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Article

Therapeutic drug monitoring of gabapentin: the applicability in patients with neuropathic pain

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Gabapentin is an antiepileptic drug prescribed for several neuropathic pain conditions. This study aimed to evaluate gabapentin (GAB) trough plasma concentration range and the applicability of therapeutic drug monitoring in patients with neuropathic pain. Fifty-three patients with neuropathic pain, aged 20 to 75, received gabapentin as treatment for at least 7 days. Gabapentin plasma concentration was sampled before GAB administration and quantified by liquid chromatography with a UV detector. GAB trough plasma concentration ranged between 0.40 and 11.94 µg/mL in patients with chronic neuropathic pain. No differences were observed in terms of GAB plasma concentrations between responsive and non-responsive patients. Our data suggest that the reference ranges suggested in the literature for patients with epilepsy should not be used for patients with neuropathic pain. Therapeutic drug monitoring of GAB was shown to be an important tool to assess treatment adherence.

Keywords: Gabapentin. Therapeutic drug monitoring. Neuropathic pain.

INTRODUCTION

Gabapentin (GAB) is an antiepileptic drug, which has shown to be an important pharmacological treatment for several pain conditions such as diabetic neuropathic pain, postherpetic neuralgia and central pain (Eisenberg *et al.*, 2007). It is recommended as first-line treatment for neuropathic pain as well as tricyclic antidepressants, pregabalin, duloxetine, venlafaxine, carbamazepine and oxcarbazepine (Attal *et al.*, 2010). Furthermore, placebo-controlled clinical studies report the efficacy of GAB for the treatment of menopausal hot flashes (Guttuso *et al.*, 2003; Butt *et al.*, 2008) and restless legs syndrome (Garcia-Borreguero *et al.*, 2002; Lee *et al.*, 2011; Lal *et al.*, 2012). The indication of therapeutic drug monitoring (TDM) has been suggested for GAB in epilepsy (Neels *et al.*, 2004; Brandt, May, 2011; Krasowski, McMillin, 2014; Landmark *et al.*, 2015; Patsalos, Spencer, Berry, 2018; Reimers *et al.*, 2018). However, the benefits and therapeutic ranges for TDM of GAB in other indications have been poorly investigated so far (Burns *et al.*, 2019).

After oral administration, GAB is rapidly absorbed with maximum plasma concentrations observed around 2-3 hours. The nonlinear pharmacokinetics of GAB with variable bioavailability suggests a saturation of the active transporters during the absorption process (Stewart *et al.*, 1993; Patsalos, Spencer, Berry, 2018). GAB does not bind to plasma proteins, is not metabolized and is eliminated mainly unchanged by renal excretion. It shows large interindividual variability in pharmacokinetics mainly due to saturable absorption and variable renal function (Patsalos, Spencer, Berry, 2018). The most frequent adverse events reported in GAB-treated patients are dizziness and somnolence, occurring in >14% of patients (Backonja *et al.*, 1998; Rice, Maton, 2001; Serpell, 2002; Arnold *et al.*, 2007). GAB has been recently described

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as a drug subject to abuse, misuse and diversion (Smith, Havens, Walsh, 2016; Evoy, Morrison, Saklad, 2017).

Therefore, GAB fulfills some requirements for TDM such as large interindividual pharmacokinetic variability, compliance concerns (which hinders diagnosing therapeutic failure or correct use following a dosing regimen change) and clinically difficult to establish efficacy (Patsalos *et al.*, 2008; Backonja, Canafax, Cundy, 2011; Krasowski, McMillin, 2014). Whereas the GAB reference range for therapeutic monitoring was proposed based on clinical studies with patients treated for epilepsy, this study aimed to evaluate trough plasma concentrations at steady state in patients with neuropathic pain.

