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Original Article

# Reduced response to gabapentin enacarbil in restless legs syndrome following long-term dopaminergic treatment

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ABSTRACT

*Objectives:* To determine whether long-term treatment with dopaminergic agents (DAs) might dampen the response to a non-dopaminergic agent, such as gabapentin enacarbil.
*Methods:* We performed a two-week randomized, double-blind, crossover, and placebo-controlled study in a single, referral center in dopamine treatment-naive patients and non-augmented patients continuously treated with dopaminergics for the last five consecutive years. Following washout from any previous CNS-active drugs, patients were randomized into one of two groups for two consecutive two-week treatment periods with gabapentin enacarbil (GBPen) and placebo. Treatment was administered at 7 PM at a fixed dose of 600 mg/day. RLS severity was measured weekly using the International RLS Scale (IRLS) and Clinical Global Improvement (CGI). An M-SIT was also performed between 6 pm and midnight at the end of each treatment condition.
*Results:* There were no significant differences between groups in age, sex, duration of disease, ferritin levels, RLS severity at baseline, or existing concomitant conditions. Both groups improved more during treatment with GBPen than during placebo on the IRLS scale, CGI and mSIT. However, improvements were greater in the DA-naïve group than in long-term treatment with DAs group on the IRLS ($p < 0.05$), CGI ($p < 0.01$), and mSIT ($p < 0.01$).
*Conclusions:* Previous long-term treatment with DAs reduces future response to GBPen in RLS patients. Potential pathiophysiological explanations are discussed. Our finding has strong implications for the initial choice of treatment in RLS and supports the notion that initial treatment should not be started with DAs.
*Classification of evidence:* The study provides class II evidence supporting reduced effects of gabapentin enacarbil in RLS patients previously exposed to long-term treatment with dopamine agonists.


## 1. Introduction

Although the short-term efficacy of dopaminergic agents is firmly established [1], the main long-term complications associated with these drugs include loss of efficacy and augmentation [1]. Loss of efficacy is a reduction of response to dopaminergic treatment in which some degree of response is still preserved [2]. In contrast to augmentation, the severity of symptoms is not worse than before treatment initiation. During augmentation [3], symptoms become more severe with dopaminergic treatment than before treatment initiation, and it is characterized by symptoms starting earlier in the afternoon and during rest, spreading to previously unaffected body parts, and showing a greater intensity [3].

Treatment failure is not uncommon under dopaminergic treatment: a number of retrospective evaluations have highlighted that over the long-term, the percentage of patients whose symptoms do not improve or even worsen despite treatment, is high. Overall, during the first 8–10 years of treatment, 40–60% of patients

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worsened or had to discontinue/change their dopaminergic medication [4–6].

The question is whether such exposure to previous long-term dopaminergic treatment modifies the fundamental pathophysiology in such a way that the future response to non-dopaminergic agents, such as α2δ ligands could also be dampened. It is conceivable that long-term dopaminergic stimulation would cause a down-regulation of dopaminergic receptors, ultimately dampening dopaminergic postsynaptic signaling with an increase in RLS symptom severity [7]. So far, no studies have reliably compared the response to α2δ ligands in untreated vs. dopamine pre-treated patients.

The present study investigates this hypothesis for the first time and seeks to determine whether there is a clinically significant reduction in treatment response to gabapentin enacarbil in RLS patients who have been treated with dopamine agonists when compared to DA-naïve RLS patients.

## 2. Methods

### 2.1. Standard protocol approvals, registrations, and patient consents

The study was performed at the Sleep Research Institute, Madrid, Spain and approved by the local institutional review board. Written informed consent was obtained from all participants. This study was registered at the EUDRA-Clinical Trials registry. EudraCT#: 2014-005111-16. Registry #: 2483.

### 2.2. Subjects

Forty subjects attending our clinic and suffering with moderate to severe, idiopathic RLS were enrolled and stratified into two groups:

*Group A* (n = 20) consisting of RLS patients not previously treated with dopaminergics, and *group B* (n = 20) consisting of RLS patients who had been continuously treated with dopaminergics at least 90% of the time during the previous five years, responding to dopaminergics and not meeting diagnostic criteria for augmentation.

