

Intravenous lacosamide and phenytoin for the treatment of acute exacerbations of trigeminal neuralgia: A retrospective analysis of 144 cases

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Abstract

Background: Scant evidence is available on the use of intravenous pain treatment in acute exacerbations of trigeminal neuralgia. The aim of this descriptive study was to evaluate the effectiveness and security of intravenous lacosamide and phenytoin in the treatment of acute trigeminal neuralgia pain.

Methods: We reviewed patients who attended the emergency department of a tertiary hospital between 2012 and 2020 for exacerbations of trigeminal neuralgia pain and were treated with either intravenous phenytoin or lacosamide for the first time. Primary endpoints were pain relief and adverse effects during the hospital stay. A comparative analysis between both treatment groups was performed.

Results: We studied 144 episodes in 121 patients (median age 61 years, 66.1% women). Trigeminal neuralgia etiology was secondary in 9.9%. Pain relief was observed in 77.8% of 63 patients receiving lacosamide infusions, and adverse effects in 1.6%. Pain relief was observed in 72.8% of 81 phenytoin infusions and adverse effects in 12.3%, all mild. No difference was observed in pain relief between groups, but the proportion of adverse effects was significantly different ($p = 0.023$). Statistically significant differences were also detected in readmissions within six months, time to readmission, and pain relief status at first follow-up visit.

Conclusion: Intravenous lacosamide and phenytoin can be effective and safe treatments for acute pain in trigeminal neuralgia. According to our series, lacosamide might be better tolerated than phenytoin and lead to lower readmissions and sustained pain relief.

Keywords

Trigeminal neuralgia, lacosamide, phenytoin, acute pain, intravenous treatment, neuropathic pain

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Introduction

Trigeminal neuralgia (TN) is defined by the third edition of the International Classification of Headache Disorders (ICHD3) (1) and the first edition of the International Classification of Orofacial Pain (ICOP) (2) as paroxysmal, short-lasting, unilateral, electric-shock-like pain, triggered by innocuous stimuli, limited to one or more divisions of the trigeminal nerve. It is categorized as classical TN, in which neurovascular compression is confirmed by magnetic resonance imaging (MRI); secondary TN, caused by multiple sclerosis, space-occupying lesions or other causes; or idiopathic

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TN, when no cause is identified (1,3). Despite the number of drugs proposed to treat TN, mainly sodium channel blockers, only carbamazepine and oxcarbazepine offer enough evidence to be considered first-line treatments (4). Nevertheless, pain is refractory in a large number of cases and therapeutic adverse events are common (5).

Pain relapses in TN are a frequent reason for consulting the emergency department, and to date evidence on effective drugs in the acute phase is scant, especially for rapid-acting or intravenous compounds that are preferred when the oral route is not tolerated due to intense pain (6). Only phenytoin or lidocaine are recommended as intravenous drugs in acute exacerbations of pain, but the quality of evidence is low (7,8). To date, only one randomized, double-blind, placebo-controlled trial using intravenous medications in TN exacerbations has been published, supporting the use of intravenous lidocaine for the reduction of pain (9). Other lidocaine preparations have also been studied, including nasal spray (10), eye drops (11), nerve blocks (12), or application to trigger points in the oral mucosa (13), all of which showed low evidence of effectiveness.

Lately, there is a growing interest in new drugs which act by blocking voltage-gated sodium channels (14,15), similar to carbamazepine or phenytoin, but with novel mechanisms of action that may decrease the very common side effects of these drugs (16,17). For instance, lacosamide blocks voltage-gated sodium channels in a slow inactivating manner (18). This compound, initially designed as an antiepileptic drug, has recently shown effectiveness in the treatment of neuropathic pain (19,20) and its effectiveness as an adjunctive treatment in TN has been suggested in small case series (21–23). Its efficacy as intravenous treatment in pain crises has scarcely been studied, but a few cases have been described in which intravenous administration has improved pain in the acute phase (24). Considering the small but mounting evidence of lacosamide in acute TN, our aim was to analyze its use in real-life situations in the emergency room and compare it with the use of phenytoin.

For this purpose, we retrospectively evaluated the effectiveness and safety of intravenous lacosamide and intravenous phenytoin in a series of patients attending a tertiary hospital due to acute exacerbations of TN pain.

