Consequences on economic outcomes of generic versus brand-name drugs used in routine clinical practice: The case of treating peripheral neuropathic pain or generalized anxiety disorder with pregabalin

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Abstract

Background: Discrepancies are seen between arguments in favor of and against prescribing generic versus brand-name drugs.

Objective: To provide real-world evidence on treatment persistence, economic and clinical outcomes of pregabalin, generic versus brand-name (Lyrica®, Pfizer), routinely used to treat neuropathic pain (NP) or generalized-anxiety-disorder (GAD).

Methods: Electronic-medical-records from subjects' first starting treatment with pregabalin between January-2015 and June-2016 were retrospectively analyzed. Persistence, resources utilization, and costs were assessed, along with remitter and responder rates.

Results: 4,860 records were analyzed. Discontinuation was lower with brand-name than with generic in NP (adjusted hazard ratio [HR]: 0.70 [95% CI: 0.58–0.85], p<0.001) and GAD patients (HR: 0.63 [0.45–0.84], p<0.001). Adjusted mean total costs were lower with brand-name: €1,500 [1,428–1,573] vs. €2,003 [1,864–2,143] in NP and €1,528 [1,322–1,734] vs. €2,150 [1,845–2,454] in GAD (both p<0.001). More patients were remitters or responders with brand-name in NP (55.0% vs. 46.7% and 59.2% vs. 48.4%, respectively; p<0.001) and GAD (58.6% vs. 48.7% and 64.6% vs. 47.2%, respectively; p<0.001).

Conclusions: As a consequence of higher persistence in routine practice, patients who first started therapy with pregabalin brand-name versus generic showed better pain or anxiety outcomes at a lower cost to payers in Spain.

Keywords: neuropathic pain, generalized anxiety disorder, persistence, costs, outcomes, effectiveness, payers.

1. Introduction

Peripheral neuropathic pain (pNP), defined by the International Association for the Study of Pain (IASP) as pain initiated or caused by a primary lesion or dysfunction of the nervous system, is a common symptom of a group or variety of diseases [1]. The estimated prevalence of pNP is 1–10% of the adult population. This condition accounts for approximately 40% of cases of chronic pain [2]. Generalized anxiety disorder (GAD) is characterized by having symptoms of anxiety most

days for at least several weeks in a row [3]. Its prevalence is around 2–7% of the general population [4]. These two clinical entities entail a great deal of demand and a great many clinical repercussions, and they tend to be chronic. Due to the chronic nature of their symptoms and the probable associated disability, they may generate considerable direct costs as well as indirect costs (productivity loss) for society as a whole [5-8]. Also, these health conditions result in a loss of quality of life that affects all aspects of living: family, friends and work. It should be noted that many patients are not properly diagnosed, do not receive suitable drug treatment or are prescribed lower doses than they should be [9].

Drug therapy represents a cornerstone of treatment for these diseases [1,3]. *Pregabalin* (a neuromodulator and gamma-aminobutyric acid analogue) is the only active substance on the market indicated in both pNP and GAD [10]. At present, both brand-name and generic presentations are available (Lyrica®, Pfizer Inc and pregabalin INN, respectively). Generic drugs are medicines that are bioequivalent to the original brand-name drug and have the same levels of efficacy, safety and quality [11,12]. Factors that may influence their use include physician awareness and healthcare intervention strategies with respect to generic drugs [12,13]. Discrepancies are seen between arguments in favor of and against prescribing generic drugs [14]. Traditionally, the primary advantage of a generic drug was its cost–effectiveness ratio compared to its reference drug, as a generic drug coupled a similar expected clinical effect with a lower cost of drug acquisition. However, since reference prices were established, this is no longer the case in Spain; now, generic and brand-name drugs come at the same cost to the Spanish National Health System (SNS) after loss of exclusivity period or patent protection [15]. The disadvantage of a generic drug is the confusion it may cause in patients with respect to its commercial name (active substance) and its presentation or form (bioappearance), especially in older people [14,16,17]. This potential confusion may lead to medication errors, which could in turn lead to treatment non-adherence, cause a possible decrease in clinical effectiveness, trigger the onset of adverse effects and generate a potential increase in associated healthcare costs [18,19]. This change in pill appearance (physical characteristics of shape, color, size and packaging that identify medicines) which occurs when generic drugs are supplied by different brands over time might result in higher

levels of treatment discontinuation or less likely to be adherent [19]. Therefore, administration of a generic drug could be considered a factor to be taken into account, particularly in some countries, like Spain, where generic substitution is allowed and their governments encourage doctors to prescribe them. Pharmacists can make a substitution between generics, choosing one from those available in the national system of reference prices, unless the doctor and/or the patient prefer another product [15].

Treatment persistence constitutes a key factor in disease progression and risk of complications. Confirming this hypothesis (link between treatment persistence vs. clinical and economic consequences) in both diseases (pNP, GAD) with the same active substance (brand-name vs. generic pregabalin) would render the conclusions more robust. While there are other data sources, including claims databases, patient registries, internet-based consumer research and prescription-based data collection, this article focuses on the evidence with respect to behaviors and attitudes collected by the Spanish Health System Research Network (*Red de Investigación en Servicios Sanitarios,* RedISS), a research-based organization which uses electronic medical records (EMRs) stored on the OMIAPWIN software application in use at many healthcare centers in Spain. This allows for an established method of researching current treatment practices across a wide range of disease areas using robust, real-world data that accurately reflect current symptom prevalence and severity as well as associated treatment practices for a number of common chronic disease areas. This article provides real-world evidence on treatment persistence as well as clinical and economic consequences of generic versus brand-name drugs used in routine clinical practice to treat pNP and GAD with pregabalin.

2. Methods

2.1 Design

This paper reports and interprets the findings of a secondary investigational analysis conducted by ClinicResearch. This investigational analysis, approved by the Institutional Research Board of the Universitat Internacional de Catalunya in Barcelona and the Spanish Agency of Medicines, used existing anonymized EMRs linked from the patient database of the RedISS Foundation (*www.rediss.es*). The RedISS Foundation is a nonprofit research network whose primary mission is to conduct research on the services provided by healthcare management organizations in Spain. RedISS is a longitudinal, anonymized research database of EMRs kept by family physicians (FPs) across Spain. The patient data included in the database are stripped of identifying details as specified in Spanish Law 15/1999, of 13 December, on Personal Data Protection. For the findings presented here, primary care practices in Spain from two regions (Catalonia and Asturias) provided patient data in the form of clinical records for over 700,000 actively registered individuals. The data are representative of the Spanish population. The data available in the RedISS database include information on demographics, medical history (including diagnoses and health contacts), results of clinical investigations, drug prescriptions and days of sick leave. Diagnostic data are recorded using the International Classification of Primary Care version 2 (ICPC-2) and/or the International Statistical Classification of Diseases and Related Health Problems (Ninth Revision) codes [20]. The RedISS database contains data on hospitalizations and emergency room visits from reference regional and tertiary health centers for such FPs and their corresponding primary care centers. The RedISS database also contains information on pharmacy drug supply through its regional pharmacy drug supply database link.

