Journal of Diabetes and Its Complications 28 (2014) 698–704

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Impact of comorbidities on pharmacotherapy of painful diabetic neuropathy in clinical practice

Dan Ziegler [a,*], Edith Schneider [b], Frank G. Boess [b], Lovisa Berggren [c], Frank Birklein [d]

[a] Institute for Clinical Diabetology, German Diabetes Center, Leibniz Institute for Diabetes Research at Heinrich Heine University; Department of Endocrinology and Diabetology, University Hospital, Düsseldorf, Germany
[b] Lilly Deutschland GmbH, Medical Department, Bad Homburg, Germany
[c] Lilly Deutschland GmbH, Global Statistical Sciences, Bad Homburg, Germany
[d] Klinik und Poliklinik für Neurologie, Johannes Gutenberg Universität, Mainz, Germany

ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form 9 April 2014
Accepted 9 April 2014
Available online 18 April 2014

Keywords:
Duloxetine
Gabapentin
Pregabalin
Anticonvulsants
DPNP

ABSTRACT

Aims: We evaluated the impact of baseline comorbidities on the effectiveness of duloxetine and anticonvulsants (pregabalin/gabapentin) in patients with painful diabetic neuropathy in clinical care.
Methods: Outcomes from a 6-month, observational study with 2575 patients initiating/switching DPNP treatment were analyzed post-hoc. Propensity scoring was used to adjust for baseline factors influencing treatment choice in 1523 patients receiving duloxetine or anticonvulsants. Analysis of covariance models with fixed effects for baseline pain, treatment, propensity score, baseline characteristics or comorbidities, and their interaction with treatment were used to estimate LSmean effects on Brief Pain Inventory (BPI) average pain and interference scores.
Results: 89.5% of patients reported comorbidities, including hypertension (70.5%), hyperlipidemia (39.2%), and depression (24.8%). Macrovascular complications (37.0%) and 'other chronic pain' (41.5%), particularly joint pain had an impact on both pain treatments, i.e. less improvement of average pain and interference of pain. Better treatment responses with duloxetine vs. anticonvulsants were observed in patients with depression, those with high baseline BPI total interference score, especially general activity, and in patients with joint pain.
Conclusions: Comorbidities such as macroangiopathy and depression as well as pain characteristics should be considered in the treatment of DPNP as they may predict the effectiveness of duloxetine and anticonvulsants.

1. Introduction

Diabetic peripheral neuropathic pain (DPNP) is a common complication of diabetes affecting 13% to 26% of the diabetic population (O'Connor & Dworkin, 2009). It has growing importance due to the aging of the population, increasing prevalence of type 2 diabetes, and higher survival rates from diabetes (Sadosky et al., 2013; Tesfaye & Boulton, 2009). Diabetes patients have a high risk of developing cardiovascular and other diabetes-related complications or comorbidities. In a recent cross-sectional survey the most common comorbid conditions were sleep disturbance/insomnia, depressive symptoms, and anxiety (Sadosky et al., 2013).

Several studies have demonstrated that DPNP is associated with substantial patient burden, decreased quality of life, and impairments in many aspects of patients' lives (Gore et al., 2005; Tölle et al., 2006). Disorders associated with chronic pain – especially depression and anxiety – also greatly complicate the clinician's efforts to achieve significant pain relief in DPNP patients (Jain, Jain, Raison, & Maletic, 2011). Thus, individual patient factors, such as comorbidities, should also be considered when choosing DPNP treatment (Argoff et al., 2006; Baron, 2006; Wallace, 2007). Screening, diagnosing and optimally treating comorbidities may not only improve quality of life, but also positively impact DPNP (Jain et al., 2011).