Both groups were closely matched for age, gender, and disease duration. Patients were 18–80 years old, met IRLSSG criteria for idiopathic RLS [10], had a history of RLS symptoms on three or more days per week for at least 12 months and had an IRLS score of ≥20 at baseline (following treatment discontinuation). Furthermore, patients with any secondary forms of RLS, patients with current or previous augmentation, with serum ferritin <18 mcg/ml, or currently suffering from other clinically relevant diseases that could confound assessments or RLS symptoms were excluded.

If treated with drugs likely to influence sleep architecture or motor manifestations during sleep, a washout period of at least five half-lives was performed. If pre-treated with levodopa or dopamine agonists, the washout period lasted two weeks. Baseline severity values were measured following treatment discontinuation in both groups.

### 2.3. Study design and procedures

The study followed a double-blind, randomized, cross-over, placebo-controlled design on gabapentin enacarbil vs. placebo. Following a washout period of two weeks for any previous RLS and psychotropic medications, patients were randomized to a fixed dose of 600 mg gabapentin enacarbil or placebo (allocation ratio: 1:1) for two weeks. Following a washout period of seven days, patients underwent another two-week treatment with the alternate treatment. Medication was administered each day as a single dose at 7 PM.

The primary endpoint was a difference across groups (DA treated vs. not DA treated) in treatment change (GBPen vs. placebo) on the IRLS scale. Severity ratings were evaluated weekly using the IRLS scale Clinical Global Index-severity (CGI), RLS-6 [8], Medical Outcomes Sleep (MOS) scale and a visual analog scale (VAS) for pain.

A Multiple Suggested Immobilization Test (m-SIT) was performed at the end of each treatment period. The m-SIT [9] is a validated test [9] that evaluates the severity of motor and subjective RLS/WED symptoms in the evening while the patient is awake and immobile. Four 1-hr SITs were performed at 6, 8, 10 pm and at midnight, during which the patients were asked to remain immobile. Periodic leg movements were measured with bilateral anterior tibialis muscle surface EMG. Every ten minutes patients completed a numerical symptom severity scale (mSIT disturbance scale, mSIT ds) (range: 0–10, with a maximum total sum of 60).

### 2.4. Randomization, allocation, and blinding

Selection and allocation of patients to both groups was performed by the first author (DGB), who had no access to the patients or their data during the entire study. All ratings and scoring of mSITs, or PSGs was performed by raters blinded to group allocation.

A randomization list for the order of treatments was obtained from an external clinical research organization using a computerized allocation schedule system with half of the patients starting with placebo and the other half with gabapentin enacarbil. Treatment assignment was implemented through an interactive voice response system. No access to the double-blind list was granted to the study investigators, site staff, patients, m-SIT scorers, or the monitoring staff during the entire study. Blinding was completed before receiving the drug at the study site; manufactured placebo capsules were equal in aspect, size, color and taste to the active compound.

### 2.5. Data analysis

Calculation of the sample size was based on the results of a similar two-week cross-over study that compared GBPen with placebo in the RLS population [11]. Thus, a clinically meaningful mean difference of 10 points (SD range: 6.1–6.5) on the IRLS-total score for GBPen compared to placebo was estimated for the DA-naive group. Furthermore, in an exploratory manner, we assumed a placebo-corrected, clinically significant difference of at least four points between the DA-naïve group and the group previously treated with dopaminergic agents. Thus, with 20 subjects per group, the study had at least 80% power to detect a difference between treatment if the true difference was at least four points. The test assumed a Type I error of 0.025 with one-sided testing.

All efficacy analyses were carried out using the intention-to-treat population (ITT) which was defined as all patients who received randomized treatment.

The Kolmogorov–Smirnoff test was used to evaluate the normality of distributions. Paired sample tests were used to analyze dependent variables (primary and secondary endpoints), with the paired t-test used if normal distribution, and the Wilcoxon test if not. Due to the experimental character of the study and small sample size, the significance levels used were 0.05 with mention of any values below 0.1.