2.2 Patient and Public Involvement

Patients or public were not involved in this work directly, but EMRs were abstracted from the database to carry out the analysis. The EMRs of patients with either pNP or GAD were identified in the RedISS database based on patients' medical and treatment history. Patients' first prescribed

pregabalin (brand-name or generic) between January 1, 2015, and June 30, 2016, were eligible to enroll. The inclusion criteria were as follows: male or female, 18 years of age or older, having been entered in the database 12 or more months before first being prescribed pregabalin, having been enrolled in the long term prescription follow up program at each healthcare center, having received ≥ 2 prescriptions for generic or brand-name pregabalin (depending on the analysis group assigned) and having been diagnosed with pNP or GAD in the 180 days before the date of enrollment, with at least 2 follow-up contacts in the database. Patients first prescribed pregabalin after June 30, 2016, and patients who might have been exposed to pregabalin within 12 months of the index date were excluded. Patients who received combination therapy with concomitant or sequential generic or brand-name pregabalin were considered ineligible for the analysis. The EMRs of patients whose healthcare was transferred out to other regions or healthcare centers during the follow-up period were also excluded. The EMRs of patients with concomitant pNP and GAD were excluded to prevent bias in estimating healthcare resource utilization and/or days of sick leave. From these data, four subgroups of therapeutic regimens were identified according to the Anatomical Therapeutic Chemical (ATC) Classification System, N03AX16 [21]: brand-name pregabalin for pNP, generic pregabalin for pNP, brand-name pregabalin for GAD and generic pregabalin for GAD. The index date was defined as the date on which a patient was first prescribed either brand-name or generic pregabalin in either the pNP group or the GAD group. Patients were followed up until the earliest date among the following options: the index date plus 12 months; the end of recorded data; the last prescription for the regimen of interest plus 30 days; or the date of regimen change. The end of recorded data was defined as the earlier date between the last date on which data was collected for the practice or the date of death.

The initial analysis plan included obtaining all available records that met all screening criteria in the enrollment period (from the index date). However, an initial predetermination of the minimum sample size was also performed. This because it was considered to have an initial estimation of the minimum sample size in each of the analyzed groups needed to achieve a sufficient statistical power, and also sufficient to calculate the effect sizes (magnitude of differences observed) to have a minimum clinical significance. Thus, the sample size was

calculated based on finding a minimum difference of €250 (standard deviation [SD]: €1000) between the brand-name drug and the generic drug in terms of non-adjusted healthcare costs, both in pNP and in GAD. These differences enabled detection, with an α error < 0.05 and a β error < 0.15 (85% statistical power), of differences of at least a small magnitude according to Cohen's *d* with a minimum effect size of 0.25 [22]. Given these parameters, it was estimated that there should recruit at least 300 medical records to each of the four groups.

2.3 Diagnosis and demographics

The records of subjects with pNP or GAD included in the database are habitually obtained according to the International Classification of Primary Care (ICPC-2) [20], codes N92-N99 or P74, and/or the International Classification of Diseases (Ninth Revision), Clinical Modification (ICD-9-CM; codes 350.1, 352.9, 353.1, 353.3, 353.8, 354.0, 355.1, 355.5, 357.2, 357.4, 357.8, 357.9, 053.13 or 300.02, respectively). The criteria followed were in all cases at the physician's discretion. pNP was considered to be pain initiated or caused by a primary lesion or dysfunction of the peripheral nervous system (nerve roots, nerve plexi or nerves)[1]. GAD was considered to be symptoms of anxiety most days for at least several weeks in a row. These symptoms had to include excessive worrying, muscle tension and autonomic hyperarousal [3].

The following demographic variables and comorbidities were considered to be extracted from the database: age (continuous and by range), sex and time since diagnosis (years), as well as prior history based on the ICPC-2 of hypertension (K86, K87), diabetes mellitus (T89, T90), obesity (T82), active smoking (P17), alcoholism (P15, P16), all types of organ failure (heart, liver and kidney), ischemic heart disease (codes: K74, K76, K75), cerebrovascular accident (K90, K91, K93), dementia (P70), depressive syndrome (P76) and malignant neoplasms (all types: A79, B72-75, D74-78, F75, H75, K72, L71, L97, N74-76, T71-73, U75-79, W72-73, X75-81, Y77-79). The following were also used for each patient cared for as a summary variable of general comorbidity: a) the Charlson comorbidity index [23], b) the number of chronic comorbidities and c) the case-mix index, based on adjusted clinical groups (ACGs), a system for classifying patients by resource isoconsumption [24]. These variables were obtained at the start of pregabalin therapy.

2.4 Treatments

Medication was obtained according to the ATC classification [21]: a) pregabalin (active substance) and b) concomitant medication: non-steroidal anti-inflammatory drugs (NSAIDs, M01), opioids (N02A), analgesics (N02B), sedatives/hypnotics (anxiolytics: N05C) and antidepressants (N06A). The information was obtained from the drug supply records for drugs. The choice of brand-name or generic drug for a specific patient was at the physician's discretion (*routine clinical practice*).

2.5 Outcomes

2.5.1 Adherence

The adherence rate was defined according to the criteria of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and calculated based on use/medication possession ratio (MPR) and treatment persistence [25]. *MPR* was assessed from the first to the last prescription and represents the number of days of medication supplied divided by the number of treatment days (from the index date). *Persistence* was defined as the time, measured in days, without stopping the initial treatment or switching to another medication at least 30 days after the initial prescription. It is expressed as the difference between the date of first supply (enrollment) and the date of last supply, plus the number of days that would be covered by the last supply (30 days).