Methods

We retrospectively reviewed consecutive patients who attended the emergency department of a tertiary reference hospital (Bellvitge University Hospital, Barcelona, Spain) between 2012 and 2020, and who were coded in

the system as trigeminal neuralgia. We reviewed clinical records, nurse medication sheets, subsequent emergency admissions and consecutive follow-up visits for at least six months for each patient. Two different neurologists trained in headache and facial pain reviewed the records, splitting the dataset review between them (AM-V and ST).

Patients were included if they met diagnostic criteria for TN according to the International Classification of Headache Disorders, third edition (1), reported facial pain exacerbation as the reason for admission in the emergency room, and received intravenous lacosamide or phenytoin for the first time during their visit to the emergency department. Patients were excluded if they had already received that specific intravenous medication before, or if not all of the required variables had been registered, including a minimum follow-up of six months after discharge.

Variables collected for each patient were: age, gender, TN etiology, time since diagnosis, ongoing treatment, time of admission to the emergency department, treatment choice (lacosamide or phenytoin), dose and start time of infusion, use of adjuvant medication, pain relief status (defined as: no pain reported by the patient, absence of further rescue medication after the infusion, and hospital discharge less than 10 hours after receiving treatment), adverse effects, time to discharge, need for hospital admission, readmissions in the next six months and time to readmission if the treatment was prescribed at discharge, pain relief status at the next follow-up visit if the medication was prescribed at discharge, and time until surgical treatment if ever needed.

Primary endpoints were pain relief (see definition criteria above) and adverse effects in each treatment group. Secondary endpoints were time to discharge after the infusion, need for emergency readmission if the treatment was prescribed at discharge and time to readmission, and improvement of pain control at the next outpatient visit if the treatment was prescribed at discharge. Additionally, a comparative analysis between both treatment groups was performed for demographic and clinical variables and primary and secondary endpoints.

Lacosamide or phenytoin treatment and doses were determined by the attending neurologist, based on clinical criteria and patient comorbidities. Prior systemic and neurological examinations and electrocardiograms were obtained for all patients. Treatment was administered by infusion pump, with continuous electrocardiographic monitoring or serial electrocardiograms. Time of infusion for both drugs was between 15 and 40 minutes depending on doses, as per the hospital emergency protocol.

The study was approved by the Ethical Committee of the Hospital Universitari de Bellvitge with reference EOM028/21. The confidential information of the patients was handled in accordance with Spanish regulations.

Statistics

Primary and secondary endpoints were assessed using a descriptive analysis. Categorical variables were presented as absolute frequencies. Demographic and clinical variables were presented as median and ranges or mean and standard deviation according to the distribution. For the secondary comparative analysis, chi-squared tests and Student's t-tests were used to describe clinical and sociodemographic differences between groups when the distribution was normal. Otherwise, non-parametric tests were used (Fisher's exact test). Kaplan-Meier survival analyses were performed to study the time to readmission in each group when treatment was prescribed at discharge. All tests were studied with confidence intervals of 95% and a significance level of 5%. Statistical analyses were performed in SPSS v.22 (SPSS Inc, Chicago, USA).

Results

An initial registry of 896 episodes in a total of 599 patients treated in the emergency department was obtained. After a review of the individual cases, 144 episodes in a total of 121 patients were finally included (see Figure 1). Each episode was a single lacosamide or phenytoin first-time infusion; as such, two different episodes were included for 23 patients—in one episode

they received first-time intravenous phenytoin, and in the other they received first-time intravenous lacosamide.

The median age of the patients was 61 years (range 26–91), and 66.1% were women. TN etiology was secondary in 9.9% (5 multiple sclerosis, 5 tumors and 2 post-surgical). Diagnosis of TN had already been established for 80.2% of the patients at the time of attendance, and the median time since diagnosis was four years. 83.3% of the patients without a previous TN diagnosis received a subsequent MRI, revealing secondary etiologies in 16.7% of patients.

Patients were stratified into two groups based on whether they received lacosamide or phenytoin. Demographic and clinical variables for each group are shown in Table 1. Mean infusion dose was 180 mg for lacosamide (range 50–400) and 757 mg (range 100–1500) for phenytoin. All patients had a follow-up of six months or more, except for one patient who was not subsequently evaluated due to death (caused by a massive medial cerebral artery aneurysmatic hemorrhage, so not attributable to TN or associated medication).