METHODS

Patients

The clinical study was designed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the School of Pharmaceutical Sciences – São Paulo State University (UNESP) – with the approval of the Ethics Committee of HCFMRP-USP (ClinicalTrials.gov identifier NCT02977208). The medical charts of 124 patients with GAB prescribed as treatment for neuropathic pain, attending the Neuropathic Pain Clinic of the General Hospital of the Ribeirão Preto Medical School (HCFMRP-USP) between September 2016 and February 2018, were analyzed. All invited patients were informed of the clinical protocol and signed a free informed consent form. In summary, patients were included after receiving the same daily dose of GAB for at least 1 week to ensure that they reached the steady state of GAB plasma concentrations. In terms of neuropathic pain treatment, all patients were classified as responsive or non-responsive by an experienced neurologist. The classification was based on the patient's declaration of pain relief improvement since the last visit. There were no restrictions on gender, weight, or race. Patients were excluded if they were pregnant or breastfeeding, using OCT2 and OCTN1 inhibitors, declared non-compliance to GAB therapy or if they declined to participate.

Blood samples were collected at steady state immediately before the dose of GAB (trough concentration) and plasma samples were stored frozen at -70 ºC until analysis. Medical charts were reviewed to obtain demographic (gender, age, weight, height) and clinical data (daily dose, dose regimen, creatinine serum concentration, comorbidities, concomitant medication).

Gabapentin plasma concentration analysis

Samples of 100 µL of plasma were spiked with 25 µL of internal standard solution (amlodipine, 200 µg/mL). For protein precipitation, 200 µL of acetonitrile were added. A total of 200 µL of organic phase were removed to a clean tube and 200 µL 0.25 M borate buffer (pH 8.2), 30 µL 0.06 M FDNB and 1 mL acetonitrile were added. The mixture was inverted and kept in a dryer block at 65 ºC for 10 min for derivatization reaction. The samples were kept at room temperature and a 25 µL 1 M HCl solution was added. After evaporated to dryness, the residues were reconstituted in 200 µL of mobile phase and 50 µL were injected into the chromatographic system.

The plasma concentration of gabapentin was analyzed by liquid chromatography with a UV detector using a reversed-phase LiChrospher® C18 RP column (125 × 4 mm, 5 µm; Merck, Darmstadt, Germany) with LiChroCART® 4-4 Purospher®RP-18 endcapped guard column (5 µm; Merck, Darmstadt, Germany). The mobile phase consisted of a mixture of 50 mM sodium phosphate buffer (pH 3.9):methanol (27:73, v/v), at a flow rate of 1.2 mL/min. Detection was performed at a wavelength of 360 nm. The method was validated following the European Medicines Agency "Guideline on Bioanalytical Method Validation" and presented linearity at the range of 0.2 to 14 µg/mL (European Medicines Agency, 2011).

Statistical analysis

Statistical analyses were performed using GraphPad Prism (version 6.0c for Macintosh, GraphPad Software, San Diego, CA, USA). The Mann-Whitney test was performed to compare the median values of GAB plasma concentration between responsive/non-responsive

patients. The statistical significance was set at 5% (*P*-value <0.05).

RESULTS

One hundred and twenty-four medical charts of patients with GAB prescription information were analyzed. However, 71 patients did not fit the inclusion criteria or could not be contacted (Figure 1). Therefore, the study was performed with 53 patients aged 20 to 75 years. The average GAB dose in the studied samples was 1553±804 mg daily and ranged from 600 to 3600 mg. Table I shows the clinical indication of GAB and the most common comorbidities in the investigated patients. Antidepressants (e.g., amitriptyline, sertraline, fluoxetine), analgesics (e.g., dipyrone, codeine, paracetamol) and antihypertensives (e.g., hydrochlorothiazide, losartan, enalapril) were the most frequent drugs prescribed concomitantly with GAB.