2.5.2 Resource utilization and cost analysis

The societal and the National Health System (NHS) perspectives were taken into account to compute healthcare and indirect costs. Healthcare costs (direct costs) were considered to be those relating to healthcare activity (medical visits, days of hospitalization, emergency visits, diagnostic and therapeutic requests, etc.) performed by healthcare professionals. Non-healthcare costs (indirect costs) were considered to be those relating to work productivity loss (days of sick leave due to temporary disability). Cost was expressed as mean cost per patient (average per unit)

throughout the analysis period (1 year). Unitary costs applied were as follows: primary care medical visit; €23.19, emergency room visit; €117.53, hospitalization (one day); €420.90, specialized care medical visit (neurology, orthopedic, psychiatry or internal medicine departments); €92.00, day hospital session; €125.55, laboratory tests; €22.30, single x-ray; €18.50; and diagnostic/therapeutic tests (related to peripheral neuropathic pain and generalized anxiety disorder); €37.12. Prices were based on the sites' analytical accounting, except medication and days of sick leave. Prescriptions were quantified by retail price per pack at the time of prescription (according to the Drug Catalogue of the General Council of Associations of Official Pharmacists of Spain. Available at: https://botplusweb.portalfarma.com/botplus.aspx). Concomitant medication (non-steroidal anti-inflammatory drugs, opioids, analgesics, anxiolytics and antidepressants) was also included in calculating costs. Days of occupational disability and productivity losses were quantified according to the average interprofessional wage (source: Spanish Statistical Office [*Instituto Nacional de Estadística*, INE]) [26]. Cost per day not worked due to sick leave was €101.21. The analysis did not taken into account non-healthcare direct costs, that is to say, "out-of-pocket" costs or costs paid by the patient/family, as these are not recorded in the database and patients themselves could not be accessed through the retrospective capture of existing records.

2.5.3 Clinical effectiveness

To approximate clinical effectiveness, information was obtained from medical histories (clinical protocols) on relative reduction in baseline symptoms (severity of pain or anxiety) using the visual analogue scale (VAS) for pain or the Hamilton Rating Scale for Anxiety (HAM-A)[27,28]. Both scales are implemented in the routine follow up of patients in participant primary healthcare centers. The VAS measures the severity of pNP on a scale from 0 (no pain) to 10 (the worst pain imaginable). The HAM-A scores responses to 14 questions from 0 to 4 points and assesses the severity and frequency of anxiety, with a maximum scoring of 56 points. The scores for the two scales (VAS, HAM-A) were compared at the initial and final visits to obtain the absolute variation (points) and the relative variation (%) of pain/anxiety severity between the two visits (reduction since initial visit). The proportion of patients with anxiety symptoms in remission

(HAM-A < 7 points) or with mild or no pain (VAS < 4 points) as well as the proportion of responders (patients with a ≥ 50% reduction in their initial score for severity of pain or anxiety at their final visit) were also obtained.

2.6 Statistical analysis

Basic descriptive statistics, such as means and proportions not requiring statistical comparisons, are presented in tables by group of interest in the analysis. Analyses requiring statistical comparisons were performed using SPSS Version 17 (SPSS Inc., Chicago, USA). Standard parametric and non-parametric univariate statistical tests suitable for both the data type and the comparison group were performed. In making comparisons across patient subgroups within the RedISS sample, maximum likelihood/regression models were applied to isolate the influence of each possible explanatory variable on the outcome parameter of interest. These included generalized linear models, which are increasingly popular means of modeling health outcome data by comparing an outcome measure between two groups while controlling for confounding factors [29,30]. A descriptive univariate statistical analysis was performed, and 95% confidence intervals (CIs) were obtained to estimate parameters (subjects not lost). The normality of the distribution was verified through the Kolmogorov–Smirnov test. The bivariate analysis used analysis of variance (ANOVA) tests, the chi-squared test and the Mann–Whitney *U* test. To measure treatment persistence, a survival analysis was performed with the Kaplan–Meier estimator (comparison: log-rank test). The multivariate models used were as follows: a) analysis of covariance (ANCOVA; procedure: estimation of marginal means; Bonferroni adjustment), to correct costs, b) Cox proportional hazards model, to correct treatment persistence (dependent variable) and c) multiple linear regression, to obtain variables associated with healthcare cost (method: consecutive stepwise). The covariables included were as follows: sex, age, general comorbidity (Charlson, Resource Utilization Band [RUB]), time since diagnosis, MPR and treatment persistence.

2.7 Reporting guidelines

CHEERS reporting guidelines were used to write this article [31].

3. Results

From an initial screening of 282,120 subjects ≥ 18 years of age assigned to the sites, 5,850 patients fulfilling enrollment criteria were recruited. Patients receiving brand-name versus generic drug treatment were compared across 4 groups: a) brand-name pregabalin (N = 3,844; 79.1%) vs. generic pregabalin (N = 1,016; 20.9%) for pNP; and b) brand-name pregabalin (N = 674; 68.1%) vs. generic pregabalin (N = 316; 31.9%) for GAD. Table 2 shows the baseline characteristics of patients analyzed. In pNP, the mean age was 59.9 (SD: 13.6) years and 61.3% were women. In GAD, the mean age was 58.3 (SD: 16.7) years and 63.9% were women. There was an acceptable level of comparability between the brand-name group and the generic group both for pNP and for GAD (Table 1).

Tables 2 and 3 list medication use characteristics, doses administered and concomitant medication. For patients with pNP treated with brand-name pregabalin, mean treatment duration (6.1 vs. 5.2 months; $p < 0.001$), MPR (83.6% vs. 78.4%; $p<0.001$) and persistence after 12 months (20.8% vs. 15.6%; $p<0.001$) were higher than for those treated with generic pregabalin. The likelihood of discontinuing to be treated with brand-name pregabalin after 12 months is significantly lower than with generic pregabalin; hazard ratio was 0.70 (95% CI: 0.58–0.85, $p<0.001$). The mean daily dose of brand-name vs. generic pregabalin was similar (208.7 vs. 209.8 mg; $p=0.823$), while concomitant medication use was significantly lower in the brand-name group (1.6 vs. 2.1; $p< 0.001$), at the expense of NSAIDs, non-narcotic analgesia and opioids. Similar results were seen for GAD. With brand-name pregabalin, mean treatment duration (8.6 vs. 7.9 months; $p=0.008$), MPR (81.8% vs. 76.5%; $p<0.001$) and persistence after 12 months (41.2% vs. 30.7%; $p=0.001$) were higher than with generic pregabalin. The hazard ratio for discontinuation with brand-name pregabalin was 0.63 (95% CI: 0.45-0.84, $p<0.001$). The mean daily dose of brand-name vs. generic pregabalin was similar (232.5 vs. 330.1 mg; $p=0.811$). The concomitant medication group average was lower (2.0 vs. 3.0; $p<0.001$), respectively, at the expense of all groups. Figure 1 lists the Kaplan–Meier curves for treatment persistence both for pNP (A) and for GAD (B). These show that persistence was significantly higher for the brand-name drug in comparison with the generic drug ($p=0.001$ and $p=0.002$ for pNP and GAD, respectively).

