Observational study

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The utility/futility of medications for neuropathic pain – an observational study

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Abstract

Background and aims: The RELIEF (Real Life) study by AstraZeneca was designed as an observational study to validate a series of Patient Reported Outcome (PRO) questionnaires in a mixed population of subjects with neuropathic pain (NP) coming from diabetes, neurology and primary care clinics. This article is an analysis of a subset of the information to include the medications used and the effects of pharmacological treatment over 6 months. The RELIEF study was performed during 2010–2013.
Methods: Subjects were recruited from various specialty clinics and one general practice clinic across Canada. The subjects were followed for a total of 2 years with repeated documentation of their status using 10 PROs. A total of 210 of the recruited subjects were entered into the data base and analyzed. Of these, 123 had examination-verified painful diabetic neuropathy (PDN) and 87 had examination-verified post-traumatic neuropathy (PTN). To evaluate the responsiveness of the PROs to change, several time points were included and this study focusses primarily on the first 6 months. Subjects also maintained a diary to document all medications, both for pain and other medical conditions, including all doses, start dates and stop dates, that could be correlated to changes in the PRO parameters.
Results: RELIEF was successful in being able to correlate the validity of the PROs and this data was used for further AstraZeneca Phase 1, 2, and 3 clinical trials of NP. To our surprise, there was very little change in pain and low levels of patient satisfaction with treatment during the trial. Approximately 15% of the subjects reported improvement, 8% worsening of pain, the remainder reported pain unchanged despite the use of multiple medications at multiple doses, alone or in combination with frequent changes of medications and doses over the study. Those taking predominantly NSAIDs (COX-inhibitors) did no worse than those taking the standard recommended medications against NP.
Conclusions: Since this is a real-life study, it reflects the clinical utility of a variety of internationally recommended medications for the treatment of NP. In positive clinical trials of these medications in selected "ideal" subjects, the effects are not overwhelming – 30% are 50% improved on average. This study shows that in the real world the results are not nearly as positive and reflects information from non-published negative clinical trials.
Implications: We still do not have very successful medications for NP. Patients probably differ in many respects from those subjects in clinical trials. This is not to negate the use of recommended medications for NP but an indication that success rates of treatment are likely to be worse than the data coming from those trials published by the pharmaceutical industry.

Keywords: neuropathic pain; real world; drug failure; diabetic neuropathy; posttraumatic neuropathy.

1 Introduction

Chronic neuropathic pain (NP), whatever the cause, is a substantial economic, emotional and physical burden for those afflicted [1–4]. Effective treatment is necessary to decrease the economic costs of health care, costs to society and costs to patients. The exact incidence and prevalence of all forms of chronic neuropathic pain are unknown although there is better information on specific syndromes such as painful diabetic polyneuropathy (PDN) that occurs in up to a 50% in patients with longstanding diabetes or 11%–20% in all diabetics [5]. A French survey

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reports a point prevalence of symptoms compatible with neuropathic pain of 6.9% in the general population [6]. A review of the problem of chronic neuropathic pain lists the average prevalence of NP in the general population at 7%, range 3%–18% in various studies [3].

Clinicians treating patients with neuropathic pain are overwhelmed with information on the pharmacological management of this problem. Treatment guidelines abound and various groups have published treatment protocols based on systematic reviews of the literature [7–15]. This "evidence-based" medicine gives the impression that a significant number of patients with various neuropathic pain problems should obtain substantial relief using the protocols. But what is the situation in real life? An editorial in the British Medical Journal [16] commenting on one of the reviews [10] gives some perspective and is sceptical. This editorial also notes that 40% of a general practice population in the UK never were offered therapy for their neuropathic pain. A more recent review of treatment solely for post herpetic neuralgia (PHN) in the US found that treatment guidelines are not always followed [17]. The less than optimum results using treatment guidelines have prompted another editorial entitled "Toward a definition of pharmaco-resistant neuropathic pain" [18]. This research-report will explore this topic further.

This paper is a report on the outcome of pharmacological treatment as usual over 1 year for 123 subjects with examination-verified painful diabetic polyneuropathy (PDN) and 87 subjects with examination-verified painful post-traumatic neuropathy (PTN) which here is defined as pain occurring after a peripheral nerve injury, either accidental or surgical.

The study was done during the years 2010–2013.