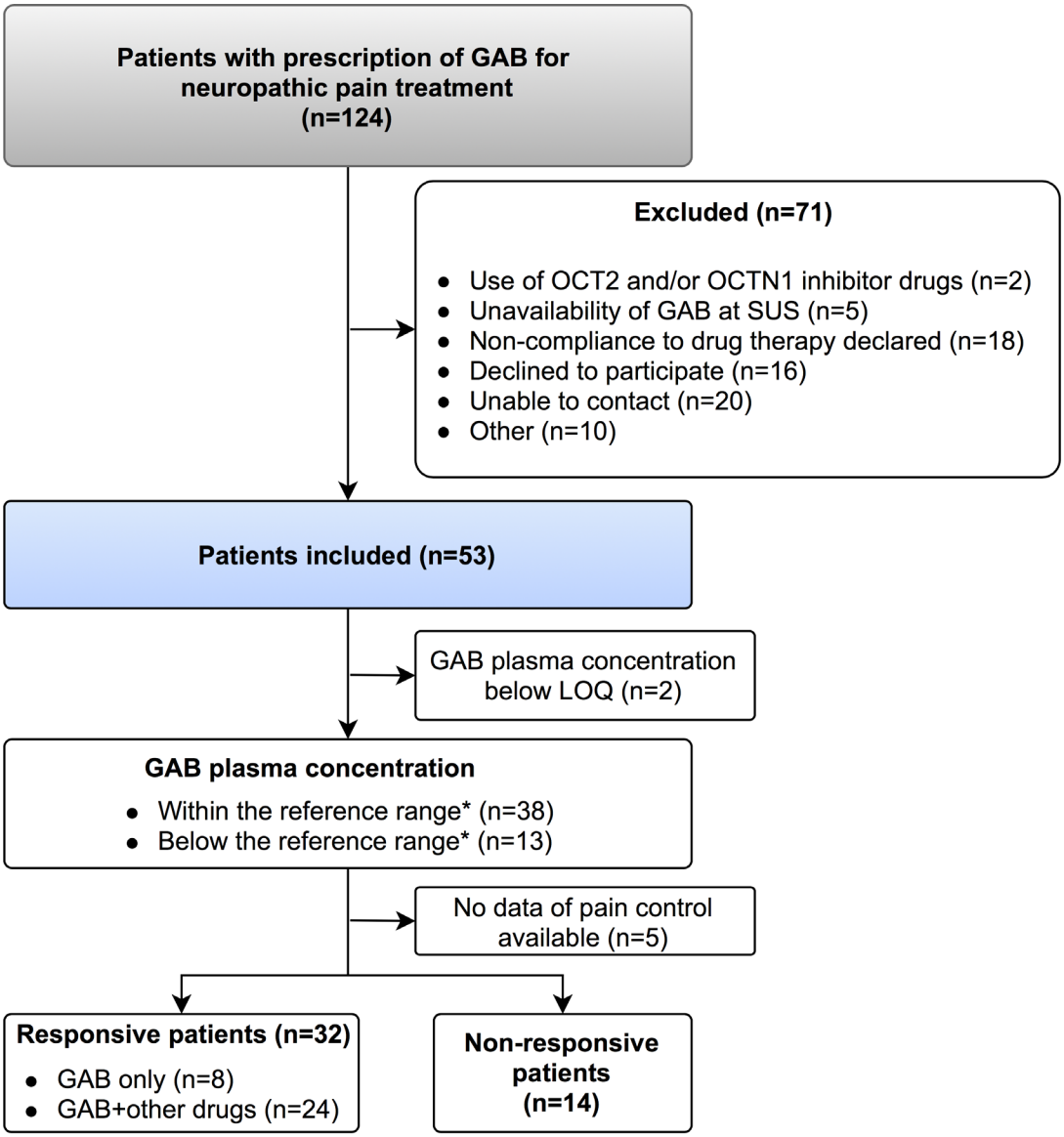

FIGURE 1 - Flowchart of enrollment and follow-up for therapeutic drug monitoring of gabapentin (GAB). Medical charts of patients with neuropathic pain were analyzed for recruitment (n=124, gray box). GAB plasma concentrations of included patients were determined (n=53, blue box). SUS: Brazil's Unified Health System; OCT2: organic cation transporter 2; OCTN1: novel organic cation transporter 1; LOQ: limit of quantification. *Reference range: 2-20 µg/mL of GAB.