Table 4 shows a comparison of brand-name vs. generic pregabalin in terms of resource utilization and costs by groups. For pNP, the total cost was €7.7 million; of this amount, 71.0% corresponded to direct healthcare costs and 29.0% corresponded to non-healthcare costs (productivity losses). Subjects being treated with brand-name vs. generic pregabalin used fewer healthcare resources, specifically in terms of primary care (PC) visits (10.6 vs. 13.2; p<0.001), specialized care visits (2.2 vs. 3.0; p< 0.001) and days of occupational disability (4.1 vs. 6.2; p=0.002). The adjusted average annual total cost of subjects being treated with brand-name vs. generic pregabalin was lower; €1,500 vs. €2,003, p < 0.001; difference: €–503. This difference was maintained for healthcare cost (€1,080 vs. €1,310, p<0.001; difference: €–230) and work productivity losses (€420 vs. €692, p=0.003; difference: €–272). For GAD, the total cost was €1.7 million; of this amount, 63.5% corresponded to direct healthcare costs and 36.4% corresponded to non-healthcare costs (productivity losses). Subjects being treated with brand-name vs. generic pregabalin used fewer healthcare resources, specifically in terms of PC visits (12.3 vs. 14.3; p=0.004) and specialized care visits (1.7 vs. 2.1; p=0.029). Days of occupational disability (5.4 vs. 8.2; p=0.100) showed no conclusive differences. The adjusted average annual total cost of subjects being treated with brand-name vs. generic pregabalin was lower; €1,528 vs. €2,150, p<0.001; difference: €–622). Differences were maintained for healthcare cost (€980 vs. €1,301, p<0.001; difference: €–321) and work productivity losses (€549 vs. €849, p=0.008; difference: €–300). Figure 2 shows total costs by patient age range and group.

In the multiple linear regression analysis, the total cost of pNP was associated with generic pregabalin (β = 0.15), therapeutic non-adherence (β = 0.15), comorbidity (β = 0.12), age (β = 0.10) and lower clinical effectiveness (β = 0.10) (p<0.001 in all cases). For GAD, the results were similar: the total cost was associated with age (β = 0.21), use of generic pregabalin (β = 0.17), therapeutic non-adherence (β = 0.13), lower clinical effectiveness (β = 0.12) and general comorbidity (β = 0.09) (p<0.001 in all cases). In pNP, treatment persistence was associated with women (odds ratio [OR] =1.6; CI: 1.3–1.9), use of brand-name pregabalin (OR = 1.2; CI: 1.1–1.3), clinical effectiveness (OR = 1.2; CI: 1.0–1.4) and age (OR = 1.1; CI: 1.0–1.3) (p<0.003). In GAD,

treatment persistence was associated with brand-name pregabalin (OR = 1.8; CI: 1.3–2.7), women (OR = 1.5; CI: 1.1–2.1) and age (OR = 1.1; CI: 1.0–1.3) ($p<0.01$).

Table 5 lists variation in severity of pain and assessment of anxiety between the start of treatment and treatment discontinuation by group. For pNP, no statistically significant differences were seen in scores on pain scales at the start visit between the brand-name drug and the generic drug (7.3 vs. 7.4 points; $p=0.093$). Compared to generic treatment, brand-name treatment showed an additional reduction in baseline pain: –10.7% (–63.4 vs. –52.7%; $p<0.001$). For GAD, the results were similar: no significant differences were seen in scores on anxiety scales at the visit start between the brand-name drug and the generic drug (27.3 vs. 27.7 points; $p=0.436$). Compared to generic treatment, brand-name treatment showed an additional reduction in baseline anxiety: –16.7% (–64.4 vs. –47.6%; $p<0.001$). In patients with remission of symptoms and in responders, similar results were seen both in pNP and in GAD, respectively.

4. Discussion

This paper provides real-world evidence on treatment persistence as well as clinical and economic consequences of generic versus brand-name drugs used in routine clinical practice to treat pNP and GAD with pregabalin. Findings observed reveal that patients who start treatment with brand-name pregabalin versus generic pregabalin, were associated with higher levels of treatment adherence, in terms of both medication possession and persistence, and better clinical outcomes (reduction in pain and anxiety), resulting in lower resource utilization and healthcare costs for the Spanish National Health System. According with Kazis et al.[22], these achieved not only statistical significance but also clinical and economic significance (effect size of the difference between the two options; Cohen's *d* of 0.33 and 0.65 in pain and anxiety, and 0.25 and 0.42 in healthcare costs for pNP and GAD, respectively). These findings were consistent both for pNP and for GAD, and are congruent with a prior published study conducted by this group also on pNP and GAD, although with gabapentin and venlafaxine [32]. However, it should be noted that there are few observational studies in real-world conditions in the literature consulted; this makes it difficult to compare results, yet highlights the fact that these findings are unique in the field of both neuropathic pain and generalized anxiety disorders. It is worth noting its representativeness (as well as its potential for application to other healthcare areas), as it includes results from health centers belonging to two regions that differ greatly in terms of both geographic location and population, yet yielded concordant outcomes (data not shown).

A great deal of evidence suggests that a generic drug has the same qualitative and quantitative composition in terms of active substance and pharmaceutical form, with demonstrated bioequivalence (bioavailability studies), in comparison with the reference (brand-name) medicinal product. It should be noted that generic versus brand-name drugs may differ in terms of excipient composition and outer appearance and that this may result in problems of bioappearance [16,17]. In Spain, the entry into the market of these drugs has contributed to a reduction in pharmaceutical expenditure in public health; however, at present, both generic and brand-name drugs have the same cost of acquisition as there is a reference price system [15]. In view of this, there should be no

pharmacological arguments that indiscriminately impede the prescription of brand-name or generic drugs.

