Neuropathic pain, back to the patient

Robert van Seventer

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	Prof. dr. R.J. Stolker
	Prof. dr. K.C.P.Vissers

Voor Mammarijke

CONTENTS

Chapter I

Introduction

INTRODUCTION

Pain can be classified in several ways. The International Association for the Study of Pain (IASP) recommends describing pain according to five categories or axes, namely its anatomical location (neck, lower back, etc.), the body system involved (gastrointestinal, nervous, etc.), temporal characteristics (intermittent, constant, etc.), intensity and time since onset, and etiology (cause). The idea to discriminate between 'nociceptive' pain and 'neuropathic' pain only came into common clinical practice in the last decade. Since then, probably due to the therapeutic consequences of this classification, the proposal has become increasingly appreciated as a meaningful way to define pain.

In nociceptive or somatic pain, the initial stimulus of the peripheral nociceptor is produced chemically as a result of (potential) tissue damage. In contrast, neuropathic pain results from complex changes in the physiology of the nerve involved; this implies an affliction anywhere along the neuraxis from cortical neurons down to neurons in the anterior horn cell or in ganglia of the peripheral nervous system. The causes of neuropathic pain include structural damage by disease, trauma, metabolic disturbance, and infection.[1]

Neuropathic pain is defined by the IASP as: *pain arising from inflammation or injury to the peripheral or central nervous system, or from dysfunction of the nervous system*.[2] However, this definition has been an ongoing subject of debate. Some argue that inclusion of the term "dysfunction" makes this definition vague and far too broad.[3,4] Moreover, a group of European neurologists have proposed a new definition for neuropathic pain, namely: *pain arising as a direct consequence of a lesion or disease affecting the somatosensory system*.[5] This new insight emphasises the neurophysiological character of neuropathic pain and may help to overcome the current lack of progress in diagnostic classification.

Neuropathic pain occurs spontaneously (non-provoked), and responses to noxious and innocuous stimuli are pathologically amplified (provoked). The pain is caused by abnormal dysfunctional plasticity, i.e. repetitive neural action is re-focused to a disease state affecting the somatosensory system. Multiple alterations distributed widely across the nervous system contribute to different pain phenotypes. These alterations include ectopic generation of action potentials, facilitation and disinhibition of synaptic transmission, loss of synaptic connectivity and formation of new synaptic circuits, and neuroimmune interactions. Although neural lesions are necessary, the lesions alone are not sufficient to generate neuropathic pain; other factors influencing the risk to develop persistent pain include genetic polymorphisms, gender and age.[6,7]

The epidemiology of neuropathic pain has not been adequately studied, partly because of the diversity of the associated conditions. Current pooled data suggest that neuropathic pain may affect as much as 3% of the population.[8–15]

Demonstrating a lesion of the nervous system that is compatible with particular signs and symptoms provides strong support for considering the pain to be neuropathic. However, when no lesion can be demonstrated the limits of current diagnostic technology make it difficult to identify neuropathic pain. Furthermore, there is broad agreement among pain clinicians and basic scientists that no suitable diagnostic tools are available to unambiguously identify which mechanisms cause neuropathic pain in any given patient. Moreover, in neuropathic pain no single mechanism, sign or symptom is pathognomonic.[6,7,16]. However, combinations of certain symptoms, pain descriptors, and bedside findings do increase the likelihood of a neuropathic pain condition.[17,18]

For the above-mentioned reasons, neuropathic pain is often under-diagnosed or recognised too late, which can result in ineffective pain management and therapeutic failure. This stimulated the development and validation of screening tools, in the form of questionnaires, based on verbal pain description with (or without) some bedside testing. A questionnaire format was selected because subjective pain experience, particularly the description of sensory pain, is often used in the identification of neuropathic pain mechanisms.[19–23]

One of the aims of this thesis is to validate and implement a questionnaire for reliable identification of specific signs and symptoms in order to accurately diagnose neuropathic pain. It is expected that this will also lead to a better understanding of the mechanisms involved in these signs and symptoms. Therefore, the DN4 (a questionnaire developed in France [23]) was translated and validated for clinical use in the Netherlands.[24,25]

In the treatment of neuropathic pain, it is important to recognize that this pain condition requires a new approach. For example, the 'classic' analgesics (e.g. NSAIDs) are generally of little benefit, [26] and none of the available pharmacological interventions produces meaningful pain relief in more than about 50% of the patients with neuropathic pain.[26] Although many medications with some evidence of efficacy are available for neuropathic pain, this condition remains under-recognized and therefore undertreated.[27]

The most common pharmacological approaches to the management of neuropathic pain include antidepressants, anti-epileptics, SSRIs, SNRIs, opioids, and other treatments such as topical lidocaine patch and topical capsaicin.[28]

Double-blinded, placebo-controlled studies have been conducted to test the efficacy and tolerability of pregabalin in the treatment of peripheral neuropathic pain, in patients suffering from postherpetic neuralgia and post-traumatic pain, respectively. Pregabalin is an α2-δ ligand with demonstrated efficacy in epilepsy, neuropathic pain, and anxiety disorders.[29] The results of two randomized controlled trials on neuropathic pain are presented in this thesis[30,31].

A study in pain management clinics showed that patients with postherpetic neuropathic pain and patients with non-neuropathic low back pain were similar in their

reports of pain, dysfunctional cognition, mood, and physical function.[32] Two population-based studies which used screening tools to identify neuropathic pain showed that it was associated with an excessive psychosocial burden compared to nociceptive pain, and that there is ample evidence that neuropathic pain impairs patients' mood, quality of life, activities of daily living and performance at work.[22,33]

In this thesis we describe a cross-sectional survey among patients with postherpetic neuralgia which investigates health impairment and treatment patterns. Postherpetic neuralgia causes substantial patient burden expressed as interference with daily functioning and reduced health status associated with pain severity.[34] Patient burden, expressed as impairment of function and reduced quality of life, was significantly associated with pain severity as indicated by poorer health status (EQ-5D) and increased pain interference with functioning (mBPI-SF Pain Interference scores) with increasing neuropathic pain severity.[35,36]

Understanding the relationship between pain severity and corresponding levels in patient-reported function can inform treatment decisions and guide assessment of outcomes. We evaluated the relationship between pain (0–10 numerical rating scale, NRS), and patient-reported outcomes of function (Pain Interference Index from the modified Brief Pain Inventory), mood (Hospital Anxiety and Depression Scale), sleep (Medical Outcomes Study Sleep Scale), and sleep interference (0–10 NRS). [37]

Postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (DPN) are common chronic neuropathic pain conditions. There is a complex relationship between chronic neuropathic pain and sleep, with pain often disturbing sleep and poor sleep exacerbating pain. We analyzed data of nine clinical trials investigating pregabalin for the treatment of PHN and DPN and showed that pregabalin has a beneficial effect on pain and sleep disturbances. [38]

This thesis is based on clinical studies which focus on identifying and treating neuropathic pain, co-morbidity and impairment of the patient's quality of life.

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Chapter II

Linguistic validation of the DN4 for use in international studies

R. Van Seventer 1, C. Vos 2, W. Meerding 3, I. Mear 4, M. Le Gal 4, D. Bouhassira 5,6, F.J. P.M. Huygen 7

Author affiliations:
1 Amphia Hospital, Department of Anaesthesiology, Breda, The Netherlands. 2 Department of General Practice, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands. 3 Pfizer bv, Rivium Westlaan 142, 2909 LD, Capelle a/d IJssel, P.O. Box 37, 2900 AA Capelle a/d IJssel, The Netherlands. 4 MAPI Group, 27, rue de la Villette, 69003 Lyon, France. 5 INSERM U-792, Boulogne-Billancourt F-92100, France. 6 Université Versailles-Saint-Quentin, Versailles F-78035, France. 7 Department of Anaesthesiology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands.

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ABSTRACT

Objectives

Traditionally, pain is divided into two main groups: nociceptive pain due to an excess of nociception and neuropathic pain associated with an injury or dysfunction of the central or peripheral nervous system. The French neuropathic pain group has developed a specific questionnaire, the DN4, to help clinicians in the differential diagnosis of neuropathic and non-neuropathic pain. In order to allow this questionnaire to be used in international studies, it has been translated and linguistically validated into Dutch, German, Greek and Hungarian, using a well-established procedure.

Methods

The same method was used for each country and involved four stages: (1) two forward translations followed by comparison and reconciliation of the translations, (2) one backward translation, (3) review by an expert clinician, and (4) cognitive testing of the first seven items on patients.

Results

The translation work produced three types of situations. Either the original wording could be translated literally or semantic issues were discussed as the original wording was not always sufficiently clear and had to be clarified by adding an explanation, or, in the case of idiomatic phrases such as "pins and needles", it was necessary to use different expressions, the challenge being to retain the original concept while doing so. The versions proposed to patients and experts were well understood.

Conclusion

The DN4 items were linguistically validated in each of the target languages, thus providing the means for standardising the diagnosis of neuropathic pain and pooling the data collected during clinical research in the different countries involved.

1. INTRODUCTION

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".

The IASP defines neuropathic pain as "initiated or caused by a primary lesion or dysfunction in the nervous system" (Backonja, 2003). Recently, the IASP's special interest group proposed another definition: "pain arising as a direct consequence of a lesion or disease of the somatosensory system" (Treede et al., 2007). Neuropathic pain can be either peripheral or central, depending on where the lesion or dysfunction occurs (Attal and Bouhassira, 2004; Hansson, 2002).

The prevalence and incidence of neuropathic pain are difficult to assess given various origins and different ways of manifestation (Bowsher, 1991). Recent population-based studies in the UK and France based on screening tools have suggested that prevalence may be as high as 7–8% (Torrance et al., 2006; Bouhassira et al., 2008). Incidence rate in the Netherlands is estimated at 1% in the general population (Dieleman et al., 2008). This type of pain is under diagnosed and therefore not treated adequately (Hall et al., 2006).

The lack of consensus on diagnostic criteria for neuropathic pain makes differential diagnosis and therefore adapted therapeutic approaches difficult in daily practice.

Early preliminary studies had suggested that some pain descriptors from the McGill Pain questionnaire could have a diagnostic value (Dubuisson and Melzack, 1976; Boureau et al., 1990). This notion was confirmed in a series of recent studies (Bennett, 2001; Krause and Backonja, 2003; Bouhassira et al., 2005; Portenoy, 2006; Freynhagen et al., 2006a,b) showing that neuropathic pain has specific semiological characteristics. It was shown that, although no symptoms and/or signs were specific or pathognomonic, the combination of a relatively small number of selected symptoms and signs has a very high discriminative value for the identification of this category of pain. This was the basis for the development and validation of screening tools in the form of simple questionnaires based on verbal pain description.

Screening tools allow identification of potential patients with neuropathic pain, particularly in daily practice. This is probably their chief clinical strength. Their ease of use by professionals and patients makes them attractive. They provide immediate information. Clinicians should then be alerted to undertake further assessment, which may subsequently influence management decisions. They fail to identify about 10–20% of patients with clinician-diagnosed neuropathic pain. They may offer guidance for further diagnostic evaluation and pain management but they do not replace clinical judgment (Bouhassira et al., 2004; Bennett et al., 2007).

Epidemiology, in the general population and in specific clinical situations (e.g. Kaki et al., 2005; Torrance et al., 2006; Freynhagen et al., 2006a,b; Bennett and Bouhassira, 2007; Bouhassira et al., 2008) has been another major application of these tools.

Currently, five different screening tools are available for neuropathic pain including the DN4, developed by the French Neuropathic Pain Group (Bouhassira et al., 2005).

The aim being to use this new tool internationally, a linguistic validation process, described below, was required to ensure the equivalence of the concepts.

2. MATERIALS AND METHODS

Interestingly, although screening tools were developed in parallel in different countries and into different languages (English, German, French), most of the items (i.e. pain descriptors) included in these clinical tools are similar, which strongly reinforces the relevance of this approach (Bennett et al., 2007). Thus, despite the specifities associated with the description of chronic pain in different cultures, the symptom-based approach for the diagnosis of neuropathic pain appears to be valid trans-culturally.

The DN4 was initially developed and tested in French, and then an English version was produced. This questionnaire consists of 10 items divided into two distinct sections: the patient interview (questions 1 and 2) and the standardised clinical examination of patients (questions 3 and 4) (Appendix A).

This questionnaire was tested, validated, and its psychometric properties verified during a study carried out in France involving 160 patients. It was noted that the seven items corresponding to the patients' interview were sufficiently discriminating for the questionnaire to be used in large clinical studies with, for example, a telephone follow-up, or as part of epidemiological studies (Bouhassira et al., 2005, 2008). A recent psychometric study on 164 patients from Spain, further confirmed the high sensitivity of specificity of a Spanish translation of the DN4 questionnaire for the identification of neuropathic pain (Perez et al., 2007).

To obtain a translation of the DN4 original instrument in a target language that is both conceptually equivalent to the original and easily understood by the people to whom the translated questionnaire is administered, the Linguistic Validation followed an internationally-accepted translation methodology was performed using a well-recognized methodology which includes of the following standard steps (Figure 1) (Wild et al., 2005; Acquadro et al., 2004).

2.1. Forward translation

The aim of this step is to produce a version in the target language that is close to the original questionnaire, both in meaning and conceptually.

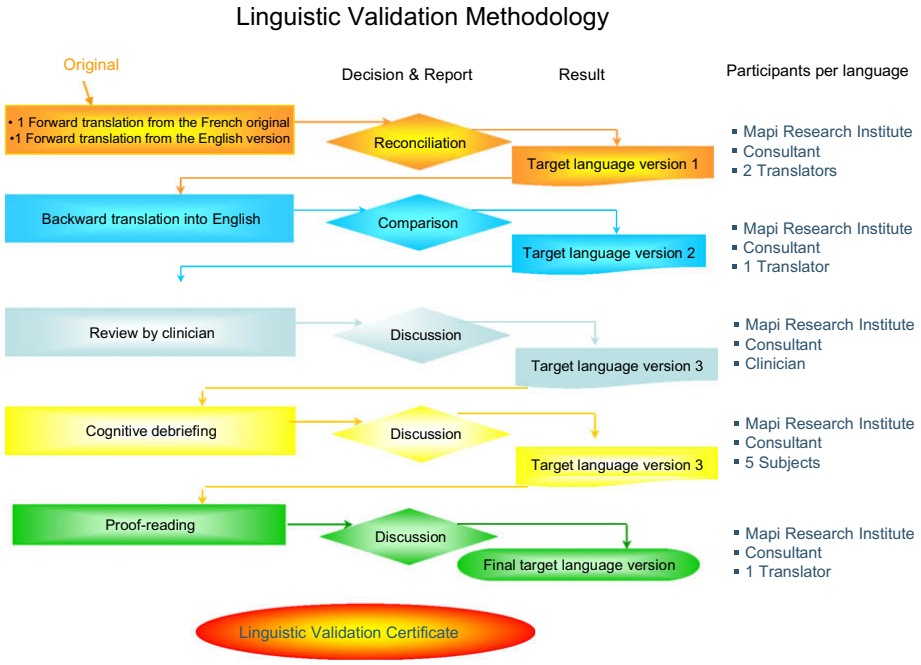

Fig. 1. Linguistic validation methodology. © MAPI Research Institute, 1995. All Rights Reserved.

The process consists of different stages.

First, the concepts of each item in the original questionnaire are clearly defined in collaboration with the author. This ensures that translators in the different languages have a common understanding of the concepts and items, thereby ensuring that the translations remain faithful to the original meaning.

Two professional translators, native speakers of the target language and fluent in the source language, undertake independent forward translations of the original questionnaire into the target language. A reconciled language version is developed on the basis of the two forward translations.

2.2. Backward translation

A backward translation of the reconciled language version is produced in the source language by a third professional translator, a native speaker of the source language and fluent in the target language. The back translation and the original version are then compared.

Any discrepancies encountered are analysed and, if necessary, changes are made to the reconciled translation in the target-language, leading to the production of a second target-language version.

2.3. Pilot testing

A clinician specialised in the treatment of neuropathic pain in the target country reviews the second target language version to obtain feedback from experts in the relevant medical field.

In the target country, the translated questionnaire is also administered to a small sample of five individuals with a low-to-average level of education, suffering from neuropathic pain and who are native target-language speakers, in order to assess the clarity, appropriateness of wording and acceptability of the translated questionnaire. The third target-language version is produced based on the results of the clinician's review and respondents' feedback.

A summary report is compiled at each stage of the process.

The methodology used to translate the DN4 was adapted slightly as the questionnaire was originally developed in French, and then an English version was produced. For that reason, both the French original and the English version were used as starting points for the linguistic validation process. Therefore, the standard methodology needed to be revised slightly was as follows:

- One forward translation was based on the French original instrument and produced by a native-speaking translator from the target country, fluent in French; the second forward translation was based on the English version of the instrument and completed by a native-speaking translator from the target country, fluent in English.
- Although the original scale was developed in French, the backward translation was in English in order to facilitate the process and allow the consultant and MAPI Research Institute to perform a quality control.
- While the consultants primarily referred to the English version, MAPI Research Institute's native French-speaking team provided input in the analyses and discussions based on the original French instrument, in order to reflect the original intended meaning.

This methodology was used to translate the DN4 into each of the four target languages.

The instructions and items 1 and 2 were translated using the complete process. In order for the Dutch version to be used both in the Netherlands and in Belgium, a harmonised version was produced after testing it on clinicians and patients both in the Netherlands and in Belgium. Items 3 and 4 were only tested on clinicians as these questions were only addressed to them.

3. RESULTS

The cognitive debriefing step was carried out in each country on five patients suffering from neuropathic pain. Patient details and the average time spent filling in these questionnaires are presented in Table 1.

Table 1
Details of patients taking part in cognitive debriefing.

	Number of patients with neuropathic pain	Age mean (min–max)	Sex male/ female	Completion time mean (min–max)
Hungary	5	51.2 (29–69)	2/3	6.8 min (3–10)
Greece	5	71.4 (60–84)	1/4	1 min (0.5–1.5)
Germany	5	45.4 (34–63)	1/4	2.2 min (2–3)
Netherlands	5	54.6 (28–75)	2/3	2.2 min (1.0–4.5)
Belgium	4	67.3 (56–83)	1/3	10 min (5–15)

– The instruction sentence: "*Please complete this questionnaire by ticking one answer for each item in the 4 questions below:*" was translated literally in each target language, although a few slight modifications were added. In Hungarian and German, the sentence was split in two to make it easier to understand. In addition, as the term for "item" in German had not been wellunderstood by patients, it was replaced by the equivalent of "point". In Hungarian, the second part of the instructions were translated using a colloquial expression "one–one square", which was confirmed to be understood well by patients, and in the Greek version, it was specified that an "X" had to be used to mark the answer (Table 2).

Table 2
Translations of the instruction sentence.

	Backward translation
English wording	*"Please complete this questionnaire by ticking one answer for each item in the 4 questions below:"*
Hungarian	Please answer the following four questions. Answer all four questions by marking one–one square
Greece	Please complete this questionnaire by marking with a X one answer for each item in the four questions below:
Germany	Please answer the following four questions. Check only one answer for each point:
Netherlands	Please complete this questionnaire by crossing one answer for each item of the four questions listed below:

– During the translation process, it is easiest when the original wording can be translated literally.

- Direct equivalents were found for items "burning" and "itching" in each of the four languages, but the Hungarian translators felt the need to add "sensation" after the word "burning" to make the meaning clearer.
- The item "tingling" also had an equivalent in the four languages, but the German translators decided to add the phrase "feeling of ants crawling" to better reflect the original concept better. In Greek, no additional phrase was necessary, as both translators used the same word in their forward translations, meaning "like when ants are walking on the skin".
- No comments were made by the clinicians concerning the translations of these three items, and they were well-understood by patients.
- The two items relating to sensory-deficit touch hypoesthesia and pricking hypoesthesia provided no translation problems as direct equivalents existed.
- Sometimes, semantic issues were discussed as the original wording was not always sufficiently clear and had to be clarified by adding an explanation.
- The items "painful cold" and "electric shocks" were modified slightly during the forward translations, for example by adding the word "sensation" or "like" to make their meaning clearer and therefore easier to understand.
- For example, the item "electric shock" was translated in Hungarian by the expression "sensation of electric-like shock" and for the Greek version, patients themselves proposed the term "like electric current" which seemed more idiomatic.
- When describing the "painful sensation of cold", all five Greek respondents spontaneously used the notion of "ice" and it was therefore suggested that a reference to this should be added.

  As this interpretation was found to be in line with the original concept, the item was consequently reworded as "painful sensation of cold as if it gets iced", as the patients' suggestion was approved by the clinician.
- The item "numbness" was translated into Hungarian and Greek using direct equivalents, with no need for modification. In German, two alternatives, "stiffness" and "numbness", were suggested in the French to German translation. The latter wording was found to be closer in meaning to the original concept. However, the consultant explained that the German term "taubheit" can refer to both "numbness" and "deafness". Consequently, to avoid any confusion, it was decided to use the alternative "feeling of numbness" in the reconciled version.
- The term "numbness" was rendered in Dutch using a direct equivalent. The clinician suggested rewording the item as "deaf/dead sensation". This change was implemented in the Dutch translation. The item was correctly interpreted during the cognitive debriefing step and was therefore implemented in the final Dutch version. However, during the additional step when the Dutch translation was harmonized with the Belgian Dutch version, the term "dead" was deleted from the Dutch translation to

be in line with the Belgian Dutch version. The revised wording "deaf sensation" was tested on 4 patients in the Netherlands and the original meaning was confirmed to be correctly understood. The change was consequently implemented in the updated Dutch for the Netherlands version.

– On the other hand, "brushing", the last item of the questionnaire, posed quite a few translation problems in each of the target languages.

A direct translation in Hungarian of "brushing" (dörzsölés) was found inappropriate in this context as this term refers to "brushing with strength". The item was therefore rendered as "touching (applying brush)" in the reconciled version. The clinician pointed out that a piece of cotton wool is more frequently used than a brush in neurological tests in Hungary. He therefore suggested rewording the item to read "touching (applying cotton wool or fine brush)". This change was implemented in the final Hungarian version.

The term "brushing" was used by the English-to-Greek translator and the word "rubbing" by the French-to-Greek translator. The former was retained in the reconciled version.

During the backward translation step, it was explained that the Greek noun for "brushing" explicitly referred to the object "brush". However, this word sounded too specific given that the original concept conveys a broader meaning and also implies rubbing with either the hand, a cloth, a brush or a piece of cotton wool. As a result, the term "brushing" was replaced with "rubbing" and this alternative was to be carefully checked with the clinician. The clinician suggested adding "or caressing" after the word "rubbing" to fully convey the original concept. Since this part of the instrument is to be completed by the physician, the suggested alternative was retained.

The German word "bürsten" meaning "brushing" was retained in the reconciled version but it was felt to be inappropriate in this context as it refers to actions requiring strength, such as cleaning shoes. The clinician suggested replacing the initial German wording with the phrase "caressing the skin with a brush". As this alternative was found to be closer to the original concept, the reconciled version was reworded accordingly.

In the reconciled Dutch version, the item was rendered with an idiomatic term "strijken", literally meaning "stroking". However, during the additional step when the Dutch translation was harmonized with the Belgian Dutch version, the Belgian Dutch version had used "wrijven". The Dutch clinicians confirmed that the latter alternative (meaning "rubbing") was closer to the original concept. The term "wrijven" was consequently implemented in the updated Dutch for the Netherlands version.

– The idiomatic expression "pins and needles" was the item that proved to be the most difficult to translate because it was necessary to use different expressions.

The expression "sensation of pins and needles" was preferred in Hungarian for the sake of clarity.

For the Greek version, both forward translators rendered this item with the noun literally meaning "pinnings". This alternative was felt to be idiomatic and was therefore retained in the reconciled version. The clinician suggested replacing "pinnings" with "needles and prickings", as the latter expression is actually used in everyday practice and is better understood by Greek patients. This change was therefore implemented in the Greek version. In German, this item proved difficult to translate and generated extensive discussion. The English to German translator rendered it as "feeling of ants crawling on the skin". However, this alternative was rejected as it was felt to be too close in meaning to item 4. The French-to-German forward translation used a German term "prickeln" (meaning prickling), which was explained to be slightly less intense than "stinging" but stronger than "tingling". This wording was retained in the reconciled German version and the developer was contacted to clarify the original concepts. The original item was confirmed to refer to a prickling sensation; consequently, the initial German wording was replaced with "stechen", a term generally used to describe a sharp pain as if caused by piercing. The clinician suggested adding the expression "like a thousand needles" in parentheses after the term "stechen". Most participants found "stechen" inaccurate and pointed out that this term would generally be used to describe a stabbing pain rather than the kind of pain caused by thin needles. It was therefore suggested that the item be reworded as "pieksen (nadelstiche)" meaning "pricking (needles)". However, to fully reflect the original concept, it was finally agreed to rephrase the item as "pricking (like a thousand needles)" as suggested by the clinician.

In the Dutch version, the term "prikkelingen", meaning "pricking", was found to be more appropriate and was consequently retained. However, it was discovered that the Dutch for "pricking" was confused with "tingling" by the patients. To avoid any misinterpretation, it was decided to replace the initial Dutch wording with "prikken". This term, meaning "stinging", was felt to better convey the original concept.

4. DISCUSSION

The DN4 is a questionnaire developed to help clinicians, who are not pain specialists, to diagnose neuropathic pain in their daily clinical practice. This questionnaire consists of pain descriptors and items relating to bedside sensory examination (Bennett et al., 2007).

When used in international studies, it is necessary to have language versions of this questionnaire available that are easily understood by patients and doctors in the different countries involved, and that measure the same concepts (Acquadro et al., 2004).

Thus, the aim, when translating any document, is to transpose the text from the original language (source language) into another language (target language), while transmitting the message contained in it as faithfully as possible.

However, there is a difference between a translation, where the ideas expressed in one language are translated into another, and linguistic validation, whose objective is to obtain a text that is conceptually equivalent without necessarily being a literal translation.

Item equivalents are found in different languages, yet it is necessary to ensure that they are correctly understood by users of the document. For example, in the DN4 questionnaire, although an item such as "itching" posed no problem to translate, as an equivalent existed in the target language, it was necessary to add the word "sensation" after the item "burning", to ensure in this case that the concept was clear and unambiguous to patients.

The instruction sentence of the DN4 questionnaire "Please complete this questionnaire by ticking one answer for each item in the four questions below:" was, at first sight, very simple to translate, yet adaptations were made. Although equivalent words existed in each of the languages, slight modifications in sentence structure or vocabulary were necessary to make it easier to understand and to adapt it to the language structure found in each target country.

To ensure conceptual equivalence, it is essential to define the concepts precisely beforehand so that there is absolutely no ambiguity in interpretation, and the interpretation is identical in every target language.

Few items in the DN4 questionnaire posed an interpretation problem, but the meaning is not easy to render in all languages. For the item "tingling", although a direct equivalent was available in German, an explanatory phrase meaning "feeling of ants crawling" was added to reflect the defined concept more closely. During cognitive debriefing, patients validated this proposal, which eliminated any comprehension difficulties.

"Brushing" posed a conceptual problem, as the concept conveyed by the word for "brushing" in certain languages did not correspond to that initially foreseen by the questionnaire's author. The point of this item was to evaluate whether stimuli that are innocuous on normal skin can induce or increase pain for the patient. In some languages, such as Hungarian or German, the literal translation of the word was inappropriate, as the action suggested by this word was stronger than the author had intended.

In a straightforward translation, the direct equivalent of "brushing" would have been used, which would have been linguistically correct. However, the linguistic validation process allowed the concept of a gentler action to be transcribed more clearly, and which also happened to correspond to what clinicians normally do when they examine the patient. The risk of ambiguity was therefore eliminated.