## 3. Results

### 3.1. Patient disposition and demographics

The recruitment period started in September 2015 and finished in June 2017. As shown in Fig. 1, 40 subjects were screened, and 39

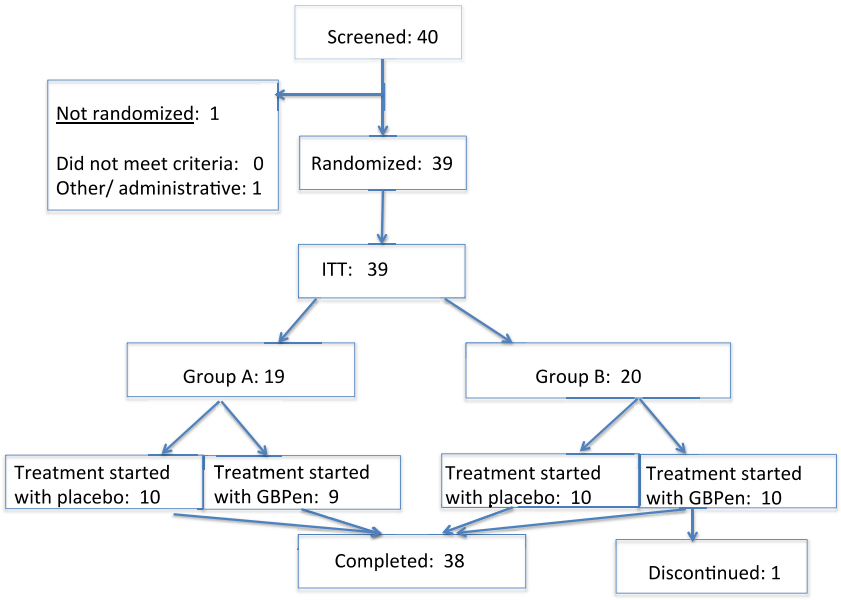


**Fig. 1.** Patient disposition.

were randomized. Thirty-eight subjects completed the entire study. Two subjects were not able to complete the study: one decided to discontinue due to the severity of symptoms during the screening period, while the other discontinued the study for personal reasons at the end of the first treatment phase.

There were no significant difference between groups (A v/s B) in age (57.74 v/s 58.26, Z: −0,7, p value n.s), sex (63% females, Z:0, p value n.s), mean duration of disease (18.11 v/s 18.58 years, Z: 0, p value n.s), duration of disease since diagnosis (4.84 v/s 6.94 years, Z: −0.3, p value n.s), serum ferritin (71.59 v/s 85.80 ng/ml, F: −1.09, p value n.s) or existing concomitant conditions. Patients in Group A had been treated with the median dose used over the previous 12 months with clonazepam (n:7, 1 mg), trazodone (n:5, 75 mg), zolpidem (n:4, 10 mg) or carbamazepine (n:2, 400 mg) (with one single case not having undergone any RLS treatment); regarding Group B, the main dopamine agonist and median dose used over the last 12 months was pramipexole (n: 7; range: 0,25–0,5; mean ± SD: 0,39 ± 0,11 mg), followed by rotigotine (n: 10; range: 1–4; mean ± SD: 2,8 ± 0,97 mg) and ropinirole (n:2, range: 1,3; mean ± SD: 2 ± 1,41). Of particular relevance was the fact that both groups had a fairly similar severity of RLS symptoms following discontinuation of dopaminergic treatment (21.34 v/21.68 IRLS severity) (see Table 1).

### 3.2. Efficacy variables

As shown in Table 2a, a greater improvement on the IRLS scale was seen in both groups (A and B) during the two-week treatment period with GBPen than with placebo ($p < 0.0001$). However, DA-naïve RLS patients improved significantly more during treatment with GBPen than the group of patients previously treated with dopaminergics ($p < 0.05$). Similar results were found on the CGI-S scale, with both groups improving more during treatment with GBPen than with placebo (Group A: $p < 0.0001$ and Group B: $p < 0.05$). Again, DA-naïve RLS patients improved significantly more during treatment with GBPen than the group of patients previously treated with dopaminergics ($p < 0.01$).

Table 2b shows the mean-values (SD) of RLS-6, item one ("sleep satisfaction"), item 2a ("RLS severity at bedtime"), and item 2b ("RLS severity during the night") across treatment and groups. As shown, the DA-treatment naïve group improved marginally more under GBPen than under placebo on items 1 and 2b, and