At the end of the follow-up period, patients being treated with brand-name for pNP were associated with greater persistence (20.8% vs. 15.6%) and MPR (83.6% vs. 78.4%). Similar results were reported for GAD patients (persistence: 41.2% vs. 30.7%; MPR: 81.8% vs. 76.5%). In a general review of the literature, Wettermark found annual treatment persistence with pregabalin of 36.3% for GAD and 21.5% for neuropathic pain [33]. Our figures are similar to or perhaps slightly higher than those reported (though still low). There might be several explanations for this: a) our method of measuring persistence/MPR, b) the fact that we considered the dose indicated by the physician at the start of therapy, c) the fact that ours analysis is more recent, d) the fact that these patients require care (regularly go in for check-ups), and/or e) the fact that these patients are subject to specific follow-up nursing care. As said, our results are consistent with these observations, although we have not found any similar findings, with the exception of the above-mentioned with gabapentin and venlafaxine [32]. In addition to known reasons for non-adherence, which may be intentional (sociodemographic factors, side effects, drug prices, lack of understanding of treatment or health status, etc.) or unintentional (failure to remember how to take the medication correctly, etc.), the results suggest that administration of a generic drug could be considered an additional factor to be taken into account. The appearance of the medicinal product (not measured here) might influence our results and affect the worse adherence seen with generic drugs, as shown previously [32]. These factors include a different appearance (in terms of color and shape), a lack of certain presentations (delayed release or delayed absorption), variability in terms of excipients, a copayment effect or even a nocebo effect [34-38].

For pNP, patients with brand-name vs. generic pregabalin were associated with lower concomitant medication (1.6 vs. 2.1, with 86% vs. 97% using 2 or more concomitant medications, $p<0.001$), total costs (€1,500 vs. 2,003; difference of €503 per patient and treatment) and pain reduction (difference of 10.7%). For GAD, concomitant medication (2.0 vs. 3.0, with 71% vs. 83% using 2 or more concomitant medications, $p<0.001$), total cost per patient (€1,528 vs. €2,150; difference of €622) and anxiety reduction (16.7%) were also lower. It´s noticeable that opioids use

was significantly lower with brand pregabalin both in pNP and GAD subjects, which is important in an era of increasing use of such drugs to treat painful health conditions. The (statistically significant) lower cost of concomitant medication offset the higher cost of primary medication which was higher with the brand-name drug than with the generic drug due to a longer treatment duration: €428 vs. €418 in pNP and €438 vs. €448 in GAD. In addition, in the multiple linear regression model, the cost (pNP, GAD) was associated with generic pregabalin, non-adherence (persistence/MPR) and lower clinical effectiveness. The temporal relationship between non-adherence, lower clinical effectiveness and greater healthcare resource utilization seems consistent in the literature reviewed [18,19,32,39].

In recent published studies, Lumbreras found that switching between pills of different appearances was associated with lower patient adherence to pharmacological treatment and a higher uncontrolled blood pressure than no change in pharmacological treatment or change only in package but not in pill appearance [19]. Cheng showed that higher suicide rates were reported in patients who used generic versus brand-name medicinal products [40]. Leclerc found that patients being treated with generic medicinal products had higher rates of adverse effects [41]. Hsu [42], in a study to determine the long-term effectiveness of brand-name vs. generic antipsychotics to treat schizophrenia, found that higher doses of generic drugs (risperidone and sulpiride) as opposed to brand-name drugs were prescribed. Tran reported that the use of generic drugs is associated with a reduction in therapeutic monitoring objectives (clinical effectiveness: LDL cholesterol) in treating dyslipidemia [43]. Gagne [44], in a prospective study, found that patients who started a treatment with generic versus brand-name statins had higher rates of non-adherence and cardiovascular episodes. While these data cannot be generalized, they are consistent with other published studies [10,32].

Arguments in favor of and against generic drugs are not without controversy. By way of example, reviews conducted by Kesselheim and Manzoli defended the similar clinical efficacy between the brand-name drug and the generic drug [45,46]. Other authors with other designs found no differences in terms of outcome variables between brand-name and generic drugs. Unnanuntana [47], in a clinical study comparing generic and brand-name alendronic acid (N = 70 per group),

found that bone mineral density increased by 2.5% vs. 5.5% and that rates of adverse reactions were 35.7% vs. 30.0%, respectively. Mano [48], in a retrospective study, reported that switching between brand-name (N = 147) and generic (N = 135) atorvastatin did not affect patients' treatment persistence (85.9% vs. 73.5%) after 180 days of treatment. Loch enrolled 266 patients in his study [49]. He concluded that brand-name vs. generic atorvastatin achieved similar results in terms of total cholesterol and low-density lipoprotein cholesterol in the clinical management of dyslipidemia, although brand-name atorvastatin achieved improvements in high-density lipoprotein cholesterol. To our understanding, the following should be assessed: whether these studies obtained a suitable sample size (statistical power), where the balance would be between statistical significance and clinical significance/repercussions, and when meta-analyses are performed based on these studies. However, other authors concluded their studies with a number of recommendations. Candido suggested that the use of a generic drug may underestimate the effect of adherence of some medicinal products (single dose, delayed absorption)[50]; therefore, medicinal products administered to patients with chronic pain should be personalized to better meet analgesic needs and ensure patient safety. Fraeyman [51], based on a survey of 1,636 patients, recommended highlighting the name of the active substance on drug pack labels to prevent health risks, especially in older patients. Colombo concluded that his results are consistent with studies supporting the possibility that a change in the appearance of the pack each time a new generic drug prescription is supplied may create confusion and reduce patient adherence [52], which may in turn influence clinical effectiveness and safety. Our results could support these contributions. Like efficacy and bioequivalence between the brand-name drug and the generic drug, our findings suggest that changes in the *appearance* of the drug may have repercussions for patient safety, especially in chronic diseases, older patients and/or polymedicated patients. A reduction in variability of appearance (image of the drug or similar) among chemically identical medicines or implementation of some procedure that would guarantee the patient receives always the same type of generic drug could help to promote a lack of treatment discontinuation [53].