This exercise is even more complex when the item is expressed by an idiomatic expression. In an ideal situation, it would be better for questionnaire developers to avoid using

idiomatic expressions, although these often express the exact concept that is sought after. It is sometimes possible to find an equivalent expression in the target language, but it is often necessary to use a circumlocutory phrase. In the DN4 questionnaire, the expression "pins and needles" was translated in each of the target languages using a phrase linguistically remote from the original, but that still conveyed the same conceptual meaning.

The linguistic exercise is difficult as there are not one but several solutions that can usually be applied to different criteria. The question, therefore, is which criterion to adopt; either staying as close as possible to the original language structure or register, ensuring that there are no ambiguities by avoiding the risk of double meanings/double negatives, or favouring the cultural aspect. Though the solutions retained in all languages are not identical, the fact that similar criteria are applied in the decision-making process ensures that the different target-language versions provide consistent and comparable results when applied in practice.

The results of the linguistic validation of the DN4 questionnaire clearly illustrate the importance of the various steps in the process.

The forward translation led to a consensus on the vocabulary, for example, with the item "tingling", for which the two Greek translators used the same word in their forward translations, meaning "like when ants are walking on the skin".

Backward translations avoid mistranslations and inaccuracies, although such problems did not arise in this case.

An adult's understanding of a questionnaire is not affected by the patients' age but rather by their level of education. Therefore, the age difference in the patients interviewed in Greece, Belgium and in the other countries did not pose a problem. On the other hand, cognitive debriefing of subjects with a low-to-average level of education ensured that all items were understood correctly, using vocabulary suggested by the patients themselves. For example, the item "painful cold", which they described as "cold as if it gets iced", perfectly conveyed the concept sought and ensured the absence of ambiguity. Finally, the clinician-review step provides an extra quality control, validating the description of pain as expressed by patients and observed during clinical examination.

The linguistic validation process enabled items of the DN4 to be linguistically validated in each of the target languages. In clinical trials or epidemiological studies, the DN4 will provide the means for standardising the diagnosis of neuropathic pain and pooling the data from the different countries involved. It will be interesting to confirm the psychometric properties of each of these versions with the patient populations included in these studies, which is already the case for the Dutch version of the DN4, which is currently undergoing clinical validation in The Netherlands

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APPENDIX A. DN4 QUESTIONNAIRE (ENGLISH VERSION)

Question 1: Does the pain have any of the following characteristics?		
	Yes	No
Burning		
Painful sensation of cold		
Electric shocks		
Question 2: Is the pain associated with any of the following symptoms in the same area		
	Yes	No
Tingling		
Pins and needles		
Numbness		
Itching		
Question 3: Is the pain located in an area where examination reveals either of the following?		
	Yes	No
Hypoesthesia to touch		
Hypoesthesia to prick		
Question 4: Is the pain provoked or increased by the following?		
	Yes	No
Brushing		

Bouhassira et al. (2005).

Chapter III

VALIDATION OF THE DUTCH VERSION OF THE DN4 DIAGNOSTIC QUESTIONNAIRE FOR NEUROPATHIC PAIN

Robert (R.) van Seventer 1, Kees (C.J.) Vos 2, Maurice (M.J.M.M.) Giezeman 3,Willem-Jan (W.J.) Meerding 4, Benoit (B.) Arnould 5, Antoine (A.) Regnault 5, Maarten (M.J.P.G.) van Eerd 1, Carola (C.) Martin 6, Frank (F.J.P.M.) Huygen 6

Author affiliations:
1 Amphia Hospital, Department of Anaesthesiology, Breda, Netherlands. 2 Erasmus Medical Center, Department of General Practice, Netherlands. 3 Diakonessen Hospital, Zeist, Netherlands. 4 Pfizer bv, Netherlands. 5 Mapi Values, Lyon, France. 6 Erasmus Medical Center, Department of Anaesthesiology Pain treatment centre, Rotterdam, Netherlands

Submitted

ABSTRACT

Difficulties in diagnosing neuropathic pain in routine clinical practice support the need for validated and easy-to-use diagnostic tools. The DN4 neuropathic pain diagnostic questionnaire aims to discriminate neuropathic pain from nociceptive pain, but needs clinical validation.

A total of 269 patients with chronic pain in three pain clinics were included in the study of which 248 had analyzable data. The mean duration of pain was 4.9 years. The most frequent etiologies were posttraumatic (36%), (pseudo) radicular (13%) and mechanical back (12%) pain. The mean intensity of patients' pain at the moment of the visit was 5.6 on a 0–10 scale.

196 out of 248 patients had an identical pain diagnosis from both physicians: 85 had neuropathic pain, 57 had nociceptive pain, and 54 had mixed pain. Among patients with identical diagnoses of neuropathic or nociceptive pain, using a receiver operating characteristic curve analysis, the area under the curve (AUC) was 0.81 for the DN4 7-item and 0.82 for the 10-item version. A cut-off point of 5/10 for the full questionnaire resulted in a sensitivity of 75% and a specificity of 79%, while a cut-off point of 4/7 for the partial questionnaire resulted in a sensitivity of 74% and a specificity of 79%. The items "brushing", "painful cold" and "numbness" were most discriminating.

The DN4 is an easy-to-use screening tool that is reliable for discriminating between neuropathic and nociceptive pain conditions in daily practice. Item-specific scores provide important information in addition to the total score.

INTRODUCTION

Pain can be classified in several ways. The International Association for the Study of Pain (IASP) recommends describing pain according to five categories or axes, namely its anatomical location (neck, lower back etc.), the body system involved (gastrointestinal, nervous etc.), temporal characteristics (intermittent, constant etc.), intensity and time since onset, and etiology (cause). From a therapeutic point of view a practical classification between nociceptive and neuropathic pain is also advisable because each group requires a different treatment strategy.

Nociceptive pain is primarily treated with analgesics as described on the WHO ladder, for example with NSAIDs or weak and strong opioids. Neuropathic pain has to be treated with the so-called co-analgesics, drugs often originally not developed for the treatment of pain but which have a positive effect on this special kind of pain, for example tricyclic antidepressants and anti-epileptics [3].

Neuropathic pain is often difficult to diagnose and therefore possibly regularly underdiagnosed or recognised too late, which may result in poor pain management strategies and therapeutic failures [9]. In a large primary care database study the incidence of neuropathic pain was estimated to be 8.2 per 1000 person years translating to more than 0.8% of the population per year or more than 130.000 cases in the Netherlands yearly [8].

In this study more than 50% of cases received pain medication within 6 months after diagnosis, mostly consisting of NSAIDs or aspirin. Anticonvulsants and tricyclic antidepressants were only used by 4.8 and 4.7% of cases respectively. Among every 1000 patients registered with a general practitioner, about 60–80 patients will have symptoms of chronic neuropathic pain; 50% of these patients require medication and regular support [11]. The difficulties in identifying neuropathic pain support the need for diagnostic tools that can be used with, or even without, bedside testing [5]. The methods for developing and validating such tools are well defined [2]. Several screening tools are available in the form of questionnaires based on verbal pain descriptions. Regularly used screening questionnaires are the PainDetect [10] the S-LANSS [4] and the DN4 [7]. These screening tools allow identification of patients with neuropathic pain with a high degree of sensitivity and specificity. They can be used by pain specialists but also by general practitioners and nurses in daily practice [6]. DN4 stands for "douleur neuropathique 4 questions" and was developed by the French Neuropathic Pain Group. The DN4 was designed as an easy to complete diagnostic questionnaire and is composed of 10 yes or no items. It was designed to compare signs and symptoms in patients with chronic pain associated with neurological (peripheral or central) or somatic tissue injuries [7]. The DN4 was linguistically validated in several languages including the Dutch and Spanish language [13,14].

The primary objective of this study was to evaluate the diagnostic value of the Dutch version of the DN4 questionnaire. The secondary objectives were to evaluate the psychometric properties and to compare these properties with those of the original French version.

METHODS

Description of the DN4 questionnaire

The DN4 is a neuropathic pain diagnostic questionnaire built in two parts. The first part is based on symptoms estimated in an interview of the patient and can be self-administered. The second part is based on a standardized clinical examination. The interview part includes 7 items corresponding to two domains. The questions initially assess pain characteristics (burning, painful cold and electric shocks), and subsequently assess associated symptoms of abnormal sensations in the same area (tingling, pins and needles, numbness, itching). The examination part includes two domains measured by 3 items that address signs identified with a neurological examination: touch hypoesthesia, pricking hypoesthesia and pain caused or increased by brushing. Examination of sensitivity to touch and pricking is made by means of a soft brush and a von Frey hair respectively. In order to evaluate the tactile allodynia the soft brush is used once more. Every item is scored on a binary scale, with a no scoring as 0 and a yes scoring as 1. The sum of the item scores leads to a global score range between 0 and 10 when the 7 item interview part as well as the 3 item examination part are included. The total score ranges between 0 and 7 when only the 7 item interview part is utilised.

PATIENTS

Eligible patients were identified during referral and asked to participate in the study. Definite recruitment took place during the first visit in one of three participating pain clinics in the Netherlands, two general hospitals and one university hospital. All consecutive patients, men or women over 18 years old, with pain complaints were asked to participate in the study. Previously sent Data Privacy Statements were collected at the first visit, signed and dated.

Patients were included when their primary reason for consulting the doctor was chronic pain, defined as having pain for more than 3 months [12]. Other inclusion criteria were: suffering from moderate to severe pain (scoring 5 or higher on a 0–10 Numerical Rating Scale), being first time visitors and not yet previously diagnosed by the investigator. Exclusion criteria were major comorbidity (e.g. malignant disorders), fibromyalgia,

headache or visceral pain, communication or language issues, cognitive impairment, intellectual disorders, severe depression or psychosis (based on DSM IV) or participating in a clinical trial. Patients had to be able to speak and read the Dutch language.

DESIGN

The study was set up as a prospective observational study. At the first visit each patient was seen by a research nurse, and the same day was independently diagnosed for nociceptive, neuropathic or mixed pain by a physician. An independent diagnostic confirmation by a second physician took place the same day or at least within 72 hours after the first visit. All physicians were experienced pain anaesthesists or neurologists familiar with diagnosis and management of pain.

Prior to the first visit, patients were asked to complete the 7 self-assessment items of the DN4 questionnaire. On the day of the first visit the research nurse checked the 7 item questionnaire for completion and completed the demographic data of the patient (date of birth, gender, ethnic origin, medication for pain). The research nurse then administered a second full 10-item DN4 questionnaire to the patient. Subsequently and without knowledge of the information from the patient and research nurse administered DN4 questionnaires, the first physician completed the last 3 DN4 items of the patient administered questionnaire. The first physician also completed a diagnosis form in which the diagnosis (neuropathic, nociceptive or mixed pain) was stated. The second physician was asked to complete the same diagnosis form. Both physicians were blinded for the completed items of the DN4 and the second physician was blinded for the diagnosis of the first physician. Both physicians used whichever diagnostic tools they felt were appropriate.

In order to compare the results of this study with the results of the previously performed validation study [7] we aimed for a comparable sample size of 70–80 patients in each of three diagnostic groups.

Statistical analysis

Frequencies, standard deviation (SD) and total scores of all items were measured. All DN4 questionnaires were checked on completion. Questionnaires missing one or more items were not used in the analysis. The demographic data of patients removed from the analysis were compared with the remaining cohort.

The inter-rater reliability (i.e. agreement between the two assesments) of the last 3 DN4 items and the reliability for self- and hetero-administrations of the first 7 DN4 items were evaluated using Kappa coefficients. Strength of agreement is seen as poor

for values of Kappa <0.20; fair 0.21–0.40; moderate 0.41–0.60, good 0.61–0.80 and very good >0.81 [1].

The analysis of the discriminatory properties of the DN4 was limited to patients who were diagnosed with neuropathic or nociceptive pain by both physicians (n=142). In these patients the least doubt exists about the type of pain, and so they therefore provide the most appropriate groups to analyze the discriminatory properties. The discriminatory properties of the DN4 were assessed individually for each item as well as for the total scores of the 7-item and 10-item questionnaires. In this procedure, similar to the original French study, the diagnosis of neuropathic pain or nociceptive pain made by the physicians was considered as the gold standard. The ability of the DN4 items to discriminate between patients with nociceptive pain and patients with neuropathic pain was assessed using odds ratios (OR).

The predictive power of the DN4 diagnostic procedures was evaluated using the sensitivity, i.e. the ability of the diagnostic procedure to correctly identify patients with neuropathic pain, and the specificity, i.e. the ability of the diagnostic procedure to correctly identify patients without neuropathic pain. Receiving operator characteristic (ROC) curve was constructed and the area under the curve (AUC) calculated. A ROC curve is a plot of sensitivity as a function of 1–specificity for the possible cut-off points. This curve usually has a concave shape connecting the points (0,0) and (1,1). The AUC is a measure of the diagnostic power of the test, independent of cut-off points. An AUC <0.60 is considered 'negative', >0.60 and < 0.80 as 'doubtful', >0.80 and < 0.90 as 'good' and >0.90 as 'very good' [1]. The Youden Index was calculated as the maximum of sensitivity plus specificity minus one for all possible cut-off points to identify the most relevant cut-off values [15]. All data processing and analyses were performed with SAS software for Windows (Statistical Analysis System, Version 9).

RESULTS

The study was performed in three different pain clinics from September 2006 until September 2008. In total 269 patients were eligible to enter the study. 19 patients did not complete all 7 DN4 self-assessment items. From the remaining 250 patients the diagnosis was missing from 1 patient, and baseline data were missing from 1 patient, resulting in 248 patients with analyzable data.Descriptions of socio-demographic characteristics in eligible patients are shown in Table 1.

Table 1 Description of socio-demographic and pain characteristics in the eligible population (N=269)

Age, median (IQR Q1-Q3)	53.3 (41.2–63.1)
Gender, female (%)	68.0
Ethnic origin	
Black (%)	0.7
Caucasian (%)	95.9
Other (%)	3.4
Pain characteristics	
Duration of pain in years, median (IQR Q1-Q3)	2.0 (0.8–6.0)
Intensity of pain, mean (SD)	5.6 (2.2)
Acceptable pain intensity, mean (SD)	3.3 (2.1)
Results of sensory tests	
Pinprick: decreased, normal, increased (%)	32.7, 33.5, 31.6
Cotton wool: decreased, normal, increased (%)	32.7, 43.5, 21.6
Cotton bud: decreased, normal, increased (%)	29.4, 42.8, 25.7

SD, standard deviation, IQR interquartile range.

The mean age was 52.3 years. A greater proportion of women entered the study (68%). The mean intensity of patients' pain at the moment of the visit was 5.6 on a 0–10 scale, and the mean acceptable pain intensity was 3.3. The mean duration of pain was 4.9 years. The most frequent etiologies of the pain were posttraumatic (36%), (pseudo) radicular (13%) and mechanical back pain (12%) as presented in Table 2.

Table 2 Pain etiology ranked by frequency in the eligible population

	Eligible population (n=269)	Patients with identical diagnosis of neuropathic pain (n=85)	Patients with identical diagnosis of nociceptive pain (n=57)
	%	%	%
Posttraumatic	36.4	38.8	24.6
(Pseudo) radicular	12.6	11.8	8.8
Mechanical back	11.9	2.4	22.8
CRPS	9.7	23.5	3.5
Nerve damage	8.2	16.5	0.0
Lumbago	5.6	1.2	14.0
Soft tissue	3.7	2.4	8.8
Spinal stenosis	3.4	0.0	5.3
FBSS	2.6	0.0	0.0
Arthrosis	1.9	2.4	3.5
Cervicobrachial pain	1.9	0.0	7.0
Other	2.2	1.2	1.8

CRPS= Complex Regional Pain Syndrome
FBSS= Failed Back Surgery Syndrome

The 19 patients that did not complete all 7 DN4 self-assessment items were on average older and had a longer duration of pain but differences were small (data not shown).

From the 248 patients with analyzable data, the first and second physicians diagnosed identical types of pain in 196 patients: 85 patients with neuropathic pain, 57 patients with nociceptive pain and 54 patients with mixed pain. In the remaining 52 patients different diagnoses were made by the first and second physician. The diagnoses from both physicians were highly correlated, as demonstrated by a Pearson correlation coefficient of 0.82 for the scores on the specific 0–10 scale ranging from 0 nociceptive pain to 10 neuropathic pain.

The majority of patients answered that pain was burning (62%) and painfully cold (52%), and that pain was associated with tingling (68%), pins and needles (61%) and numbness (66%). Only 38% answered that pain was like electric shocks and 21% that pain was associated with itching. Regarding the 3 examination items completed by the first physician, a majority answered that pain was not associated with touch hypoesthesia (63%), pricking hypoesthesia (64%) or by brushing (60%).

The overall agreement between the patient-administered and nurse-administered information was very good for 'burning', 'painful cold' 'and 'itching' (Table 3).

Table 3 Inter-rater reliability for the DN4 items in patients with complete DN4 data (n=249)

	Kappa coefficient Patient — nurse	Kappa coefficient Nurse — first physician
1. Burning	0.81	—
2. Painful cold	0.81	—
3. Electric shocks	0.69	—
4. Tingling	0.71	—
5. Pins and Needles	0.63	—
6. Numbness	0.67	—
7. Itching	0.82	—
8. Touch hypoesthesia	—	0.51
9. Pricking hypoesthesia	—	0.42
10. Brushing	—	0.56

Agreements for the other items were good. Inter-rater agreements for the last three items of the DN4 that were administered by the nurse and the first physician were moderate, with Kappa coefficients between 0.42 and 0.56.

Because the aim of the study was to determine the discriminatory properties of the DN4, only patients with an identical diagnosis of neuropathic or nociceptive pain from both physicians were included in the analysis (n=142), using the scores from the patient administered questionnaire. The differences in DN4 item scores between neuropathic and nociceptive pain patients are shown in Table 4.

Table 4 Description of DN4 items in patients with neuropathic pain (n=85) and nociceptive pain (n=57)

Item answered with yes	Neuropathic pain (%)	Nociceptive pain (%)
1. burning	68.2	35.1
2. Painful cold	63.5	19.3
3. Electric shocks	42.2	29.8
4. Tingling	77.7	43.9
5. Pins and Needles	72.9	38.6
6.Numbness	74.1	31.6
7. Itching	29.4	19.3
8. Touch hypoesthesia	38.8	24.6
9. Pricking hypoesthesia	41.2	35.1
10. Brushing	50.6	8.8

Compared to nociceptive pain patients, neuropathic pain patients scored more positively on all the items, although not much higher on the itching and pricking hypoesthesia items. Moreover neuropathic pain patients showed higher total scores on the DN4 7-item and 10-item questionnaire compared to nociceptive patients (Figure 1a, 1b).
Six of the 10 DN4 items were individually and significantly able to discriminate between patients with neuropathic pain and those with nociceptive pain (Figure 2).

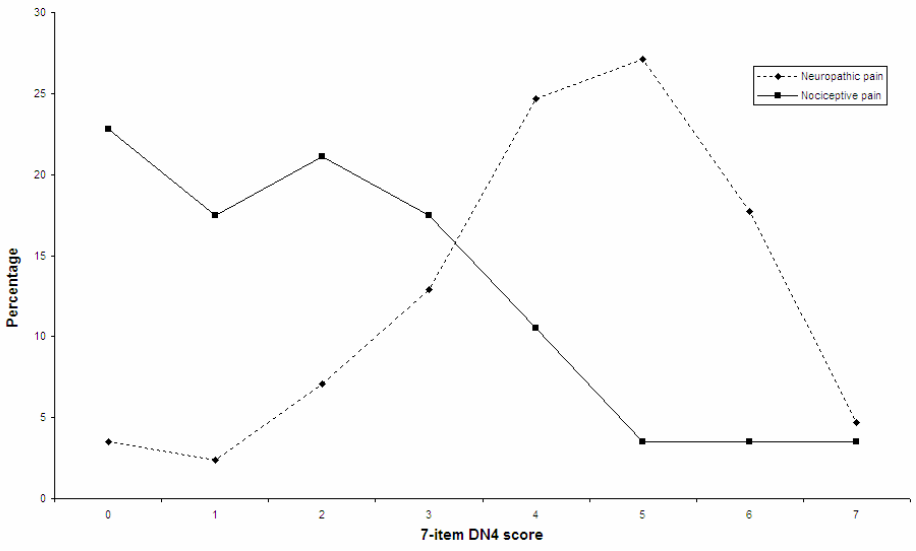

Figure 1a Distribution of the 7-item DN4 score in the neuropathic and nociceptive pain groups (n=142)
— — ◆ — — Neuropathic pain group — ■ — Nociceptive pain group

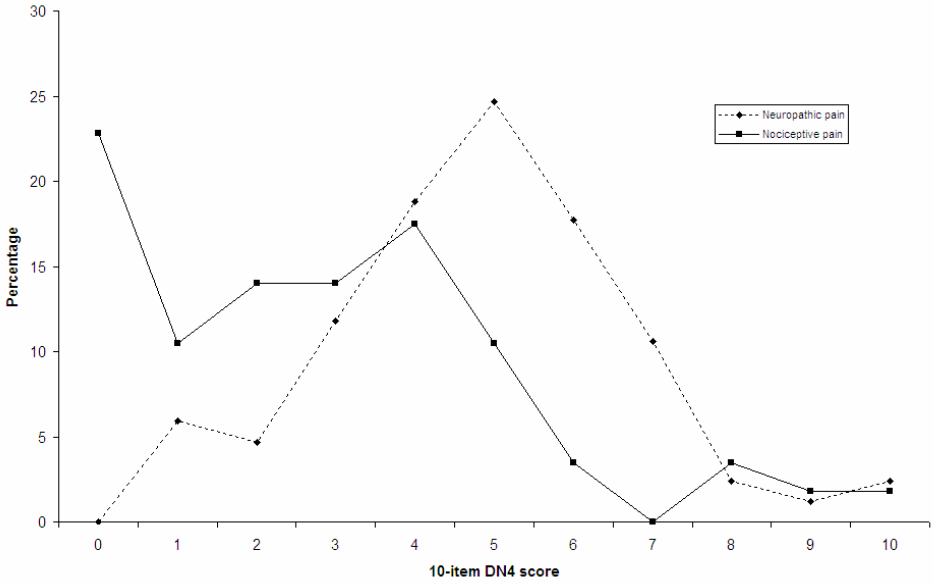

Figure 1b Distribution of the 10-item DN4 score in the neuropathic and nociceptive pain groups (n=142)
— — ◆ — — Neuropathic pain group — ■ — Nociceptive pain group

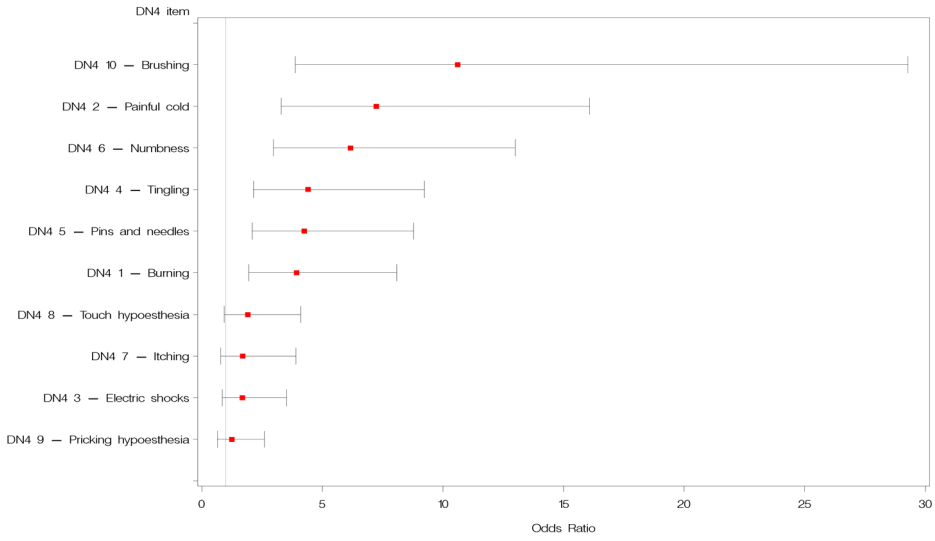

Figure 2 Discriminant property of the DN4 items in the neuropathic and nociceptive pain groups (n=142)

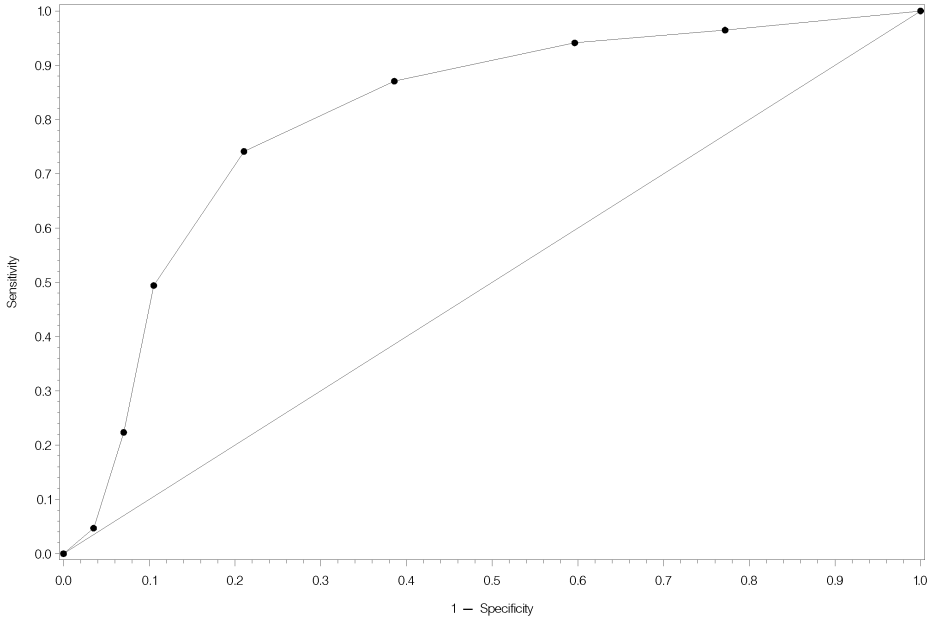

Figure 3a ROC curve for the 7-item DN4 score in the neuropathic and nociceptive pain groups (n=142)

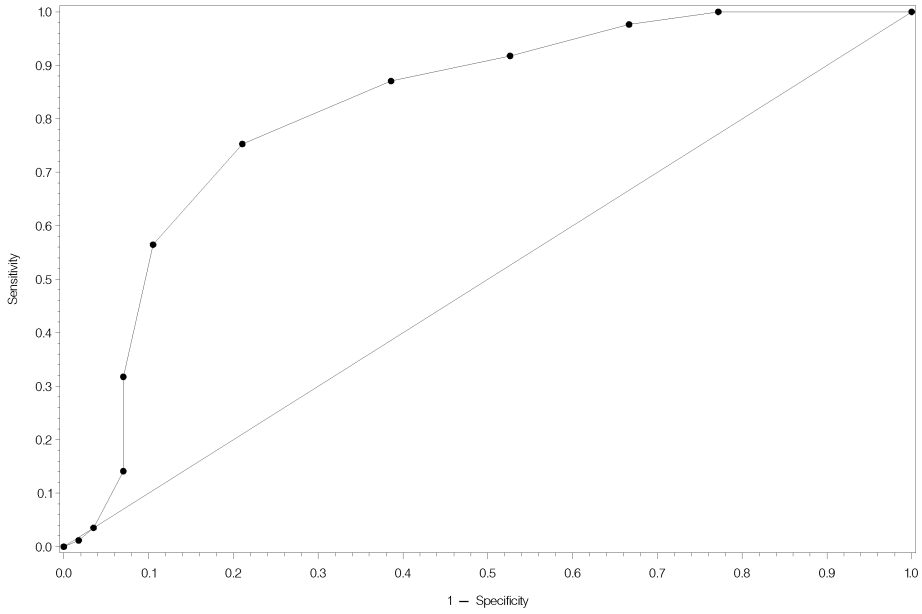

Figure 3b ROC curve for the 10-item DN4 score in the neuropathic and nociceptive pain groups (n=142)

These items are: 'burning', 'painful cold', ''tingling",pins and needles', 'numbness' and 'brushing'. The largest odds ratios observed were "brushing", "painful cold" and "numbness" (OR 10.6, 7.3 and 6.2, respectively).