**Table 1**
Summary of clinical characteristics, demographics (mean ± SD), and concomitant diseases.

| | Group A: treatment naïve | Group B: DA treated | Z | P value |
|---|---|---|---|---|
| Age | 57,74 ± 7,4 | 58.26 ± 12,4 | Z: −0.7 | n.s. |
| Sex (% females) | 63 | 63 | Z: 0 | n.s. |
| Mean Duration of disease (yrs) | 18.11 ± 15,9 | 18.58 ± 8,1 | Z: −0,14 | n.s. |
| Duration of disease -since diagnosis- (yrs) | 4.84 ± 5,7 | 6.94 ± 6,7 | Z: −0,3 | n.s. |
| Family History (%) | 57.90 | 70.00 | Chi-sq.: 0.62 | n.s. |
| Serum ferritin (ng/ml) | 71.59 ± 53,3 | 85.80 ± 63,9 | F: −1.09 | n.s. |
| Pain at baseline | 8/19 (42%) | 5/19 (26.3%) | | n.s. |
| Duration of previous treatment (yrs) | 4,23 ± 6,6 | 7,36 ± 2,3 | | n.a. |
| Levodopa equivalent dose[a] | n/a | 56,2 ± 35,4 mg | | n/a |
| Last type of treatment and dose (n, range) before study treatment | None (n: 1) | Ropinirole (2; 1–3 mg) | n.a. | n.a. |
| *for Group A: mean treatment and median dose of treatment used over the last 12 months | Carbamacepine (n:2, 400 mg)<br>Trazodone (n:5, 75 mg) | Pramipexole (7; 0,25–0,5 mg)<br>Rotigotine (10; 1–4 mg) | | |
| **for group B: number of patients using it as a main drug and median dose used over the last 12 months | Zolpidem (n:4, 10 mg)<br>Clonacepam (n:7, 1 mg) | | | |
| IRLS severity at screening visit | 24.15 (±4,6) | 21.68 (±4,2) | Z: −0.8 | n.s. |
| IRLS severity at baseline | 23.15 (±5,1) | 22.68 (±5,5) | | n.s. |

[a] Source: University of Birmingham Clinical Trial Unit, 2012.

**Table 2a**
Mean (±SD) values of the IRLS total score (main endpoint) and CGI-severity scale score in both groups of patients and under both treatment conditions.

| | | | | Gabapentin enacarbil vs. placebo | | Group A vs. Group B | |
|---|---|---|---|---|---|---|---|
| | BL mean* | Week 1 | Week 2 | Z | P | Z | P |
| **IRLS mean scores (±SD)** | | | | | | | |
| Group A (DA naive) gabapentin enacarbil | 24.45 (±4.64) | 12.94 (±5.66) | 11.14 (±7.17) | −3.71 | <0.0001 | −2.01 | 0.045 |
| Group A (DA naive) placebo | 21.85 (±8.23) | 21.22 (±8.71) | 20.51 (±8.92) | | | | |
| Group B (DA treated) gabapentin enacarbil | 24.40 (±6.26) | 17.52 (±5.93) | 14.27 (±5.88) | −3.62 | | | |
| Group B (DA treated) placebo | 21.07 (±4.36) | 15.35 (±6.58) | 15.01 (±6.78) | | | | |
| **CGI mean scores (±SD)** | | | | | | | |
| Group A (DA naive) gabapentin enacarbil | 5.21 (±0.78) | 4.26 (±1.24) | 3.47 (±1.50) | −3.49 | <0.001 | −2.75 | 0.006 |
| Group A (DA naive) placebo | 5.47 (±0.51) | 4.94 (±0.91) | 4.94 (±0.84) | | | | |
| Group B (DA treated) gabapentin enacarbil | 4.68 (±0.74) | 3.52 (±0.69) | 3.26 (±0.73) | −2.04 | <0.041 | | |
| Group B (DA treated) placebo | 5.05 (±0.75) | 4.45 (±1.23) | 4.36 (±1.06) | | | | |

* In contrast to Table 1, baseline means are divided into four subgroups, showing the mean IRLS value at the initiation of each treatment condition.