2 Methods

The RELIEF (Real Life) study was a prospective, non-interventional, explorative study to document the clinical state at baseline and with treatment as usual of subjects with PDN and PTN. The subject groups were recruited in Canada from various pain clinics, diabetes clinics and family practice clinics. Recruitment of subjects with neuropathic pain was from a pool of patients when they came for initiation of neuropathic pain treatment, to have changes in this treatment or for routine follow up when treatment was ongoing and unchanged. The intent of the study in Part I (the first 6 months) was to assess the characteristics of a group of patient reported outcome questionnaires (PROs) in neuropathic pain patients. Part II (the second 18 months) was to assess the health care costs of management of PDN and PTN (unpublished data). As a part of the assessment of PRO performance, an evaluation of "responsiveness" of the PROs to changes in the subjects' pain over time was necessary to document the sensitivity to change of the PROs. It was assumed that there would be improvements in a majority of subjects followed over the first 6 months and this would allow measurement of the responsiveness to change of all the PROs.

2.1 Ethical issues

One hundred and twenty three PDN subjects and 87 PTN subjects were eligible for statistical analysis in the RELIEF study. The protocol was approved by local Ethics Committees. Included were male and female English-speaking subjects of 18 years and older with a minimum of 3 months duration of PDN or PTN.

The demographics of the groups are seen in Table 1.

At inclusion, a physical examination was done to document the presence of neuropathic pain, and informed the patients about this observational study.

2.2 Diagnostic criteria for neuropathic pain

2.2.1 The diagnostic criteria for PDN

1) a medical history of diabetes mellitus type 1 or 2,
2) pain with a distal symmetric distribution, arterial occlusion excluded, of at least 3 months' duration,
3) a diagnosed sensory disturbance with a distal symmetric distribution of at least 3 months' duration involving one or more of the following senses;
   a) light touch (examined with a brush [SENSELab Brush-05, Somedic]),
   b) pinprick (examined with a cocktail pin),

Table 1: Demographics of painful diabetic neuropathy (PDN) and post-traumatic neuropathy (PTN).

Demographic characteristics		PDN	PTN	Total
Number of subjects		123	87	210
Age (years)	Mean	59.8	48.8	55.2
	Std	12.14	11.75	13.13
	Median	60.0	49.0	56.0
	Min	30.0	23.0	23.0
	Max	84.0	70.0	84.0
Sex *n* (%)	Male	79 (61.8)	5 (51.7)	121 (57.6)
	Female	47 (38.2)	42 (48.3)	89 (42.4)

c) warmth (examined with a metallic roller at 40 °C [Somedic]),
d) cold (examined with a metallic roller at 20 °C [Somedic]).

In addition, tests for peripheral pulses (those with absent pulses were excluded), tendon stretch reflexes and vibration sense were tested and recorded and a monofilament examination for tactile hyperalgesia was also done and recorded.

2.2.2 The diagnostic criteria for PTN

1) a history of pain due to injury (accidental or surgical) to one or several well-defined peripheral nerves,
2) pain localized to the area of the specific nerve(s),
3) a diagnosed sensory disturbance of the affected area of one or more of the following senses;
   a) light touch (examined with a brush [SENSELab Brush-05, Somedic])
   b) pinprick (examined with a cocktail pin)
   c) warmth (examined with a metallic roller at 40 °C [Somedic])
   d) cold (examined with a metallic roller at 20 °C [Somedic])

In addition, tendon stretch reflexes and vibration sense were tested and recorded and a monofilament examination for tactile hyperalgesia was done and recorded.

2.2.3 Patient reported outcomes

Also at inclusion, a battery of PROs was completed by both the PDN and PTN groups. The PROs chosen were based on the guidelines of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [19, 20] prior to the publication of more specific guidelines from both IMMPACT and the US Food and Drug Administration. Both groups repeated the PROs 1 week after inclusion for test-retest reliability and again at three and 6 months. A subset of these PROs was repeated at 2 years. The primary reason for the use of these PROs was to assess their suitability for use in future neuropathic pain studies and to validate their performance in neuropathic pain.

2.2.4 The PROs comprised

1) The intensity of pain measured on an 11-point Numerical Rating Scale (NRS) where "0" is "no pain" and "10" is "worst possible pain",
2) Patient Global Impression of Change (PGIC), except at visit one,
3) Short Form McGill Pain Questionnaire (MPQ-SF),
4) Brief Pain Inventory Short Form (BPI-SF),
5) Medical Outcomes Study (MOS) Sleep Scale,
6) Hospital Anxiety and Depression Scale (HADS),
7) Modified Work Productivity and Activity Impairment Questionnaire for pain (WPAI-pain),
8) 36-item Short Form Health Survey, version 2 acute form (SF-36v2 acute),
9) European Quality of Life Index – 5D (EQ-5D),
10) Health Utility Index Mark 3 (HUI3).