We constructed two different ROC-curves, one for the 7-item and one for the 10-item questionnaire (Figure 3a, 3b).

Both the DN4 7-items and 10-items questionnaires showed good ability to discriminate between patients' type of pain, with an AUC of 0.81 and 0.82, respectively. For the partial 7-item questionnaire the Youden index was 0.53, corresponding with a cut-off point of 4/7, a sensitivity of 74% and a specificity of 79%. Similarly, for the DN4 10-item questionnaire the Youden index was 0.54, corresponding with a cut-off score of 5/10, and the sensitivity and specificity of this cut-off score were 75% and 79%, respectively.

DISCUSSION

Our study showed that the DN4 questionnaire is a diagnostic tool with a good ability to discriminate between neuropathic and nociceptive pain as shown by the ROC analysis, with an AUC of 0.81 and 0.82 for the 7-item and 10-item version, respectively.

There are two key characteristics of our study that strengthen the findings. Firstly, the patients in our study were a representative sample of a population presenting with chronic pain complaints in pain clinics. Secondly, we excluded patients with mixed pain and patients with noncorresponding diagnoses from two physicians. This enabled the analysis of the discriminatory ability of the DN4 in patients with a high likelihood of pain from a predominantly neuropathic or nociceptive origin. It is unlikely that the differences in diagnoses by two physicians were due to autonomous dynamics in pain symptoms because in practice all patients were seen by both physicians on the same day, although the protocol gave the opportunity for an interval of 72 hours. Our findings slightly differ from those of the French and Spanish validation studies [5,7]. For the 7-item version the cut-off score corresponding with the Youden index was higher than that defined on the original French data (4/7 vs. 3/7). For the 10-item DN4 we found a cut-off point of 5/10 while the French as well as the Spanish version both found a cut-off point of 4/10. Compared to the French study the diagnostic power was slightly lower as indicated by an AUC of 0.81 compared to 0.87 for the 7-item questionnaire and an AUC of 0.82 compared to 0.92 for the 10-item questionnaire. These differences may be explained by differences in the study design. As noted earlier, in our study patients with mixed pain were identified and excluded from the analysis of the diagnostic power. In addition, we used an unselected patient population of first time visitors with undiagnosed pain complaints that visited one of the three pain clinics involved in the study. The French study included patients who were already diagnosed. Also, patients with

a variety of chronic pain syndromes were included whereas these were more narrowly defined (e.g. CRPS patients were excluded) before inclusion in the French study. Finally, we used a Dutch translation of the DN4 that was derived from the French and English original. The Dutch version has been linguistically validated with a state-of-the-art methodology to solve semantic issues because of unclear wording in the original or because of equivalent alternative wordings in the target language with similar though slightly different meanings [14]. Nevertheless, slight differences in scoring because of different interpretations of items cannot be excluded.

The level of agreement between the patient-administered and nurse-administered questionnaire was good for the items "electric shocks", "tingling", "pins and needles" and "numbness" and very good for the items "burning", "painful cold" and "itching". Except for the item "tingling", Kappa coefficients were lower than those observed in the French study. This reflects a lower level of agreement between the Dutch physician and nurse than between the two French physicians. The agreement between the first physician and the nurse was considered moderate for the 3 items in the examination part. These three examination items did not add significantly to the sensitivity and specificity of the questionnaire. These findings are important in several ways. They support the idea that the DN4 produces reliable results with different modes of administration with no differences in diagnostic power, and can be applied in a flexible manner in clinical practice, in secondary as well as primary care settings. For daily practice the use of the 7-item questionnaire could be considered in order to make the DN4 also applicable outside the immediate physician consultation e.g. for pre-consultation and postal use. These applications could accelerate the use of the questionnaire. An easy-to-use questionnaire is also important for primary care settings. The findings also open the possibility that the three examination items are used as a second step if uncertainty remains for some patients with intermediate scores of 3 or 4 out of 7.

An alternative strategy for addressing uncertainty in diagnosis, particularly in patients with intermediate scores (e.g. 3 or 4 in the 7-item and 4 or 5 in the 10-item questionnaire), is provided by the differences in diagnostic power per item. In our study the examination item "brushing" and the items "painful cold" and "numbness" were identified as very discriminating between neuropathic and nociceptive pain. So the scores on these items may provide important information particularly when uncertainty exists about the diagnosis.

Compared to other neuropathic pain questionnaires the DN4 provided similar sensitivity and specificity figures [6]. The choice as to which screening questionnaire is used also depends on the local acceptance of it. The DN4's main advantages are that it is brief, and that a total score can be derived rapidly. It is also easy to apply any decision algorithm based on the total score, whereas the information on the discriminatory ability of the different items provides further flexibility in shaping these decisions.

Of particular interest was the high level of acceptable pain in our study, with a mean score of 3.3 on a 0–10 numerical rating scale. It would be worth investigating the relationship between acceptable pain, pain intensity and the DN4 scores. Another issue for further research is whether DN4 response patterns would differ by age and sex, given the same type and level of pain. In our study we identified a substantial number of patients with mixed pain (n=54) and with different diagnoses (n=52) made by the two physicians. This indicates that it is important to provide physicians with reliable and validated tools to assist diagnosing. Now that the ability of the DN4 to discriminate between patients with clear neuropathic and nociceptive pain has been investigated and confirmed in several studies, a logical next step would be to investigate the performance of the DN4 in patients with a less clear diagnosis or with mixed pain.

Whereas the DN4 has been identified as a useful tool to discriminate patients with neuropathic pain, it is worthwhile to investigate whether it is predictive for treatment response. Patients with a higher total score are hypothesized to be more responsive to therapy that is specific for the treatment of neuropathic pain.

We conclude that the DN4 is an easy-to-use screening tool that is reliable in daily practice to discriminate between neuropathic and nociceptive pain conditions. Item-specific scores provide important information in addition to the total score.

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Ethics of Human Experiment

The study was permitted by the medical ethical committee. (METC-Amphia hospital CO/BS/232.06//no.3)

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Chapter IV

Efficacy and tolerability of pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13 week, randomized trial

Robert van Seventer 1, Hilary A Feister 2, James P Young, Jr 2,
Malcolm Stoker 3, Mark Versavel 4 and Laurence Rigaudy 5

Author affiliations:
1 Amphia Hospital, Department of Anaesthesiology, The Netherlands. 2 Pfizer Global Research and Development, Ann Arbor, MI, USA. 3 Pfizer Global Research and Development, Sandwich, Kent, UK. 4 Pfizer Global Research and Development, New London, CT, USA. 5 Pfizer Global Research and Development, Fresnes, France.

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ABSTRACT

Objective

This trial evaluated the efficacy andsafety of pregabalin dosed twice daily (BID) for relief of neuropathic pain associated with postherpetic neuralgia (PHN).

Research design and methods

The 13-week, double-blind, placebo-controlled study randomized 370 patients with PHN to pregabalin (150, 300, or 600 mg/day BID) or placebo.

Main outcome measures

Primary efficacy measure was endpoint mean pain score from daily pain diaries. The secondary efficacy measure was endpoint mean sleep-interference score from daily sleep diaries. Safety evaluations included adverse events (AEs), physical and neurologic examinations, 12-lead ECG, vital signs, and laboratory testing.

Results

Pregabalin provided significant pain relief at endpoint: difference from placebo in mean pain score, 150 mg/day, –0.88, $p = 0.0077$; 300 mg/day, –1.07, $p = 0.0016$; 600 mg/day, –1.79, $p = 0.0003$. Weekly mean pain scores significantly improved as early as week 1. Sleep interference was also significantly improved at endpoint, compared with placebo ($p < 0.001$), beginning at week 1 ($p < 0.01$). More patients in the 150 (22.6%, $p = 0.02$), 300 (27.2%, $p = 0.085$), and 600 (36.5%, $p = 0.003$) mg/day pregabalin groups rated themselves 'very much' or 'much' improved than did patients in the placebo (16.2%) group.

Most AEs were mild or moderate. Among pregabalin-treated patients, 13.5% withdrew due to AEs, most commonly for dizziness (16 patients, 5.8%), somnolence (8, 2.9%), or ataxia (7, 2.5%).

Conclusions

Pregabalin, dosed BID, reduced neuropathic pain associated with PHN and was well tolerated. It also reduced the extent to which pain interfered with sleep. Pregabalin's effects were seen as early as week 1 and were sustained throughout the 13-week study

INTRODUCTION

Ten to fifteen per cent of all patients with herpes zoster (HZ) have postherpetic neuralgia (PHN), persistent pain for > 3 months beyond the resolution of the HZ rash[1]. This often chronic pain resulting from HZ is neuropathic in nature. Neuropathic pain is differentiated from nociceptive pain in that neuropathic pain is a direct result of damage to or dysfunction of the nervous system, while nociceptive pain is a neural response to injury to body tissues. PHN can be intensely painful, significantly interferes with sleep in > 50% of patients, and often impairs physical and psychosocial functioning[2,3].

Treatment for PHN is often suboptimal. Tricyclic antidepressants have been first-choice therapy for PHN[4–7], but their side-effects profiles may render their use in the elderly Problematic[4,8,9]. Some opioid analgesics[10] and local anesthetic preparations (lidocaine patch)[11] have shown some efficacy for relief of PHN. Drugs indicated for acute or nociceptive pain, including non-steroidal anti-inflammatories, have been used to treat PHN with limited success. Gabapentin is approved for treatment of PHN in several countries[12], however, gabapentin is relatively difficult to use clinically: it must be started at low doses, titrated to effective doses, and dosed three times daily (TID), adding complications for physicians and patients, which may affect compliance. There is a need for alternative treatments, the efficacy of which are supported by consistent clinical evidence. Pregabalin is an alpha2-delta (α2-δ) ligand with analgesic, anxiolytic, and anticonvulsant activity. The compound binds potently to the α2-δ subunit protein of voltage-gated calcium channels[13]. Potent binding at this site reduces calcium influx at nerve terminals and reduces the release of several neurotransmitters, including glutamate, norepinephrine, and substance P, from activated neurons[14–17]. Pregabalin is inactive at $GABA_A$ and $GABA_B$ receptors, is not converted metabolically into GABA or a GABA antagonist, and does not alter GABA uptake or degradation[18,19]. Pregabalin's *T*max is 1 h, its *T*. is 6 h, and it exhibits linear pharmacokinetics with low inter-subject variability. Pregabalin dosing does not require lengthy titration, and its starting dose of 150 mg/day significantly relieves pain in many patients.

Pregabalin — at dosages of 300 or 600 mg/day — has been shown to be safe and well tolerated, to reduce pain, and to improve sleep disturbance associated with chronic neuropathic pain in three studies totaling over 700 patients who had painful diabetic peripheral neuropathy[20–22]. Similarly, dosages of 150, 300, and 600 mg/day (TID) pregabalin were shown to relieve pain and related sleep interference in two PHN studies of over 400 patients[23,24]. Most recently, in a study of 338 patients with either painful DPN or PHN who received 600 mg/day or flexibly-dosed (150–600 mg/day) pregabalin (BID) or placebo, treatment with pregabalin was associated with significant improvements in both pain and pain-related sleep interference[25]. In 2004, the American Academy of Neurology issued practice parameters for the treatment of PHN which identified prega-

balin as a first-line treatment option for PHN[1]. This study was designed to evaluate the efficacy and tolerability of pregabalin dosed twice daily (BID) to enhance its ease of use in patients with PHN across its therapeutic dosing range.

PATIENTS AND METHODS

Study 1008–196 was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter, phase 3 trial, conducted from November 9, 2001 to October 30, 2002. Patients were randomized to one of four treatments: placebo, 150, 300, or 600 mg/day pregabalin, administered in two doses each day. Because pregabalin is renally excreted (98% as unchanged drug), and because a doubling of exposure can be expected with a 50% reduction in creatinine clearance (CLcr)[26], patients randomized to the 600 mg/day group were stratified based on each patient's CLcr: in this group, patients with CLcr > 60 mL/min received 600 mg/day pregabalin, while patients who had CLcr > 30 and ≤ 60 mL/min received 300 mg/day, a dosage providing equivalent exposure to 600 mg/day in patients with CLcr > 60 mL/min, based on pharmacokinetic modeling studies[27]. Creatinine clearance was estimated from serum creatinine, body weight, age, and sex using the Cockcroft and Gault equation.

The study consisted of three phases: 1-week baseline,13-week double-blind treatment (including 1-week titration and 12-week fixed-dose phases for patients receiving 300 or 600 mg/day), and 1-week follow-up for patients not entering the open-label follow-on study. Patients were seen at six scheduled visits plus one follow-up visit (if not entering open label).

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and US Food and Drug Administration regulations. Written informed consent was required from each patient (or their authorized representative) prior to enrolment. The protocol, consent documents, and protocol amendments were approved by each of the 76 participating centers' Institutional Review Boards. Patients were eligible if they were ≥ 18 years old, had pain for > 3 months after healing of HZ lesions, had a visual analogue scale pain score ≥ 40 mm at baseline and at randomization, and had at least four daily pain diary entries with mean daily pain score ≥ 4 prior to randomization.

Patients were excluded for the following reasons: malignancy (with the exception of basal cell carcinoma) within the past 2 years; WBC < 2500 mm3, neutrophil count < 1500 mm3, or platelet count < 100 × 103/mm3; clinically significant or unstable hepatic, respiratory, or hematologic illnesses or psychologic conditions; unstable cardiovascular disease; abnormal 12-lead ECG; history of chronic hepatitis B or C, hepatitis B or C within the past 3 months, or HIV infection; immunocompromise; history of alcohol or illicit drug

abuse within the last 2 years; or participation in a clinical trial for an investigational drug or agent within 30 days prior to baseline or participation in a previous trial of pregabalin. Patients with CLcr ≤ 30 mL/min were also excluded, as were patients who had previous surgical therapy for PHN, who had other severe pain or skin conditions in the affected dermatome that could alter sensation or that might compromise PHN assessment, or who had used prohibited medications, including long-acting benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromethorphan, amantadine, alpha-lipoic acid, hydroxychloroquine, thioridazine, deferoxamine, and antiepileptics (including carbamazepine, clonazepam, phenytoin, valproic acid, lamotrigine, topiramate, vigabatrin, and gabapentin) without appropriate washout (at least 7 days prior to entry to baseline phase). Stable regimens (of ≥ 30 days prior to study entry; therapy not to be initiated during study period) of non-narcotic analgesics, e.g., noramidopyrine and paracetamol, and stable regimens of opioids, anti-inflammatories, and antidepressants were allowed.

The primary efficacy parameter was endpoint mean pain score, based on the last 7 days of patients' daily pain diaries. Daily pain diaries consisted of an 11-point numerical rating scale (NRS), in which 0 = 'nopain' and 10 = 'worst possible pain'. Each morning, patients rated the severity of their pain during the past 24 h by circling the appropriate number on the NRS. Supplemental analyses of the primary efficacy parameter included proportion of responders (patients with ≥ 50% reduction and patients with ≥ 30% reduction in mean pain score from baseline) and weekly mean pain scores. Secondary efficacy parameters included endpoint mean sleep-interference scores and weekly mean sleep-interference scores. These measures were derived from daily sleep-interference diaries, consisting of an 11-point NRS, with 0 = 'pain does not interfere with sleep' through 10 = 'pain completely interferes with sleep'. At study termination, patients were also administered the Patient Global Impression of Change (PGIC), a patient-rated instrument measuring change in patients' overall health status on a 7-point scale ranging from 1 ('very much improved') to 7 ('very much worse').

Efficacy analyses were performed on modified intent to-treat (ITT) patients — randomized patients who took at least one dose of study medication and who had one or more post-baseline scores. Patients with no data for a parameter at baseline or at the time-point analyzed were excluded from that analysis. The sample size calculation was based on the primary efficacy parameter. Based on the results of previous pregabalin PHN trials, a common standard deviation of 2.15 was assumed[23,24]. Assuming two-sided testing at the 0.0167 level (to control for multiple comparisons), 88 patients per treatment group would provide over 90% power to detect a difference of at least 1.3 between at least one pregabalin group and placebo. This difference from placebo is consistent with the design of other pregabalin PHN studies. Under the assumption of equal alloca-

tion between the four treatment groups, a total sample size of 352 randomized patients is required.

The primary analysis of the primary parameter was an ANCOVA, including effects for treatment, cluster, CLcr stratum, and baseline mean pain score as the covariate. In addition, repeated-measures analysis was performed for the weekly mean pain scores and the weekly mean sleep interference scores. In each case, adjusted (leastsquares) means were obtained from the model and 95% confidence intervals on the difference in least-squares means between each pregabalin treatment group and placebo were constructed. *p* values were adjusted using the Hochberg procedure for the three pairwise comparisons versus placebo in order to protect the type I error rate at the 0.05 level. All statistical testing was done using SAS Version 6.12. Safety was assessed via adverse events (AEs) reporting (assessed as 'mild', 'moderate', or 'severe' by the investigators), laboratory testing, physical and neurologic exams, and 12-lead ECGs.

RESULTS

The four treatment groups were similar in gender (54% were female), age (mean = 70.7 ±10.6 years), duration of PHN (mean = 40.7 months, median = 27 months), height, weight, and CLcr (Table 1). Four hundred and thirty-five patients entered the baseline phase, and 65 withdrew during the baseline phase: one patient experienced an adverse event, 48 patients (11%) did not meet the inclusion criteria, and 16 patients (4%) withdrew due to other/administrative reasons.

Three hundred and seventy patients completed the baseline phase and were randomized (2 patients, one assigned to placebo and one to pregabalin 600 mg/day, did not receive study medication after randomization, Figure 1), and 368 patients were included in the modified ITT population. (The results and discussion below refer to this population.) Despite concurrent use of pain-relief medications by 53% of patients — with paracetamol the most commonly reported (23%), followed by amitriptyline (12%) and tramadol (6%)– baseline mean pain scores for such patients were > 6 (as they were for patients not using concurrent medications), indicating continued moderate-to-severe pain. Thirty-four per cent of patients who received study medication withdrew during the double-blind phase: 13% because of an AE, 16% for lack of efficacy, 1% for lack of compliance, and 6% for other reasons (Figure 1). Two hundred and seventy-five patients (75%) entered the open-label, follow-on study: 63 (70%) from the pregabalin 600 mg/day, 70 (71%) from the 300 mg/day, 68 (78%) from the 150 mg/day, and 74 (80%) from the placebo groups.

Endpoint mean pain score was significantly improved for each pregabalin dosage group compared with placebo (Table 2). Mean pain scores were also analyzed at each

Table 1. *Patient characteristics (ITT population)*

	Placebo (*n* = 93)	Pregabalin 150 mg/day (*n* = 87)	Pregabalin 300 mg/day (*n* = 98)	Pregabalin 300/600 mg/day (*n* = 90)	All patients (*n* = 368)
Gender					
Male, *n* (%)	40 (43)	36 (41.4)	54 (55.1)	38 (42.2)	168 (45.7)
Female, *n* (%)	53 (57)	51 (58.6)	44 (44.9)	52 (57.8)	200 (54.3)
Premenopausal, *n* (%)	1 (1.9)	2 (3.9)	2 (3.9)	4 (7.7)	9 (4.5)
Postmenopausal, *n* (%)	52 (98.1)	49 (96.1)	42 (95.5)	48 (92.3)	191 (95.5)
Race					
White, *n* (%)	92 (98.9)	86 (98.9)	98 (100)	88 (97.8)	364 (98.9)
Black, *n* (%)	0	1 (1.1)	0	1 (1.1)	2 (0.5)
Other, *n* (%)	1 (1.1)	0	0	1 (1.1)	2 (0.5)
Age categories					
18–64 years, *n* (%)	20 (21.5)	20 (23.0)	25 (25.5)	23 (25.6)	88 (23.9)
65, *n* (%)	73 (78.5)	67 (77.0)	73 (74.5)	67 (74.4)	280 (76.1)
Age (years)					
Mean (SD)	70.9 (10.4)	70.5 (9.3)	70.7 (11.9)	70.7 (10.6)	70.7 (10.6)
Median	72.0	73.0	73.0	72.5	73.0
Min–max	42–89	38–88	18–92	38–90	18–92
Weight (kg)					
Mean (SD)	73.03 (15.95)	72.27 (14.72)	73.72 (14.07)	72.71 (14.72)	72.96 (14.82)
Median	72.00	72.00	74.35	71.45	72.00
Min–max	36.0–154.0	44.8–111.1	45.0–111.0	44.5–105.8	36.0–154.0
Baseline mean pain score					
Mean (SD)	6.85 (1.49)	6.44 (1.58)	6.72 (1.41)	6.65 (1.44)	6.67 (1.48)
Median	7	6.57	6.93	6.71	6.79
Min–max	1.71–10.00	2.57–10.00	3.71–9.71	3.86–10.00	1.71–10.00
Duration of PHN (months)					
Mean (SD)	43.3 (44.8)	36.3 (43.1)	48.2 (53.1)	34.1 (37.3)	40.7 (45.3)
Median	31	22	29	22.5	27
Min–max	2–263	2–224	3–262	2–180	2–263
Baseline CL_{cr} (mL/min)					
Mean (SD)	76.80 (31.68)	74.34 (21.13)	75.33 (26.26)	76.34 (25.90)	75.71 (26.50)
Median	68.00	71.00	70.50	72.50	71.00
Min–max	32.0–229.0	36.0–126.0	37.0–201.0	33.0–152.0	32.0–229.0
CL_{cr} stratum					
Low (30-60 mL/min), *n* (%)	31 (33.3)	26 (29.9)	33 (33.7)	26 (28.9)	116 (31.5)
Normal (> 60 mL/min), *n* (%)	62 (66.7)	61 (70.1)	65 (66.3)	64 (71.1)	252 (68.5)

Table 2. *Endpoint* mean pain and sleep interference scores for patients treated with placebo and three dosages of pregabalin (PGB)*

	N	Least-squares means	SE	Treatment comparisons, pregabalin vs. placebo			
				Difference	95% CI	Unadjusted *p* value	Adjusted† *p* value
Pain							
Placebo	93	6.14	0.23				
PGB 150	87	5.26	0.24	–0.88	(–1.53, –0.23)	0.0077	0.0077
PGB 300	98	5.07	0.23	–1.07	(–1.70, –0.45)	0.0008	0.0016
PGB 600	88	4.35	0.24	–1.79	(–2.43, –1.15)	0.0001	0.0003
Sleep							
Placebo	93	4.10	0.21				
PGB 150	87	3.07	0.22	–1.03	(–1.62, –0.44)	0.0007	0.0007
PGB 300	98	2.84	0.21	–1.26	(–1.84, –0.68)	0.0001	0.0002
PGB 600	88	2.17	0.22	–1.93	(–2.52, –1.34)	0.0001	0.0002

SE = standard error; CI = confidence interval; PGB = pregabalin

*Endpoint = last 7 available scores while on study medication, up to and including the day after the last dose. Based on LS Means using ANCOVA model (including effects for treatment, cluster, CL_{cr} stratum, and the baseline score value as covariate)

†Adjustment based on Hochberg's procedure

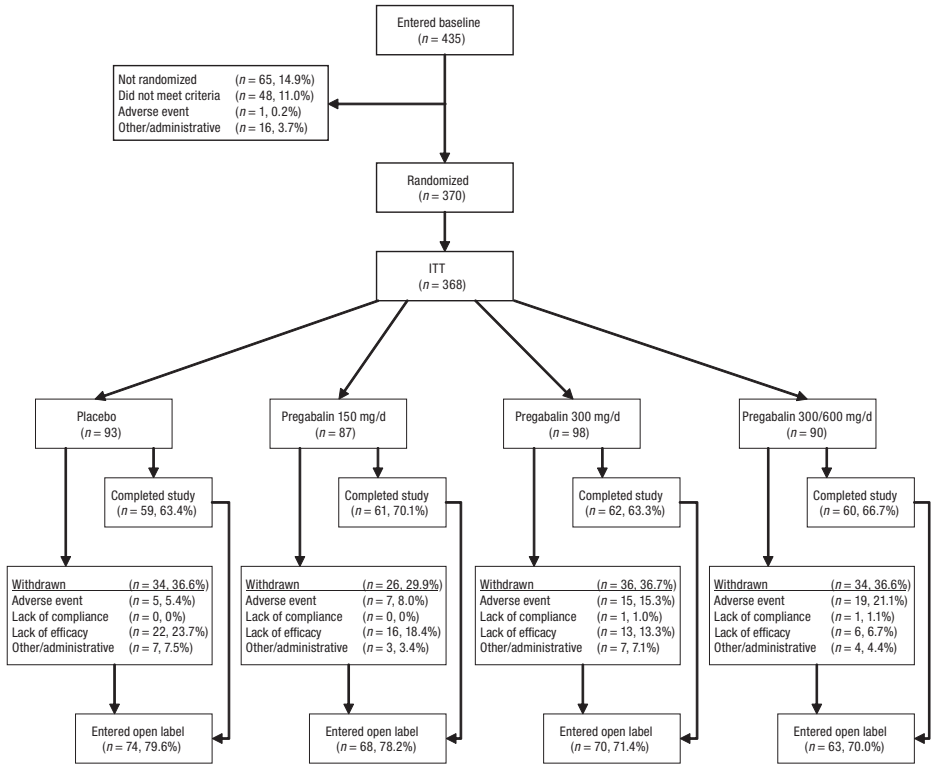

Figure 1. *Patient disposition cohort diagram*

study week, and, compared with placebo, all three pregabalin groups demonstrated significantly superior improvements in weekly mean pain score beginning at Week 1 ($p = 0.0005$ for 150 mg/day; $p = 0.0002$ for 300 and 600 mg/day).

These significant improvements were maintained at every weekly timepoint and persisted throughout the study's 13-week duration (Figure 2), with maximum pain relief (peak effect) beginning at week 3.

The proportion of 50% responders (≥ 50% reduction from baseline) was 26.4% for the 150 mg/day, 26.5% for the 300 mg/day, and 37.5% for the 600 mg/day pregabalin groups and 7.5% for the placebo group ($p = 0.001$ for each pregabalin group compared withplacebo). Number needed to treat (NNT) based on ≥ 50% responder rates was 5.3 for the 150 mg/day, 5.3 for the 300 mg/day, and 3.3 for the 600 mg/day pregabalin groups. The NNT for all pregabalin doses combined (150–600 mg/day), was 4.4. The proportion of patients with ≥ 30% pain reduction from baseline, a clinically meaningful degree of improvement, as reported by Farrar *et al*.[28], was 39.1% for the 150 mg/day, 40.8% for the 300 mg/day, and 52.3% for the 600 mg/day pregabalin groups and 17.2% for placebo ($p \leq 0.001$, Figure 3).