**Table 2b**
Mean RLS-6 Scores. Z: Mann–Whitney test.

| RLS-6 mean scores (±SD) | | | | Gabapentin enacarbil vs. placebo | | Group A vs. Group B | |
|---|---|---|---|---|---|---|---|
| | BL mean | Week 1 | Week 2 | Z | P | Z | P |
| **Item 1, sleep satisfaction** | | | | | | | |
| Group A (DA naive) gabapentin enacarbil | 5,94 (±1,98) | 3,83 (±2,33) | 3,94 (±2,98) | −1.82 | <0,1 | −0.09 | n.s. |
| Group A (DA naive) placebo | 5,06 (±2,96) | 5,06 (±2,46) | 5,22 (±2,53) | | | | |
| Group B (DA treated) gabapentin enacarbil | 4,28 (±2,14) | 2,56 (±1,79) | 4,74 (±2,75) | −1.56 | n.s. | | |
| Group B (DA treated) placebo | 6,79 (±2,44) | 4,79 (±2,42) | 5,06 (±2,44) | | | | |
| **Item 2a, RLS at bedtime** | | | | | | | |
| Group A (DA naive) gabapentin enacarbil | 5,17 (±2.75) | 2,83 (±1,86) | 1,94 (±1,35) | −2.85 | <0,01 | −0.075 | n.s. |
| Group A (DA naive) placebo | 4,22 (±3,56) | 4,22 (±2,58) | 4,56 (±2,75) | | | | |
| Group B (DA treated) gabapentin enacarbil | 3,39 (±2,7) | 2,33 (±1,91) | 3,63 (±2,95) | −1.21 | n.s. | | |
| Group B (DA treated) placebo | 5,42 (±3,32) | 3,95 (±2,99) | 3,39 (±2,98) | | | | |
| **Item 2b RLS symptoms during the night** | | | | | | | |
| Group A (DA naive) gabapentin enacarbil | 3,94 (±3,02) | 2,11 (±2,06) | 1,33 (±1,82) | −1.82 | <0.1 | −0.29 | n.s. |
| Group A (DA naive) placebo | 4,67 (±3,58) | 3,89 (±2,90) | 4,67 (±3,50) | | | | |
| Group B (DA treated) gabapentin enacarbil | 4,00 (±2,25) | 2,17 (±2,28) | 3,95 (±2,84) | −0.02 | n.s. | | |
| Group B (DA treated) placebo | 5,16 (±3,25) | 3,95 (±2,90) | 3,72 (±2,40) | | | | |

Z: Mann-Whitney test

significantly on item 2a. No significant differences occurred between treatment phases in the DA-treated group. The response to GBPen did not differ significantly between the two groups of patients. There were no significant differences between treatment or groups on the other items of the RLS-6 scale.

### 3.3. Multiple Suggested Immobilization Test (m-SIT)

#### 3.3.1. MSIT disturbance scale

As shown in Fig. 2a, the DA-treatment naïve group improved more under GBPen than under placebo ($p < 0.01$). No significant differences occurred between either treatment phase in the DA-treated group. Overall, DA-naïve patients (group A) had a greater response to GBPen (compared to placebo) than the group of patients previously treated with dopaminergics ($p < 0.01$).

#### 3.3.2. Periodic Legs Movements while awake (PLMW)

PLMW decreased more in both groups with GBPen than placebo, although the response in the DA-treated group was only marginally greater for GBPen compared to placebo ($p < 0.1$) (Fig. 2b).

When comparing the placebo-corrected response across groups, the response to GBPen was marginally greater for patients in the DA-naïve group compared to the DA-treated group.

Overall, dopaminergic DA-naïve patients responded better to GBPen than those previously treated over the long-term with dopoaminergics. Such improvement in response involved not only fewer dysesthesias but also improved motor symptoms (PLMW).

#### 3.3.3. Pain-VAS and MOS-sleep scales

8/19 (42%) of patients in Group A and 5/19 (26.3%) patients in Group B reported some degree of pain at baseline. However, no significant differences were reported in painful symptoms between either treatment phase, or between groups of patients (n.s.).

There was a greater improvement in the MOS subscore “sleep disturbance” for the DA-treatment naïve group under GBPen than under placebo ($p < 0.01$), but not in the DA-treated group. No differences were seen between treatments or groups on the subscore sleep adequacy (Table 2c).

#### 3.3.4. Toxicity

As shown in Table 3, both groups of patients suffered more side-effects during treatment with GBPen than during placebo, with drowsiness, postural instability, headache, dry mouth, dizziness, occurring in more than 10% of the sample. Side effects were similarly distributed across both groups.

The distribution of severity of side-effects was fairly similar across groups (Table 3). In three cases (7.89%), side effects were reported as severe during at least one of the visits. These three patients suffered from an upper airway infection, severe headache and myocardial infarction, all of which were considered to be unrelated to the study medication.