2.2.5 Clinicians' impressions of change of pain from treatment

In addition, except at the first visit, the subjects' physicians completed a Clinical Global Impression of Change (CGIC).

2.2.6 Medications used for neuropathic pain

At the first visit, subjects recorded all medications being taken, those for pain as well as for other conditions, and the dose of each. Subsequently, all medication changes, additions or subtractions and the dates of same were recorded by the subjects in a diary during the first 6 months and entered for analysis. Because of the very large variety of medications taken by the subjects, a modified classification system of the medications was used. It was felt that analysis by individual medication would not be statistically possible.

2.2.7 Medications were grouped under

1) COX inhibitors, COX-1 and COX-2 inhibitors (=NSAIDs), ASA, specific COX-2 inhibitors, and acetaminophen/paracetamol,
2) opioids,
3) tricyclic antidepressants (TCAs),
4) other antidepressants,
5) anti-epileptics,
6) combinations, primarily COX inhibitors combined with opioids,
7) others.

2.3 Statistical analysis

Statistics were calculated on input data and at each visit interval. Descriptive statistics included listings, summary

tables (mean, standard deviation, median, minimum, maximum, q1 and q3) and were presented by subject group, gender and age, among others (see Table 1).

The primary outcome variable for assessing improvement was Patient's Global Impression of Change – PGIC that is a global measure indicating the degree of change in the overall status of the subject as noted by the subjects themselves [21].

3 Results

3.1 Changes in pain-intensity

Although the RELIEF study did allow for appropriate statistical evaluation of the PROs, including sensitivity to change of PGIC, surprisingly few of the subjects were actually improved by treatment over the course of the study. A high number of subjects included had a NRS/VAS above 4/10, the arbitrary level that indicates at least moderate pain and inadequate pain control. This was an indication that any treatment offered before the initiation of the RELIEF study had not had much effect. The median NRS score was 6.0 for both PDN and PTN at intake. These scores did not change significantly throughout the 2 years of the study despite efforts through medication change in many subjects to control the pain.

3.2 Patient's Global Impression of Change

The PGIC data show that very few subjects were improved between visits (see Table 2). PGIC used in the study had a seven-point Likert scale: "Very much improved", "Much improved", "Minimally improved", "No change", "Minimally worse", "Much worse", "Very much worse". The frequency of subjects who reported "Much improved" or "Very much improved" from Visit 1–3 was 14.3% in the PDN group and 16.0% in the PTN group. From visit 1–4, the numbers were 14.3% in the PDN group and 11.5% in the PTN group.

Table 2: Patient global impression of change (PGIC).

	PDN		PTN	
	Worse	**Better**	**Worse**	**Better**
Time points				
Visit 1–3	8.0%	14.3%	3.7%	16.0%
Visit 1–4	8.6%	14.3%	7.7%	11.5%

Worse = worse + much worse; Better = somewhat better + much improved.

The PGIC data show also that some subjects were worse over the course of the study (see Table 2). The frequency of subjects who reported "Much worse" or "Very much worse" from Visit 1–3, was 8.0% in the PDN group and 3.7% in the PTN group. From Visit 1–4, the numbers were 8.6% in the PDN group and 7.7% in the PTN group.

There was a statistically moderate correlation between PGIC and CGIC (Clinical Global Impression of Change – the clinicians' impression of the treatment effect) at all visits with the CGIC indicating less improvement than the subjects reported themselves.

3.3 Effects of medications

Despite the above grouping of medications to simplify statistics, it was impossible to correlate any improvement with specific medication changes. A part of the problem is that there were often multiple changes in medications at a single visit.

A surprising finding was the high use of COX inhibitors (43.3% overall and 80.6% in the general practice group at visit 3), and opioids combined with COX inhibitors (29.5% overall and 43.1% in the general practice group). Also surprising, was the rather low use of antidepressants and antiepileptics – see Table 3.