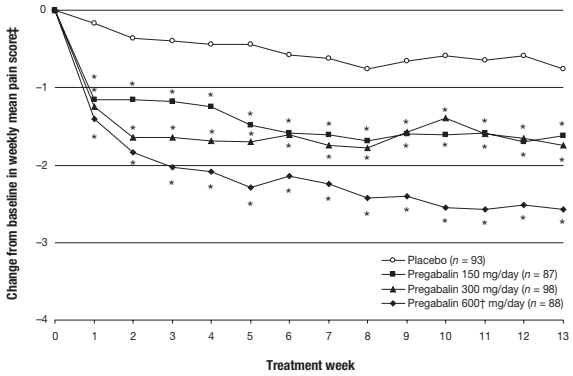

Figure 2. *Change from baseline in weekly mean pain scores, weeks 1–13. *p ≤ 0.01 vs. placebo. †600 mg/day arm stratified according to CL_{cr}. Patients with CL_{cr} > 30 and ≤ 60 mL/min received 300 mg/day pregabalin; patients with CL_{cr} > 60 mL/min received 600 mg/day. ‡Greater negative change from baseline indicates greater pain relief*

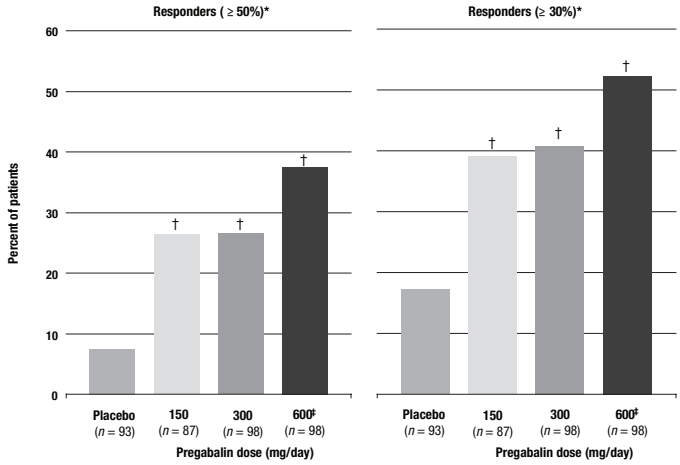

Figure 3. *Proportion of responders to treatment. *≥ 50% and ≥ 30% reduction from baseline. †p ≤ 0.001 vs. placebo. ‡600 mg/day arm stratified according to CL_{cr}. Patients with CL_{cr} > 30 and ≤ 60 mL/min received 300 mg/day; patients with CL_{cr} > 60 mL/min received 600 mg/day*

Mean sleep-interference scores at endpoint were significantly improved, compared with placebo, in all three pregabalin groups ($p = 0.0007$ for 150 mg/day; $p = 0.0002$ for 300 and for 600 mg/day, Table 2). Weekly mean sleep-interference scores were significantly better than placebo beginning at week 1 and for every study week thereafter ($p < 0.01$ for all pregabalin groups, Figure 4).

At study termination, more patients in the 150 mg/day (22.6%, $p = 0.02$), 300 mg/day (27.2%, $p = 0.085$), and 600 mg/day (36.5%, $p = 0.003$) pregabalin groups rated themselves 'very much' or 'much' improved on the PGIC than did patients in the placebo (16.2%) group. At least minimal improvement was reported by 51.2%, 47.9%, and 67.1%

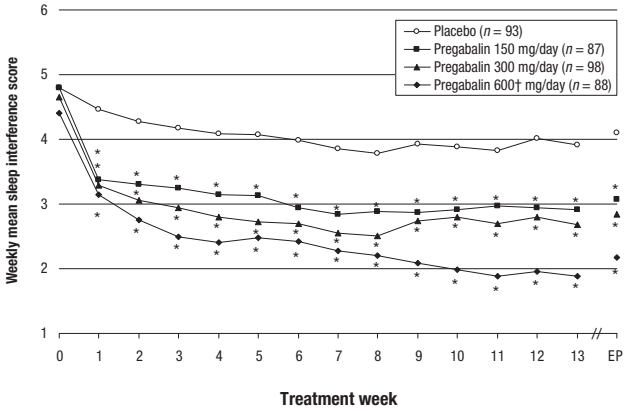

Figure 4. *Mean weekly pain-related sleep-interference scores in postherpetic neuralgia at all dosages. *p ≤ 0.01 vs. placebo. †600 mg/day arm stratified according to CL_{cr}. Patients with CL_{cr} > 30 and ≤ 60 mL/min received 300 mg/day pregabalin; patients with CL_{cr} > 60 mL/min received 600 mg/day*

of patients treated with 150, 300, and 600 mg/day pregabalin, respectively compared with 35.6% of those treated with placebo.

SAFETY AND TOLERABILITY

The most commonly reported treatment-associated AEs (Table 3) for the pregabalin groups were dizziness (16.1%, 32.7%, 36.7% of patients in the 150, 300, and 600 mg/day groups, respectively; 9.7% for placebo), somnolence (9.2%, 11.2%, 25.6% of patients in the 150, 300, and 600 mg/day groups, respectively; 4.3% for placebo), and peripheral edema (12.6%, 14.3%, 13.3% of patients in the 150, 300, and 600 mg/day groups, respectively; 10.8% for placebo). Most AEs were mild or moderate in intensity. There were no patient deaths reported during this double-blind study. Sixteen per cent of the 275 patients in the three pregabalin groups and 13% of the 93 placebogroup patients had severe AEs. Serious AEs (defined as congenital anomaly/birth defect, persistent or significant disability/incapacity, any AE resulting in patient hospitalization or prolongation of existing hospitalization, immediately life-threatening, death, or any medically significant event, including laboratory abnormalities) occurred in 3.6% of pregabalin patients and 2.2% of placebo patients. A total of 13.5% of pregabalin patients and 4.3% of placebo patients withdrew because of AEs considered associated with treatment. Among pregabalin-treated patients, AEs most frequently leading to withdrawal were dizziness (5.8%), somnolence (2.9%), and ataxia (2.5%), while among placebo-treated patients, dizziness (3.2%) most frequently led to withdrawal (no patients in the placebo group withdrew because of somnolence or ataxia). Only 1.5% of pregabalin-treated

Table 3. *Summary of associated* treatment-emergent adverse events (ITT population)*

Adverse event/preferred term	Placebo (*N* = 93)		Pregabalin 150 mg/day (*N* = 87)		Pregabalin 300 mg/day (*N* = 98)		Pregabalin 600 mg/day (*N* = 90)	
	Number of patients (%)							
Dizziness	9	(9.7)	14	(16.1)	32	(32.7)	33	(36.7)
Somnolence	4	(4.3)	8	(9.2)	11	(11.2)	23	(25.6)
Peripheral edema	10	(10.8)	11	(12.6)	14	(14.3)	12	(13.3)
Ataxia	0	(0.0)	3	(3.4)	6	(6.1)	11	(12.2)
Dry mouth	0	(0.0)	5	(5.7)	4	(4.1)	11	(12.2)
Constipation	2	(2.2)	1	(1.1)	8	(8.2)	8	(8.9)
Weight gain	0	(0.0)	3	(3.4)	8	(8.2)	8	(8.9)
Amblyopia	1	(1.1)	2	(2.3)	3	(3.1)	5	(5.6)
Asthenia	5	(5.4)	4	(4.6)	3	(3.1)	5	(5.6)
Edema	3	(3.2)	3	(3.4)	3	(3.1)	5	(5.6)
Abnormal gait	0	(0.0)	1	(1.1)	2	(2.0)	4	(4.4)
Abnormal vision	0	(0.0)	0	(0.0)	2	(2.0)	4	(4.4)
Face edema	2	(2.2)	3	(3.4)	1	(1.0)	4	(4.4)
Headache	3	(3.2)	4	(4.6)	1	(1.0)	4	(4.4)
Thinking abnormal	1	(1.1)	2	(2.3)	2	(2.0)	4	(4.4)
Confusion	1	(1.1)	3	(3.4)	3	(3.1)	3	(3.3)
Diplopia	0	(0.0)	0	(0.0)	0	(0.0)	3	(3.3)
Flatulence	2	(2.2)	1	(1.1)	0	(0.0)	3	(3.3)
Incoordination	0	(0.0)	2	(2.3)	1	(1.0)	3	(3.3)
Nausea	5	(5.4)	1	(1.1)	0	(0.0)	2	(2.2)
Diarrhea	1	(1.1)	5	(5.7)	0	(0.0)	0	(0.0)
Pain	2	(2.2)	2	(2.3)	3	(3.1)	0	(0.0)
Sweating	3	(3.2)	1	(1.1)	0	(0.0)	0	(0.0)

*AEs that were possibly, probably, or definitely related – and those for which the relationship was unknown – reported in at least 3% of patients in any treatment group. Events are sorted by decreasing frequency in the 600 mg/day pregabalin treatment group

patients and 1.1% of placebo-treated patients withdrew from the study because of peripheral edema. Of pregabalintreated patients, 6.9% reported weight gain as an AE that was considered associated with treatment. None of the AEs of weight gain was considered severe, and none led to withdrawal from the study.

Two patients had abnormal ECG findings that were present at termination, with no previous clinically significant findings detected at baseline. One patient's abnormal ECG findings were considered unrelated to pregabalin (the patient had a history of hypertension and stroke and showed evidence of myocardial infarction at baseline); findings for the other patient (who was in the placebo group) were considered of unknown causality. Neither of these findings led to withdrawal.

DISCUSSION

In this 13-week study of patients with PHN — more than half of whom had high (> 6) baseline mean pain scores despite the use of pain-relief medications — all three BID dosages of pregabalin were associated with a statistically significant reduction in endpoint mean pain score versus placebo. Onset of statistically significant reduction of pain was rapid — beginning as early as Week 1, the first post-baseline time-point analyzed

— and remained statistically significant throughout the study's 13 weeks. This finding is consistent with results reported from previous studies of pregabalin in both painful DPN and PHN. Pregabalin showed a positive increase in effect with increasing dosage. At exposure equivalent to 600 mg/day BID, 37.5% of pregabalin-treated patients met the strict criterion for response (≥ 50% improvement). The NNT for this level of reduction in pain for the dosage range of 150–600 mg/day was 4.4 (consistent with that observed in other studies of pregabalin for neuropathic pain), while the NNT to achieve a similar reduction in pain for gabapentin across a dosage range of 900–3600 mg/day has been calculated, from two studies, to be 5.3–5.8. Further, 52% of patients in the 600 mg/day BID pregabalin group experienced ≥ 30% improvement, a level also considered to be clinically meaningful pain relief[28].

Improvement of sleep interference began by week 1 for each of the three dosage groups, and it was significantly superior to placebo at each weekly timepoint throughout the study. Because sleep interference is frequently co-morbid with PHN (in > 50% of patients)[2], pregabalin's effect on sleep interference represents an important benefit to patients being treated for PHN.

Pregabalin's effect of reducing pain and improving pain-related sleep interference in patients with PHN has been established in two previous studies using TID dosing[23,24] and in one study using BID dosing[25]. In this trial of BID dosing of longer duration (13 weeks versus 8 weeks in the two previous TID-dosing PHN trials), pregabalin demonstrated similar efficacy and tolerability. Further, while the trial reported by Dworkin *et al.*[23] had a single treatment arm (300 or 600 mg/day based on creatinine clearance) and the trial reported by Sabatowksi *et al.*[24] included 150- and 300-mg/day treatment arms, this is the first pregabalin PHN trial to include three treatment arms spanning pregabalin's effective dosing range, 150–600 mg/day, each of which was associated with significant efficacy and favorable tolerability. Importantly, even at the high end of pregabalin's dosing range, using a BID as opposed to a TID schedule, most AEs were mild to moderate, and the low withdrawal rate due to AEs suggests the clinical benefit of treatment may have outweighed the discomfort of patients' AEs.

CONCLUSION

In addition to confirming previous data demonstrating pregabalin's sustained, beneficial effects for relief of neuropathic pain and associated sleep interference, this 13-week study supports a more convenient BID dosing schedule in PHN. Pregabalin represents a rapid-onset treatment option for PHN that is easy to use, shows low intersubject variability, and is well tolerated.

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Investigators of the CI-1008–196 Study Group:

Australia: Dr David Cherry, Dr Martin Robinson, Adelaide; Dr Christopher Bladin, Box Hill; Dr Graham Schapel, Maroochydore; Dr Allan Molloy, St Leonards.

Austria: Dr Thomas Berger, Innsbruck; Dr Dieter Klingler, Linz; Dr Anna Spacek, Wien.

Belgium: Dr Marie-Christine Payen, Brussels; Dr Martine Puylaert, Genk; Dr Jacques Devulder, Gent; Dr Bart Morlion, Leuven; Dr Dominique Libbrecht, Liege.

France: Dr Bruno Brochet, Bordeaux Cedex; Dr Patrick Mangin, Mulhouse Cedex; Dr Michel Lanteri-Minet, Nice Cedex; Dr Jean Bruxelle, Dr Anne Margot-Duclot, Dr Julie Revnic, Dr Alain Serrie, Paris.

Germany: Dr Georgi Tontschev, Bemau; Dr Rainer Freynhagen, Dusseldorf; Professor Andreas Hufnagel, Essen; Professor Jan Hildebrandt, Goettingen; Dr IngoMar Conrad, Hanover; Dr Norbert Matzek, Karlsnuhe; Professor Ralf Baron, Kiel; Dr Gerhard Hege-Scheuing, Ulm; Dr Martin Klein, Wuerzburg.

The Netherlands: Dr Robert van Seventer, Breda; Dr Gerrit Keizer, Kampen; Dr Andre Paul Wolff, Oss; Dr Paul Jozef W. Zomers, Roosendaal; Dr Frank JPM Huygen, Dr AJ Mulder, Rotterdam; Dr Theodoor Stijn Michiel Euverman, Stadskanaal.

Poland: Dr Marek Suchorzewski, Gdansk; Dr Piotr Lyczak, Gdansk-Oliwa; Dr Cezary Strugala, Grudziadz; Dr Stanislaw Ochudlo, Katowice; Dr Andrzej Tutaj, Olsztyn; Dr Teofan Domzal, Professor Jacek Jastrzebski, Warsaw; Dr Andrzej Kuebler, Wroclaw.

Portugal: Dr Maria Georgina Coucelo, Amadora; Dr Laurinda Lemos, Guimaraes; Dr Rosa Mario Miguel, Lisbon; Dr Jorge Manuel Cortez, Setubal.

Spain: Dr Elena Catala, Dr Mauro Sinche Yupanqui, Barcelona; Dr Luis Miguel Torres Monera, Cadiz; Dr Manuel Camba Rodriguez, El Ferrol; Dr Andres Castro Mendez, Ourense.

United Kingdom: Dr Andrew Souter, Bath; Dr John O'Hanlon, Belfast; Dr John Macleod, Birmingham; Dr Hany Khalil, Darlington; Dr Alan Semple, Falkirk; Dr Michael Serpell, Glasgow; Dr Margaret Carlin Thomas, Greenock; Dr Manmatha KuMar Roy, Hartlepool; Dr Patrick McGowan, Herts; Dr Karen Simpson, Leeds; Dr Timothy Nash, Liverpool; Dr Lachlan Morrison, Livingston; Dr Andrew Baranowski, Dr Jayne Gallagher, Dr Wolfgang Hamann, Dr Pierluigi Di Vadi, London; Dr Keith Milligan, Middlesborough; Dr Michael Gregory, Oldham; Dr Adrian Dashfield, Plymouth; Dr Ian Yellowlees, Roxburghshire; Dr Barbara Hoggart, West Midlands; Dr Simon Dolin, WestSussex; Dr Raouf George Ghaly, Wigan.

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Chapter V

Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: A randomized double-blind trial

Robert van Seventer 1, Flemming W. Bach 2, Cory C. Toth 3, Michael Serpell 4, Jane Temple 5, T. Kevin Murphy 6 , Meryem Nimour 7

Author affiliations:
1 Amphia Hospital, Department of Anaesthesiology, Breda, Netherlands. 2 Danish Pain Research Center, Department of Neurology, Aarhus University Hospital, Aarhus, Denmark. 3 Department of Clinical Neurosciences, The Hotchkiss Brain Institute, and the University of Calgary, Calgary, Alberta, Canada. 4 Pain Clinic Gartnavel General Hospital, University of Glasgow, UK. 5 Pfizer Global Research and Development, Sandwich, Kent, UK. 6 Pfizer Inc, New York, NY, USA. 7 Pfizer Limited, Tadworth, Surrey, UK

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ABSTRACT

Background

Pregabalin is effective in the treatment of peripheral and central neuropathic pain. This study evaluated pregabalin in the treatment of post-traumatic peripheral neuropathic pain (including post-surgical).

Methods

Patients with a pain score ≥4 (0–10 scale) were randomized and treated with either flexible-dose pregabalin 150–600 mg/day (n=127) or placebo (n=127) in an 8-week double-blind treatment period preceded by a 2-week placebo run-in.

Results

Pregabalin was associated with a significantly greater improvement in the mean endpoint pain score vs. placebo; mean treatment difference was -0.62 (95% CI -1.09 to -0.15) (P=0.01). The average pregabalin dose at endpoint was ~326 mg/day. Pregabalin was also associated with significant improvements from baseline in pain-related sleep interference, and the Medical Outcomes Study Sleep Scale sleep problems index and sleep disturbance subscale (all P<0.001). In the all patient group (ITT), pregabalin was associated with a statistically significant improvement in the Hospital Anxiety and Depression Scale anxiety subscale (P<0.05). In total, 29% of patients had moderate/severe baseline anxiety; treatment with pregabalin in this subset did not significantly improve anxiety. More patients reported global improvement at endpoint with pregabalin than with placebo (68% vs. 43%; overall P<0.01). Adverse events led to discontinuation of 20% of patients from pregabalin and 7% from placebo. Mild or moderate dizziness and somnolence were the most common adverse events in the pregabalin group.

Conclusion

Flexible-dose pregabalin 150–600 mg/day was effective in relieving neuropathic pain, improving disturbed sleep, improving overall patient status and was generally well tolerated in patients with post-traumatic peripheral neuropathic pain.

INTRODUCTION

Pregabalin demonstrated analgesic efficacy in the treatment of painful diabetic neuropathy (DPN) [1–3], postherpetic neuralgia (PHN) [3–6] central neuropathic pain [7], and fibromyalgia [8]. The analgesic efficacy of pregabalin in peripheral and central neuropathic pain models, as well as in fibromyalgia, a disorder in which central sensitization is thought to be an important component [10], has been linked to its ability to modulate neurotransmitter release from hyperexcited neurons via binding to the alpha-2-delta site, mediating calcium influx [9,10].

In addition to significant analgesic efficacy, pregabalin also improves pain-related sleep interference in neuropathic pain and is associated with significant patient-reported global improvement [1–7]. The anxiolytic activity of pregabalin has been demonstrated in several clinical trials in generalized anxiety disorder (GAD) in which pregabalin was associated with a significant improvement in the Hamilton Anxiety Rating Scale [11].

To date, the most rigorous evaluations of pregabalin in neuropathic pain have been undertaken in studies in patients with a single underlying cause. The study we report extends the findings from DPN and PHN studies by evaluating the efficacy of pregabalin in patients with post-traumatic peripheral neuropathic pain. A further objective was to evaluate the effect of pregabalin on anxiety in those patients with clinically relevant anxiety symptoms.

METHODS

Patients

Men or women aged 18 to 80 years with post-traumatic peripheral neuropathic pain, confirmed by a pain specialist, and which had persisted for at least 3 months following the traumatic event, were eligible. Patients with DPN, PHN, radiculopathy, trigeminal neuralgia, carpal tunnel syndrome, central neuropathic pain or Complex Regional Pain Syndromes I or II were excluded. Patients with creatinine clearance ≤60 mL/min or a positive urine illicit drug screen were also excluded. Women who were breastfeeding or pregnant were excluded and those able to conceive were required to use reliable contraception.

All patients were required to have a score greater than 40mm on the 100mm visual analog scale (VAS) of the Short-Form-McGill Pain Questionnaire [12] at screening (before a 2-week, single-blind, placebo run-in period) and at randomization. To be randomized, patients were also required to have completed a daily pain diary upon awakening in the 2 weeks before treatment in which pain in the last 24h was rated on an 11-point numerical rating scale (NRS) from 0=no pain to 10=worst possible pain, and to have

an average score of at least 4 based on at least four daily entries during the week prior to randomization. Patients were allowed to be taking non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 inhibitors (COX-2s), opioid and non-opioid analgesics, antiepileptic drugs (AEDs) and antidepressant medications concomitant pain medications if they had been stable for at least 1 month before the study and would remain so during the study. Those taking gabapentin were required to discontinue treatment at the screening visit and those previously exposed to pregabalin were excluded.

All patients gave written, informed consent. Institutional review boards reviewed and approved the protocol and the study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local laws and regulations.

Study design and treatment

This was an international, multicenter, parallel-group, double-blind, randomized clinical trial comparing 8 weeks of flexible-dose pregabalin 150–600 mg/day with placebo, taken as two daily doses (Clintrial.gov Identifier: NCT00292188). Randomization was preceded by a 2-week, single blind, placebo run-in period; baseline data were collected at randomization. Patients who did not meet both pain entry criteria at randomization (i.e. NRS and VAS assessments) specified above were not randomized.

Study medication was initiated at 150 mg/day for the first week and was then increased to 300 mg/day for the second week. Investigators were encouraged to have patients take their first dose in the morning. The 300 mg/day dose could be further increased to 600 mg/day from the beginning of week 3 if needed for efficacy. Only one dose reduction was allowed. A 450 mg/day dose increment was not included as 225 mg capsules had not been manufactured at the time of the study. Medication was blinded by using capsules of identical size, color, taste and smell for placebo and pregabalin. An Interactive Voice Recognition System was used to randomize patients. Clinic visits were scheduled for screening, baseline and the end of weeks 1, 2, 3, 4, 5 and 8, or upon discontinuation. There was a 1-week double-blind taper period at the end of the study.

Efficacy assessments

The endpoint mean pain score was the primary efficacy variable and this was based on the last seven entries in the daily pain diary described above, which was completed by the patient during the placebo run-in and each day during the 8-week, double-blind treatment period. Patients also rated the extent to which pain interfered with sleep in a daily diary on an 11-point NRS from 0=pain does not interfere with sleep to 10=pain completely interferes with sleep.

Other secondary efficacy assessments included the Medical Outcomes Study (MOS)-sleep scale [13] which was based on a 1-week recall period and was completed at baseline and week 8 or upon early discontinuation (endpoint) and the Hospital Anxiety

and Depression Scale (HADS) [14] which was completed at baseline, weeks 1 and 5 and at endpoint. The modified Brief Pain Inventory short-form (mBPI-sf) [15] was completed at baseline and endpoint and the Patient Global Impression of Change (PGIC), in which patients rated their overall status on a 7-point scale from 1=very much improved to 7=very much worse [16] was completed at endpoint.

Tolerability and safety assessments

All spontaneously reported and observed adverse events, vital signs, and body weight were recorded at each clinic visit. Routine clinical laboratory tests were conducted at screening and endpoint. Peripheral edema was monitored.

Data analysis

The sample size estimation, based on the between group comparison of the mean pain score at endpoint, assumed a two-sided comparison with a tolerance for type I error at alpha = 0.05. Based on the results of a previous flexible-dose study in PHN and DPN [4], the mean endpoint pain difference was estimated to be 1.2 with a standard deviation (SD) of 2.3. Because our study recruited patients with peripheral neuropathic pain of different etiologies, we sought to detect a smaller effect size than the previous study. It was calculated that 113 patients per group would provide 90% power to detect a treatment difference of 1.0 assuming the same SD. Assuming a dropout rate of 13% we estimated 130 per patients group should be enrolled. We also estimated based on previous studies [7, 24] that to detect a mean difference (SD) of 2.3 (3.0) in the endpoint HADS anxiety subscale score in the subset of patients with a baseline score >10 (moderate to severe anxiety) that 39 patients (i.e. 30%) in each group would have to meet this criterion.

All analyses were based on the intention-to-treat population (ITT). In post-hoc analyses, a model was fitted which also adjusted for gender and tested for a treatment by gender interaction. The proportions of patients with a ≥30% and ≥50% reduction in pain score between baseline and endpoint (responder analyses) were calculated. Mean changes from baseline to endpoint in the secondary efficacy variables were determined.

All analyses were based on two-sided tests using SAS procedures without adjustment for testing multiple measures. All continuous variables were analyzed using ANCOVA, controlling for pooled country, and baseline values. The analysis of weekly mean pain and sleep interference scores was based on a mixed model repeated measures (MMRM) analysis and least squares (LS) means were compared between groups each week. The MMRM analysis used all of the available data from sequential observations in patients to impute missing values. Categorical variables were analyzed using the Cochran-Mantel-Haenszel test. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) terminology.

RESULTS

Patients

A total of 367 patients took single-blind placebo during the 2-week run-in period (Figure 1). Of the 367 treated in the single-blind run in, 254 were randomized and received either placebo (n=127) or pregabalin (n=127). One patient from each group was excluded from the ITT analysis because they did not have post-baseline efficacy data. Of the 113 patients who were not randomized, 28 did not meet pain entry criteria.

Baseline demographic and clinical characteristics were generally similar in the two randomized treatment groups, except there was a greater proportion of women in the pregabalin group (60.6%) than in the placebo group (40.9%) (Table 1). All patients had post-traumatic pain. The cause of pain was collected in an open field where the investigators

Table 1 Patient demographics and baseline characteristics

	Placebo (n=127)	**Pregabalin (n=127)**
Women, n (%)	52 (40.9)	77 (60.6)
Age, yr, mean (SD)	51 (13)	52 (14)
Aged ≥65–80 yr, n (%)	25 (19.7)	29 (22.8)
White race, n (%)	120 (94.5)	124 (97.6)
Weight, kg, mean	81 (17)	78 (15)
Mean duration of neuropathic pain, yr (range)	4.4 (0.2–29)	4.3 (0.3–26)
Primary neuropathic pain diagnosis[a]		
Trauma	*59 (46.5)*	*62 (48.8)*
Surgical	*41 (32.3)*	*44 (34.6)*
Amputation	*6 (4.7)*	*3 (2.4)*
Nerve injury	*12 (9.4)*	*8 (6.3)*
Other	*9 (7.1)*	*10 (7.9)*
Concomitant pain medications, n (%)[b]	101 (79.5)	102 (80.3)
NSAIDs/Cox-2s	*46 (36.2)*	*57 (44.9)*
TCAs	*39 (30.7)*	*41 (32.3)*
SNRIs	*7 (5.5)*	*2 (1.6)*
Opioids	*15 (11.8)*	*20 (15.8)*
Tramadol	*41 (32.3)*	*42 (33.1)*
AEDs[c]	*46 (36.2)*	*41 (32.3)*

Abbreviations: NSAID — non-steroidal anti-inflammatory drug; COX-2 -cyclooxygenase-2 inhibitor; TCA — tricyclic antidepressant; SNRI selective norepinephrine receptor inhibitor, AEDs — anti-epileptic drugs.
[a]Categorized based on the open field description on the cause of pain recorded by the investigator
[b]Medications may not have been specifically prescribed for neuropathic pain
[c]AEDs, excluding gabapentin, were allowed

recorded what they felt was an appropriate description. Generally the statements in this field lacked sufficient detail to further classify the trauma causing the post traumatic pain precisely. Investigators recorded that almost half the patients had "trauma" as the cause of the neuropathic pain and a further one-third as having developed pain as a result of surgery.

The overall discontinuation rate from randomized treatment was similar in both treatment groups (Figure 1). Lack of efficacy resulted in the discontinuation of 9.4% from placebo and 1.6% from pregabalin. Adverse events were given as the reason for the discontinuation of 7.1% and 19.7% from the placebo and pregabalin groups, respectively.

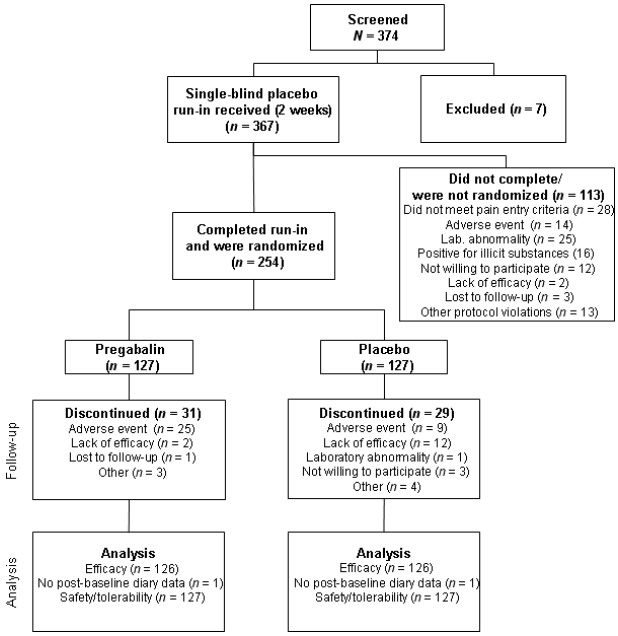

Figure 1 Patient disposition. The other protocol violations listed as the reason for not completing the single-blind run-in period/not being randomized included medical and procedural reasons.