The potential limitations of this work may be related with retrospective capturing of data, such as disease under-recording and potential variability between professionals at the time of treatment

(the selection bias on the part of the treating physician when starting a brand-name or generic treatment, since this was not done randomly), the system of measurement used for the main variables, and the potential existence of a classification bias. In this regard, potentially inaccurate diagnostic coding in the diagnosis of pNP or GAD, or the absence of any data that might influence the final results (patient socioeconomic status, changes in drug dose prescribed, changes in form and presentation of generic drugs, prior acquisition of concomitant medication, lack of recording "out-of-pocket" costs, etc.), might be considered a limitation. In addition, the measurement of clinical effectiveness (pain or anxiety) could not be obtained in all patients, especially in the final period; however, this deficiency was uniformly distributed among the different patient subgroups.

In conclusion, and taking into account that results should be interpreted with caution, this work provide real-world evidence about starting treatment with brand-name pregabalin when compared with generic pregabalin for both pNP and GAD health conditions. Results showed brand-name pregabalin to be associated with higher levels of treatment persistence and adherence, resulting in lower healthcare costs, and, at the same time, higher levels of therapeutic effectiveness (greater reductions in pain and anxiety).

5. Key issues

- This was a secondary analysis of a retrospective investigation conducted using existing electronic medical records (EMRs) that evaluates for the first time the impact on economic and clinical consequences of treating two health conditions with pregabalin brand-mane (Lyrica®) or its generic formulation under real-world routine medical practice.
- The strength of this paper is that shows how the use of pregabalin brand-name or its generic counterpack associates with drug adherence in term of discontinuation and medication possesion ratio and how this, after adjusting by covariates, translates into meaningfull economic and clinic consequences for the patients and the national health system.
- A sufficient quantity of data from sixteen healthcare centers from two different regions were abstracted and assesed, then, supporting the ability of the findings to be generalized, altholugh with caution, to other settings in the country.
- The potential limitations of this work may be related with retrospective capturing of data, such as disease under-recording, errors in disease classification and potential variability between healthcare professionals at the time of treatment (the selection bias on the part of the treating physician when starting a brand-name or generic treatment). Nonetheless, the multivariate statistical analysis included adjustment for potential covariates.

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Legend to Figures

Figure 1: Kaplan–Meier curves for persistence and cumulative likelihood of remaining with treatment after 12 months of follow-up.

Figure 2: Total costs (healthcare and non-healthcare, in EUR) by patient age range and by group.

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Table 1: Characteristics (demographics and comorbidity) at start of therapy with pregabalin by group and indication.

Groups	Peripheral neuropathic pain				Generalized anxiety disorder			
Subgroups	Brand-name	Generic	Total	p	Brand-name	Generic	Total	p
Number of patients (%)	3,844 (79.1%)	1,016 (20.9%)	4,860 (100%)		674 (68.1%)	316 (31.9%)	990 (100%)	
Sociodemographic characteristics								
Average age (years)	59.7 (13.7)	60.6 (13.3)	59.9 (13.6)	0.066	58.8 (17.4)	57.4 (15.1)	58.3 (16.7)	0.218
Ranges: 18–44 years	15.6%	13.2%	15.1%		22.1%	19.0%	21.1%	
45–64 years	43.3%	41.4%	42.9%		38.7%	49.4%	42.1%	
65–74 years	29.9%	33.8%	30.7%		15.9%	15.5%	15.8%	
≥ 75 years	11.2%	11.6%	11.3%	0.054	23.3%	16.1%	21.0%	0.305
Sex (female)	61.6%	60.0%	61.3%	0.355	63.5%	64.9%	63.9%	0.675
Pensioners	59.2%	60.8%	59.6%	0.358	55.0%	54.4%	54.8%	0.856
General comorbidity								
Average diagnoses	6.6 (3.9)	6.9 (3.6)	6.6 (3.8)	0.036	7.3 (4.1)	7.0 (3.8)	7.2 (4.0)	0.276
Charlson index	0.6 (1.0)	0.7 (1.1)	0.6 (1.0)	0.191	0.6 (0.8)	0.6 (0.8)	0.6 (0.8)	0.998
Average RUB	2.8 (0.6)	2.9 (0.7)	2.8 (0.7)	0.018	2.9 (0.6)	2.9 (0.7)	2.9 (0.7)	0.647
1 (very low comorbidity)	4.4%	5.7%	4.7%		3.7%	6.0%	4.4%	
2 (low comorbidity)	17.0%	11.4%	15.9%		11.3%	12.3%	11.6%	
3 (moderate comorbidity)	70.7%	73.2%	71.2%		75.1%	68.4%	72.9%	
4 (high comorbidity)	7.2%	8.2%	7.4%		8.6%	11.7%	9.6%	
5 (very high comorbidity)	0.7%	1.5%	0.9%	0.018	1.3%	1.6%	1.4%	0.174
Associated comorbidities								
Hypertension	51.8%	51.2%	51.6%	0.754	45.8%	45.8%	45.8%	0.999
Diabetes mellitus	22.7%	21.7%	22.5%	0.462	16.9%	16.5%	16.8%	0.857
Dyslipidemia	44.0%	44.4%	44.1%	0.831	45.7%	44.9%	45.5%	0.823
Obesity	17.8%	17.5%	17.8%	0.824	17.1%	16.7%	17.0%	0.432
Active smokers	22.3%	22.8%	22.4%	0.759	18.4%	19.9%	18.9%	0.564
Alcoholism	2.7%	2.8%	2.7%	0.914	4.6%	5.1%	4.7%	0.749
Ischemic heart disease	7.2%	7.1%	7.2%	0.918	6.7%	6.3%	6.6%	0.837
Cerebrovascular accident	13.1%	12.3%	12.9%	0.495	12.9%	12.3%	12.7%	0.803
Organ failure	14.6%	16.7%	15.0%	0.093	12.7%	12.0%	12.6%	0.537

Dementia	3.3%	2.2%	3.1%	0.071	4.5%	4.7%	4.5%	0.835
Depressive syndrome	26.0%	26.3%	26.0%	0.838	47.5%	47.2%	47.4%	0.924
Malignant neoplasms	13.5%	12.8%	13.3%	0.571	10.7%	11.1%	10.8%	0.853
Categories of neuropathic pain								
Radiculopathy	49.9%	50.6%	50.0%			---		
Diabetic neuropathy	22.1%	22.1%	22.1%			---		
Postherpetic/trigeminal neuralgia	14.0%	12.8%	13.8%			---		
Other types of neuropathic pain	14.0%	14.5%	14.1%	0.758		---		

Values expressed as percentage or mean (standard deviation); p: statistical significance between brand-name vs. generic. RUB: resource utilization band.