Table I. Demographic and clinical characteristics (n=53)

Characteristics	
Gender (men/women)	25/28
Age (years)†	54±13 (20-75)
Daily dose (mg)†	1553±804 (600-3600)
Body weight (kg)†	78.3±14.3 (51.5-118.6)
BMI (kg/m²)†	28.47±5.59 (20.12-44.89)
Indication	**n (%)**
Lumbar/cervical disc herniation	19 (35.85)
Central pain	7 (13.21)
Traumatic/postsurgical nerve injury pain	5 (9.43)
Complex regional pain syndrome	4 (7.55)
Trigeminal neuralgia	3 (5.66)
Diabetic neuropathic pain	2 (3.77)
Others chronic pain	13 (24.53)
Comorbidities	**n (%)**
Hypertension	27 (50.9 %)
Dyslipidemia	20 (37.7 %)
Diabetes mellitus	9 (17.0 %)
Co-medication	**n (%)**
Antidepressants	34 (64.2 %)
Antihypertensives	29 (54.7 %)
Analgesics	24 (45.3 %)
Antiulcer	19 (35.8 %)
Antihyperlipidemic	19 (35.8 %)
Anticonvulsants	19 (35.8 %)

Data are expressed as mean ± standard deviation (range). BMI: body mass index.

All patients included in this study declared to use GAB every day as prescribed, but GAB was below the lower limit of quantification in the plasma samples of three patients. These patients were invited for a second sampling and new samples were collected. In the second sampling, GAB was detected in only one patient indicating that the two other patients were not using GAB correctly. GAB observed through plasma concentration ranged between 0.40 and 11.94 μg/mL in patients treated with 600 to 3600 mg/day. The plasma concentration/daily dose (Cp/D) ratio observed ranged between 0.00028 and 0.01410 μg/mL/mg. As GAB has non-linear pharmacokinetics due to saturable drug absorption, the steady-state plasma concentration observed did not increase proportionally with dose escalation (Figure 2).