The other protocol violations listed as the reason for not completing the single-blind run-in period/ not being randomized included medical and procedural reasons.

Study medication

Pregabalin dosing at endpoint was as follows; 38 patients (30.2%) received 150 mg/day, 58 (46.0%) received 300 mg/day and 30 (23.8%) received 600 mg/day. The corresponding percentages in the placebo group for these "dose groups" were 10.3%, 14.3% and 75.4%, respectively. The mean endpoint pregabalin dose was 326 mg/day.

Efficacy

In the evaluation of the primary endpoint, pregabalin was statistically significantly more effective than placebo in improving pain at endpoint (Table 2). The treatment by gender

interaction was not statistically significant and the findings of the primary efficacy analysis were upheld when the model was adjusted for gender.

The percentage of patients with ≥30% reduction in pain from baseline to endpoint was significantly greater in the pregabalin group (39.7%) than in the placebo group (25.4%; $P<0.05$). In the MMRM analysis of weekly mean pain scores a statistically significant difference in favor of pregabalin was first apparent at week 3 ($P=0.01$) and then weekly from week 5 to week 8 ($P<0.05$). The mBPI-sf pain interference and severity indices, which were not subject to formal statistical analysis, showed improvement in both groups which were numerically greater in the pregabalin group than the placebo group.

In total 25.4% in the pregabalin group and 32.5% in the placebo group had a baseline HADS anxiety subscale score >10. In this subset of patients there was modest but insignificant difference between groups in the change in the HADS anxiety score between baseline and endpoint. (Table 2). In the all patient group, the difference between groups did achieve statistical significance.

Table 2 Mean (SD) primary and secondary efficacy variables at baseline and endpoint, differences between treatment groups and statistical analysis.

	Placebo			**Pregabalin**			**Endpoint comparison placebo — pregabalin[a]**		
	N	Baseline	Endpoint	N	Baseline	Endpoint	Adjusted difference	95% CI	*p* value
Pain[b]	125	6.3 (1.7)	5.5 (2.3)	126	6.0 (1.6)	4.6 (2.4)	-0.62	-1.09;-0.15	0.01
Sleep interference[b]	125	4.8 (2.6)	4.13 (2.8)	126	4.1 (2.4)	2.73 (2.4)	-0.79	-1.25;-0.34	0.001
MOS-sleep scale problems index[c]	112	45.9 (21.9)	44.6 (21.0)	116	43.4 (20.2)	35.9 (21.1)	-7.54	-11.52; -3.56	<0.001
HADS Anxiety score[d] all patients	124	8.4 (4.9)	7.5 (4.9)	124	7.6 (4.5)	6.2 (4.5)	-0.84	-1.6; -0.08	0.031
Patients with baseline HADS Anxiety subscale >10	*41*	*14.3 (2.5)*	*12.1 (4.1)*	*32*	*13.7 (2.4)*	*10.3 (4.6)*	*-1.68*	*-3.69; 0.32*	*0.099*
HADs Depression score[d]	124	6.8 (4.5)	6.5 (4.5)	124	6.3 (4.2)	5.1 (4.5)	-0.97	-1.61; -0.33	0.003
Patients with baseline HADS Depression subscale >10	*23*	*13.9 (2.7)*	*12.3 (4.1)*	*17*	*13.9 (2.8)*	*12.1 (4.5)*	*0.24*	*-1.87; 2.34*	*0.819*

Abbreviations: NSAID — non-steroidal anti-inflammatory drug; COX-2 -cyclooxygenase-2 inhibitor; TCA — tricyclic antidepressant; SNRI selective norepinephrine receptor inhibitor, AEDs — anti-epileptic drugs.

[a]Categorized based on the open field description on the cause of pain recorded by the investigator

[b]Medications may not have been specifically prescribed for neuropathic pain

[c]AEDs, excluding gabapentin, were allowed

In the weekly analysis of pain-related sleep interference, a statistically significant improvement in the pregabalin group was apparent from week 1 onwards and (P<0.05) and at endpoint (Table 2). In the evaluation of sleep using the MOS sleep scale there was a statistically significant improvement in the overall sleep problems index in the pregabalin group (Table 2) as well as in the sleep disturbance and sleep adequacy subscales (both P<0.001; data not shown). The mean MOS sleep scale somnolence score at endpoint was 33.6 in the placebo group and 35.4 in the pregabalin and the adjusted mean endpoint difference (2.31) was not statistically significant (P=0.32). At endpoint, most patients in the pregabalin treatment group rated themselves as improved (Figure 2), with only 7.5% rating themselves as worse than baseline. In the placebo group over half the patients rated themselves as either unchanged or worse. The distribution of responses across the seven PGIC categories was statistically significant (P=0.006) in favor of improvement in the pregabalin group (Figure 2).

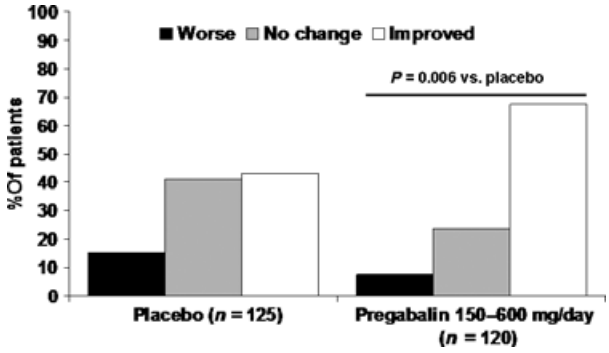

Figure 2 Patient Global Impression of Change (PGIC) of overall change experienced by patients at endpoint since receiving randomized medication
(PGIC) rated on a seven-point scale 1=very much improved; 2=much improved, 3=minimally improved; 4=no change, 5=minimally worse, 6=much worse, 7=very much worse; condensed into 3 categories for presentation

TOLERABILITY AND SAFETY

In total, treatment-emergent adverse events were reported in 58.3% of patients in the placebo group and 85.8% in the pregabalin group. Most adverse events were either mild or moderate in intensity; 9% in the placebo group and 10% in the pregabalin were rated as severe in intensity. The most common adverse events and the associated discontinuation rates are summarized in Table 3.

Serious adverse events were reported in four patients in the pregabalin group, one of which was considered related to treatment, and two in the placebo group. The event

Table3 Most frequently reported adverse events; n(%)[a]

	Placebo (n=127)		Pregabalin (n=127)	
	Incidence	Discontinuation	Incidence	Discontinuation
Dizziness	12 (9.4)	2 (1.6)	55 (43.3)	11 (8.7)
Somnolence	8 (6.3)	1 (0.8)	20 (15.7)	1 (0.8)
Headache	14 (11.0)	2 (1.6)	15 (11.8)	1 (0.8)
Fatigue	10 (7.9)	0	15 (11.8)	2 (1.6)
Dry mouth	6 (4.7)	0	14 (11.0)	0
Nausea	8 (6.3)	1 (0.8)	12 (9.4)	2 (1.6)
Constipation	4 (3.1)	0	9 (7.1)	0
Peripheral edema	3 (2.4)	0	9 (7.1)	2 (1.6)
Disturbance in attention	4 (3.1)	1 (0.8)	9 (7.1)	0
Blurred vision	3 (2.4)	0	8 (6.3)	1 (0.8)

[a]Treatment-emergent adverse events occurring in ≥5% of patients in either treatment group and with greater frequency in the pregabalin group than the placebo group.

considered related to pregabalin was a patient with tremor and dyspnoea who was on 600 mg/day who discontinued and recovered. Weight gain was reported as an adverse event in five patients on pregabalin and two on placebo. Four patients on pregabalin and two on placebo had ≥7% weight gain. The mean weight change at endpoint was 1 kg in the pregabalin group and 0.2 kg in the placebo group. No patterns of changes in vital signs or laboratory assessments were observed.

DISCUSSION

This 8-week, placebo-controlled study of a heterogeneous group of patients with post-traumatic peripheral neuropathic pain demonstrated that pregabalin was significantly effective in reducing pain. In addition, pregabalin was associated with significant improvement in disturbed sleep, and was generally well tolerated. The findings from the present study are largely consistent with results from previous studies of pregabalin in peripheral neuropathic pain [1–5].

This study, unlike previous studies of pregabalin in neuropathic pain, included a 2-week placebo-run-in period. It has been suggested that this approach be explored as a means of minimizing the placebo-response rate in neuropathic pain trials [18]. In total, 7.3% of those entered into the study were not randomized because they failed to meet both pain entry criteria (NRS and VAS assessments). The mean baseline pain score in this study (~6.1) was a little lower than the mean scores in pregabalin DPN (~6.4) and PHN (~6.7) pre-registration trials [24] in which no placebo-run-in was employed. The treatment difference for pregabalin versus placebo in the primary pain endpoint in this study

was modest (-0.62) but of statistical significance. The lower baseline score might in part explain the relatively modest improvement observed with pregabalin. The mean dose in this study was 326 mg/day. Compared with fixed doses of pregabalin such as with 300 mg/day, the difference from placebo in primary pain endpoint in this study was generally less than other studies in DPN [1,2] and PHN [4], in which a significant improvement was observed, but similar to that in another PHN study [5]. A recent cross-over study of gabapentin up to 2400 mg/day in a similar patient population failed to find a significant difference from placebo on the primary endpoint, the mean change in pain intensity score, suggesting that this type of neuropathic pain may be more difficult to treat than the classic DPN and PHN models [19]. The placebo response rate in this study (14.3%), as shown by the proportion of patients with a ≥50% reduction in their pain score between baseline and endpoint was similar to or greater than in several other studies in peripheral neuropathic pain that did not employ a placebo run-in period [2,4,5]. Thus, it appears that the placebo run-in period with the use of an absolute entry threshold regardless of percentage improvement between screening and randomization did not demonstrate a marked impact on reducing the placebo response rate during the randomized treatment period.

Although the 50% responder rate with pregabalin was not significantly different from placebo, the difference between groups in the 30% response rate was significant. When putting the results from the assessment of pain in this study into context it is important to be cognisant of the population under study. This was a very heterogeneous group of patients with post-traumatic pain of many differing causes which had been present for, on average, 4.4 years. The refractory nature of the sample was evident when it is considered that 80% were taking concomitant pain medications, several classes of which have demonstrated efficacy in neuropathic pain, but nonetheless pain persisted at a level such they were able to enter the study. The very heterogeneity of the sample may also contribute to the fact that the effect size in this study was not as great as studies of pregabalin in more "pure" DPN and PHN samples [1,2,4]. Rowbotham noted that clinical trials in specific disease cohorts have less variability than trials in relatively unselected groups with chronic pain [20], and this may be relevant to the heterogeneous population in the present study.

A secondary objective of this study was to evaluate the effects of pregabalin on anxiety in a subset of patient with clinically relevant baseline anxiety symptoms, defined as having a HADS anxiety subscale score >10. Slightly fewer patients than expected actually met this criterion, and therefore statistical power was lacking. Although a numerical difference that is likely to be clinically relevant was observed in favour of improvement in anxiety in the pregabalin group, the finding did not achieve statistical significance. The all patient group did reach statistical significant improvement despite the low overall baseline anxiety scores, which suggests very mild anxiety and little room for im-

provement. Nonetheless, the significant improvement in the HADS anxiety subscale is consistent with a study in central neuropathic pain [6] and with the fact that pregabalin is effective in GAD [11]. Consistent with other studies in neuropathic pain, pregabalin was also associated with a rapid and significant improvement in pain-related sleep interference [1–6], which was reflected in the significant improvements in the MOS sleep problems index, as well as in the sleep disturbance and sleep adequacy subscales.

Pregabalin was generally well tolerated with adverse events mostly mild or moderate in intensity and resulting in the discontinuation of 19.6% from pregabalin compared with 7.1% from placebo. Consistent with the broader pregabalin database [1–6], dizziness and somnolence were the two most common adverse events. Dizziness among pregabalin-treated patients, at placebo-corrected incidence of 34%, was reported slightly more frequently than in pooled DPN studies [21] and more than 300 mg/day arms in PHN studies [4,5], but most patients who reported dizziness remained on treatment. The reason for the relatively higher incidence of mostly mild or moderate dizziness in this population is not known. Peripheral edema, which was proactively measured, was slightly more frequent with pregabalin than with placebo but only resulted in two patients discontinuing treatment. There were no remarkable findings in any of the laboratory or safety assessments.

The evaluation of change as rated by the PGIC reflected the overall benefits of pregabalin treatment as perceived by the patients. Two thirds of subjects receiving pregabalin rated themselves as improved at endpoint, and the distribution of PGIC responses was significantly in favour of improvement in the pregabalin group versus placebo. This suggests that the improvement in pain and sleep disturbance, along with the fact that pregabalin was generally well tolerated, provided meaningful patient benefit. In conclusion, the results of this study in post-traumatic peripheral neuropathic pain are generally consistent with earlier studies in other peripheral neuropathic pain states, DPN and PHN, and underlie the effectiveness of pregabalin in the treatment of peripheral neuropathic pain.

TRIAL REGISTRATION

Clintrial.gov Identifier: NCT00292188

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Chapter VI

A cross-sectional survey of health state impairment and treatment patterns in patients with postherpetic neuralgia

Robert van Seventer 1, Alesia Adoski 2, Melanie Lucero 3, Ellen Dukes 2

Author affiliations:
1 Amphia Hospital, Department of Anaesthesiology, Breda, The Netherlands. 2 Global Outcomes Research, Pfizer Global Pharmaceuticals, 235 East 42nd Street, Mailstop 235/9/2, New York, NY 10017, USA. 3 Pfizer Consultant

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ABSTRACT

Background

Postherpetic neuralgia (PHN) develops in 8–24% of patients with herpes zoster. Few studies have evaluated the patient burden and treatment of PHN in general practice.

Objectives

To determine the patient burden of PHN with respect to pain intensity and impact on patient functioning and to characterise treatment patterns and health resource utilisation in general practice.

Methods

Eighty-four patients with PHN were identified in general practice settings during an observational survey of neuropathic pain syndromes in six European countries. Patients answered a questionnaire that included pain severity and interference items from the modified short form brief pain inventory (mBPI-SF), EuroQol (EQ-5D) survey and questions related to current treatment, health status and resource utilisation. Physicians provided information on medications prescribed for PHN and pain-related co-morbidities (anxiety, depression and sleep disturbance).

Results

Mean patient age was 71.0 } 12.8 years, 76% were ≥65 years and 45% of patients had PHN ≥1 year. The mean pain severity index was 4.2, reflecting moderate pain despite 89% of patients taking prescription medications for PHN. Few medications with demonstrated efficacy against PHN (e.g. carbamazepine and gabapentin) were prescribed, often at suboptimal doses. Pain severity was associated with reduced EQ-5D health state valuation ($P<0.001$), greater pain interference on all domains ($P<0.001$) and increased health resource utilisation ($P = 0.008$).

Conclusions

PHN causes substantial patient burden expressed as interference with daily functioning and reduced health status associated with pain severity. This burden may result in part from suboptimal management strategies and suggests a need for more effective pain management.

INTRODUCTION

Herpes zoster (HZ) is characterised by painful blisters that erupt along a nerve path after reactivation of latent varicella zoster virus. HZ has an estimated incidence in the United States and Europe of 3.9–11.8/1,000 person-years in persons aged ≥60 years [1]. The acute pain of HZ significantly impacts patient function and quality of life [2, 3].

Postherpetic neuralgia (PHN), the most common complication of HZ, is a neuropathic pain frequently reported as lancinating, burning, shooting, stabbing, paroxysmal or electrical. It is often associated with abnormal sensory perception (e.g. allodynia and/or hyperalgesia) and may persist as chronic pain after resolution of the HZ rash. Because different criteria are used to define PHN (pain at rash healing, 1 month after rash onset or 3 months after rash onset), the estimated incidence varies from 8 to 24% [4, 5]. The prevalence of PHN increases with older age [6, 7]; 47 and 73% of untreated adults with HZ over 60 and 70 years of age, respectively, may have PHN [8]. With the ageing of the population, a larger proportion of persons are at a risk of developing HZ and PHN. Medical management of pain presents unique challenges in an older population, and care is needed in the choice of therapies for neuropathic pain conditions [9].

The high incidence of HZ in older persons combined with the recognised impact of PHN on patient functioning and quality of life [1, 4, 5, 10–13] suggests that PHN may present a significant patient burden in a population already impaired in health status. Patient functioning and quality of life have been incorporated as outcomes in several studies of PHN [14–16]. However, few studies evaluated the patient burden and treatment of PHN in primary care, the usual locus of chronic pain management [17]. A US study conducted by postal questionnaire in patients recruited through advertisements showed substantial impact of PHN on health status domains related to patient functioning [13]. A second US study, adapting the brief pain inventory to assess HZ pain in patients recruited from different health care settings, showed an association between PHN and reduced patient function and quality of life [18].

These considerations suggested a need to better understand treatment patterns and patient burden in general practice settings in Europe. The purpose of the present analysis was to evaluate the impact of PHN on patient functioning and to characterise associated treatment patterns in patients recruited from primary care settings in six European countries.

SUBJECTS AND METHODS

The sample consisted of 84 patients with PHN identified during a larger observational, cross-sectional study of broad neuropathic pain syndromes [19]. Sampling was limited to

general practitioners and non-pain specialists. Patients were recruited from community-based practices in France, Germany, Italy, the Netherlands, Spain and United Kingdom.

We assessed patient-reported functional health and wellbeing, pain experience, medication use and health resource utilisation specifically for PHN (e.g. physician visits and telephone consultations).

Physicians were screened for their interest in study participation, and a feasibility assessment was conducted to determine their ability to identify patients for inclusion. Physician training by teleconference included reviewing the study objectives, physician responsibilities, patient eligibility criteria and administrative procedures. The clinical case report form provided definitions of PHN with reference to patient-reported pain descriptors and pain location.

The study protocol was approved by local ethics committees. Participating physicians invited patients to participate in the study during routine care visits. Eligible patients were identified by physicians based on the presence of neuropathic pain and report of symptoms consistent with allodynia (pain in reaction to non-noxious stimuli such as the light touch of a cotton ball) and hyperalgesia (exaggerated pain reaction to mild pain stimuli) and/or the patient's use of specific words (e.g. burning, shooting, stabbing or tingling) that typically describe neuropathic pain. PHN was defined as neuropathic pain in the area of a spinal nerve dermatome or cranial nerve tract lasting >3 months after crusting of the skin lesions associated with HZ. Symptom duration of ≥3 months and up to the week before the survey was required.

Exclusion criteria were participation in an investigational drug study within the past 30 days, presentation with or a history of a serious or unstable medical or psychological condition that would compromise participation in the study and presence of a concomitant illness unrelated to PHN (e.g. neurological disorder or other pain condition) that would likely confound the assessment of PHN.

Patients were eligible if they had other chronic pain conditions such as osteoarthritis or migraine headaches, provided they could distinguish between PHN pain and the other conditions. Patients who consented completed a questionnaire as described below. Physicians provided clinical information regarding the duration of disease and prescribed medications for PHN and common pain-related co-morbid conditions (e.g. anxiety, depression or sleep disturbance).

PATIENT QUESTIONNAIRE

The questionnaire included 11 items from the modified short form brief pain inventory (mBPI-SF) [20–22], the EuroQol (EQ-5D) [23] and additional questions as described below.

Validated translations of the mBPI-SF and EQ-5D survey were used, and the remaining questions were translated and reviewed for accuracy by native speakers.

Modified short form brief pain inventory

Pain severity, assessed using the mBPI-SF, was measured using an 11-point numeric rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). Items included current pain, worst, least and average pain over the previous 24 hours. The pain severity index was calculated as the average of the four ratings. Pain severity cut-points were 1–3 for mild pain, 4–6 for moderate pain and 7–10 for severe pain [24].

The remaining items measured pain-related interference over seven health status domains using 11-point numeric rating scales ranging from 0 (does not interfere) to 10 (completely interferes). The mean of these seven ratings measured the patient's overall level of pain interference (pain interference index).

EuroQol survey

The EQ-5D survey assessed the overall functioning and well-being with respect to mobility, self-care, usual activities, pain or discomfort and anxiety or depression [23]. Domains were rated using a 3-point ordinal scale, and the resulting profile was used to calculate health state valuations based on precalculated scoring coefficients [25]. We used scoring coefficients generated in the United Kingdom to assign health state valuations to patients. Health state valuations ranged from –0.59 (worst health state) to 1.00 (best health state).

ADDITIONAL QUESTIONS

Specific questions addressed patients' overall health rating and health resource utilisation. Patients rated their current health on a scale of 0–100, where 0 represented 'worst possible health' and 100 represented 'perfect health'; patients also provided a health rating under the hypothetical scenario of having complete relief of PHN pain.

Physicians provided information about current prescription medications for PHN, and patients provided information about the use of non-prescription medications and other therapies including acupuncture, topical lotions, herbs or vitamins, devices such as those for electroneural stimulation (e.g. transcutaneous electroneural stimulation [TENS] or spinal cord stimulation) and exercise. Patients also evaluated the efficacy of prescription medications (extremely effective, very effective, somewhat effective, a little effective and not effective) including information on treatment adherence and medication satisfaction. Other questions included the frequency of neuropathic pain-related

physician visits and telephone consultations during the past 4 weeks and evaluation by pain specialists.

STATISTICAL ANALYSES

Summary statistics were utilised to describe the study sample: means ± standard deviations were provided for continuous variables and frequency distributions for categorical variables.

One-way analysis of variance models for continuous outcomes and chi-square tests for categorical outcomes were used to evaluate the association between pain severity (categorized as mild, moderate or severe) [24] and other outcomes.

Statistical significance was evaluated at the 0.05 level, with no adjustments for multiple comparisons, given the descriptive nature of the study. All analyses were performed using PC-SAS version 8.0 (SAS Institute, Cary, NC, USA).

RESULTS

The sample consisted of 84 patients: 48% males and 52% females. The mean age was 71.0 ± 12.8 years: 76% of patients were ≥65 years of age. Sixty-five percent of patients were retired, 12.6% employed at least part-time and the rest disabled (3.8%), full-time homemakers (17.5%) or other (1.3%). Almost half the patients (45%) had PHN for >1 year.

The mean pain severity index was 4.2 indicating moderate pain. Fifty-nine per cent of patients reported moderateto- severe pain as their overall pain within the prior 24 hours

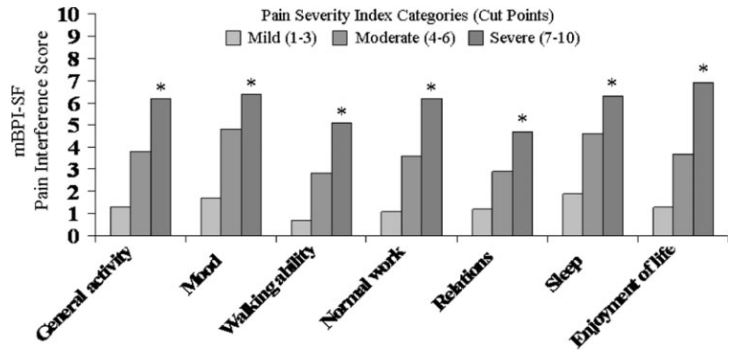

Figure 1. Mean pain interference scores for domains of daily functioning on the modified short form brief pain inventory (mBPISF) by pain severity; *P<0.001 for the association between pain severity and interference.

Table 1. Patterns of treatment for postherpetic neuralgia

Treatment[a]	*n* (%)
Physician-reported NP prescription medications	
Current NP prescription medication	75 (89.3)
Amitriptyline	18 (21.4)
Other antidepressants	22 (26.2)
Sedatives/hypnotics	27 (32.1)
Analgesics	54 (64.3)
Opioids and opioid compounds	17 (20.2)
NSAIDs or COX-2s	28 (33.3)
Antiepileptic medications	44 (52.4)
Gabapentin	32 (38.1)
Carbamazepine	19 (22.6)
Duration of NP prescription medication use	
<3 months	24 (29.6)
3–6 months	19 (23.5)
7–12 months	8 (9.9)
13–35 months	17 (21.0)
≥36 months	13 (16.0)
Physician-reported concomitant prescription medications	
Current concomitant prescription medications[b]	31 (36.9)
Prescribed medications for anxiety	12 (14.3)
Prescribed medications for sleep disturbance	14 (16.7)
Prescribed medication for depression	5 (6.0)
Patient-reported other NP medications	
Non-prescription medications	31 (36.9)
Physical treatments	24 (28.6)
Topical lotions/creams	36 (42.9)
Herbs, vitamins and supplements	21 (25.0)
Devices	16 (19.0)
Exercise	14 (16.7)

NP, neuropathic pain; NSAIDs, non-steroidal anti-inflammatory drugs.
[a]Neither the treatment categories nor the subcategories are mutually exclusive.
[b]Prescribed either antidepressants, sedatives/hypnotics (benzodiazepines, buspirone or other hypnotics) or analgesics (tramadol, any opioids or opioid compounds, non-steroidal anti-inflammatory drugs or COX-2 inhibitors) for concomitant anxiety, depression or sleep disturbance.

as indicated by their pain index severity scores; 78% of patients reported their worst pain within the prior 24 hours as moderate or severe in intensity.

Patients reported pain interference on all seven health status domains that was significantly associated with greater pain severity (Figure 1; $P<0.001$). The most affected domains were mood, sleep and general activity; the least affected domains were walking ability and relations with other people.

Most patients (89%) received at least one prescription medication for neuropathic pain, and polypharmacy was common (Table 1). More than half of the patients (52%) were prescribed antiepileptic medications (Table 1) including gabapentin (38%) and carbamazepine (23%), which are recommended for neuropathic pain [9]. Mean daily doses were low; 1032.3±508.2 mg of gabapentin and 500.0 ±309.1 mg of carbamazepine. Other commonly prescribed medications for PHN included anti-inflammatory and opioid agents (64%), sedative or hypnotic medications (32%), amitriptyline (21%) and other antidepressants (26%). More than one-third of patients (37%) received some form of prescription medication for PHN for >1 year, and a similar proportion (37%) received concomitant prescription medications for anxiety, depression or sleep disturbance related to PHN (Table 1).

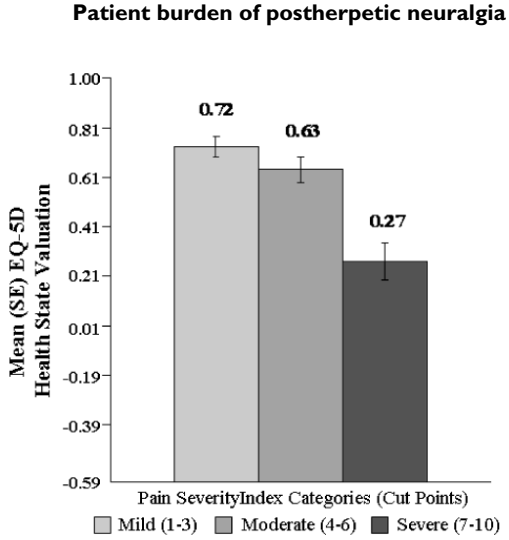

Figure 2. Association between pain severity and EuroQol (EQ-5D) health state valuation. *P*<0.001 using one-way ANOVA

Eighty-five per cent of patients reported taking their prescription medication for PHN 'all' or 'most of the time'. Only 39% of patients reported their prescription medication as 'extremely effective' or 'very effective'.

Many patients reported using other medications/treatments for their PHN (Table 1); 37% reported taking overthe-counter medications (e.g. paracetamol or aspirin), and similar proportions reported use of topical lotions or creams (43%), physical treatments (29%) or herbs/vitamins/supplements (25%).

