were no differences in the reduction of hot flash duration. The quality of the clinical trials included was classified as low to moderate. Estrogen was more effective than gabapentin in reducing the frequency of hot flashes (SD: 1.11; 95%CI: 0.69 to 1.52, at 4 weeks) but the number of studies was low and they were classified as poor quality studies. Gabapentin could not be compared to antidepressants. Conclusions could not be drawn due to the low number of studies included and their heterogeneity.[32]

The most common adverse events associated with gabapentin included dizziness, somnolence, and migraine, significant with respect to placebo, which resulted in a higher rate of drop-outs in the group of gabapentin.[32]

There is paucity of evidence supporting the use of gabapentinoids in the treatment of hot flushes in menopause.

As explained above, the off-label use of gabapentinoids is not recommended (table 4) due to the lack of solid evidence and its potential risks (sedation, dizziness or respiratory depression).

Table 4. Summary of the evidence available on off-label indications in Spain.

Off-label use	Evidence	Comments
Fibromyalgia	✗	Pregabalin: FDA-approved. EMA unfavorable benefit/risk balance
Migraine prophylaxis	✗	
Low back pain	✗	
Restless legs syndrome	✓	Gabapentin enacarbil: FDA-approved after failure of dopaminergic agonists
Essential tremor	✗	
Prevention of postoperative pain	✗	
Hot flushes in menopause	✗	

Gabapentinoids' risks

The most common side effects of pregabalin include somnolence, dizziness, ataxia, weight gain, peripheral edema, blurred vision, diplopia and headache.[1] Gabapentin increases somnolence, dizziness, confusion, ataxia, lethargy and edema.[2]

These adverse events are more common at high doses. However, pain relief does not improve with high doses. Additionally, fragile patients with renal failure or in treatment with other central nervous system depressants, or alcohol-users, are prone to experience a higher number and more severe adverse events.[33]

During post-marketing experience, cases of edema and congestive heart failure were reported in some patients taking pregabalin. These reactions are mostly observed in elderly patients (older than 65 years) with cardiovascular disease, and subside after treatment withdrawal.[1,10]

Hyponatremia is another adverse event associated with the use of gabapentinoids.[34,35,36] According to data available on EudraVigilance,[37] 151 cases of hyponatremia associated with pregabalin and 146 cases associated with gabapentin have been reported. When administered concomitantly to other drugs causing hyponatremia (such as serotonin reuptake inhibitors, diuretics, etc...), this side effect can be exacerbated. It is important to take this into account when used in elderly patients with polypharmacy.

These drugs have also been associated with depression, behavior disorders and suicidal ideation. In a Swedish cohort of 191,973 patients treated with gabapentinoids, 5.2% of patients received treatment for suicidal behaviors or committed suicide. Gabapentinoids were associated with a higher risk of suicide (HR: 1.26; 95%CI: 1.2 to 1.32), unintended overdose (HR: 1.24; 95%CI: 1.19 to 1.28), self-harm (HR: 1.22; 95%CI: 1.2 to 1.32) and car accidents (HR: 1.12; 95%CI: 1.062 to 1.20).[38]

According to clinically relevant interactions, it is worth mentioning that concomitant administration with central nervous system depressants may cause severe adverse events such as respiratory depression.[1,2] The relevance of this severe adverse event led the FDA to issue the warning detailed below.

Risk of respiratory depression when combined with other depressants of the Central Nervous System

In December 2019, the FDA issued a warning that a high rate of patients would be at a higher risk of developing respiratory depression during treatment with gabapentin or pregabalin.[39] The patients at a higher risk included those with Chronic Obstructive Pulmonary Disease (COPD) or patients receiving concomitantly central nervous system depressants such as opioids, anxiolytics, antidepressants and antihistamines. Additional depressor effects may occur, causing somnolence, sedation or respiratory depression. Therefore, this combination should be avoided.