Pain relief was achieved in 49 out of 63 patients who received lacosamide (77.8%), and in 59 out of 81 patients who received phenytoin (72.8%). Immediate adverse effects were detected in one patient in the lacosamide group (1.6%) and 10 patients in the phenytoin group (12.3%). Secondary endpoint results are shown in Table 2.

Reported adverse effects were mild in all cases. In the lacosamide group, the single adverse effect reported was sleepiness, in one patient. In the phenytoin group, 10 patients reported the following adverse effects: dizziness (5), nausea (2), hypotension (2),

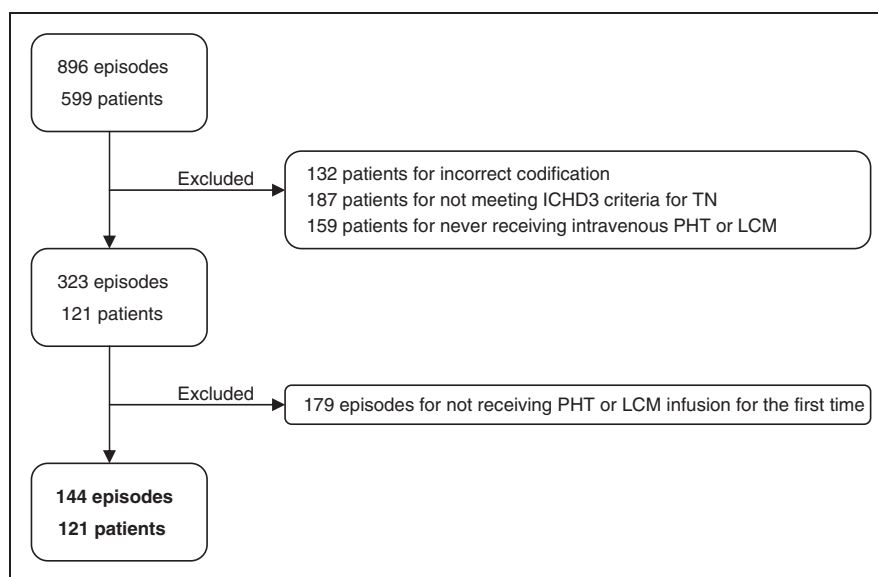


Figure 1. Flowchart for patient inclusion.

Table 1. Demographic and clinical variables for each treatment group.

	Lacosamide	Phenytoin	p
N	63	81	
Age in years [median (range)]	63 (28–92)	60 (26–91)	0.959
Women [n (%)]	37 (58.7)	57 (70.4)	0.146
Secondary etiology [n (%)]	7 (11.1)	8 (9.9)	
Previous TN diagnosis [n (%)]	55 (87.3)	63 (77.8)	0.141
Time since TN diagnosis in years [median (IQR)]	3 (7)	1.5 (6)	
Previous TN surgery [n (%)]	7 (11.1)	17 (21)	0.115
Subsequent TN surgery [n (%)]	21/63 (33.3)	28/80 (35.0) ^a	0.835
Time to TN surgery (days) [mean ± SD]	318.6 ± 496.1	454.61 ± 642.6	0.424
Ongoing treatment with CBZ, OXC or ESL [n (%)]	44 (69.8)	45 (55.6)	0.080
Adjuvant treatment received [n (%)] ^b	40 (63.5)	55 (67.9)	0.580
Opiates [n (%)]	15 (23.8)	20 (24.7)	0.903
Others [n (%)]	25 (39.7)	35 (43.2)	0.670
Dose (mg) [mean (range)]	180 (50–400)	757 (100–1500)	
Prescribed treatment at discharge [n (%)]	36 (57.1)	19 (23.5)	0.000

CBZ, carbamazepine; ESL, eslicarbazepine; IQR, interquartile range; mg, milligrams, OXC, oxcarbazepine; SD, standard deviation; TN, trigeminal neuralgia.

^aOne patient was lost to follow-up and was not included.