Table 2: Treatment persistence, medication possession ratio and doses administered by group.

Groups	Peripheral neuropathic pain				Generalized anxiety disorder			
Subgroups	Brand-name	Generic	Total	p	Brand-name	Generic	Total	p
Number of patients (%)	3,844 (79.1%)	1,016 (20.9%)	4,860 (100%)		674 (68.1%)	316 (31.9%)	990 (100%)	
Time since diagnosis (months)	1.7 (1.2)	1.6 (1.2)	1.7 (1.2)	0.605	2.3 (1.4)	2.8 (1.7)	2.4 (1.5)	0.467
Median (P25–P75)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)		2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	
Treatment possession (months)	6.1 (3.4)	5.2 (3.5)	5.9 (3.4)	< 0.001	6.9 (3.5)	5.9 (3.6)	6.6 (3.6)	< 0.001
Median (P25–P75)	5.0 (4.0–8.0)	5.0 (2.0–8.0)	5.0 (4.0–8.0)		6.0 (4.0–11.0)	4.0 (4.0–10.0)	6.0 (4.0–10.0)	
Treatment duration (months)	7.0 (3.4)	6.2 (3.3)	6.8 (3.4)	< 0.001	8.6 (3.5)	7.9 (3.6)	8.4 (3.5)	0.008
Median (P25–P75)	6.0 (5.0–9.0)	6.0 (3.0–9.0)	6.0 (5.0–10.0)		9.0 (6.0–12.0)	8.0 (6.0–12.0)	9.0 (6.0–12.0)	
Medication Possession Ratio								
Average	83.6%	78.4%	82.5%	< 0.001	81.8%	76.5%	80.1%	< 0.001
95% CI	82.4–84.8%	75.9–80.9%	81.4–83.6%		78.9–84.7%	71.8–81.2%	77.6–82.6%	
Treatment persistence								
3 months	89.0%	83.5%	87.9%	< 0.001	92.3%	84.5%	89.8%	< 0.001
Hazard ratio compared to brand-name*		0.62 (0.51–0.76)		< 0.002		0.45 (0.30–0.69)		< 0.001
6 months	56.8%	52.8%	56.0%	0.020	80.0%	75.9%	78.7%	0.150
Hazard ratio compared to brand-name*		0.83 (0.72–0.96)		0.010		0.78 (0.57–1.08)		0.148
9 months	35.5%	28.4%	34.0%	< 0.001	55.3%	44.9%	52.0%	0.002
Hazard ratio compared to brand-name*		0.71 (0.61–0.83)		0.002		0.66 (0.50–0.86)		0.004
12 months	20.8%	15.6%	19.7%	< 0.001	41.2%	30.7%	37.9%	0.001
Hazard ratio compared to brand-name*		0.70 (0.58–0.85)		0.001		0.63 (0.45–0.84)		0.002
Pregabalin dosage (mg/day)	208.7 (142.7)	209.8 (140.2)	209.0 (142.2)	0.823	232.5 (151.3)	230.1 (127.8)	231.7 (144.1)	0.811
75 mg/day	3.9%	4.7%	4.1%		0.1%	1.6%	0.5%	
100 mg/day	8.6%	7.0%	8.2%		0.6%	1.6%	0.9%	
150 mg/day	63.6%	62.6%	63.4%		69.7%	57.3%	65.8%	
300 mg/day	14.0%	16.2%	14.4%		16.9%	32.0%	21.7%	
600 mg/day	10.0%	9.4%	9.9%	0.132	12.8%	7.6%	11.1%	< 0.001

Values expressed as percentage or mean (SD: standard deviation); p: brand-name vs. generic; CI: confidence interval.

*: Cox proportional hazards regression (corrected for covariables). Reference drug: brand-name pregabalin. P: percentile.

Table 3: Concomitant medication by group.

Groups	Peripheral neuropathic pain				Generalized anxiety disorder			
Subgroups	Brand-name	Generic	Total	p	Brand-name	Generic	Total	p
Number of patients (%)	3,844 (79.1%)	1,016 (20.9%)	4,860 (100%)		674 (68.1%)	316 (31.9%)	990 (100%)	
Concomitant medication (average)	1.6 (1.0)	2.1 (1.2)	1.7 (1.1)	< 0.001	2.0 (1.0)	3.0 (1.0)	2.0 (1.0)	< 0.001
1	13.9%	3.1%	11.6%		28.9%	17.4%	25.3%	
2	23.7%	22.8%	23.5%		21.8%	22.2%	21.9%	
3	28.3%	36.3%	30.0%		26.9%	33.5%	29.0%	
4	22.7%	24.7%	23.1%		12.2%	22.8%	15.6%	
5	9.8%	11.0%	10.0%	< 0.001	2.4%	3.5%	2.7%	< 0.001
Concomitant medication groups								
NSAIDs	48.3%	60.0%	50.7%	< 0.001	44.7%	54.7%	47.9%	0.003
Analgesics	71.0%	80.6%	73.0%	< 0.001	41.8%	55.4%	46.2%	< 0.001
Anxiolytics	17.2%	19.0%	17.6%	0.193	72.4%	87.7%	77.3%	< 0.001
Antidepressants	32.8%	34.1%	33.1%	0.461	41.8%	54.7%	46.0%	< 0.001
Opioids	25.9%	30.3%	26.9%	0.005	12.9%	18.4%	14.6%	0.031

NSAID: Non-steroidal anti-inflammatory drugs. Values expressed as percentage or mean (standard deviation); p: brand-name vs. generic.

Table 4: Resource utilization and associated costs (€) by group.