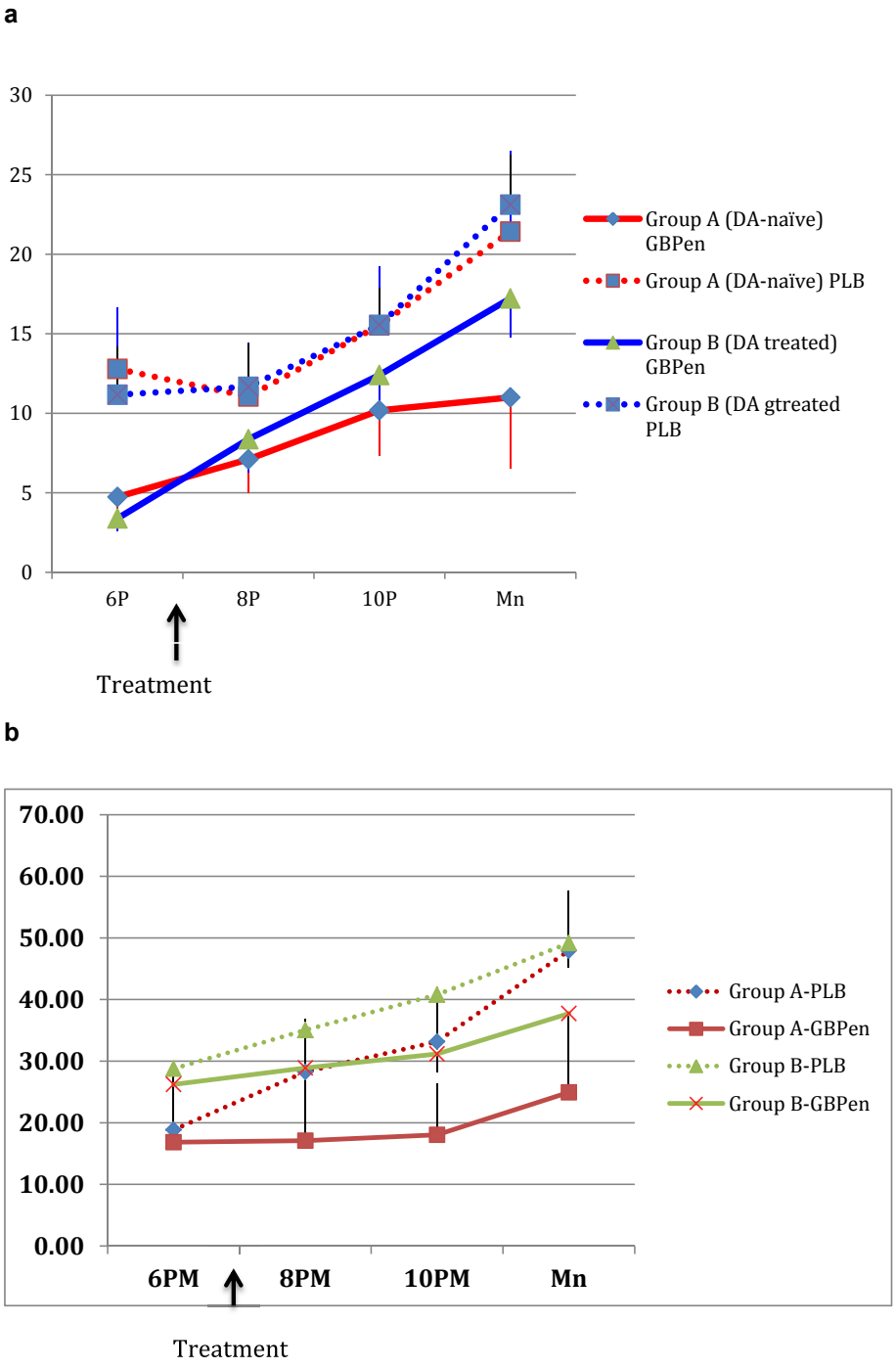


**Fig. 2.** (a) Mean-values (SEM) of the mSIT discomfort scale across treatment, groups and time of day. (b) Mean-values (SD) of the PLMW-index across treatments, groups and time of day.

As shown in Table 3, the distribution of side-effects potentially attributed to the study medication was similar across both groups of patients.

## 4. Discussion

As could be expected, both groups of patients improved following a two-week treatment with GBPen compared to placebo. However, the main finding in our study was to show, for the first time, a difference in the therapeutic response to an α2δ ligand between RLS patients never treated with DAs and those who had received treatment beyond five years with dopaminergics. These findings were obtained not only on the IRLS and CGI scales but also on the mSIT. In our opinion, the absence of similar differences on the RLS-6 can be attributed to the lower sensitivity of this scale to show treatment change in previous DA-treated patients [8].