^bAdjuvant treatment was considered if the patient received one or more of the following medications: dexketoprofen, metamizole, paracetamol, sumatriptan, tramadol, fentanyl, morphine, pethidine, diazepam or clonazepam. We sub-analyzed opioids separately (patients who received at least one of tramadol, fentanyl, morphine, or pethidine).

Table 2. Primary and secondary endpoints.

	Lacosamide	Phenytoin	p
Primary endpoints			
Pain relief [n (%)]	49 (77.8)	59 (72.8)	0.497
Adverse effects [n (%)]	1 (1.6)	10 (12.3)	0.023^a
Secondary endpoints			
Time to discharge (min) [mean ± SD]	477.4 ± 640.4	479.2 ± 592.1	0.986
Readmission in 6 months if prescribed treatment [n (%)]	9/36 (25.0)	13/19 (68.4)	0.002
Time to readmission if prescribed treatment (days) [mean ± SD]	146.8 ± 63.6	74.58 ± 79.0	0.001
Pain relief status at first follow-up visit if prescribed treatment [n (%)]	22/36 (61.1)	3/18 (16.7) ^b	0.003

Statistically significant differences in each variable between groups are marked in bold.

^aBecause of a low number of cases in one group, a non-parametric test (Fisher's exact test) was used.

^bOne patient was lost to follow-up and was not included.
min, minutes; SD, standard deviation.

infusion pain (2), cutaneous rash (2), paresthesia (1) and itchiness (1); 6 patients presented more than one symptom. No difference in dosage was detected in patients who presented adverse events (850 mg for phenytoin [range 500–1000] and 200 mg for the single lacosamide infusion) when compared to those who did not (744 mg [range 100–1500] for phenytoin and 179.8 mg [range 50–400] for lacosamide). In a similar manner, the proportion of patients who received adjuvant medication was not different in this subgroup of patients with adverse effects (72.7%) compared to those without (65.4%) ($p=0.242$); and neither the concomitance of ongoing treatment with carbamazepine or derivatives (62.4% for patients without adverse

events, 54.5% for patients with adverse events, $p=0.266$).

A secondary analysis was performed to compare both treatment groups. Demographic variables and clinical characteristics of TN did not differ between groups. Pain relief was similar but the proportion of adverse effects was significantly higher in the phenytoin group (1 of 63 patients with lacosamide vs 10 of 81 patients with phenytoin, $p=0.023$). Statistically significant differences were also found when comparing the secondary endpoints of readmissions in the following six months if the treatment was prescribed at discharge (25% for lacosamide vs 68.4% for phenytoin, $p=0.002$), time to readmission if the treatment was

prescribed at discharge (147 days for lacosamide vs 75 days for phenytoin, $p=0.001$), and proportion of pain relief at the next follow-up visit if the treatment was prescribed at discharge (61.1% for lacosamide vs 16.7% for phenytoin, $p=0.003$). Time to readmission if the treatment was prescribed in each group is presented in Figure 2.

Discussion

Treatment of acute pain exacerbations in TN is still controversial. Although many antiepileptic or anesthetic drugs have been proposed, evidence-based studies are scarce, and many neurologists prescribe treatments based mostly on their own clinical experience (7). In this study, retrospective analysis shows how lacosamide and phenytoin administered intravenously as a rescue situation can be effective and safe options in controlling pain.

Phenytoin or fosphenytoin has been proposed as a treatment for neuropathic pain for years, and its intravenous preparation has aroused special interest (25). Nonetheless, only small case series have been published in patients with TN (26–28). A retrospective series of cases has been published recently, in which 65

intravenous phenytoin infusions in 39 patients were effective as acute rescue treatment in 89.2% of cases (29), 15.4% of whom reported mild adverse effects. These results are consistent with our study.

As for lacosamide, its potential effect in alleviating neuropathic pain, its intravenous preparation and its generally good tolerance have made it a modern and attractive option for the treatment of TN pain. However, few studies have evaluated its real effectiveness and safety: only small case series on oral lacosamide in adjunctive treatment (21–23) and one case report on intravenous administration have been published (24).