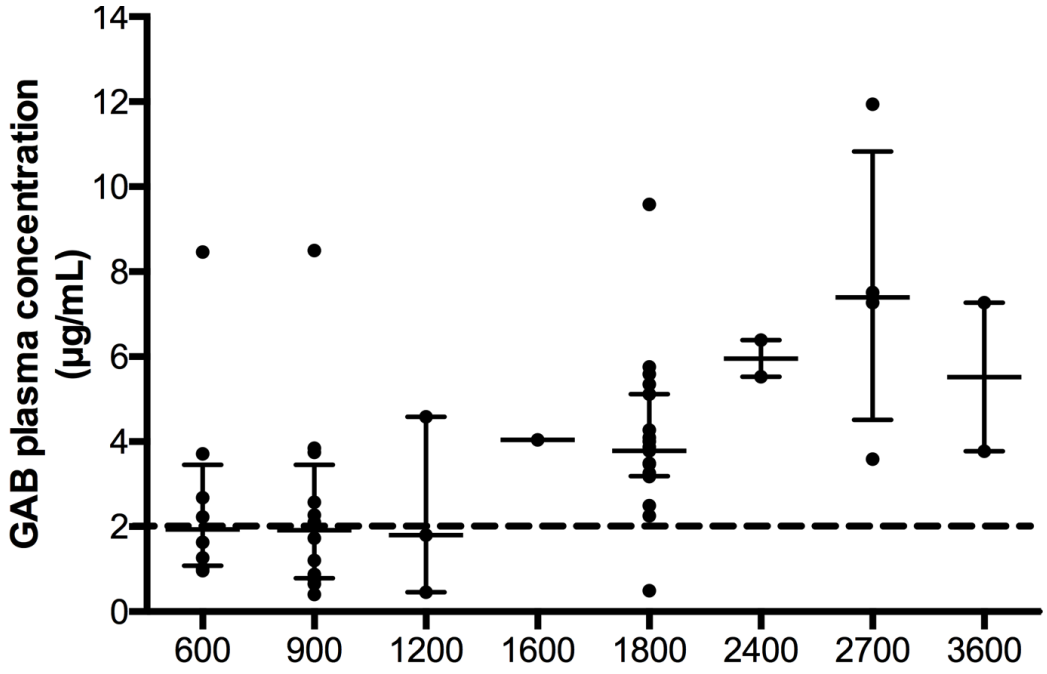

FIGURE 2 - Steady-state plasma concentration of gabapentin (GAB, n=51). The data show the median and interquartile range. The dashed line represents the lower limit of the reference range for gabapentin concentration (2 µg/mL).

In terms of neuropathic pain control, no difference in median GAB through plasma concentration was observed between responsive (3.48 µg/mL, n=32) and non-responsive (3.97 µg/mL, n=14) patients (*P*-value= 0.0503; Figure 3A). The median GAB plasma concentration did not differ between responsive patients who received GAB only (Responsive, 1.93 µg/mL, n=8) and those who received other drugs for pain relief (Responsive+, 3.62 µg/mL, n=24) (Figure 3B). There was also no difference between responsive and non-responsive patients when plasma concentration was normalized by dose with median Cp/D ratio of 0.00213 and 0.00272 µg/mL/mg, respectively (*P*-value= 0.1590) (Figure 3C). Within responsive patients, those treated with GAB only showed a median Cp/D ratio of 0.00243 µg/mL/mg. Meanwhile, those treated with GAB associated with other drugs presented median Cp/D ratio of 0.00206 µg/mL/mg (Figure 3D). Pain control data of five patients were not available in their medical charts.