The risk of respiratory depression increases when combined with other depressants of the Central Nervous System

Gabapentinoids are routinely used as coadjuvants for pain control. A cohort study was recently conducted in USA assessing side effects of the postoperative use of gabapentinoids in combination with opioids (n=892,484 patients). A higher number of patients receiving the combination developed symptoms of overdose as compared with the group that received opioids alone (HR: 1.95; 95%CI: 1.49 to 2.55), and a higher rate of patients who received the combination experienced respiratory complications (HR: 1.68; 95%CI: 1.59 to 1.78). Nevertheless, as the incidence of these events was low, the NNH were very high.[30]

A case-control study was carried out in Ontario assessing opioid users and mortality due to the use of opioids. It associated the combination of opioids and gabapentin with an increased risk of mortality related to the use of opioids (OR: 1.49; 95%CI: 1.19 to 1.88) as compared to opioids alone, with higher effects at higher doses of gabapentin. In addition, a 44% increase was reported in systemic exposure to gabapentin when administered in combination with morphine, probably due to the reduced intestinal motility, which leads to a higher absorption of this drug.[40]

Risk of abuse and addiction

In the recent years, mortality associated with the abuse and addiction to gabapentinoids has increased. Thus, in some countries such as UK, France or USA, pregabalin and gabapentin are now considered psychotropic substances and have been included in the list of controlled substances.[41,42] For example, in France, the duration of pregabalin treatments is limited to a maximum of six months.[43]

In 2019, the updated NICE guidelines for the treatment of neuropathic pain included a warning on the risk of abuse and dependence associated with gabapentin and pregabalin.[7]

A systematic review on the abuse of gabapentinoids concluded that the abuse or inadequate use of gabapentinoids is more prevalent in patients engaged in opioid replacement programs or opioid-dependent, with inadequate use, having been detected in one out of three or four patients.[11] The review highlights that evidence is not solid enough to determine the level and severity of abuse and dependency on these drugs.

Several reasons could explain why gabapentinoids abuse is higher in opioid users. Apparently, they might be useful for opioid withdrawal. Gabapentin could be considered as part of pain control in chronic patients receiving opioids, since it could facilitate opioid withdrawal after surgery.[44] However, further studies are needed to confirm this hypothesis. In addition, they may be used as a strategy to reduce the prescription of benzodiazepines.[45,46]

There seems to be a higher risk of abuse associated with pregabalin than with gabapentin due to its rapid absorption and high bioavailability, causing an earlier feeling of well-being and euphoria.[46] The last analysis available on EUDRA Vigilance[37] database contains 4,301 and 7,639 reports of gabapentin and pregabalin addiction, respectively.

They are associated with risk of suicidal ideation, abuse and addiction.

Safe prescription of gabapentinoids

BEFORE PRESCRIBING

Concomitant medication (CNS depressants)

Kidney function

Comorbidities (heart failure)

Previous suicidal ideation

WHEN PRESCRIBING

Approved indications

Minimum effective dose

Shortest duration

DURING TREATMENT

Monitor risk/benefit during the first 2 weeks

Monitor adverse events (somnolence, sedation, respiratory depression, suicidal ideation)

New concomitant treatments (CNS depressants)

Deprescribing gabapentinoids

To develop a strategy for deprescribing gabapentinoids, we based on NHS recommendations.[47] Candidates for deprescription of these drugs are patients who:

- Do not comply with approved indications.
- Do not respond to treatment.
- Have intolerable adverse events.
- Have poor treatment adherence.
- Are on chronic treatments (>6 months).
- Are pregnant and breastfeeding women.

It is important to mention that the treatment must be regularly reviewed to assess aspects such as efficacy, tolerability, adverse effects and adherence. Revisions can be performed with the following periodicity:

- Monthly in patients with a history of abuse
- Quarterly if the patient is receiving concomitant opioid therapy.
- Quarterly or biannually in all patients.

Gradual dose tapering must be about 25% each week (table 5). If the patient experiences intolerable withdrawal symptoms (generally 1-3 days after a dose reduction), continue in the previous tolerable dose until symptoms subside. In this case, a slower dose reduction should be considered (i.e. 10% reductions of the daily dose). If complete withdrawal is not successful, continue on the last tolerated dose reached in the reduction regimen and consider withdrawal after 3-6 months.[47]

DEPRESCRIBING

Progressive withdrawal (to prevent withdrawal symptoms such as anxiety, confusion...)