Groups	Peripheral neuropathic pain				Generalized anxiety disorder			
Subgroups	Brand-name	Generic	Total	P	Brand-name	Generic	Total	p
Number of patients (%)	3,844 (79.1%)	1,016 (20.9%)	4,860 (100%)		674 (68.1%)	316 (31.9%)	990 (100%)	
Resource utilization								
Medical visits (primary care)	10.6 (5.5)	13.2 (4.6)	11.1 (5.4)	<0.001	12.3 (10.3)	14.3 (9.6)	12.9 (10.1)	0.004
Laboratory tests	1.1 (1.2)	1.3 (1.4)	1.1 (1.2)	<0.001	0.8 (1.1)	1.2 (1.5)	0.9 (1.2)	<0.001
Conventional radiology	0.8 (1.0)	1.0 (1.1)	0.8 (1.1)	<0.001	0.5 (0.9)	1.6 (1.7)	0.8 (1.3)	<0.001
Complementary tests	0.3 (0.6)	0.3 (0.6)	0.3 (0.6)	0.306	0.1 (0.6)	0.3 (0.7)	0.2 (0.6)	<0.001
Days of hospitalization	0.2 (1.3)	0.3 (2.0)	0.2 (1.4)	0.010	0.1 (0.8)	0.3 (1.1)	0.2 (0.9)	0.020
Medical visits (hospital)	2.2 (3.3)	3.0 (3.2)	2.4 (3.3)	<0.001	1.7 (3.1)	2.1 (2.9)	1.8 (3.1)	0.029
Day hospital sessions	0.2 (1.1)	0.3 (1.8)	0.2 (1.3)	<0.001	0.1 (0.4)	0.2 (1.1)	0.1 (0.7)	<0.001
Emergency visits (hospital)	0.4 (0.7)	0.8 (0.9)	0.5 (0.7)	<0.001	0.5 (0.8)	1.1 (1.1)	0.7 (1.0)	<0.001
Days of occupational disability	4.1 (18.9)	6.2 (22.6)	4.6 (19.8)	0.002	5.4 (24.7)	8.2 (23.5)	6.3 (24.3)	0.100
Unadjusted costs								
Healthcare costs	1,079 (854)	1,328 (1,126)	1,131 (923)	<0.001	1,013 (728)	1,311 (933)	1,108 (811)	<0.001
Costs in primary care	722 (437)	782 (332)	735 (418)	<0.001	753 (410)	845 (433)	783 (420)	0.001
Medical visits	245 (127)	306 (107)	258 (126)	<0.001	285 (238)	331 (222)	300 (234)	0.004
Laboratory tests	24 (26)	29 (31)	25 (27)	<0.001	18 (24)	27 (33)	21 (28)	<0.001
Conventional radiology	15 (19)	18 (21)	16 (19)	<0.001	9 (16)	29 (32)	15 (24)	<0.001
Complementary tests	10 (23)	11 (23)	10 (23)	0.306	4 (22)	10 (26)	6 (24)	<0.001
Concomitant medication[1]	182 (371)	217 (254)	189 (350)	0.005	171 (190)	215 (180)	185 (188)	<0.001
Baseline medication	246 (116)	201 (118)	236 (118)	<0.001	267 (177)	233 (192)	256 (183)	0.006
Costs in specialized care	357 (706)	547 (1028)	396 (788)	<0.001	260 (503)	466 (685)	326 (575)	<0.001
Days of hospitalization	90 (534)	145 (834)	102 (609)	0.010	45 (327)	106 (483)	65 (384)	0.020
Day hospital sessions	202 (308)	272 (299)	217 (307)	<0.001	155 (287)	197 (266)	168 (281)	0.029
Medical visits	19 (132)	41 (227)	23 (157)	<0.001	7 (56)	31 (136)	15 (90)	<0.001
Emergency visits	46 (79)	89 (107)	55 (88)	<0.001	53 (96)	132 (125)	78 (113)	<0.001
Non-healthcare costs (productivity loss)	418 (1,915)	632 (2,288)	463 (2,000)	0.002	548 (2,496)	824 (2,371)	636 (2,459)	0.100
Total costs (EUR)	1,497 (2,115)	1,961 (2,611)	1,594 (2,235)	< 0.001	1,562 (2,618)	2,135 (2599)	1,745 (2,624)	0.001

Adjusted costs[2]			Difference*				Difference*	
Healthcare costs	1,080	1,310	–230	< 0.001	980	1,301	–321	0.001
95% CI	1,051–1,110	1,254–1,367			921–1,038	1,214–1,387		
Non-healthcare costs (productivity loss)	420	692	–272	0.003	549	849	–300	0.008
95% CI	356–484	569–817			357–741	565–1,132		
Total costs (€)	1,500	2,003	–503	< 0.001	1,528	2,150	–622	< 0.001
95% CI	1,428–1,573	1,864–2,143			1,322–1,734	1,845–2,454		

Values expressed as mean (SD: standard deviation); p: brand-name vs. generic; CI: confidence interval. *Difference: brand-name versus generic.

[1] Concomitant medication (non-steroidal anti-inflammatory drugs, analgesics, anxiolytics, antidepressants and opioids).

[2] Adjusted by covariates age, sex, BUR, Charlson severity index, comorbidities and baseline score in pain or HAM-A scales.

Table 5: Variation in pain severity and anxiety assessment between the start of treatment and treatment discontinuation by group.

Subgroups	Brand-name	Generic	p
Number of patients (%)	3,844 (79.1%)	1,016 (20.9%)	
*Peripheral neuropathic pain (VAS)**			
Start of treatment	7.3 (1.2)	7.4 (1.2)	0.093
Treatment discontinuation	3.0 (1.1)	4.5 (1.2)	< 0.001
Absolute variation (score)	–4.3 (1.3)	–3.9 (1.3)	< 0.001
Relative variation (%)	–63.4%	–52.7%	< 0.001
Remission (< 4 points in a 0-10 scored scale)	55.0%	46.7%	< 0.001
95% CI	53.4%–56.6%	43.6%–49.7%	
Responders (reduction ≥ 50% of baseline score)	59.2%	48.4%	< 0.001
95% CI	57.7%–60.8%	45.4%–51.5%	
Subgroups	Brand-name	Generic	p
Number of patients (%)	674 (68.1%)	316 (31.9%)	
*Generalized anxiety disorder (HAM-A)**			
Start of treatment	27.3 (6.9)	27.7 (6.7)	0.436
Treatment discontinuation	9.7 (4.8)	14.5 (5.0)	< 0.001
Absolute variation (score)	–17.6 (6.0)	–13.2 (5.6)	< 0.001
Relative variation (%)	–64.4%	–47.6%	< 0.001
Remission (< 7 points in a 0-56 scored scale)	58.6%	48.7%	< 0.001
95% CI	54.9%–62.3%	43.2%–53.3%	
Responders (reduction ≥ 50% of baseline score)	64.6%	47.2%	< 0.001
95% CI	60.9%–68.1%	41.7%–52.7%	

Values expressed as mean (SD: standard deviation); p: brand-name vs. generic. CI: confidence interval.
VAS: visual analogue scale for pain. HAM-A: Hamilton Rating Scale for Anxiety.