Pain had a significant impact on health status including functioning and well-being. Patients reported an overall mean EQ-5D health state valuation of 0.60±0.29 (–0.59 to +1.00 scale), and a significant association was observed between increasing pain severity and decreasing EQ-5D health state valuation (Figure 2; *P*<0.001). Similarly, a significant association was observed between increasing pain severity and pain interference; pain interference index scores were 1.3, 3.8 and 6.2 for mild, moderate and severe pain, respectively (*P*<0.001).

Patients placed significant value on obtaining relief from their PHN. On a 0–100 scale, patients estimated a 29% increase in their health-rating score (improvement from 61.7±20.3 to 79.7±19.8; *P*<0.0001, paired *t*-test) if they could experience complete relief from their PHN.

PHN directly impacted medical resource utilization within the past 4 weeks; 68% of patients visited their physician at least once, 30% had telephone consultations for their PHN and 30% saw a pain specialist. A significant association was observed between

increasing pain severity and greater number of telephone consults ($P = 0.008$), with a similar trend between pain severity and physician visits ($P = 0.078$).

DISCUSSION

These findings demonstrate a substantial patient burden of PHN, consistent with previously reported neuropathic pain conditions including diabetic peripheral neuropathy [12, 19, 26] and PHN [13]. Patient burden, expressed as impairment of function and reduced quality of life, was significantly associated with pain severity as indicated by poorer health status (EQ-5D) and increased pain interference with functioning (mBPI-SF Pain Interference scores) with increasing neuropathic pain severity. Additionally, a substantial proportion of patients were prescribed medications for depression, anxiety and sleep disturbance related to PHN, conditions considered co-morbid with chronic pain including neuropathic syndromes [11, 27].

The sustained moderate-to-severe pain levels suggest suboptimal pain management. This is supported by the considerable patient burden observed despite most patients receiving prescription medications for their PHN. This finding may in part be attributed to the use of agents having no demonstrated efficacy for the treatment of neuropathic pain (e.g. 33% of patients were taking non-steroidal anti-inflammatory drugs or COX-2 inhibitors for their PHN).

Similarly, suboptimal doses of neuropathic pain medications including gabapentin and carbamazepine may have contributed to inadequate pain management [9, 10]. Few patients reported adequate therapeutic efficacy of their prescribed medications, which may explain why non-prescription adjunctive treatments including over-the-counter analgesics, topicals and supplements were taken to obtain pain relief.

Twenty-one per cent of patients were taking amitriptyline, which has demonstrated efficacy in neuropathic pain, albeit at higher doses than the mean daily dose of 32.4±17.4 mg observed here. According to the Beer's modified criteria [28], amitriptyline is considered inappropriate for use in the age group represented in this analysis (≥65 years) and is not recommended for treatment of neuropathic pain in older patients [9]. Potentially inappropriate use of medications for painful neuropathic disorders was recently reported in older adults, where 35% of patients with PHN were prescribed amitriptyline [29].

Our observation of inadequate pain control, pain interference with functioning and suboptimal treatment was consistent with a US postal survey of patients with PHN, where only half of patients reported taking prescription medication for PHN in the prior week, despite moderate levels of pain severity and pain interference [13]. The association of pain severity with pain interference and EQ-5D health state valuation observed

in both the postal survey and current study suggest that suboptimal treatment of PHN is common.

Suboptimal pain management and patient burden were similarly reported by Gilron *et al*. [30] in a Canadian study of patients with neuropathic pain treated by general practitioners. Seventy-three per cent of patients complained of inadequate pain control and only 16% tried any of the newer pharmacologic agents available for neuropathic pain. Approximately 30% of patients saw a pain specialist, similar to the present study, indicating that few patients were being referred to and treated by physicians familiar with new and/or appropriate treatment options. In the current analysis, inadequate management of PHN and increased resource utilisation were demonstrated by the significant association between pain severity and telephone consults and the trend towards more physician visits with increasing pain severity.

This study has several limitations. The small number of patients may limit the ability to detect potentially significant associations. Other limitations include the potential for selection and recall bias, where patients were actively seeking medical care (possible selection bias), and some information from the survey was collected by self report (possible recall bias). Furthermore, pain is a complex and multidimensional experience, and our focus on pain severity may not have captured the full impact of pain on patient burden. The use of >3 to distinguish between moderate and mild pain severity and interference was consistent with that reported in other studies. The cut-point correlated with resource utilisation and patient outcomes in diabetic peripheral neuropathy [20, 24] and demonstrated agreement with activities of daily living and quality of life in an HZ-specific adaptation of the BPI [18].

In conclusion, this study demonstrates substantial patient burden associated with PHN. The burden was significantly greater when pain was less controlled and likely resulted from suboptimal or inappropriate management strategies. Our results demonstrate a need for more effective management strategies in patients presenting with PHN, such as physician education related to neuropathic pain mechanisms and treatment options, and familiarity with current neuropathic pain management guidelines.

KEY POINTS

- Most patients with postherpetic neuralgia (PHN) reported moderate or severe pain and suboptimal health and functioning despite taking prescribed medications for the treatment of PHN.
- Patient burden was significantly associated with pain severity: health valuation was poorer and pain interference with functioning was greater with increasing pain levels.

- Use of prescription medications with no known efficacy in neuropathic pain and in general lower than recommended doses of medications with neuropathic pain efficacy was reported.
- Better management strategies including physician education could reduce the burden of PHN.

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Chapter VII

Relationships Between Changes in Pain Severity and other Patient-Reported Outcomes: An Analysis in Patients With Posttraumatic Peripheral Neuropathic Pain

Robert van Seventer 1, Michael Serpell 2, Flemming W. Bach 3,4, Bart Morlion 5, Gergana Zlateva 6, Andrew G. Bushmakin 7, Joseph C. Cappelleri 7, and Meryem Nimour 8

Author affiliations:
1 Amphia Hospital, Department of Anaesthesiology, Breda, The Netherlands. 2 Pain Clinic, Gartnavel General Hospital, Glasgow, UK. 3 Danish Pain Research Center, Aarhus, University Hospital, Aarhus Denmark. 4 Department of Neurology, Hospital of Aalborg, Aarhus University Hospital, Aalborg, Denmark. 5 The Leuven Centre for Algology and Pain Management, University Hospitals Leuven, Belgium. 6Pfizer Inc., New York, NY, USA. 7 Pfizer Inc., Global Research & Development, New London, CT, USA. 8 Pfizer Ltd, Walton Oaks, Tadworth, Surrey, England, UK

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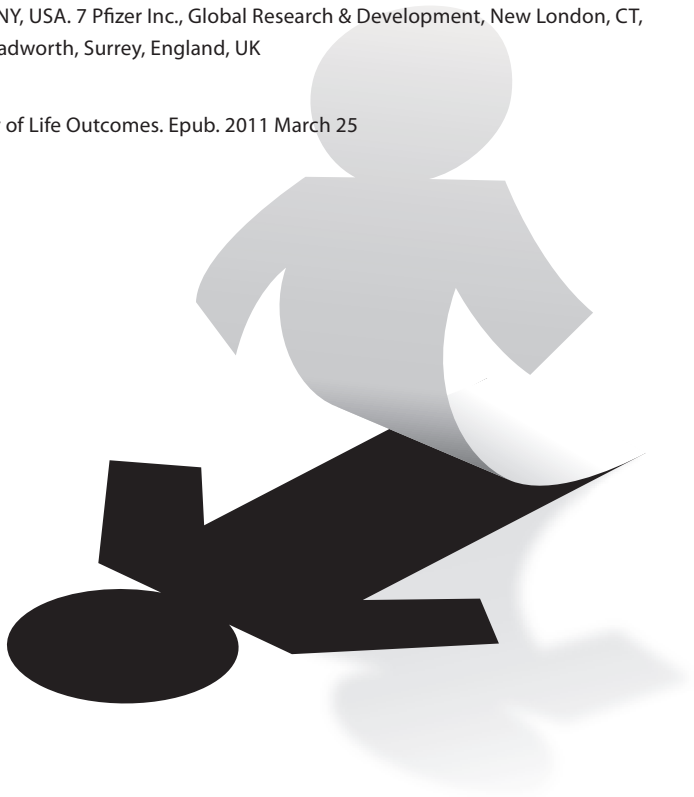

ABSTRACT

Background

The objective of this study is to use the pain numeric rating scale (NRS) to evaluate associations between change in pain severity and changes in sleep, function, and mood assessed via patient-reported outcomes (PROs) in patients with posttraumatic pain.

Methods

This is a secondary analysis of a clinical trial evaluating pregabalin in patients with posttraumatic peripheral neuropathic pain (N=254). Regression models were used to determine associations between changes in pain (0–10 NRS) as the predictor and scores on the following PRO measures as the outcome: Pain Interference Index; Hospital Anxiety and Depression Scale anxiety and depression subscales; Medical Outcomes Study–Sleep Scale 9-item Sleep Problems Index and Sleep Disturbance subscale; and Daily Sleep Interference Scale (0–10 NRS).

Results

Change in pain severity showed clear, direct relationships with changes in function, anxiety, depression, and sleep PROs, all of which were statistically significant ($P<.001$). Results from subgroup analyses (≥30% or ≥50% pain responders, pregabalin or placebo treatment, age ≤ 51 years or >51 years) tended to be consistent with results from the overall sample.

Conclusions

Overall, a direct relationship exists between pain and various aspects of patient's well-being and functioning, which can provide a quantitative assessment of how improvements in pain may be expected to relate to other patient outcomes. (ClinicalTrials.gov Identifier number NCT00292188; EudraCT #2005-003048-78).

BACKGROUND

Because the complexity and subjective nature of pain complicates evaluation of its severity and impact, various patient self-report instruments have been developed to assess pain and other patient-reported outcomes (PROs) in the research and clinical settings [1]. The 11-point numeric rating scale (NRS), which ranges from 0 (no pain) to 10 (worst possible pain), has become one of the most frequently used instruments for evaluating pain based on its simplicity and ease of comprehension by patients.

This NRS is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) as one of the core outcomes for assessment in clinical trials of chronic pain [2]. Additionally, IMMPACT recommends that function and mood should be included as core outcomes. The presence and increased severity of pain often results in reduced function and increased mood disturbance [3, 4]. Although not included in the IMMPACT recommendations, sleep is another outcome that is affected adversely by pain, with consistent evidence endorsing this relationship [5–7].

When evaluating these outcomes, we believe that because the presence of pain generally interferes with daily functions, improvement in pain will be associated with improved functioning and other health benefits such as sleep and mood — specific outcomes that can be quantified and expressed. Therefore, characterizing and quantifying the relationship between pain severity and corresponding levels of interference with daily function, sleep, and mood can inform treatment decisions and guide assessment of outcomes. Previous studies in painful diabetic peripheral neuropathy have evaluated the relationship between pain and other PROs to categorize patients with mild, moderate, and severe pain [8, 9]. One of these studies suggested that changes across severity categories correlate with specific score changes in PROs [9]. The purpose of the current study is to use the pain NRS to characterize and quantify in a clinical and meaningful way the extent of the relationship between pain severity scores and scores on other PROs that measure sleep, pain interference on daily functions, and mood.

METHODS

This study is a secondary analysis using data derived from a placebo-controlled clinical trial evaluating the efficacy of pregabalin in patients with posttraumatic peripheral neuropathic pain (N=254). The methodology and primary analysis of the trial have been reported elsewhere [10].

All patients gave written, informed consent. Institutional review boards reviewed and approved the protocol and the study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and local laws and regulations. Patients

were eligible for participation if they received a diagnosis of posttraumatic peripheral neuropathic pain (including post-surgical neuropathic pain, neuropathic pain due to peripheral nerve injury, and phantom limb pain) that was confirmed by a qualified pain specialist and persisted for a minimum of three months following the traumatic event. Patients were enrolled if they had a score of ≥40 mm on the visual analog scale of the short-form McGill Pain Questionnaire and completed ≥ 4 daily pain diaries during the last week of the screening period prior to randomization, with the mean score being ≥4 on the 11-point (0–10) NRS.

Patients with neuropathic pain that was not due to trauma (e.g. diabetic peripheral neuropathy, postherpetic neuralgia, radiculopathy, trigeminal neuralgia or carpal tunnel syndrome), was central rather than peripheral (e.g. spinal cord injury) or was due to Complex Regional Pain Syndrome (Type 1 or Type II) were excluded. Also, patients suffering from clinically significant or unstable conditions that, in the opinion of the investigators, would compromise participation in the study were excluded.

The current report focuses on the association between changes in pain severity and changes in PROs of pain interference on daily functions, sleep, and mood; these analyses are independent of the treatment allocation (pregabalin or placebo) and comparative results reported in the primary analysis.

We evaluated the association between change in pain, assessed daily using a 0-to-10 NRS (0 = no pain, 10 = worst possible pain) and then averaged to give a weekly result, and several other PROs assessed at baseline and end of double-blind treatment at week 8. These PROs included the following: the Pain Interference Index (PII) from the modified Brief Pain Inventory — short form (mBPI-sf) [11], a composite score of the 7 interference items assessed using a 0-to-10 NRS anchored at 0 = does not interfere and 10 = completely interferes (recall period of the past 24 hours); the anxiety and depression subscales of the Hospital Anxiety and Depression Scale (HADS) [12], with each subscale consisting of 7 items scored using a 4-point Likerttype scale (1-week recall period) and higher scores indicating greater severity; the Medical Outcomes Study–Sleep Scale (MOS-SS) 9-item Sleep Problems Index and 4-item Sleep Disturbance subscale [13], both based on a 1-week recall period with higher scores indicating greater sleep problems; and the Daily Sleep Interference Scale that uses an 11-point NRS to describe how pain has interfered with sleep during the past 24 hours (0 = no interference, 10 = completely interferes). Linear models were applied to evaluate the relationship between the change in each of these PROs as the outcome and the change in pain used as a continuous predictor.

The above-specified relationships between change in pain and PROs were examined using linear regression models. The changes in PRO scores were evaluated as a function of the change in pain NRS score (from baseline to end point).

The model was populated with all available patients who provided data in the clinical trial regardless of treatment allocation or treatment effects. To evaluate the model for consistency and robustness, six sensitivity analyses were performed using subgroups from the clinical trial. These cohorts included patients achieving ≥30% pain response (30% responders), patients achieving ≥50% pain response (50% responders), pregabalin-treated patients, placebo-treated patients, patients aged ≤ 51 years and patients >51 years. Fifty-one years was chosen as the cut-off value since it is the median age of all patients. The 30% and 50% responders are those patients who achieved at least a 30% and 50% reduction in pain NRS scores, respectively, from baseline to endpoint.

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA). A *P* value <.05 was taken to confer statistical significance.

RESULTS

The population consisted of 254 patients with a mean age of 51.7 years; 50.8% of the patients were female. In the original placebo-controlled clinical study [10], pregabalin was associated with a statistically significant improvement in pain compared to placebo, and significant improvements in other PRO scores that included pain-related sleep interference, the MOS sleep scale (overall sleep problems index, as well as the sleep disturbance and sleep adequacy subscales), and the anxiety and depression subscales of the HADS.

In this secondary analysis, changes in PRO scores were evaluated as a function of change in pain severity. Regression models resulted in linear plots (see Table 1 for slope and intercept estimates) that showed significant associations (*P*<.001) between changes in pain and changes in patient-reported sleep disruption (Figure 1), pain interference

Tables

Table 1 - Slope and intercept estimates from models predicting relationships between changes in pain severity and PROs for all patients

	Estimate (95% CI)					
	MOS-SS Disturbance	MOS-SS 9-Item Sleep Problems Index	Sleep Interference (NRS)	HADS Anxiety	HADS Depression	PII
Intercept	–4.30 (–7.31, –1.28)	–2.07 (–4.42, 0.27)	–0.27 (–0.49 ,–0.05)	–0.76 (–1.22 ,–0.30)	–0.27 (–0.63, 0.08)	–0.32 (–0.56, –0.08)
Slope	3.79 (2.44, 5.13)	2.76 (1.71, 3.80)	0.68 (0.59, 0.78)	0.38 (0.17, 0.59)	0.48 (0.32, 0.64)	0.58 (0.47, 0.69)

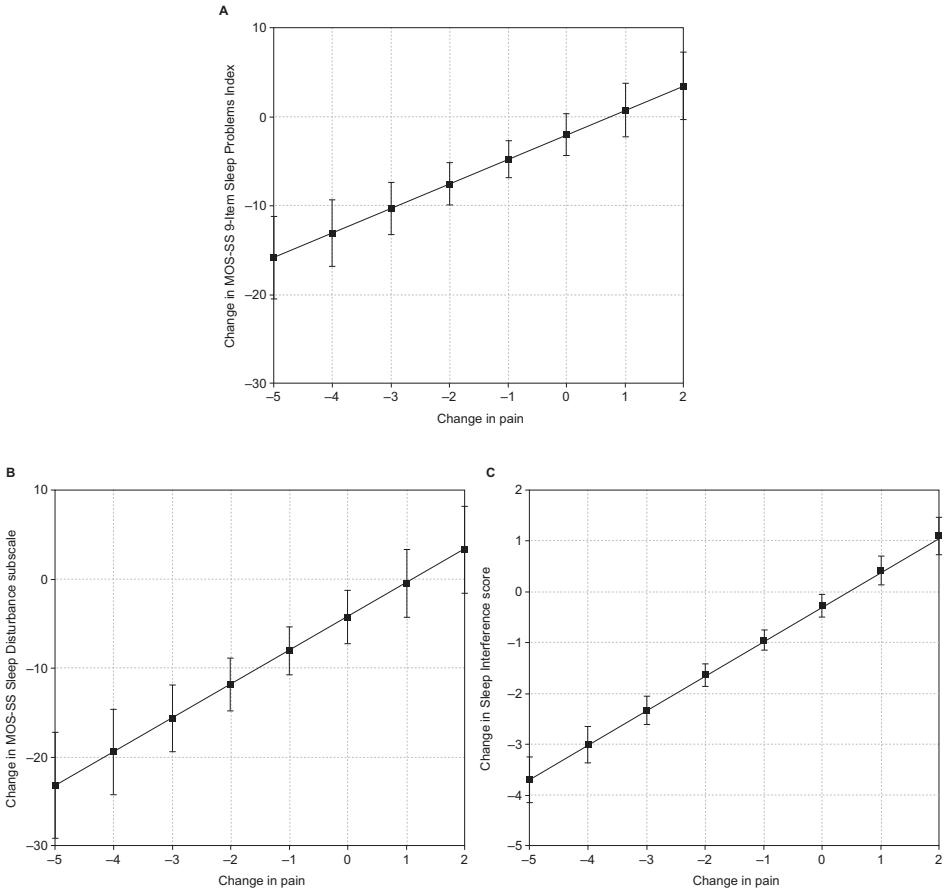

Figure 1

on daily functions (Figure 2), and mood (anxiety and depression; Figure 3). For example, a 2-point decrease (improvement) in pain corresponded to an estimated 7.6-point decrease (improvement) in the MOS Sleep Problem Index 9, 11.9-point decrease in MOS Sleep Disturbance, and 1.6-point decrease in Sleep Interference (Figure 1). A 2-point decrease in pain was associated with an estimated 1.5-point decrease in pain interference on daily function or PII (Figure 2). A 2-point decrease in pain was associated with an estimated 1.5-point decrease in HADS anxiety and a 1.2-point decrease in HADS depression (Figure 3). The derived plots can be interpreted as showing, at the individual patient level, the mean change in PRO score (y-axis) that can be expected with the various incremental changes in pain severity (x-axis).

Table 2 presents the mean improvement (decrease) in PROs corresponding to a 2-point improvement (decrease) in pain for the total sample. The mean improvement values were estimated as intercept + slope*(-2). For example, using data from Table 1, mean improvement in MOS-SS disturbance that corresponded to a 2-point improve-

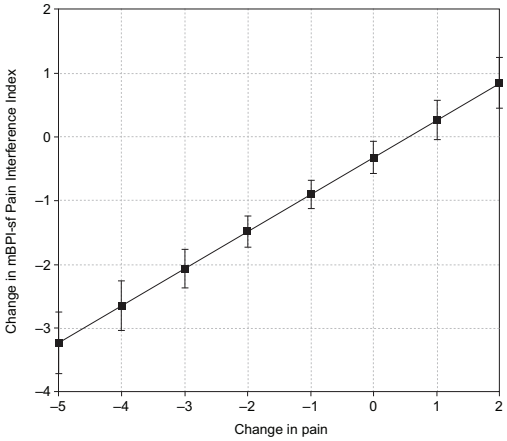

Figure 2

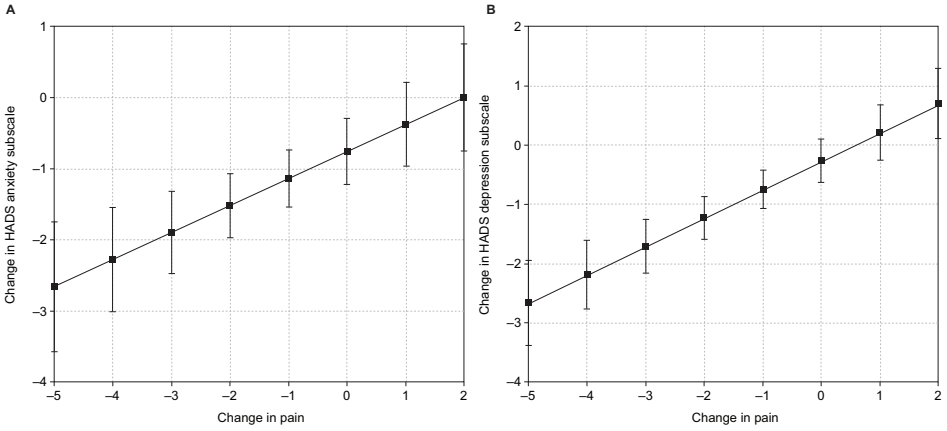

Figure 3

ment in pain is -4.3 + 3.79*(-2), which is equal to -11.87, taking into account rounding errors in intercept and slope (Table 2).

Table 2 also presents the results of the subgroup sensitivity analyses for 30% and 50% pain responders as well as for individuals in the pregabalin and placebo groups, and individuals aged ≤ 51 years and > 51 years. In general, these sensitivity analyses tended to support the results of the main analysis of the total sample, with some exceptions, for example, 50% responders on the PII scale, and placebo-treated patients as well as patients ≤ 51 years of age on the HADS depression subscale, the MOS-SS Disturbance subscale and the MOS-SS 9-item Sleep Problems Index.

Table 2 - **Mean Improvement in PROs Corresponding to a 2-Point Improvement in Pain for Patients and Preselected Subgroups**

	Mean (95% CI) Improvement in PRO That Corresponded to a 2-Point Improvement in Pain					
Group	MOS-SS Disturbance	MOS-SS 9-Item Sleep Problems Index	Sleep Interference (NRS)	HADS Anxiety	HADS Depression	PII
All patients	–11.87	–7.59	–1.64	–1.52	–1.23	–1.48
(N=254)	(–14.83, –8.91)	(–9.91, –5.27)	(–1.86 ,–1.43)	(–1.97 ,–1.07)	(–1.58,–0.88)	(–1.72, –1.25)
Subgroups						
30% responders	–11.57	–7.41	–1.54	–1.57	–1.39	–1.68
(n=82)*	(–19.17, –3.98)	(–13.31, –1.50)	(–2.05, –1.03)	(–2.61, –0.53)	(–2.13,–0.65)	(–2.22 ,–1.14)
50% responders	–13.12	–8.37	–1.70	–2.04	–1.25	–2.21
(n=48)*	(–25.04, –1.19)	(–18.07,1.32)	(–2.70,–0.70)	(–3.88, –0.21)	(–2.50,0)	(–3.13,–1.28)
Pregabalin-treated patients (n=127)	–15.79 (–19.76, –11.83)	–9.85 (–13.14, –6.57)	–1.67 (–1.96, –1.38)	–1.64 (–2.25,–1.03)	–1.56 (–2.00,–1.12)	–1.71 (–2.05,–1.38)
Placebo-treated patients (n=127)	–7.09 (–11.51,–2.68)	–4.93 (–8.22, –1.65)	–1.62 (–1.95, –1.29)	–1.41 (–2.09, –0.74)	–0.83 (–1.39,–0.27)	–1.18 (–1.51,–0.85)
Age ≤ 51 y (n=127)	-8.12 (-12.35, -3.89)	-5.16 (-8.41, -1.91)	-1.59 (-1.89, -1.30)	-1.17 (-1.83, -0.51)	-0.75 (-1.28, -0.22)	-1.47 (-1.79, -1.15)
Age > 51 y (n=124)	-15.64 (-19.74, -11.54)	-10.17 (-13.48, -6.86)	-1.69 (-2.01, -1.38)	-1.87 (-2.48, -1.27)	-1.71 (-2.16, -1.26)	-1.50 (-1.85, -1.15)

Mean Improvement = decrease; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; MOS-SS, Medical Outcomes Study–Sleep Scale; NRS, numeric rating scale; PII, Pain Interference Index; PROs, patient-reported outcomes.

*30% and 50% responders are those patients who achieved at least a 30% and 50% reduction in pain, respectively, in the clinical trial on which this analysis was based.

DISCUSSION

It is well-recognized that pain affects patient function and may have a reciprocal relationship with specific outcomes such as sleep and mood [3–7]. The results of this study expand our knowledge of the relationship between pain and PRO by suggesting that a clear, direct relationship exists between change in pain and change in patients' self-report of daily function, sleep, and mood. To our knowledge, this is the first study that provides evidence for such a relationship. This study demonstrates a direct quantitative linkage of these relationships, whereby specific changes in pain severity can be mapped to the specific magnitude of a change in a PRO.

Pain severity is not necessarily linearly related to functional impairment [14]. Nevertheless, our imposition of linearity on the relationship between change in pain and change in functional impairment is useful because it enables us to predict and quantify

the functional improvement that may be expected to result from successful analgesic treatments. The strength of our results is that they are hypothesis- and empirically-driven findings that are independent of treatment allocation. This model for evaluating change in pain severity can be interpreted at the individual patient level over time, and can be used to determine the expected change in PRO score that corresponds to a particular incremental change in pain severity for a particular patient in the current study from baseline to week 8. This relationship can be explained to the patient and can help to convey the level of improvements that may be achievable, thereby enabling the patients to form more realistic and objective goals.

Even though there were fewer patients in the sensitivity analyses, the results were generally consistent with the main analysis, indicating the invariance of the observed relationships. The few exceptions may be owing to the smaller number of observations and the curtailment of distribution of responses, which resulted in a narrower range in change scores in the subgroups. While the reason for these exceptions warrants further investigation, the overall comparability of the values among the evaluated samples suggests the model's robustness.

Of particular interest is the observation that for some of the PROs, there was a change in score even with no change in pain severity. For example, individuals with no change in pain severity still showed a 4.3-point improvement on the MOS-SS Sleep Disturbance subscale. This can be taken to suggest that there may exist effects of treatment that are independent of the effects on pain, which in this case, can be specific effects on sleep.

Further support for this comes from the sensitivity analyses, for which pregabalin treated patients with no change in pain improved by 7.50 points on the MOS-SS Sleep Disturbance subscale, whereas placebo-treated patients with no pain change improved only by 1.35 points. Direct effects of pregabalin on sleep improvement have previously been suggested using mediation analysis in a study of patients with fibromyalgia [15]. The relationship between pain and sleep is considered to be bidirectional [6, 16], and while studies have suggested that sleep disruption may enhance the pain experience [17–19], it is not clear whether sleep improvement in itself can directly improve pain scores or if the improved sleep increases the patient's ability to cope with the pain.