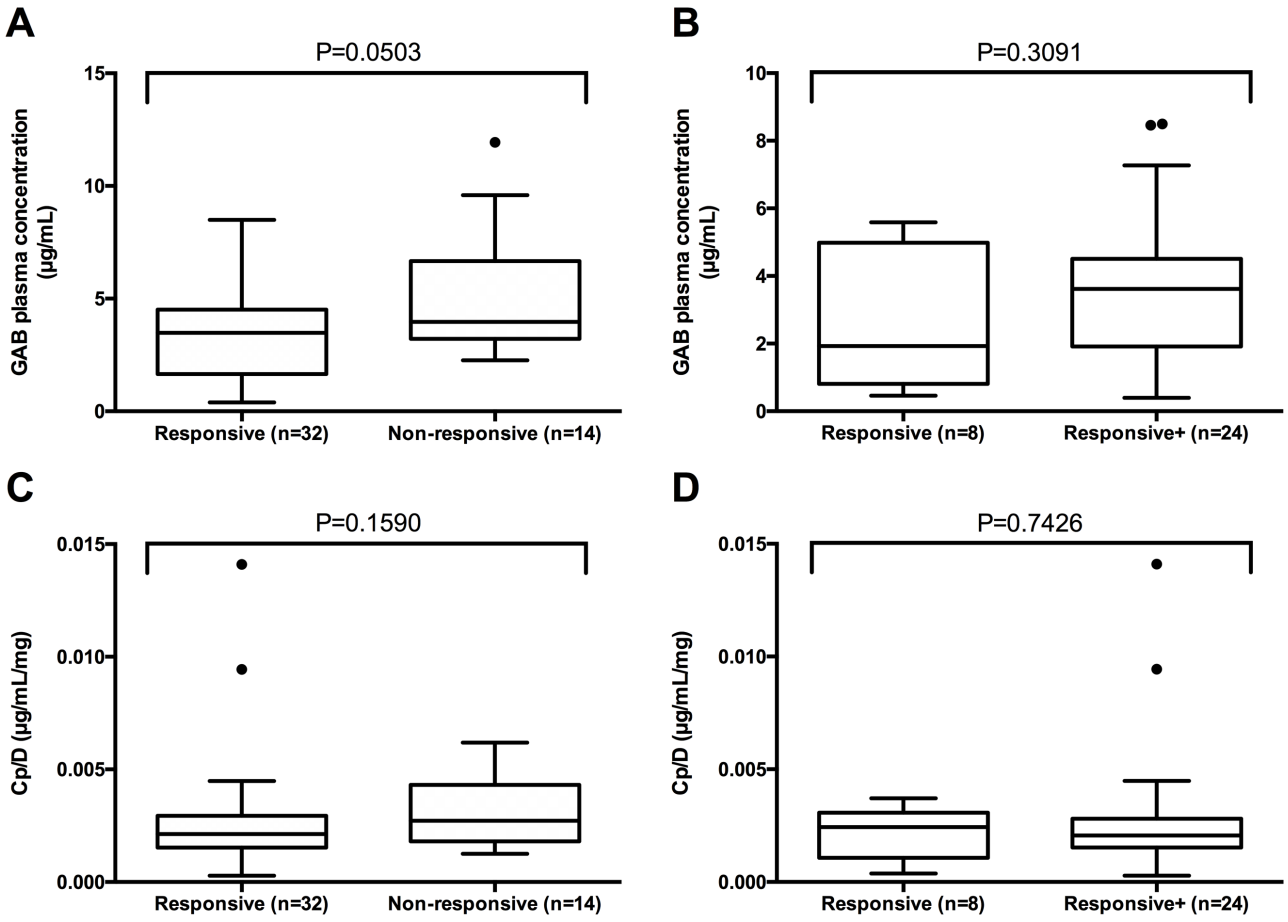

FIGURE 3- Gabapentin (GAB) plasma levels in patients with neuropathic pain presented as absolute plasma concentration (A and B) or plasma concentrations normalized by dose (Cp/D, C and D). GAB plasma concentration and Cp/D ratio were compared between responsive and non-responsive patients (n=46, A and C) or between responsive patients treated with GAB only (Responsive, n=8) and patients receiving associated drugs for neuropathic pain (Responsive+, n=24). Data were presented as median (middle line), 25th percentile (lower line), 75th percentile (upper line) and outliers (·). The statistical significance was set at 5% (*P*-value <0.05).

DISCUSSION

The extensive pharmacokinetic variability of GAB is an indication for TDM. After the TDM of patients treated with GAB for epilepsy and other indications, a 22- and >100-fold pharmacokinetic variability in Cp/D ratios of GAB was observed (Landmark *et al*., 2015; Burns *et al*., 2019). Large pharmacokinetic variability was also observed in this study, with a Cp/D ratio variability of 51-fold. This variability is due to the GAB dose-dependent bioavailability and the saturation of active transport during the absorption (Stewart *et al*., 1993; Gidal *et al*., 1998). Furthermore, age/glomerular filtration rate or renal drug transporters activity can influence GAB pharmacokinetics (Boyd *et al*., 1999; Urban *et al*., 2008; Lal *et al*., 2010; Ahmed *et al*., 2017; Yamamoto *et al*., 2019). In this study, patients using OCT2 and OCTN1 inhibitors were excluded, since these drug transporters were reported to be involved in GAB elimination (Urban *et al*., 2008; Lal *et al*., 2010). Renal function can partially explain the pharmacokinetic variability observed. Considering the current information in the literature regarding GAB renal excretion (Lal *et al*., 2010; Yamamoto *et al*., 2019; Costa *et al*., 2020), there are no expected drug-drug interactions at renal level between GAB and the concomitant drugs prescribed in this study.