Clinical and demographic factors known to affect therapeutic response were similar across groups. That is, both groups had been closely matched for age, sex, and previous duration of illness. Also, serum ferritin levels, the severity of illness when untreated (IRLS or CGI scores), and concomitant conditions at baseline were similar across groups. There were no differences between groups in the

**Table 2c**
Mean (±SD) values of the MOS Scale in both groups of patients and under both treatment conditions.

| MOS Scale | | | Gabapentin enacarbil vs. placebo | | Group A vs. Group B | |
|---|---|---|---|---|---|---|
| | BL mean | Week 2 | Z | P | Z | P |
| **Sleep disturbance** | | | | | | |
| Group A (DA naive) gabapentin enacarbil | 2,89 (±1,41) | 2.43 (±1.24) | −2,1 | 0,05 | −2,51 | 0.01 |
| Group A (DA naive) placebo | 2,93 (±1,39) | 3,34 (±1,06) | | | | |
| Group B (DA treated) gabapentin enacarbil | 2,84 (±1,06) | 2,39 (±1,21) | −0,3 | n.s. | | |
| Group B (DA treated) placebo | 2,94 (±1,64) | 2,62 (±1,28) | | | | |
| **Sleep adequacy** | | | | | | |
| Group A (DA naive) gabapentin enacarbil | 3.06 (±1.36) | 3,49 (±1,66) | −1,4 | n.s. | −,027 | n.s. |
| Group A (DA naive) placebo | 2,59 (±1,39) | 2,5 (±1,53) | | | | |
| Group B (DA treated) gabapentin enacarbil | 3,54 (±1,7) | 3,82 (±1,73) | −0,3 | n.s. | | |
| Group B (DA treated) placebo | 2,65 (±1,23) | 2,69 (±1,73) | | | | |

Z: Mann–Whitney test.

**Table 3**
Severity of side-effects under the active treatment in both groups.

| Side effects | Group A | | | | Group B | | | |
|---|---|---|---|---|---|---|---|---|
| | GBPen | | PLB | | GBPen | | PLB | |
| | N | % | N | % | N | % | N | % |
| Drowsiness | 3 | 15.79 | 2 | 10.53 | 6 | 31.58 | 2 | 10.53 |
| Ataxia | 3 | 15.79 | 3 | 15.79 | 3 | 15.79 | 2 | 10.53 |
| Headache | 3 | 15.79 | 2 | 10.53 | 1 | 5.26 | 1 | 5.26 |
| Dry mouth | 2 | 10.53 | 0 | 0 | 1 | 5.26 | 0 | 0 |
| Dizziness | 3 | 15.79 | 0 | 0 | 0 | 0 | 0 | 0 |
| Others: | | | | | | | | |
| **Group A:** | | | | | | | | |
| • **GBPen:** rhinitis, fluid retention, nausea, gastroesophageal reflux, conjunctivitis, feeling of satiety, retrosternal pain, hot flashes. | 8 | <10% | | | | | | |
| • **PLB:** gastroesophageal reflux, conjunctivitis, photopsias, nightmares, retrosternal pain, hot flushes. | | | 6 | <10% | | | | |
| **Group B:** | | | | | | | | |
| • **GBPen:** rhinitis, hypertension, fluid retention, bronchitis, acute gastroenteritis, nausea, stomach ache, tachycardia, fainting, infection. | | | | | 10 | <10% | | |
| • **PLB:** rhinitis, bronchitis, acute gastroenteritis, stomach ache, cervical pain, infection, tinnitus, myocardial infarct, leg cramps. | | | | | | | 9 | <10% |
| **TOTAL** | **22** | | **13** | | **21** | | **14** | |

effects of GBPen on sleep, pain, nor in toxicity. Moreover, patients with current or past episodes of augmentation were excluded from participation in this study. As expected, with the exception of one case, all other patients were undergoing treatment for RLS at least over the previous year before study initiation. Nevertheless, given the nonrandom assignment of patients to both groups, it is always possible that some unmeasured clinical feature might have influenced them to initiate, or not, treatment with dopaminergic drugs. However, such a possibility is in our view highly unlikely given the similarity of both groups in all relevant clinical features that might affect response to gabapentin such as pain, anxiety or sleep disturbance [1].