The data in the present study are consistent with results from a recent study by Hoffman et al. [9]. Using data from a randomized, placebo-controlled trial of pregabalin in patients with painful diabetic peripheral neuropathy, a different population from ours, researchers derived pain severity cutpoint categories on a 0–10 point pain numerical rating scale (NRS), and compared the magnitude of within patient change in pain severity with corresponding changes in function and health status. The cutpoint analysis indicated that pain severity ratings of 1–3, 4–6, and 7–10 corresponded to mild, moderate and severe pain, respectively. For each change category, mean (± standard deviation, SD) score changes were examined for the mBPI-sf Pain Interference Index (PII)

and the Euro-Qol (EQ-5D). On the mBPI-sf PII (0–10 NRS), mean changes of -5.5 (± 2.1) corresponded to a shift from severe pain to no/mild pain; -3.3 (± 2.1), severe to moderate; -3.2 (± 2.1), moderate to no/mild; -0.9 (± 2.0), no change; and 0.4 (± 2.6), worsening ($P < .0001$). Mean changes in the PII ranged from -4.5 (± 2.2) for patients with ≥ 50% NRS reduction and -0.2 (± 2.0) for patients with < 10% NRS reduction ($P < .0001$). Similar differences were observed for the EQ-5D. Thus, changes in pain severity were associated with changes in daily functioning and health status, findings similar to those reported in the presented study.

A two-point reduction on pain is taken to correspond to a clinically meaningful improvement on the other PROs. Psychometric studies on specific PRO scales provide evidence supporting the clinical importance of these changes. For example, a large study assessing the psychometric properties of the Daily Sleep Interference Scale demonstrated significant correlations between this scale and other outcome measures, including pain, and the results suggest that a 1–2 point change from baseline to end of treatment may be interpreted as clinically important [20], a change consistent with values reported in the present study.

In a similar study that evaluated the reliability and validity of the MOS Sleep Scale in patients with painful diabetic neuropathy [21], the MOS Sleep Problems Index was shown to be responsive to clinical changes, with improvements being greater as the pain and sleep of patients improved. Minimal improvement in health status (on measures of pain, sleep, patient or clinical global impression of change) corresponded to mean changes on the MOS Sleep Problems Index that ranged from -10 to -14, a range that overlaps with the mean ± 95% CI reported herein, particularly in pregabalin-treated patients.

A study evaluating the psychometric properties of the BPI for painful diabetic peripheral neuropathy showed that scores on the PII (subscale of BPI) correlate highly and significantly with other outcome measures related to pain, sleep, health status, quality of life and mood [11]. Furthermore, in patients with painful diabetic neuropathy treated with pregabalin, a one-grade reduction in pain level, either "severe-to-moderate" or "moderate-to-no/mild" corresponded to mean (± SD) reductions in the PII of -3.3 (± 2.1) and -3.2 (± 2.1), respectively [9]. The PII values reported herein for all patients and subgroups are below these values but within the mean ± SD range, and therefore may be associated with clinically meaningful changes in pain levels. According to IMMPACT recommendations, a 1-point reduction in the PII may reflect minimally important improvement [22].

An important limitation of this study is that while it may be reasonable to expect that reductions in pain severity will result in improvements in other outcomes, the associations demonstrated by the reported data do not imply causation. Furthermore, these data are derived from patients with nonmalignant chronic pain and do not imply a general physiologic or pathophysiologic parallel regulation. For example, it has been

shown that change in depression scores are not necessarily paralleled by changes in pain thresholds in patients treated for major depression [23]. The use of other analytic techniques, such as path or mediation analysis, may help further characterize the causal relationship of these associations.

The generalizability of this study is another limitation that should be considered when interpreting the results within the context of clinical trials or clinical practice. Consequently, these results should be used as a guide for further exploring the relationships underlying pain and pain interference with function.

Models with pain as a categorical predictor, which do not impose any functional relationship between outcome and predictor, were also investigated. Results of these models (not reported here) supported the results with pain as a continuous predictor. We believe that the best choice to depict the appropriateness of a model is through probability plots and residual plots. If the probability plot forms a linear pattern and the residual plot forms no pattern, then we can conclude that the fitted relationship (in this case linear) is appropriate. We extensively studied these two types of plots and found the model to be suitable. The use of pain as a continuous predictor not only increases the sensitivity of observed relationships but also lends a simplified and meaningful interpretation of the relationship through the slope as a measure of change.

CONCLUSIONS

In summary, the results reported here provide evidence of a direct and tangible relationship between pain and PROs in patients with chronic, nonmalignant neuropathic pain. Importantly, the data additionally demonstrate that pain responders show other benefits that are quantifiable in relation to the change in pain severity and are clinically significant. This novel analysis can be applied for determining individual responses that can be expected in patients being treated for pain, with the observed relationships providing a framework for quantitatively assessing how improvements in pain may be expected to result in improvement in other patient-centered outcomes. Such information may be useful in the research setting for trial design and in the clinical setting for informing treatment decisions and enhancing assessment of outcomes. Additional confirmatory studies are encouraged.

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Chapter VIII

The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or postherpetic neuralgia: a review of nine clinical trials

Thomas Roth 1, Robert van Seventer 2, T. Kevin Murphy 3.

Author affiliations:
1 Director, Division of Sleep Medicine and Research Center, Henry Ford Health System, Detroit, MI, USA. 2 Amphia Ziekenhuis, Department of Anaesthesiology, Langendijk Breda, The Netherlands. 3 Medical Director, Global Medical, Pfizer Inc., New York, NY, USA

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ABSTRACT

Objective

Postherpetic neuralgia and painful diabetic peripheral neuropathy are common chronic neuropathic pain conditions associated with sleep disturbances. Pregabalin is indicated in the treatment of neuropathic pain. The objective of this review is to summarize the efficacy and safety of pregabalin in painful diabetic peripheral neuropathy and postherpetic neuralgia and the effect of pregabalin on sleep interference in these patients.

Methods

MEDLINE and ISI Web of Knowledge databases were searched for randomized double-blind, placebocontrolled clinical trials of pregabalin reporting sleep measures in addition to pain endpoints in patients with painful diabetic peripheral neuropathy and postherpetic neuralgia published from inception through March 2009.

Results

Nine trials met the inclusion criteria, providing data for a total of 2399 patients with painful diabetic peripheral neuropathy or postherpetic neuralgia treated twice or three times per day with pregabalin (75–600 mg/day) or placebo on a fixed or flexible schedule. Interpretation of sleep outcomes in two studies may be limited by trial inclusion criteria which permitted benzodiazepines for sleep problems. Also, none of the studies reported objective sleep measures. Pregabalin was well tolerated. Pregabalin (150–600 mg/day) significantly reduced pain and improved pain-related sleep interference.

Conclusions

In addition to an analgesic benefit, pregabalin may decrease pain-related sleep interference in patients with painful diabetic peripheral neuropathy and postherpetic neuralgia.

INTRODUCTION

Neuropathic pain results from a primary lesion or dysfunction in the nervous system[1,2], with multiple mechanisms underlying painful symptoms, including changes in the peripheral nervous system, spinal cord, or brainstem[3]. Tricyclic antidepressants, opioids, selective serotonin reuptake inhibitors (SSRIs), selective serotonin–norepinephrine reuptake inhibitors, topical lidocaine, and antiepileptic drugs (AEDs) each have a different mode of action impacting neuropathic pain and are among the commonly used pharmacotherapies in painful diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN)[2,4–6].

Patients with neuropathic pain often experience sleep interference described as difficulties in initiating sleep and remaining asleep[7–10]. Surveys of patients with painful DPN found that more than half of patients reported substantial interference with sleep[11,12] and greater sleep problems compared with the general US population (respective mean Sleep Problems Index scores, 47.1±21.1 vs. 25.8±18.6)[13]. Most patients reported suboptimal sleep (57 hours/night), and patients with severe pain reported greater sleep problems[13]. Sleep disturbance is also a comorbid disorder in patients with PHN and can lead to anxiety and depression, both of which can further exacerbate pain and sleep interference[12,14].

Pharmacologic management of sleep disturbances in neuropathic pain is complex. AEDs have demonstrated both detrimental and beneficial effects on sleep quality and sleep architecture[15,16]. Pregabalin binds potently to the a2d subunit protein of voltage-gated calcium channels in central nervous system (CNS) tissues[17–19]. High-affinity binding to the a2d subunit results in a reduction of calcium influx, modulates the release of several excitatory neurotransmitters (including glutamate, noradrenaline, and substance P)[20–24] from presynaptic neurons, and may lead to subsequent analgesia[25]. Awakening during nonrapid eye movement (NREM) sleep contributes to sleep disturbances [26,27]. Pregabalin increases the duration of NREM sleep, and therefore, may consolidate sleep and reduce sleep interference.

Pregabalin has been shown to reduce awakenings and improve sleep dysfunction in patients with epilepsy and fibromyalgia[28,29]. The purpose of the present paper is to review the efficacy and tolerability data from clinical trials of pregabalin in painful DPN or PHN and to summarize the effect of pregabalin on sleep interference in these patients.

METHODS

Literature search

A literature search was conducted in March 2009 using MEDLINE (PubMed) and ISI Web of Knowledge to identify publications where pregabalin was evaluated in randomized, placebo-controlled clinical trials in DPN or PHN. The search criteria were customized to each database. For PubMed, the following queries were used: pregabalin AND (diabetic neuropath* OR postherpetic neuralgia OR post-herpetic neuralgia) AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Multicenter Study[ptyp]) AND English[lang] NOT ('anesthetics'[MeSH Terms] OR 'anesthetics'[All Fields] OR 'anesthetic'[All Fields] OR 'anesthetics' [Pharmacological Action]). For ISI Web of Knowledge, the search terms were: Title¼pregabalin AND (diabetic neuropath* OR postherpetic neuralgia OR postherpetic neuralgia) AND (study or trial) AND Language¼English. Literature searches were not restricted to specific dates.

Inclusion criteria

Primary reports on randomized, double blind, placebo controlled clinical trials that evaluated pregabalin on pain and pain-related sleep interference in patients with DPN or PHN were included.

Data extraction

Outcome measures on pain and pain-related sleep interference were extracted, along with demographics, adverse events and discontinuation rates.

RESULTS

The literature search yielded 27 publications, nine of which met the inclusion criteria (Table 1)[30–38]. Each of the nine clinical trials was conducted in accordance with good clinical practice guidelines and received Institutional Review Board approval. The trials were 5 to 13 weeks in duration, including the baseline phase. The mean age of patients ranged from 70 to 73 years in the PHN studies[30,35,37], compared with a mean age of 56 to 62 years in painful DPN studies[32–34,36,38]. Eligible patients receiving prohibited medications (e.g., benzodiazepines, skeletal muscle relaxants, steroids, local and topical agents, nonsteroidal anti-inflammatory drugs, and anticonvulsants) completed a washout period prior to randomization. Upon randomization, 2399 patients received pregabalin (75–600 mg/day) or placebo, twice-daily (BID) or three-times-a-day (TID) dosing on a fixed or flexible schedule (Table 1).

Table 1. Efficacy parameters at endpoint: clinical trials of pregabalin in painful DPN and PHN.

Treatment arm	Baseline mean (SD) pain score	Endpoint[a] least squares mean (SE) pain score[b]	Treatment difference [95% CI] in endpoint[a] pain score from placebo	*p* value[c]	Treatment difference [95% CI] in endpoint[a] sleep interference score from placebo[b]	*p* value[c]	PGIC,[d] %			*p* value	Responders[d,e], *n* (%)	*p* value
							Worse	No change	Improved			
Painful DPN trials												
Richter *et al.* (2005), 6 weeks, TID (including 2-week dosage escalation)[33]												
Placebo, $n=82$[f]	6.9 (1.6)	5.55 (0.23)					10.3	42.3	47.3		12 (14.6)	
Pregabalin 150 mg/day, $n=79$	6.5 (1.3)	5.11 (0.24)	−0.440 [−1.080, 0.099]	0.1763	−0.43 [−1.04, 0.18]	0.1670	9.1	35.1	59.9	NS	15 (19.0)	0.423
Pregabalin 600 mg/day, $n=82$	6.7 (1.7)	4.29 (0.26)	−1.264 [−1.890, 0.639]	0.0002	−1.15 [−1.75, −0.55]	0.0004	2.4	12.4	85.1	0.002	32 (39.0)	0.002
Lesser *et al.* (2004), 5 weeks, TID (including 1-week dosage escalation for 600 mg/day group only)[32]												
Placebo, $n=97$	6.6 (1.5)	5.06 (0.21)					10.6	33.7	55.8		17 (17.5)	
Pregabalin 75 mg/day, $n=77$	6.7 (1.3)	4.91 (0.24)	−0.151 [−0.76, 0.458]	0.6267[g]	−0.43 [−1.02, 0.17]	NS	14.9	27.0	58.1	NS	17 (22.1)	NS
Pregabalin 300 mg/day, $n=81$	6.2 (1.4)	3.80 (0.23)	−1.257 [−1.862, −0.651]	0.0001	−1.30 [−1.89, −0.71]	0.0001	5.0	15.2	79.8	0.001	37 (45.7)	0.001
Pregabalin 600 mg/day, $n=81$[h]	6.2 (1.5)	3.60 (0.23)	−1.454 [−2.056, −0.852]	0.0001	−1.55 [−2.14, −0.96]	0.0001	3.9	7.7	88.5	0.001	39 (48.1)	0.001
Rosenstock *et al.* (2004), 8 weeks, TID[34]												
Placebo, $n=69$[i]	6.1 (1.5)	5.46 (0.28)					19	42	39		10 (14.5)	
Pregabalin 300 mg/day, $n=75$[j]	6.5 (1.7)	3.99 (0.26)	−1.47 [−2.19, −0.75]	0.0001	−1.54 [−2.28, −0.80]	0.0001	8	25	67	0.001	30 (40.0)	0.001
Tölle *et al.* (2008), 11 weeks, BID[36]												
Placebo, $n=96$	6.4	4.5							33.3		28.9 (30.1)	
Pregabalin 150 mg/day, $n=99$	6.2	4.1	−0.33 [−0.94, 0.28]	0.5580	−0.45 [−1.05, 0.15]	0.1444			45.8		34.1 (34.4)	
Pregabalin 300 mg/day, $n=99$	6.4	4.4	−0.18 [−0.79, 0.43]	0.5580	−0.62 [−1.22, −0.02]	0.0844			42.5		33.0 (33.3)	
Pregabalin 300/600 mg/day[k], $n=101$	6.6	3.7	−0.97 [−1.58, −0.36]	0.0054	−1.01 [−1.6, −0.41]	0.003			50.5	0.021	46.4 (45.9)	0.036

Table 1. Continued.

Treatment arm	Baseline mean (SD) pain score	Endpoint[a] least squares mean (SE) pain score[b]	Treatment difference [95% CI] in endpoint[a] pain score from placebo	*p* value[c]	Treatment difference [95% CI] in endpoint[a] sleep interference score from placebo[b]	*p* value[c]	PGIC,[d] %			*p* value	Responders[d,e], *n* (%)	*p* value
							Worse	No change	Improved			
Arezzo *et al.* (2008), 13 weeks, BID[38]												
Placebo, $n = 85$	6.58 (1.58)	4.82					12	35	50		19.6 (23)	
Pregabalin 600 mg/day, $n = 82$	6.28 (1.47)	3.54	−1.28 [−1.96, −0.60]	0.0003	−1.08 [−1.75, −0.41]	0.0019	5	15	80	0.002	40.2 (49)	0.001
PHN trials												
Dworkin *et al.* (2003), 8 weeks, TID (including 1-week dosage escalation)[30]												
Placebo, $n = 84$	6.4 (1.5)	5.29 (0.24)					14	60	26		17 (20.2)	
Pregabalin 300/600 mg/day, [k] $n = 88$[l]	6.3 (1.4)	3.60 (0.24)	−1.69 [−2.33, −1.05]	0.0001	−1.58 [−2.19, −0.97]	0.0001	4	12	84	0.001	44 (50.0)	NR
Sabatowski *et al.* (2004), 8 weeks, TID (including 1-week dosage escalation)[35]												
Placebo, $n = 81$	6.6 (1.6)	6.33 (0.22)					26.9	38.5	34.6		8 (9.9)	
Pregabalin 150 mg/day, $n = 81$	6.9 (1.7)	5.14 (0.22)	−1.20 [−1.81, −0.58]	0.0002	−1.11 [−1.71, −0.51]	0.0003	21.3	23.8	55.1	0.064	21 (25.9)	0.006
Pregabalin 300 mg/day, $n = 76$	7.0 (1.6)	4.76 (0.23)	−1.57 [−2.20, −0.95]	0.0002	−1.43 [−2.04, −0.82]	0.0001	15.1	24.7	60.3	0.002	21 (27.6)	0.006
van Seventer *et al.* (2006), 13 weeks, BID (including 1-week dosage escalation)[37]												
Placebo, $n = 93$	6.9 (1.5)	6.14 (0.23)					NR	NR	35.6		7 (7.5)	

Pregabalin 150 mg/day, $n=87$	6.4 (1.6)		5.26 (0.24)	−0.88 [−1.53, −0.23]	0.0077	−1.03 [−1.62, −0.44]	0.0007	NR	NR	51.2	0.02	23 (26.4)	0.001
Pregabalin 300 mg/day, $n=98$	6.7 (1.4)		5.07 (0.23)	−1.07 [−1.70, −0.45]	0.0016	−1.26 [−1.84, −0.68]	0.0002	NR	NR	47.9	NS	26 (26.5)	0.001
Pregabalin 300/600 mg/day,[k] $n=88$[m]	6.6 (1.4)		4.35 (0.24)	−1.79 [−2.43, −1.15]	0.0003	−1.93 [−2.52, −1.34]	0.0002	NR	NR	67.1	0.003	33 (37.5)	0.001
Painful DPN or PHN trial													
Freynhagen *et al.* (2005), 12 weeks, BID (including 1-week dosage escalation for 600 mg/day group and 4-week dosage optimization for flexible-dosing[n] group)[31]													
Placebo, $n=65$	6.7 (1.7) PHN	6.6 (1.7) DPN	5.00 (0.3)					16.9	35.6	47.4		15 (24.2)	
Pregabalin 150–600 mg/day, $n=141$	7.0 (1.5) PHN	6.7 (1.6) DPN	3.80 (0.23)	−1.174 [−1.897, 0.452]	0.002	−1.36 [−2.04, −0.68]	<0.001	9.3	16.3	74.5	<0.01	67 (48.2)	<0.001
Pregabalin fixed 600 mg/day, $n=132$	7.1 (1.7) PHN	6.7 (1.5) DPN	3.60 (0.24)	−1.380 [−2.113, 0.647]	<0.001	−1.48 [−2.17, −0.79]	<0.001	12.8	16.0	71.2	<0.01	67 (52.3)	<0.001

SD = standard deviation; SE = standard error; CI = confidence interval; PGIC = Patient Global Impression of Change; DPN = diabetic peripheral neuropathy; TID = three times a day; NS = not significant; PHN = postherpetic neuralgia; NR = not reported; BID = twice a day.

[a] Last seven available scores while on study medication, up to and including day after last dose.

[b] Analysis of covariance.

[c] Adjustment based on Hochberg's procedure.

[d] Cochran–Mantel–Haenszel.

[e] Responder, patients with ≥50% decrease in pain.

[f] Eighty-five at baseline.

[g] Adjustment based on Hochberg's procedure for 300 and 600 mg/day only.

[h] Eighty-two at baseline.

[i] Seventy at baseline.

[j] Seventy-six at baseline.

[k] Pregabalin dosage was 600 mg/day for patients with creatinine clearance (CL_{cr}) > 60 mL/min and 300 mg/day for patients with CL_{cr} > 30 mL/min but ≤60 mL/min.

[l] Eighty-nine at baseline.

[m] Ninety at baseline.

[n] Patients randomized to flexible dosing had dosage escalations at weekly intervals in increments of 150 mg/day to a maximum of 600 mg/day. Patients were allowed to decrease their dosage once during this 4-week period. At the conclusion of the 4-week optimization period, patients received their optimized fixed dosage.

Concomitant medications including aspirin 325 mg/day, acetaminophen ≤ 3 g/day, and SSRIs were allowed, provided the dosing was stable for 30 days prior to baseline and throughout the study. In two studies[36,38], benzodiazepines were allowed for 'sleep problems.'

Efficacy

The primary efficacy measure in each study was the change from baseline of the least squares mean pain score at endpoint (defined as the last seven available daily scores while on study medication), which was rated on an 11-point numeric rating scale (0 = no pain to 10 = worst possible pain) and recorded by the patient in a daily diary. Across these studies, patients with painful DPN or PHN reported moderate-to-severe pain at baseline (mean pain scores ranged from 6.1 to 7.1)[30–38]. Each study reported endpoint least squares mean pain-related sleep interference scores as a secondary efficacy measure. Daily pain-related sleep interference scores were based on an 11-point numeric rating scale (0 = pain does not interfere with sleep to 10 = pain completely interferes with sleep) and recorded by the patient in a daily sleep diary[30–38]. In addition to the patient diary, two trials (one PHN and one trial with both PHN and DPN patients) also assessed sleep interference using Medical Outcomes Study (MOS)–Sleep Scale scores[30,31]. The MOS–Sleep Scale is a validated, reliable, 12-item, self-administered instrument evaluating quantity of sleep, sleep disturbance, sleep adequacy, daytime somnolence, snoring, and awakening with shortness of breath or headache, with higher scores reflecting worse sleep[39,40].

Pain

In patients with painful DPN, five randomized controlled trials assessed efficacy of pregabalin administered TID or BID. Treatment with pregabalin 300 or 600 mg/day significantly decreased endpoint mean pain scores compared with placebo (Table 1)32–34,36,38. Doses of 75 and 150 mg/day (and 300 mg/day BID) did not produce significant pain relief vs. placebo[32,33,36]. Patients with PHN experienced significant reductions in mean pain scores with both TID and BID regimens across all pregabalin dosages (150–600 mg/day; Table 1)[30,35,37]. One study included patients with either DPN or PHN. Both flexible-dose (150–600 mg/day) and fixed-dose (600 mg/day) pregabalin significantly improved the mean pain score compared with placebo (Table 1)[31].

Sleep

Pregabalin 300 and 600 mg/day significantly decreased endpoint mean sleep interference scores compared with placebo in patients with painful DPN[32–34,36,38], while lower doses of pregabalin (75 and 150 mg/day) did not differ from placebo[32,33,36] (Table 1 and Figure 1).

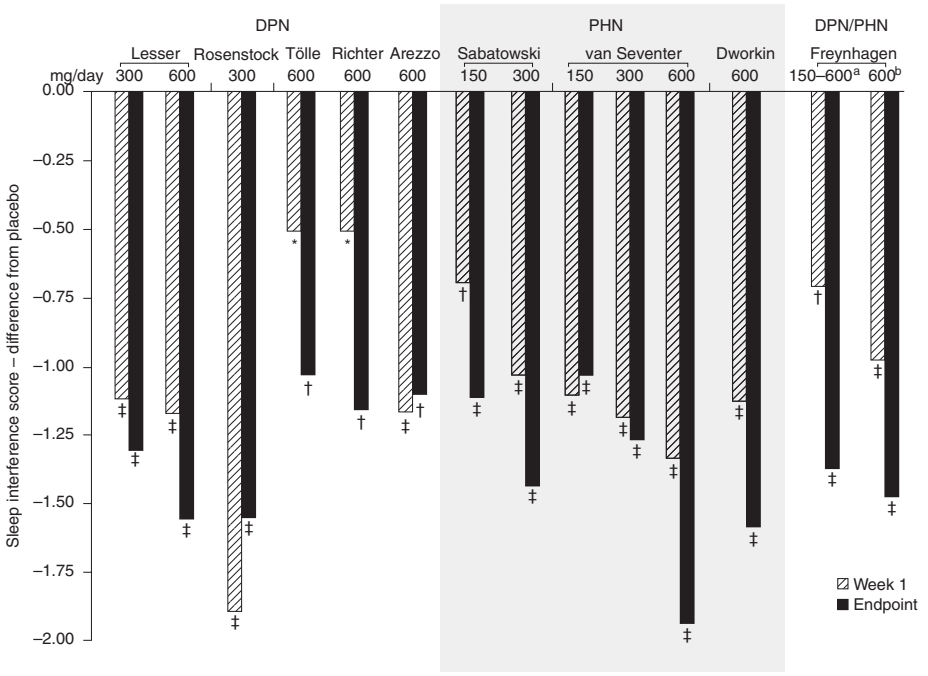

Figure 1 Difference from placebo in least squares mean sleep interference scores at week 1 and endpoint with pregabalin treatment for painful DPN and PHN. Significant improvement in sleep interference was maintained in all nine trials at every time point from week 1 through endpoint. **p*50.05; *yp*50.01; *zp*50.001. [a]Flexible-dose pregabalin. [b]Fixed-dose pregabalin

Significant improvements in sleep interference scores were seen as early as week 1 (Figure 1). In patients with PHN, compared with placebo, 150, 300 and 600 mg/day pregabalin significantly improved endpoint mean sleep interference scores[30,35,37] and these effects were seen as early as week 1 (Figure 1). A significant improvement on the MOS-Sleep scale sleep problem index was alsoobserved[30]. In the study that included patients with either DPN or PHN[31], flexible-dose (150–600 mg/day) and fixed-dose (600 mg/day) pregabalin significantly improved endpoint mean sleep interference scores, and the improvements were observed as early as week 1 (Figure 1). Significant improvements relative to placebo on sleep disturbance and overall sleep problem index of the MOS–Sleep scale were also observed.

DISCUSSION

Pregabalin 150 to 600 mg/day is well tolerated and relieves pain and pain-related sleep disturbances associated with DPN or PHN30–38. Pregabalin 600 mg/day (TID or BID) was consistently superior to placebo in patients with PHN or DPN30–38. Doses ≤150 mg/day

TID or ≤300 mg/day BID were not effective in the DPN studies[32,33,36] while pregabalin 300 mg/day TID showed statistically significant reductions in pain and sleep vs. placebo[32,34]. In the trial of pregabalin in patients with PHN or painful DPN, the BID flexible-dose regimen (150–600 mg/day) was superior to placebo[31]. Pregabalin (150–600 mg/day) demonstrated significant reductions in pain and pain-related sleep interference in PHN across all TID and BID dosages (150–600 mg/day).

All trials included in this review were randomized, double-blind, and placebo-controlled, with sleep outcomes as secondary endpoints. From objective analyses, such as polysomnography, it is known that patients with DPN and PHN show reduced sleep efficiency, more fragmented sleep, reductions in stages 3, 4, and REM sleep, and an increase in stage 1 sleep when compared with normal healthy volunteers[41,42]. However, none of the studies reviewed here included an objective sleep assessment[30–38]. Patient diaries were used as a subjective assessment of pain-related sleep interference; although these diaries are a reliable tool, they may have introduced self-report bias. One additional potential limitation was that not all studies prohibited the use of benzodiazepines for 'sleep problems'. The two trials that permitted benzodiazepines for 'sleep problems' did not assess the impact of concomitant medications on sleep quality[36,38].

Somnolence was a commonly reported adverse event in the pregabalin treatment arms and may have contributed to the decreased pain-related sleep interference scores. Post hoc analysis suggested the presence of somnolence did not impact pain scores. However, an analysis of the effect of somnolence on sleep interference scores was not performed[32].

While pregabalin improved both pain and pain-related sleep interference in patients with painful DPN and PHN, there have been studies that suggest the effects are independent of each other. In patients with osteoarthritis, pain scores were similar for pregabalin and placebo immediately following total knee arthroplasty, but pregabalin significantly decreased pain-related sleep interference scores postoperatively[43]. This suggests that further examination of pregabalin is warranted to clarify its effect on sleep. Nonetheless, pregabalin's ability to improve sleep may provide additional benefits as better sleep has been shown to decrease the prolongation of herpes zoster pain[44] and improve glycemic control in diabetes[45–49].

CONCLUSIONS

The results of these nine trials provide clinicians with safe and efficacious dosing regimens for pregabalin in the treatment of comorbid neuropathic pain and sleep disturbances in patients with painful DPN and PHN. Pregabalin 150 to 600 mg/day demonstrated a statistically and clinically significant decrease in pain scores, pain-related

sleep interference scores, sleep disturbance, and overall sleep problems indices on the MOS-Sleep Scale. Because the mechanism of pregabalin on sleep in the reviewed trials of PHN and painful DPN remains unclear, future research on the effect of pregabalin in sleep disorders associated with DPN and PHN may also be indicated.