The reference range of GAB through plasma concentrations at a steady state of 2-20 μg/mL (10-120 μmol/L) is suggested in the literature for epilepsy (Sivenius *et al*., 1991; Wilson *et al*., 1998; Gatti *et al*., 2003; Lindberger *et al*., 2003; Patsalos *et al*., 2008; Nonoda, Iwasaki, Ishii, 2014; Reimers *et al*., 2018, Burns *et al*., 2019). Although plasma concentrations of GAB in all patients with epilepsy considered responsive were within this range, no difference was observed between responsive and non-responsive patients in terms of plasma concentrations in both adults and children (Gatti *et al*., 2003; Lindberger *et al*., 2003). A TDM study with 223 Norwegian patients, diagnosed with epilepsy or not, showed that 31% (n=69) had GAB concentrations below the reference range proposed for epilepsy (Burns *et al*., 2019). Our results showed that 24.5% (n=13) of patients with neuropathic pain present GAB plasma concentration below 2 μg/mL (Figure 2). Due to the different physiopathology of epilepsy and neuropathic pain, the reference range proposed for patients with epilepsy cannot be used for patients with neuropathic pain.

TDM could play a relevant role in optimizing GAB regimen to reach the best clinical outcome with lower daily doses. However, no significant correlations were found between GAB plasma concentrations and pain intensity in 39 patients with chronic lower back pain (Atkinson *et al*., 2016). Similarly, no correlations between GAB plasma concentration and treatment response were observed here (Figure 3). Gabapentin efficacy is difficult to determine in patients with pain because pain is a subjective symptom reported by the patient and due to the concomitant use of other drugs for pain control, such as amitriptyline, nortriptyline, venlafaxine, baclofen, opioids, pregabalin and carbamazepine. Furthermore, the high inter-individual variability in pain modulation mechanisms can lead to different responses (Colloca *et al*., 2017).

In clinical practice, some patients did not use the prescribed dose of GAB correctly. During recruitment, patients complained about: a) adverse events (somnolence, gastric intolerance, swelling) which, even if not serious, were the reason for them to stop the treatment (n=3) or not follow it correctly (n=5); b) no pain relief – almost 30% of the participants do not respond to the treatment; c) the high number of medications – 32 patients included in this study used five or more medications (polypharmacy); and d) the unavailability of GAB in the public health system (Brazil's Unified Health System – SUS) (n=5). Abuse and misuse of gabapentinoids have been reported particularly in subjects with a history of opioid abuse or psychiatric disorders (Bastiaens, Galus, Mazur, 2016; Smith, Havens, Walsh, 2016; Evoy, Morrison, Saklad, 2017).

TDM is an important tool to verify GAB treatment compliance. Compliance with treatment was self-reported in this trial. The absence of other compliance evaluations is a limitation of this study. We detected that two patients were not using GAB by observing the plasma concentration below the limit of quantification. Since, they declared the correct use of GAB and its inefficacy, other interventions were made to relieve pain, such as the addition of other drugs and nerve blocks. The false inefficacy declared by the patients can lead to unnecessary risks for them from other procedures and more complex drugs.

Even without observable associations between drug concentration and response, the TDM of GAB has a significant clinical role in avoiding misdiagnosis of therapeutic failure of GAB, especially when patients are using high doses of GAB and no pain relief is observed. The small sample size is a limitation of this study. Only patients with prescriptions of the same amount of GAB in each dose interval were included, thus limiting the inclusion of other patients.

Therapeutic drug monitoring of GAB has proven to be an important tool to assess treatment adherence. The reference ranges suggested in the literature are for patients with epilepsy and should not be applied to patients with neuropathic pain. The dose adjustment based on GAB plasma concentration for neuropathic pain treatment cannot be supported by our results, since there are no differences in trough plasma concentration and treatment response.

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