There was a further difference in medications used in general practice as compared to the specialty clinics. For the total number of participants in the study, the percentage NOT receiving first or second line drugs (excluding opioids) for neuropathic pain (TCAs, other SSRIs and NSRIs and anticonvulsants) was 80.3% in the general practice group while in the specialty clinics it was 33.8%. Of those subjects in specialty clinics (138 subjects), there were 80 new trials of first line therapies during the course of RELIEF Part 1 (the first 6 months). There were only six new trials of these medications in the general practice group (72 subjects).

A proportion of the subjects appeared to have appropriate trials of medications recognized as first, second- and third-line medications for the treatment of neuropathic pain [6–8]. Sixty-six subjects had combined therapy of medications from at least two classes of those recommended.

3.4 Low health-related quality of life

Another perspective on the lack of treatment effect was the low quality of life of the subjects as reflected in the

Table 3: Medication use.

Visit	Medication group	Number (%) subjects	
		PDN *n*=123	PTN *n*=87
1	Opioids	14 (11.4)	26 (29.9)
	COX inhibitors	61 (49.6)	38 (43.7)
	Anti-epileptics	33 (26.8)	32 (36.8)
	Tricyclic antidepressants	28 (22.8)	19 (21.8)
	Other antidepressants	1 (0.8)	4 (4.6)
	Benzodiazepines	3 (2.4)	7 (8.0)
	Combinations	30 (24.4)	39 (44.8)
	Others	8 (6.5)	12 (13.8)
3	Opioids	13 (10.6)	24 (27.6)
	COX inhibitors	55 (44.7)	36 (41.4)
	Anti-epileptics	36 (29.3)	39 (44.8)
	Tricyclic antidepressants	24 (19.5)	24 (27.6)
	Other antidepressants	1 (0.8)	4 (4.6)
	Benzodiazepines	3 (2.4)	8 (9.2)
	Combinations	29 (23.6)	36 (41.4)
	Others	8 (6.5)	12 (13.8)
4	Opioids	9 (6.5)	27 (13.8)
	COX inhibitors	53 (43.1)	37 (42.5)
	Anti-epileptics	37 (30.1)	43 (49.4)
	Tricyclic antidepressants	24 (19.5)	19 (21.8)
	Other antidepressants	1 (0.8)	4 (4.6)
	Benzodiazepines	3 (2.4)	8 (9.2)
	Combinations	28 (22.8)	36 (41.4)
	Others	8 (6.5)	12 (13.8)

evaluations using the EQ-5D weighted index and overall health related quality of life at the conclusion of the study. Subjects were divided into three groups: mild pain (NRS 0–4), moderate pain (NRS 4–7) and Severe pain (NRS > 7). There were 38 PDN subjects with severe pain and they had a median EQ-5D weighted index of 0.4/1.0 and an overall quality of life median score of 0.3/1.0. There were 29 PTN subjects with severe pain and the median score for this group with the EQ-5D was 0.6/1.0 for the Weighted Index and with 0.5/1.0 for the Overall Quality of Life Index.

4 Discussion

In the current study, a large percentage of participants had no improvement despite a wide variety of pharmacological treatments. This was reflected not only in pain scores but also in other aspects of health measured, including quality of life.

4.1 Why did so few patients experience global improvement?

Was this due to inadequate treatment or are there other explanations? Treatment guidelines for neuropathic pain in Canada, published for all medical practitioners, exist but they were first published during this study [7, 8]. Some physicians involved in RELIEF were also practice guideline authors [8]. It is assumed that they were using the guidelines but this is unknown as there was neither an expectation nor a stipulation that specific guidelines should be followed in RELIEF. RELIEF was purely a 2-years observational study of treatment and outcome of patients with neuropathic pain treated mostly in pain clinics, diabetes clinics but also in one large general practice clinic in Canada.

Other guidelines have been published and were also available; a comprehensive one was published at the start of this study [12] and newer reviews have not modified guidelines to any significant extent nor have they added more effective medications [14, 22, 23]. This is also true for the SNRIs venlafaxine and duloxetine that have rather high “numbers needed to treat” (NNT), and they do increase risks of serious serotonergic symptoms, especially when co-administered with other serotonergic drugs, tramadol in particular.

The RELIEF subjects attending pain specialty clinics were taking a variety of medications indicated as first, second- and third-line therapies recommended by the then existing and current guidelines without effect. Many were on combination therapy which is currently recommended, specifically, antiepileptic and antidepressant drugs plus or minus opioids [24–27], but this was also without effect. Data from the study indicate that 44 subjects were on two first line therapy drugs at study start and 12 were on three. In all, 77 subjects continued some form of combined therapy for at least a month. Those subjects in the general practice group not taking recommended drugs, i.e. not on combination therapy, did no worse, which is surprising.