Taken together, neither duration of disease nor baseline severity dampen the response to GBPen in RLS patients, but previous treatment with dopaminergic medication does. Thus, our results support the notion that previous long-term treatment with dopaminergic agents reduces, not just the response to any other dopaminergic drugs, but also to α2δ ligands. These results contradict a previous study that found GBPen to be equally effective in dopamine-naïve and dopamine-treated patients [12]. This previous study did not control for the length of dopaminergic treatment or the doses used. In our view, the length of previous dopaminergic treatment becomes a key factor in establishing differences between the two groups.

The question is why long-term treatment with DAs would dampen the response to α2δ ligands, given the different mechanisms of action of both classes of drugs (dopaminergic for the DAs; mainly glutamatergic for the α2δ ligands). Although included subjects did not meet the criteria for past or present augmentation, they might well have been already suffering from initial changes in dopaminergic function as a result of the long-term exposure to dopaminergic medications. Such latent dopaminergic dysfunction would prepare the ground for future episodes of augmentation, should dopaminergic treatment be continued. Indeed, glutamatergic medium spiny neurons (MSNs) which constitute more than 95% of the striatal neuronal population [13], contain dopamine type-2 (D2-R) and dopamine type-4 presynaptic receptors (D4-R) forming heteromers [14–16] and allow dopamine to exert a tonic inhibitory role on striatal glutamate release [15,16]. Long-term administration of dopamine D2/D3 agonists might result in a downregulation of these D2R-D4R presynaptic heteromers, along with an upregulation in presynaptic D1 receptors [17,18] worsening the hyperglutamatergic state, and that might further reduce the therapeutic effects of α2δ ligands.

The main limitations of our study were the reduced and selected sample and a short period of treatment. Also, the allocation of patients into groups undergoing identical treatment was performed by an unblinded investigator. Nevertheless, any scorings of rating scales and sleep laboratory assessments were done by blind raters. All these shortcomings were intrinsic limitations imposed by the study design. But the fact is that to date, no other comparative, cross-over study has been performed comparing DAs and α2δ ligands.

Our results have far-reaching clinical implications: Both dopamine agonists and α2δ ligands are approved treatments for RLS. Due to their immediate therapeutic onset and relatively low toxicity profile, dopamine agonists are more commonly used in Western countries. However, over the first 10 years of treatment, these type of drugs lead, to loss of response and to augmentation in

at least 40–60% of cases. Our study shows that, even before this process takes place, the response to alternative medication is already reduced. Thus, to preserve a full response of symptoms to medication, this study supports the notion that initial treatment for RLS should be started with non-dopaminergic medications, something in line with the most current treatment recommendations from the IRLSSG expert group [19]. In conclusion, further investigation is needed.

## Financial disclosures

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Dr. Cano reports no disclosures.

Dr. Garcia Malo reports no disclosures.

Dr. Cruz Velarde reports no disclosures.

Dr. Granizo reports no disclosures.

Dr. Wanner reports no disclosures.

## Author contributions

Dr. Garcia-Borreguero: study concept and design, study supervision, acquisition of data, first draft of manuscript, revisions.

Dr. Cano: acquisition of data, first draft of manuscript, revisions.

Dr. Garcia Malo: acquisition, of data, first draft of manuscript, revisions.

Dr. Cruz Velarde: acquisition, of data, first draft of manuscript, revisions.

Dr. Granizo: statistical analysis and interpretation of data, critical revision of manuscript for intellectual content.

Dr. Wanner: data analysis, acquisition of data, first draft of manuscript, revisions.

## Abbreviations

| | |
|---|---|
| CNS | Central nervous system |
| CGI | Clinical Global Improvement |
| DAs | Dopaminergic agents |
| D2-R | Dopamine type-2 receptor |
| D4-R | Dopamine type-4 receptor |
| GBPen | Gabapentin enacarbil |
| IRLS | International restless legs syndrome scale |
| IRLSSG | International restless legs syndrome study group |
| ITT | Intention-to-treat population |
| MOS | Medical Outcomes Scale |
| MSNs | Medium spiny neurons |
| mSIT | Multiple Suggested Immobilization Test |
| PLMW | Periodic Legs Movements while Awake |
| VAS | Visual analog scale |

## Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.11.025.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.11.025.

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