Disclosures: Dan Ziegler has worked as a consultant for Lilly, Pfizer, Meda, Abbott, Takeda, AstraZeneca, Wörwag, Daiichi-Sankyo, Roche, Servier, and Merck Serono. He held presentations for Lilly, Pfizer, Meda, Takeda, Eisai, Berlin-Chemie, Wörwag, and MedUpdate, and has received financial support for research projects from Abbott, Eisai, and Quintiles. Edith Schneider, Frank G. Boess, and Lovisa Berggren own stock in Lilly and are Lilly employees. Frank Birklein has received institutional grants from the German Research Foundation, Rheinland-Pfalz Innovation Foundation, the German Physicians Society for Acupuncture, and an unrestricted educational grant from Lilly Germany. He is a member of scientific advisory boards for Pfizer, Lilly, Astellas and Grünenthal. He has received speakers' fees from Lilly, Pfizer, MedUpdate and Shire. He is a field editor of the European Journal of Pain and serves as a member of the editorial boards of Neurology, Pain Medicine and The Open Neurology Journal.

* Corresponding author at: German Diabetes Center, Auf'm Hennekamp 65, 40225 Düsseldorf, Germany. Tel.: +49 21133820; fax: +49 2113382244.
E-mail address: dan.ziegler@ddz.uni-duesseldorf.de (D. Ziegler).

http://dx.doi.org/10.1016/j.jdiacomp.2014.04.004
1056-8727/

The anticonvulsants (ACVs) pregabalin (PGB) and gabapentin (GBP) as well as tricyclic antidepressants and selective serotonin and norepinephrine re-uptake inhibitors (SNRIs) have been recommended to treat DPNP in a number of current guidelines (Attal et al., 2010; NICE guideline, 2013; O'Connor & Dworkin, 2009). The SNRI duloxetine (DLX) and the calcium channel modulator PGB are the only drugs approved by both the US Food and Drug Administration and the European Medicines Agency for the treatment of neuropathic pain in diabetes (Tesfaye et al., 2011). Since most of the randomized clinical trials (RCTs) excluded patients with certain comorbid patients, the outcomes of these studies may not be representative of a significant proportion of DPNP patients treated in routine clinical care. Moreover, traditional reporting of regulatory trials is not helpful in choosing whom to treat with which drug (Moore et al., 2010).

For example, there is little information on the effect of comorbidities on treatment effectiveness of DLX and PGB or GBP. Therefore, we characterized the comorbidities in patients treated in clinical practice in Germany with the SNRI DLX or the ACVs PGB and GBP. In particular, we addressed the question whether certain comorbidities were associated with a better or worse outcome in the treatment of DPNP.

In addition, the predictive value of different comorbidities and other baseline parameters on the effectiveness of treatment with DLX or ACVs was evaluated comparing the improvement in the Brief Pain Inventory (BPI) average pain score and the BPI interference score. This analysis may identify patient groups who will be more likely to benefit from a particular treatment.

2. Materials and methods

2.1. Study design

The present study was a 6-month, multicenter, prospective, non-interventional study. Adult patients diagnosed with diabetic peripheral neuropathy (DPN) and suffering from related chronic pain (i.e. pain for at least 3 months due to their DPN) starting a new or switching their pharmacological DPNP treatment (any medication according to investigator's decision) were eligible for participation in the study. Investigators were office based physicians of various specialties who usually treat DPNP in clinical practice, i.e. general practitioners, neurologists, diabetologists/endocrinologists, and pain specialists.

Documentation started at the baseline visit and during the further course of standard clinical care at approximately 1, 3, and 6 months after the initial documentation (or at early discontinuation of observation). Reasons for discontinuation of the DPNP treatment were also to be documented.

The study was approved by the appropriate ethics committee and patients provided written consent to the collection and release of anonymized data.

The primary objective of this non-interventional study was to investigate which interference item from the BPI was most relevant from the patients' perspective when starting or switching DPNP treatment. These results have been published elsewhere (Schneider, Ziegler, Wilhelm, Schacht, & Birklein, 2014).