Severe adverse events (respiratory depression) require immediate withdrawal

Treatment must be revised on a regular basis

Deprescribing must be progressive

Evolution of use and suitability of treatments in the Community of Navarre

In the Community of Navarre, the use of gabapentin and pregabalin increased by 17% and 18%, respectively between 2015 and 2020. In 2020, more than 1.6 million defined daily doses (DDD) of gabapentinoids were administered, with a cost of 1.4 million euros for the public health system of Navarre -Osasunbidea.

By early 2020, a total of 9,778 patients were receiving gabapentin and/or pregabalin. Half of these patients (56%) received gabapentinoids for off-label indications. In addition to the approved indications for gabapentin and pregabalin, type 1 and 2 diabetes mellitus and generalized chronic pain were considered to reduce potential bias in diagnosis record.

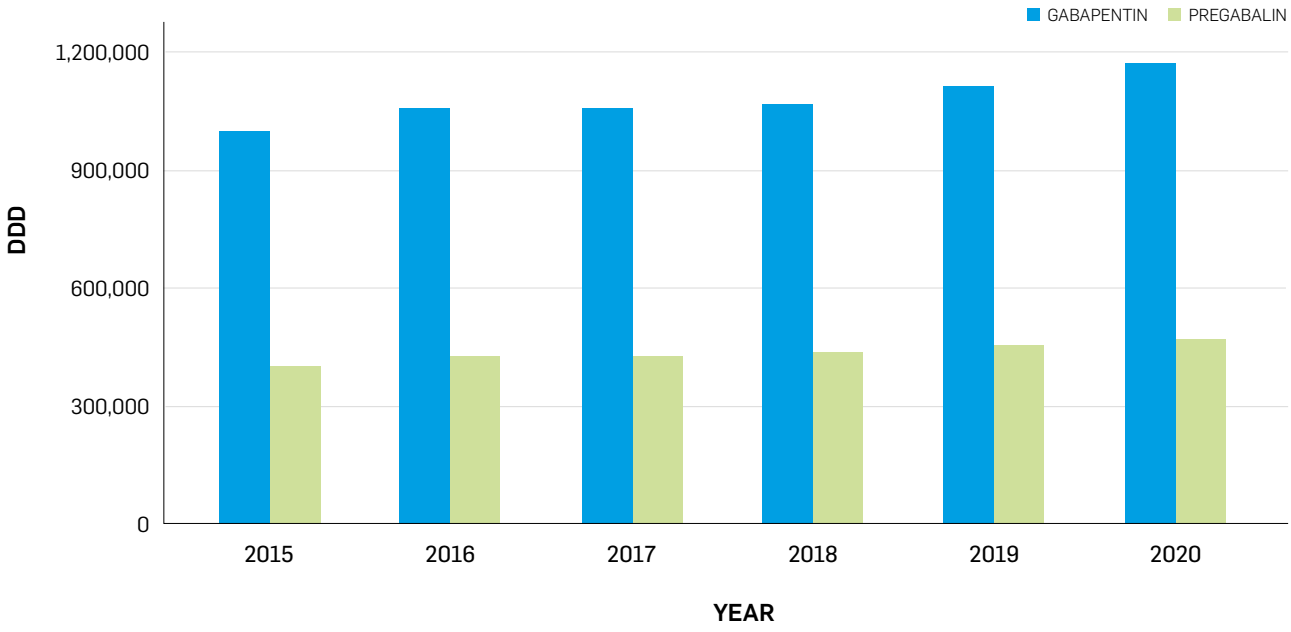
The most frequent diagnoses in patients with off-label use were analysed, and 54% had recorded signs or symptoms of low back pain, 7% migraine and 2% restless legs syndrome.

These data demonstrate that the increased use of gabapentinoids is largely due to off-label uses, despite the absence of solid evidence supporting their use for these indications, which compromises patient safety.