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Chapter IX

General discussion

GENERAL DISCUSSION

Although neuropathic pain has been relatively well defined, it remains difficult to apply this definition in clinical practice. The wide variability in the neuropathic pain conditions, the different underlying etiologies, and differences in pain complaints and sensory findings all play a pivotal role. Due to lack of knowledge on the pathophysiology of neuropathic pain, it is almost impossible to make a reliable link between signs and symptoms and the underlying mechanisms. All these factors make neuropathic pain a difficult condition to manage.[1]

The challenge in both research and clinical practice is to translate the signs and symptoms into specific pathophysiologic mechanisms, each of which have implications for treatment. The development of specific and selective treatments may well depend on a mechanism-based classification. The assumption is that common mechanisms initiated by diverse etiologic factors may elicit common pain symptoms.[2,3] However, what may appear to be the same lesion may induce pain complaints, or no pain at all. For example, in some patients the same etiology may result in complaints of numbness or an absence of sensation, and in others in painful spontaneous activity and hyperexcitability. A critical analysis of previous clinical trials showed that, despite the logic of a mechanism-based approach of therapy, evidence supporting its success remains inconclusive.[4]

Translational research should reduce the gap between the rapid progress made by basic science, which has revealed a multitude of underlying mechanisms, and the slow progress in clinical practice. One of the problems to be tackled is that standardized measurement approaches are either lacking or difficult to apply. [5]

Attempting to apply a differentiation between 'peripheral' and 'central' neuropathic pain is questionable. Rather, the mechanisms and origins of the nerve damage or dysfunction are the main discriminative factors. It is not possible to determine the origin of neuropathic pain from clinical characteristics of the pain.[6] Neuropathic pain is the result of activation, modulation and modification of the nervous system as a whole after nerve damage.[7] It seems that current treatment needs to move away from merely suppressing 'peripherally' or 'centrally' generated symptoms, to a disease-modifying strategy aimed at both preventing maladaptive plasticity and reducing intrinsic risk.[8]

Nowadays, neuropathic pain is mainly treated with antidepressants and anti-epileptics; the 'classic' analgesics show no efficacy for this type of pain. However, patients suffering from neuropathic pain may show a wide variation in response to one specific drug therapy. One reason for this is that neuropathic pain can co-exist with nociceptive and idiopathic types of pain. Therefore, patients may have different clinical pain components that need to be addressed, apart from the multiple neuropathic mechanisms involved.[9]

One step towards individually-tailored treatment strategies should be the use and validation of screening tools that can differentiate between the different types of pain.

Pain is a subjective phenomenon and therefore difficult to evaluate and/or measure with the currently available tools and equipment. The development of the DN4 questionnaire is a step towards clearly identifying patients with neuropathic pain. The questionnaire might also be used to determine neuropathic components in conditions such as malignant pain, low back pain and post-traumatic disorders. The borderline between definite, probable, possible and unlikely with regard to different types of pain conditions, in particular nociceptive and neuropathic pain, still needs to be elucidated. In addition, the term 'mixed pain' should either be avoided or more clearly defined.

Most controlled trials have focused on the relief of pain, rather than on the highly distressing symptoms of allodynia or hyperalgesia, or the effect of treatment on the patient's quality of life. This makes a comparative interpretation of the effects of the available treatments difficult. Monitoring treatment with questionnaires (such as the DN4) may help to measure the effect of treatment, and also make trial outcomes easier to compare. Moreover, because pain is generally not a static condition, the signs and symptoms may change during the course of the disease. A questionnaire might also allow to monitor these dynamic changes as well as the sometimes unpredictable responses to different types of treatment. Pain intensity scales (particularly the Visual Analogue Scale) and pain quality evaluation by monitoring specific pain symptoms (e.g. burning pain, pain paroxysms, or allodynia) may help to reveal preferential effects of different treatments.[10]

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Chapter X

Summary / Samenvatting

CHAPTER I INTRODUCTION

It is important to discriminate between 'nociceptive' pain and 'neuropathic' pain due to the important therapeutic consequences of this classification.

Neuropathic pain may affect as much as 3% of the population.

Pregabalin is an α2-δ ligand with demonstrated efficacy in neuropathic pain disorders.

Neuropathic pain is under-diagnosed, which results in ineffective pain management. Therefore, the DN4 questionnaire was validated as a screening tool.

Neuropathic pain impairs patients' mood, quality of life, activities of daily living and performance at work.

CHAPTER II LINGUISTIC VALIDATION OF THE DN4 FOR USE IN INTERNATIONAL STUDIES

A French Neuropathic Pain Group has developed a specific questionnaire, the DN4, to help clinicians in the differential diagnosis of neuropathic and non-neuropathic pain. In order to allow this questionnaire to be used in international studies, it has been translated and linguistically validated into Dutch, German, Greek and Hungarian, using a well-established procedure.

The DN4 items were linguistically validated in each of the target languages, thus providing the means for standardising the diagnosis of neuropathic pain and pooling the data collected during clinical trials in the different countries involved.

CHAPTER III VALIDATION OF THE DUTCH VERSION OF THE DN4: A DIAGNOSTIC QUESTIONNAIRE FOR NEUROPATHIC PAIN

From a therapeutic point of view, the most pragmatic classification of pain is a differentiation in nociceptive and neuropathic pain.

Difficulties to diagnose neuropathic pain in routine clinical practice urge the need for validated and easy-to-use diagnostic tools.

DN4 stands for "Douleur Neuropathique 4 questions" and was developed by the French Neuropathic Pain Group. The DN4 was designed as an easy to fulfill diagnostic questionnaire and is composed of 10 yes/no items. This neuropathic pain diagnostic questionnaire is build in two parts. The first part is based on symptoms estimated in an interview of the patient; this part can also be self-administered. The second part is based on a standardized clinical examination.

The interview part includes 7 items corresponding to 2 domains. The questions address pain characteristics: burning, painful cold and electric shocks, and subsequently associated symptoms of abnormal sensations in the same area: tingling, pins and needles, numbness, itching.

The examination part includes 2 domains measured by 3 items that address to signs estimated with a neurological examination: touch hypoesthesia, pricking hypoesthesia and pain caused or increased by brushing. The DN4 neuropathic pain diagnostic questionnaire aims to discriminate neuropathic pain from nociceptive pain.

The primary objective of this study was to evaluate the diagnostic value of the Dutch version of the DN4 questionnaire.

Both the DN4 7-item and 10-item scores showed in a statistical analysis, using a receiver operating characteristic curve, a good ability to discriminate between patients' type of pain, with an area under the curve (AUC) of 0.81 and 0.82, respectively. The cut-off point of 5/10 for the full questionnaire resulted in a sensitivity of 75% and a specificity of 79%, while the cut-off point of 4/7 for the partial questionnaire resulted in a sensitivity of 74% and a specificity of 79%.

The items "brushing", "painful cold" and "numbness" were most discriminating.

CHAPTER IV EFFICACY AND TOLERABILITY OF TWICE-DAILY PREGABALIN FOR TREATING PAIN AND RELATED SLEEP INTERFERENCE IN POSTHERPETIC NEURALGIA: A 13-WEEK, RANDOMIZED TRIAL.

The 13-week, double-blind, placebo-controlled study randomized 370 patients with PHN to pregabalin (150, 300, or 600 mg/day BID) or placebo.

This international, multicenter trial evaluated the efficacy and safety of pregabalin dosed twice daily (BID) for relief of neuro-pathic pain associated with postherpetic neuralgia (PHN).

Primary efficacy measure was endpoint mean pain score from daily pain diaries. Secondary efficacy measures included endpoint mean sleep-interference score from daily sleep diaries and Patient Global Impression of Change (PGIC).

Pregabalin provided significant, dose-proportional pain relief at endpoint: difference from placebo in mean pain score, 150 mg/day, -0.88, $p = 0.0077$; 300 mg/day, -1.07, $p = 0.0016$; 600 mg/day, -1.79, $p = 0.0003$.

Sleep interference in all pregabalin groups was also significantly improved at endpoint, compared with placebo ($p < 0.001$).

Pregabalin, dosed BID, reduced neuropathic pain associated with PHN and was well tolerated. It also reduced the extent to which pain interfered with sleep. Pregabalin's effects were seen as early as week 1 and were sustained throughout the 13-week study.

CHAPTER V PREGABALIN IN THE TREATMENT OF POST-TRAUMATIC PERIPHERAL NEUROPATHIC PAIN: A RANDOMIZED DOUBLE-BLIND TRIAL

This study evaluated pregabalin in the treatment of post-traumatic peripheral neuropathic pain (including post-surgical). The study was an international, multicenter, parallel-group, double-blind, randomized clinical trial comparing 8 weeks of flexible-dose pregabalin 150–600 mg/day with placebo, taken as two daily doses. Randomization was preceded by a 2-week, single blind, placebo run-in period; baseline data were collected at randomization. Patients who did not meet both pain entry criteria at randomization (i.e. NRS and VAS assessments) were not randomized. Of the 367 treated in the single-blind run in, 254 were randomized and received either placebo (n=127) or pregabalin (n=127).

Pregabalin was associated with a significantly greater improvement in the mean endpoint pain score vs. placebo. Pregabalin was also associated with significant improvements from baseline in pain-related sleep interference, and was associated with a statistically significant improvement in the Hospital Anxiety and Depression Scale anxiety subscale.

It was concluded that a flexible-dose pregabalin 150–600 mg/day was effective in relieving neuropathic pain, improving disturbed sleep, and improving overall patient status and was generally well tolerated in patients with post-traumatic peripheral neuropathic pain.

CHAPTER VI A CROSS-SECTIONAL SURVEY OF HEALTH STATE IMPAIRMENT AND TREATMENT PATTERNS IN PATIENTS WITH POSTHERPETIC NEURALGIA.

Postherpetic neuralgia (PHN) develops in 8–24% of patients with herpes zoster. Few studies have evaluated the patient burden and treatment of PHN in general practice. The purpose of this study was to determine the patient burden of PHN with respect to pain intensity and impact on patient functioning and to characterize treatment patterns and health resource utilization in general practice.

Eighty-four patients with PHN were identified in general practice settings. Patients answered a questionnaire that included: pain severity and interference items from the modified short form brief pain inventory (mBPI-SF); EuroQol (EQ-5D) survey; and questions related to current treatment, health status and resource utilization. Physicians provided information on medications prescribed for PHN and pain-related co-morbidities (anxiety, depression and sleep disturbance).

It was concluded that PHN causes substantial patient burden expressed as interference with daily functioning and reduced health status associated with pain severity. This

burden may result in part from suboptimal management strategies, increased health resource utilization and suggests a need for more effective pain management.

CHAPTER VII RELATIONSHIPS BETWEEN CHANGES IN PAIN SEVERITY AND OTHER PATIENT-REPORTED OUTCOMES: AN ANALYSIS IN PATIENTS WITH POSTTRAUMATIC PERIPHERAL NEUROPATHIC PAIN

This study is evaluating in patients a relationship between change in pain severity and changes on patient-reported outcomes (PROs) assessing sleep, function, and mood in patients with post-traumatic pain.

A secondary analysis is presented using data from a clinical trial evaluating pregabalin in patients with posttraumatic peripheral neuropathic pain (N=254). Regression models were used to determine the association between changes in pain (0–10 NRS) as the predictor and scores on patient-reported measures as the outcome.

Change in pain severity as a continuous predictor resulted in plots that showed clear and direct relationships with change in the other PROs, all of which were statistically significant ($P<0.001$). It was concluded that a direct relationship exists between pain and various aspects of patient's well-being and functioning, which can provide a quantitative assessment of how improvements in pain may be expected to relate to other patient outcomes.

CHAPTER VIII THE EFFECT OF PREGABALIN ON PAIN-RELATED SLEEP INTERFERENCE IN DIABETIC PERIPHERAL NEUROPATHY OR POSTHERPETIC NEURALGIA: A REVIEW OF 9 PUBLISHED CLINICAL TRIALS

Postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (DPN) are common chronic neuropathic pain conditions. Frequently, there is a complex relationship between chronic neuropathic pain and sleep; often with pain disturbing sleep, and poor sleep exacerbating pain. Pain and sleep can also have a significant impact on mood, and a greater benefit for patients with PHN or painful DPN is often found in treatments that both relieve pain and improve sleep quality.

This manuscript reviews efficacy and tolerability data from 9 published clinical trials of pregabalin for the treatment of DPN and PHN demonstrating the beneficial effect of pregabalin on pain and sleep disturbances in these patients.

Pregabalin was well tolerated and significantly reduced endpoint mean pain scores and also significantly improved pain-related sleep interference.

CHAPTER IX GENERAL DISCUSSION

In neuropathic pain it is almost impossible to make a reliable link between signs and symptoms and the underlying mechanisms. Translational research should reduce the gap between basic science, which has revealed a multitude of underlying mechanisms, and the application in clinical practice.

Treatment of neuropathic pain needs to aim at a disease-modifying strategy.

The validation of the DN4 questionnaire is a step towards clearly identifying patients with neuropathic pain. The borderline between definite, probable, possible and unlikely with regard to different types of pain conditions, still needs to be elucidated.

Samenvatting

HOOFDSTUK I INLEIDING

Het is belangrijk om nociceptieve pijn te onderscheiden van neuropatische pijn wegens de verschillen in behandeling.

Neuropathische pijn komt waarschijnlijk bij ongeveer 3% van de bevolking voor.

Pregabaline is als pijnstiller een geschikt middel bij de behandeling van neuropatische pijn en wordt over het algemeen goed verdragen door de patiënt.

De diagnose neuropatische pijn wordt te weinig gesteld, waardoor de behandeling te kort schiet. De DN4 vragenlijst werd gevalideerd om neuropatische pijn beter te kunnen opsporen.

Neuropatische pijn heeft een bijzonder negatieve invloed op het dagelijks functioneren en de kwaliteit van leven.

HOOFDSTUK II TAALKUNDIGE VALIDATIE VAN DE DN4 VOOR GEBRUIK IN INTERNATIONALE STUDIES

Een Franse groep artsen die zich bezig houdt met neuropatische pijn heeft een specifieke vragenlijst ontwikkeld, de DN4, om clinici te helpen bij de differentiële diagnose van neuropathische en niet-neuropathische pijn. Om deze vragenlijst te kunnen gebruiken in internationale studies, is de vragenlijst vertaald en taalkundig gevalideerd in het Nederlands, Duits, Grieks en Hongaars, met behulp van een goed vastgestelde procedure.

De DN4 vragen werden taalkundig gevalideerd in elk van de doeltalen, waardoor het vergelijken en bundelen van de gegevens over de diagnose en behandeling van neuropatische pijn, verzameld tijdens klinische proeven in de verschillende betrokken landen, mogelijk wordt.

HOOFDSTUK III VALIDATIE VAN DE NEDERLANDSE VERSIE VAN DE DN4: EEN DIAGNOSTISCHE VRAGENLIJST VOOR NEUROPATHISCHE PIJN.

Vanuit een therapeutisch oogpunt is de meest pragmatische indeling van pijn een differentiatie tussen nociceptieve en neuropathische pijn. De DN4 diagnostische vragenlijst is bedoeld om onderscheid te maken tussen neuropathische pijn en nociceptieve pijn.

Het is lastig om neuropathische pijn in de dagelijkse praktijk te diagnostiseren. Er bestaat behoefte aan gevalideerde en eenvoudig te gebruiken diagnostische hulpmiddelen.

De DN4 vragenlijst staat voor "Douleur Neuropathique 4 vragen" en is ontwikkeld door de Franse neuropathische pijngroep. De DN4 is ontworpen als een makkelijk in te vullen diagnostische vragenlijst en bestaat uit 10 ja / nee vragen. De vragenlijst is opgebouwd uit twee delen. Het eerste deel is gebaseerd op de symptomen uitgedrukt in de vorm van vragen aan de patiënt; dit deel kan ook zelf worden ingevuld door de patiënt. Het tweede deel is gebaseerd op een gestandaardiseerd klinisch onderzoek.

Het interview deel omvat 7 vragen overeenkomend met 2 domeinen. De vragen gaan over pijn kenmerken: branderig, pijnlijk koude gevoel en elektrische schokken, en vervolgens over bijbehorende symptomen van abnormale gewaarwordingen in hetzelfde gebied: tintelingen, prikken, doof gevoel, jeuk.

Het lichamelijk onderzoek deel omvat eveneens 2 domeinen gemeten door 3 items: hypo-esthesie bij aanraking, hypo-esthesie bij prikken en pijn veroorzaakt of verergerd door wrijven.

Het primaire doel van deze studie was het evalueren van de diagnostische waarde van de Nederlandse versie van de DN4 vragenlijst.

Zowel de DN4 7 vragen en 10 vragen uitkomsten toonden in een statistische analyse, met behulp van de ROC (Receiver Operating Characteristic), een duidelijk onderscheid tussen het type pijn bij patiënten, met een AUC (Area Under the Curve) respectievelijk van 0,81 en 0,82. De cut-off waarde van 5 uit 10 voor de volledige vragenlijst resulteerde in een gevoeligheid van 75% en een specificiteit van 79%, terwijl de cut-off waarde van 4 uit 7 voor de gedeeltelijke vragenlijst resulteerde in een gevoeligheid van 74% en een specificiteit van 79%. De items "wrijven", "pijnlijk koude gevoel" en "doof gevoel" waren de meest onderscheidende symptomen.

HOOFDSTUK IV DE WERKZAAMHEID EN VERDRAAGBAARHEID VAN TWEEMAAL DAAGS PREGABALINE VOOR DE BEHANDELING VAN PIJN EN AANVERWANTE SLAAPSTOORNIS IN POSTHERPETISCHE NEURALGIE: EEN 13 WEKEN DURENDE, GERANDOMISEERDE TRIAL.

Tijdens een 13 weken durend, dubbelblind, placebo-gecontroleerd gerandomiseerd en internationaal uitgevoerd onderzoek werden 370 patiënten met PHN (Post Herpetische Neuralgie) behandeld met pregabaline (150, 300, of 600 mg / dag tweemaal daags) of een placebo.

De werkzaamheid en veiligheid van pregabaline ter verlichting van postherpetische pijn werd geevalueerd.

Het primaire eindpunt was de gemiddelde dagelijkse pijnscore genoteerd in een dagboekje. Secundaire eindpunten waren onder meer de dagelijkse slaaponderbreking of slaapstoornis en de Patient Global Impression of Change (PGIC). Daarnaast werden bijwerkingen geregistreerd.

Pregabaline verminderde significant en dosis-proportioneel de post herpetische pijn op eindpunt: verschil versus placebo in gemiddelde pijnscore: 150 mg / dag, -0,88, p = 0,0077; 300 mg / dag, -1,07, p = 0,0016; 600 mg / dag, — 1,79, p = 0,0003.

Slaapstoornissen in alle groepen waren ook significant verbeterd op eindpunt bij inname van Pregabaline, vergeleken met placebo (p <0,001).

Pregabaline, tweemaal daags gedoceerd, verminderde neuropathische pijn als gevolg van PHN en werd goed verdragen. Het verminderde ook de slaapstoornissen ten gevolge van de pijn. De positieve effecten van Pregabaline werden in week 1 al duidelijk en vervolgens bleken deze effecten onverminderd meetbaar in de 13 weken durende studie.

HOOFDSTUK V PREGABALINE BIJ DE BEHANDELING VAN POST-TRAUMATISCHE PERIFERE NEUROPATHISCHE PIJN: EEN GERANDOMISEERDE DUBBELBLINDE TRIAL

Deze studie evalueerde pregabaline bij de behandeling van post-traumatische perifere neuropathische pijn (met inbegrip van post-operatieve pijn). Het onderzoek was een internationaal, multicentrum uitgevoerde, met parallel-groep, dubbelblind, gerandomiseerde klinische studie. Gedurende 8 weken werd een flexibele dosering pregabaline 150–600 mg / dag met placebo vergeleken. De dosering was tweemaal daags. Randomisatie werd voorafgegaan door een twee weken durende, eenzijdig geblindeerde, placebo run-in periode; baseline gegevens werden verzameld bij randomisatie. Patiënten die niet voldeden aan de beide pijn criteria voor randomisatie (dwz NRS en de VAS evaluaties) werden niet in het onderzoek betrokken. Van de 367 behandelde in de single-blind run-in periode, werden 254 patiënten gerandomiseerd en deze kregen ofwel een placebo (n = 127) of pregabaline (n = 127).

Pregabaline groep toonde een significante verbetering in de gemiddelde pijnscore bij eindpunt versus de placebo groep. Patiënten die Pregabaline gebruikten toonden een significante verbetering ten opzichte van baseline bij pijn-gerelateerde slaapstoornissen, en er werd een statistisch significante verbetering in de Hospital Anxiety and Depression Scale vastgesteld.

Er werd geconcludeerd dat een flexibele dosering pregabaline 150–600 mg / dag effectief was in het verlichten van neuropathische pijn, het verbeteren van verstoorde

slaap en algehele verbetering van de patiënt. Pregabaline werd over het algemeen goed verdragen door patiënten met post-traumatische perifere neuropathische pijn.

HOOFDSTUK VI EEN CROSS-SECTIONEEL ONDERZOEK OVER DE VERMINDERDE GEZONDHEID EN DE MANIER VAN BEHANDELING BIJ PATIËNTEN MET POSTHERPETISCHE NEURALGIE.

Postherpetische neuralgie (PHN) komt voor bij 8–24% van de patiënten met herpes zoster. Weinig studies hebben de aan pijn gerelateerde problemen van de patiënt en de behandeling van PHN in de huisartspraktijk geevalueerd. Het doel van dit onderzoek was het bepalen van de functionele gevolgen bij de patiënt met PHN in samenhang met de pijn intensiteit. Getracht werd een beeld te krijgen van behandelingspatronen en benutting van gezondheidsvoorzieningen in de huisartspraktijk.

Vierentachtig patiënten met PHN werden geïdentificeerd in de huisartspraktijk. Patiënten beantwoorden een vragenlijst: Ernst van de pijn en interferentie items uit het aangepaste formulier korte pijn inventaris (mBPI-SF), EuroQol (EQ-5D) onderzoek, en vragen met betrekking tot de huidige behandeling, de gezondheidstoestand en de benutting van de zorg. Artsen verstrekten informatie over medicijnen voorgeschreven voor PHN en pijn-gerelateerde co-morbiditeit (angst, depressie en slaapstoornissen).

Er werd geconcludeerd dat PHN aanzienlijke last veroorzaakt voor de patiënt uitgedrukt in verminderd dagelijks functioneren en een verminderde gezondheidstoestand geassocieerd met de ernst van de pijn. Deze last kan voor een deel het resultaat zijn van suboptimale behandelstrategieën. Ook wordt, mede hierdoor, een verhoogd beroep op zorg gedaan. Uit de studie blijkt dat er behoefte is aan effectievere pijnbehandeling.

HOOFDSTUK VII RELATIES TUSSEN DE VERANDERINGEN IN DE ERNST VAN DE PIJN EN ANDERE DOOR DE PATIËNT GERAPPORTEERDE UITKOMSTEN: EEN ANALYSE BIJ PATIËNTEN MET POSTTRAUMATISCHE PERIFERE NEUROPATHISCHE PIJN

Deze studie evaluateert bij patiënten de relatie tussen verandering in de ernst van de pijn en veranderingen bij patiënt-gerapporteerde uitkomsten over de slaap, het functioneren en de stemming bij patiënten met post-traumatische pijn.

Een secundaire analyse wordt gepresenteerd met behulp van gegevens uit een klinisch onderzoek met pregabaline bij patiënten met een posttraumatische perifere neuropathische pijn (N = 254). Regressie modellen werden gebruikt om het verband te

bepalen tussen de veranderingen in pijn (0–10 NRS) als de voorspeller van veranderende scores op door de patiënt gerapporteerde uitkomsten.

Verandering in de ernst van de pijn als een continue voorspeller resulteerde in duidelijke en directe, aantoonbare relaties met veranderingen in de andere door de patient gerapporteerde uitkomsten, die alle statistisch significant ($p < 0{,}001$) waren. Er werd geconcludeerd dat een directe relatie bestaat tussen de pijn en de diverse aspecten van het welzijn en functioneren van de patiënt. Misschien dat verandering van de ernst van de pijn kwantitatief beoordeelt kan worden door het meten van veranderingen van andere klachten van de patient.

HOOFDSTUK VIII HET EFFECT VAN PREGABALINE OP PIJN GERELATEERDE SLAAPONDERBREKING BIJ PERIFERE DIABETISCHE NEUROPATHIE OF POSTHERPETISCHE NEURALGIA: EEN OVERZICHT VAN 9 GEPUBLICEERDE KLINISCHE ONDERZOEKEN

Postherpetische neuralgie (PHN) en pijnlijke diabetische perifere neuropathie (DPN) zijn vormen van neuropathische pijn die veel voorkomen. Vaak is er een complexe relatie tussen chronische neuropatische pijn en slaap, waarbij pijn de slaap verstoord en slecht slapen de pijn verergert. Pijn en slaap kunnen in belangrijke mate de stemming beïnvloeden. Patiënten lijdend aan PHN of DPN zouden beter behandeld kunnen worden indien tegelijkertijd de pijn en slaapstoornissen verminderen kunnen worden.

Dit artikel geeft een overzicht van gegevens en uitkomsten van negen gepubliceerde klinische studies over pregabaline voor de behandeling van DPN en PHN. Behandeling met pregabaline heeft een gunstig effect op de pijn en slaapstoornissen bij patiënten lijdend aan DPN of PHN.

Pregabaline werd goed verdragen en gemiddelde eindpunt pijnscores werden aanzienlijk verlaagd. Tevens verbeterde ook sterk de aan pijn gerelateerde slaapstoornissen tijdens de behandeling.

HOOFDSTUK IX ALGEMENE DISCUSSIE

Het is bijna onmogelijk om een verband te leggen tussen klachten en symptomen en de veronderstelde mechanismen als oorzaak van neuropatische pijn.

De ontdekkingen uit de basiswetenschappen moeten worden vertaald in klinische toepasbaarheid.

Behandeling van neuropatische pijn moet gericht zijn op het resetten van het dysfunctionerende zenuwstelsel.

De validatie van de DN4 vragenlijst is een stap vooruit om patienten met neuropatische pijn duidelijk te onderscheiden. De grens tussen definitief, waarschijnlijk, mogelijk en onwaarschijnlijk met betrekking tot de verschillende soorten pijn moet nog vastgesteld worden.

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Curriculum Vitae

Rob van Seventer werd geboren op 4 november 1946 te Dordrecht. Het HBS-B examen werd behaald in 1966 aan de Nassau HBS te Breda. In hetzelfde jaar werd de studie geneeskunde gestart aan de RU te Leiden. Na het artsexamen in 1973 begon hij, aanvankelijk tijdens de vervulling van de militaire dienstplicht, de opleiding tot anesthesioloog in het AZL te Leiden, afdeling anesthesiologie (Hoofd Prof. Dr. Joh. Spierdijk). In 1976 was hij mede oprichter van de Nederlandse Vereniging ter Bestudering van Pijn (NVBP) en een aantal jaren secretaris/penningmeester van deze vereniging. De opleiding tot anesthesioloog werd in 1977 afgerond. In 1977 werd hij maat in de maatschap anesthesiologie van het Diaconessenziekenhuis te Breda en tevens staflid van het Laurensziekenhuis te Breda als pijnspecialist. Beide instellingen fuseerden in 1986 tot Baronie ziekenhuis. Van Seventer was, met korte onderbrekingen, bijna tien jaar voorzitter van de medische staf. Na wederom een fusie met het Ignatius ziekenhuis te Breda in 2001 is hij thans, als lid van de maatschap anesthesiologie, werkzaam als pijnspecialist van het Amphia ziekenhuis te Breda.