Here we report post-hoc analyses focused on comorbidities of the observed DPNP population and their potential influence on the effectiveness of DPNP treatment with DLX and ACVs (PGB or GBP).

2.2. Assessments

In this study, the following scales were used:

The BPI (Modified Short Form) (Cleeland & Ryan, 1994) is a self-reported scale measuring the severity of pain and the interference of pain on patient functioning. The BPI pain severity score includes 4 items assessing the severity for worst pain, least pain, average pain in the past 24 h, and the severity of pain right now. Outcomes for each item range from 0 (no pain) to 10 (pain as bad as you can imagine). The BPI interference score measures the interference of pain with the patient's functioning based on the mean of 7 items assessing the interference of pain with functioning in the past 24 h (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life). Each item can be scored from 0 (does not interfere) to 10 (completely interferes).

The Hospital Anxiety and Depression Scale (HADS) Zigmond & Snaith, 1983) is a patient-rated instrument to assess both anxiety and depression symptoms. It was developed for non-psychiatric clinical settings as addressed in this study. It consists of 14 items: 7 items for the depression subscale (HADS-D) and 7 items for the anxiety subscale (HADS-A). Sum scores for both depression and anxiety (ranging from 0 to 21) indicate the degree of depression or anxiety. The HADS cut-off criteria have been defined at ≥ 8 (possible cases) and ≥ 11 (probable cases). Since the scale has well-proven and accepted validity and takes little time for the patient to complete (approximately 2 min), it is well suited to estimate depression and anxiety in a naturalistic study.

Additional questionnaires included Clinical and Patient Global Impression (Guy, 1976), Sheehan Disability Scale (Sheehan, 2000), and Short Form Health Survey (SF 12) (Ware, Kosinski, & Keller, 1996). These results are reported elsewhere (Happich et al., 2014).

Investigators were asked to document patient demographics and other baseline characteristics, such as medical history, concomitant medications, and DPNP treatment history, including time of the initial diagnosis of the underlying diabetic neuropathy and DPNP. Furthermore, comorbidities were documented according to a pre-defined checklist. In particular, the presence of pain not related to DPN was assessed using an open question "other chronic pain (Yes/No)" with the possibility to specify headache, back pain, and joint pain.

2.3. Statistics

Sample size was determined for the primary objective (Schneider et al., 2014) and based on the proportion of patients choosing 1 of the 7 BPI interference items as the most relevant one. Its precision (95% confidence interval [CI]) of $\pm 4.4\%$ to $\pm 6.0\%$ depended on the overall proportion of patients choosing the most frequent BPI interference item within the smallest group of interest (mild pain <30 mm as measured on BPI severity).

This manuscript presents post-hoc analyses, including patients initiating DLX, PGB, or GBP as monotherapy at baseline. Data analyses were performed using SAS version 9.1.3 statistical software (SAS Institute, Cary NC, USA).

Patient disposition, demographics, baseline disease characteristics, and medical history were summarized by descriptive statistics and were compared between the groups using t-test, chi-square test, or Fishers exact test as appropriate.

As this study was naturalistic (i.e. not randomized), we applied a 2-step procedure using propensity scores to adjust for baseline differences between treatments. In a first step, we analyzed factors that influenced the choice of therapy possibly leading to differences in treatment groups. Available factors were patient baseline characteristics, physician characteristics, disease characteristics, reason for choice of treatment, and disease severity. In particular, a logistic regression was used to determine the propensity score for each patient (D'Agostino, 1998), which indicates the probability of being treated with DLX based on the information of the baseline factors included. Higher propensity scores indicate a higher likelihood of being treated with DLX. A full model and a reduced model were calculated based on backward selection including only covariates with a p-value <0.05.

In a second step subcategories (baseline characteristics or comorbidities) were evaluated using an ANCOVA model. One ANCOVA model using adjusted means obtained after controlling for covariates (least square means) was calculated for each subcategory