Table 5. Gabapentinoids withdrawal strategy (adapted from NHS).[47]

Medicinal product		Withdrawal strategy
Gabapentin	> 900 mg/day	Reduce 300 mg every 10 days (range 7-14 days) until withdrawal
	≤ 900 mg/day	Reduce 100 mg every 10 days (range 7-14 days) until withdrawal
Pregabalin		Reduce 50-100 mg every 10 days (range 7-14 days) until withdrawal

Figure 4. Evolution of use of gabapentinoids in the Autonomous Community of Navarre between 2015 and 2020 (DDD: defined daily doses).



Conclusions

Gabapentinoids are indicated for epilepsy and neuropathic pain. Pregabalin is also indicated for generalized anxiety disorder.

Gabapentinoids are not effective for fibromyalgia, migraine, low back pain, essential tremor, postoperative pain and postmenopausal hot flushes. Therefore, its use is not recommended for these indications.

Gabapentinoids are associated with a higher risk of suicidal ideation, abuse and addiction.

The combination of gabapentinoids with other central nervous system depressants such as opioids may cause respiratory depression.

Off-label use of gabapentin and pregabalin is very common despite the absence of solid evidence supporting its use that may compromise patient safety.

Treatment should be regularly revised to assess aspects such as efficacy, tolerability, adverse effects and adherence.

References

1. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica Lyrica® 150 mg cápsulas duras.
2. Agencia Española de Medicamentos y Productos Sanitarios. Ficha técnica Neurontin® 400 mg cápsulas duras.
3. Federico CA, Wang T, Doussau A, Mogil JS, Fergusson D, Kimmelman J. Assessment of Pregabalin Postapproval Trials and the Suggestion of Efficacy for New Indications: A Systematic Review. JAMA Intern Med. 2019;179:90-97.
4. Steinman MA, Bero LA, Chren M-M, Landefeld CS. Narrative Review: The Promotion of Gabapentin: An Analysis of Internal Industry Documents. Ann Intern Med. 2006 15;145:284-93.
5. Pfizer adds another $325M to Neurontin settlement tally. Total $945M.
6. U.S. Department of Justice. Justice Department Announces Largest Health Care Fraud Settlement in Its History: Pfizer to Pay $2.3 Billion for Fraudulent Marketing. Washington 2014.
7. Neuropathic pain in adults: pharmacological management in non-specialist settings. London: National Institute for Health and Care Excellence (UK); September 22, 2020.
8. Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. BMJ. 2013;346:7-9.
9. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database Syst Rev. 2019;23:1: CD007076.
10. Wiffen PJ, Derry S, Bell RF, Rice AS, Tölle TR, Phillips T, Moore RA. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6:CD007938.
11. Mathieson S, Lin CWC, Underwood M, Eldabe S. Pregabalin and gabapentin for pain. BMJ. 2020;369:1-9.
12. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. Lancet. 2019;393:768-777.
13. Generalised anxiety disorder and panic disorder in adults: management. London: National Institute for Health and Care Excellence (UK); Jul 2019.
14. European Medicines Agency: EPAR Lyrica®. Scientific Discussion. 2006.
15. Generoso MB, Trevizol AP, Kasper S, Cho HJ, Cordeiro Q, Shiozawa P. Pregabalin for generalized anxiety disorder: An updated systematic review and meta-analysis. Int Clin Psychopharmacol. 2017;32:49-55.
16. Clauw DJ. Fibromyalgia: A clinical review. JAMA. 2014;311:1547-1555.
17. Arnold LM, Clauw DJ. Challenges of implementing fibromyalgia treatment guidelines in current clinical practice. Postgrad Med. 2017;129:709-714.
18. Food and Drug Administration: Lyrica® product information.
19. European Medicines Agency: Refusal assesment report for Lyrica®. 2009.
20. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane database Syst Rev. 2016;9:CD011790.
21. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. Cochrane Database Syst Rev. 2017;3:1.
22. Linde M, Mulleners WM, Chronicle EP, Mccrory DC. Gabapentin or pregabalin for the prophylaxis of episodic migraine in adults. Cochrane Database Syst Rev. 2013;6. CD010609
23. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: an updated Cochrane review. Cephalalgia. 2015;35:51-62.
24. Shanthanna H, Gilron I, Rajarathinam M, et al. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2017;14:1-21.
25. Enke O, New HA, New CH, et al. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: A systematic review and meta-analysis. CMAJ. 2018;190:E786-E793.
26. Iftikhar IH, Alghothani L, Trotti LM. Gabapentin enacarbil, pregabalin and rotigotine are equally effective in restless legs syndrome: a comparative meta-analysis. Eur J Neurol. 2017;24:1446-1456.
27. Allen RP. Minimal clinically significant change for the International Restless Legs Syndrome Study Group rating scale in clinical trials is a score of 3. Sleep Med. 2013;14:1229.
28. Silber MH. Treatment of restless legs syndrome and periodic limb movement disorder in adults. UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accedido en mayo 2021.
29. Bruno E, Nicoletti A, Quattrocchi G, Filippini G, Colosimo C, Zappia M. Pregabalin for essential tremor. Cochrane Database Syst Rev. 2016;10: CD009682
30. Bykov K, Bateman BT, Franklin JM, Vine SM, Patorno E. Association of Gabapentinoids With the Risk of Opioid-Related Adverse Events in Surgical Patients in the United States. JAMA Netw open. 2020;3:e2031647.
31. Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: A systematic review and meta-analysis. Anesthesiology. 2020;133:265-279.
32. Shan D, Zou L, Liu X, Shen Y, Cai Y, Zhang J. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020;222(6):564-579.e12.
33. Gabapentin and pregabalin: Are high doses justified? Therapeutics Initiative. 2019;(January):1-4.