Our study suggests that both lacosamide and phenytoin are useful options for acute pain exacerbations in TN, with similar effectiveness rates of around 75%. It is important to highlight that most patients in both groups were already receiving regular treatment with carbamazepine or one of its derivatives, so our series comprised cases of refractory TN. This reinforces the potential role of these treatments as rescue medications in refractory cases when the standard oral treatments fail to work properly. We should point out that more patients in the lacosamide group were receiving ongoing treatment with carbamazepine or derivatives than

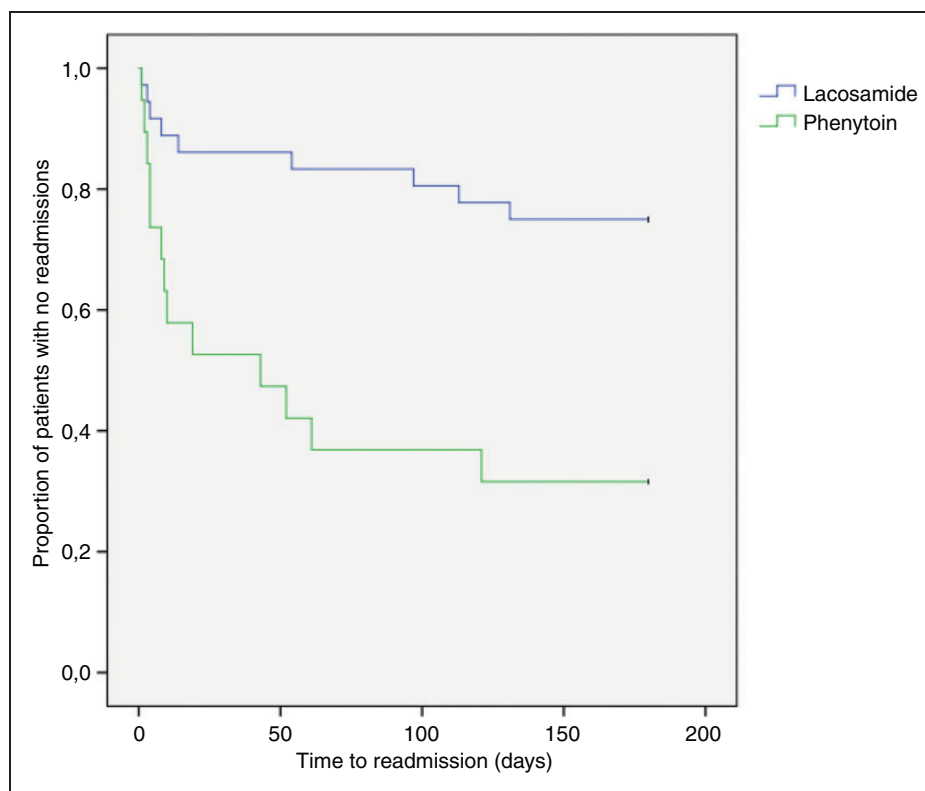


Figure 2. Kaplan-Meier analysis of differences in time to readmission in each group.

in the phenytoin group (70% vs 55% respectively, difference not statistically significant), which might have conferred better outcomes for the follow-up variables in the lacosamide group.

It should be remarked 23 patients received both drugs at two different emergency admissions. Specifically, 19 of these 23 patients first received phenytoin and 4 received lacosamide, with pain relief proportions of 78.9% and 100%, respectively. Of those who did not respond to phenytoin, 50% responded at their second admission to a lacosamide infusion. Curiously, among patients who responded to the first treatment, only half of them responded when changing drug at their second admission (50% pain relief with lacosamide after phenytoin and 40% pain relief with phenytoin after lacosamide). This fact led us to suggest not changing the rescue medication chosen if it was effective at its first infusion.

Adverse events in our series were relatively rare, and those reported for phenytoin were mild and in line with previous series (29). No adverse effects other than sleepiness in one patient were reported for lacosamide. However, it must not be forgotten that potential severe complications have been described, specially related to atrioventricular blocks (30), the risk of which can be multiplied when associated with other sodium channel blockers.