34. Falhammar H, Lindh JD, Calissendorff J, et al. Differences in associations of antiepileptic drugs and hospitalization due to hyponatremia: A population–based case–control study. Seizure. 2018;59:28-33.

35. Canadian Product Monograph: Lyrica® (pregabalin capsules). Accedido mayo 2021.

36. Canadian Product Monograph: Neurontin® (gabapentina capsules). Accedido mayo 2021.

37. European Medicines Agency; EudraVigilance.

38. Molero Y, Larsson H, D'Onofrio BM, Sharp DJ, Fazel S. Associations between gabapentinoids and suicidal behaviour, unintentional overdoses, injuries, road traffic incidents, and violent crime: Population based cohort study in Sweden. BMJ. 2019;365.

39. Food and Drug Administration: La FDA advierte acerca de problemas respiratorios graves con los medicamentos para convulsiones y dolor neural gabapentina (Neurontin, Gralise, Horizant) y pregabalina (Lyrica, Lyrica CR). 2019.

40. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case–control study. PLoS Med. 2017;14(10).

41. Driot D, Jouanjus E, Oustric S, Dupouy J, Lapeyre-Mestre M. Patterns of gabapentin and pregabalin use and misuse: Results of a population-based cohort study in France. Br J Clin Pharmacol. 2019;85:1260-1269.

42. Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. Eur Neuropsychopharmacol. 2017;27:1185-1215.

43. Prégabaline (Lyrica et génériques) : modification des conditions de prescription et délivrance pour limiter le mésusage. ANSM 2021.

44. Hah J, Mackey SC, Schmidt P, et al. Effect of perioperative gabapentin on postoperative pain resolution and opioid cessation in a mixed surgical cohort a randomized clinical trial. JAMA Surg. 2018;153:303-311.

45. Evoy KE, Morrison MD, Saklad SR. Abuse and Misuse of Pregabalin and Gabapentin. Drugs. 2017;77:403-426.

46. Hägg S, Jönsson AK, Ahlner J. Current Evidence on Abuse and Misuse of Gabapentinoids. Drug Saf. 2020;43:1235-1254.

47. Pregabalin and Gabapentin : Withdrawal Summary Guidance for NON-CANCER pain in adults in primary care. West Suffolk Clinical Commissioning Group NHS. 2021.

Alzueta N, García P, Irigoyen I. Risks and uncertainties about gabapentinoids. *Riesgos e incertidumbres de los gabapentinoides*. Bol Inf Farmacoter Navar. 2021;29(2):1-14. English. Spanish.

Servicio Navarro de Salud
Osasunbidea

ISSN
1138-1043

COPYRIGHT
NA-1263/1997

INFORMATION AND SUSCRIPTION
Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

Web site
www.bit.navarra.es