A potential bias in our study is that only immediate adverse events were registered, so perhaps not all possible delayed reactions occurring after patient discharge were obtained, and as such, the proportion of adverse effects could have been underestimated. In fact, previous incidence studies suggest approximately 25% of patients treated with lacosamide reported dizziness, though its time of onset is usually after three months of initiation (31). Another source of bias may be dosing. There is no established dose for these drugs in the treatment of TN, so large differences were recorded between infusions in each group, making it difficult to stratify cases by dosing for a controlled analysis (see doses for each group in Table 1). However, in our sample, higher doses were not related with the presence of adverse events, as mean treatment doses were similar when comparing patients who reported adverse reactions and those who did not. Also, no difference was found in the proportion of adjuvant medication received or in the proportion of ongoing treatment with carbamazepine or derivatives between these groups, thus not suggesting a synergic effect of drugs that could lead to the adverse event.

Other limitations for this study are intrinsic to a retrospective analysis. We attempted to control for the possibility of a diagnostic bias by reviewing each

clinical record and checking that the case met the diagnostic criteria. Furthermore, most patients had received a previous diagnosis of TN before their emergency admission. Similarly, time to discharge is associated with multiple confounders, such as workload in the emergency department. We tried to control this by measuring time from drug infusion and not from arrival, assuming that the immeasurable confounders will be similarly present in both groups.

It is also difficult to quantify pain in a retrospective manner, as no specific pain scales or questionnaires were used. To minimize this bias, we defined pain relief based on the available objective data, including hospital discharge within less than 10 hours, time to discharge after infusion, and need for further treatment.

Finally, a difference emerged in treatment prescription at discharge between treatments. Lacosamide was prescribed in 57% of cases, while phenytoin was only prescribed in 24%. This constitutes a notable size difference between groups when analyzing readmissions in patients who were prescribed treatment (36 for lacosamide vs 19 for phenytoin); however, this difference does not affect our primary endpoints, as these relate only to the emergency episode and not the follow-up. In spite of this, a survival analysis was performed in both groups, and the proportion of patients with no readmissions at the six month follow-up was significantly higher for lacosamide. This is probably due to the better long-term tolerance of lacosamide fostering better adherence.

To summarize, we provide evidence of the potential role of lacosamide and phenytoin in trigeminal neuralgia exacerbations. Our results pave the way for further prospective studies or randomized controlled trials, which are needed to confirm these findings and our main hypothesis. In this line, and according to our results, a therapeutic proposal could begin by applying 150 to 200 mg of lacosamide or 750 to 1000 mg of phenytoin in a 30 to 40 minutes infusion, depending on patient weight and comorbidities, with continuous cardiac monitoring and a strict surveillance of adverse effects and pain control. Regarding our results, lacosamide should be preferred over phenytoin due to a better adverse effect profile.

Conclusion

Intravenous lacosamide and phenytoin can be effective, safe treatments for acute pain in trigeminal neuralgia. According to our series, lacosamide might be better tolerated than phenytoin.

Article highlights

- Intravenous lacosamide and phenytoin can be effective and safe treatments for acute pain in trigeminal neuralgia.
- Lacosamide can be an effective option as intravenous treatment of pain in trigeminal neuralgia, with low proportion of adverse effects.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the Hospital Universitari de Bellvitge with reference EOM028/21. The confidential information of the patients was handled in accordance with Spanish regulations.

Availability of data and materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' contributions

AM-V contributed to the collection, analysis and interpretation of data and the writing of the report; ST to the collection and analysis of the data; JS-P to the analysis and interpretation of data and the correction of the report; SC to the analysis and interpretation of data and the correction of the report; MH-V to the correction of the report. All authors read and approved the final manuscript.

Declaration of conflicting interests

AM-V, ST, JS-P and SC received honoraria for participating on advisory boards and for collaborations as consultants and scientific communications; they also received research support as well as funding for travel and congress-attending expenses from Teva, Lilly, Roche, UCB, Bial, Chiesi, Allergan, Esai, Zambon, Kern Pharma, Pfizer, Biogen Idec, Novartis, TEVA, Merck, Neuraxpharm, Genzyme, Sanofi, Bayer, Almirall and Celgene. MH-V has received honoraria for participating on advisory boards and for collaborations as consultant, scientific communications, speaker, research support as well as funding for travel and congress-attending expenses for Abbie-Allergan, Novartis, Lilly, Almirall, Chiesi, Esai, Kern Pharma, TEVA and Zambon. His research group has received research grants from Abbie-Allergan; and has received funding for clinical trials from Lilly, Novartis, TEVA. In relation with this paper the authors have nothing to disclose.

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