4.2 Other negative studies?

Is this failure to respond to treatment despite the high use of recommended pharmacotherapy new or unusual? Toelle et al. [28] found a similar problem in looking at PDN in a survey across six European countries including patients from general practitioners and non-pain specialists. Despite a higher use of antiepileptic drugs than in the RELIEF study, 57% of the European subjects had a Pain Severity Index in the 4–6/10 range and 25% in the 7–10/10

range. This represents a substantial percentage which had inadequate pain relief.

Toelle et al. reported a lower use of opioids/"opioid compounds" (16.4%) than seen in RELIEF (51.9% at visit 1, 47.6% at visit 4), but as was also found in RELIEF, a high use of COX inhibitors (41.4%) and "standard analgesics" (62%), although these "standard analgesics" were not described and it could be assumed that they were over-the-counter preparations such as paracetamol and ibuprofen. Forty four percent were also taking "over the counter" medications in Toelle's group. In the RELIEF study, Toelle's two medication classes ("NSAIDS or COX-2 inhibitors" plus "over the counter medications") were grouped together and in RELIEF, 47.1% at visit 1, 43.3% at visit 4 were taking these medications. Nine percent of the Toelle subjects were not treated with prescription medications. In the RELIEF study, 11.4% of the subjects were not treated with prescription medications and all of the non-treated were in the general practice group. This is similar information to that in two previous English surveys where only 44%–72% of the patients from a general practice population had pharmacologic treatment initiated when they presented with different neuropathic pain diagnoses [29, 30].

4.3 Satisfaction with treatment versus pain relief

In assessing subject satisfaction with medications in the RELIEF study, the numbers were 12.5% completely satisfied ("much improved" on the PGIC), 34.0% moderately satisfied ("improved" Table 2), 31.6% neutral and 16.7% moderately/completely dissatisfied ("worse"/"much worse" on the PGIC – Table 2). This is similar to the Toelle study although a higher percentage in that study was "satisfied". The Toelle study reported 15% completely satisfied, 47% moderately satisfied, 10% neutral and 22% moderately or completely dissatisfied. It is surprising that so many of the European subjects were satisfied despite not reporting any pain relief from treatment. This could represent an overall assessment of treatment, not just the effect of the medication. Patients are often "satisfied" if they have been well taken care of even though they may not have less pain. The Patient Global Impression of Satisfaction (PGIS) is not as good an outcome measure; Patient Global Impression of Change, the PGIC, is more precise.

This question of poor response to treatment was also raised at the Investigators' Meeting held after completion of the statistical analysis of data from RELIEF, Part I. The investigators suggested that the high use of "COX inhibitors" and "combination/compounds" was due to these medications being available without prescription in Canada or without the need to write a triplicate prescription as was necessary for strong opioids. Investigators from the specialty clinics also suggested that many subjects received simultaneous care from general practitioners for the pain problems. The use of "COX inhibitors" and "combination/compound" medications was not standard practice for the investigators who are specialists.

4.4 Low effectiveness of guidelines-recommended drug treatments

The information that the PDN/PTN subjects were self medicating and also seeking treatment from general practitioners is another indication that more specialized treatment in pain and diabetes clinics was not effective, not because expertise was not available but that the best pharmacological treatments presently available are not very effective.

From a critical viewpoint of the literature on pharmacological therapy for neuropathic pain, there are several points to consider. A source of bias on the publicized effectiveness of medications for a variety of medical diagnoses is the report of better efficacy in clinical studies sponsored by "for profit organizations" than in those from independent sources [31, 32]. This can, in some studies, be due to selection-bias, when trials are focused on specific patient groups chosen specifically so that the trial drugs may be more effective. This means that the data from studies reporting the effectiveness of medications for treating neuropathic pain are optimistic and in reality, these medications are less effective than the pharmaceutical industry reports. This is also in part due to publication-bias: positive studies are more often published, whereas "negative" studies (like the present study) are often not published, especially if the study was funded by industry.

There is also the problem of unmasking effects in drug studies using inert placebos [33]. Lack of effect and lack of side effects of the placebo treatment mean that subjects are able to correctly identify being on the placebo arm. Although this would tend to decrease the placebo effect of treatment, it could also increase the nonspecific ("placebo") positive effect for the investigational drug which does have side effects.

The publication-bias problem is that all drug trial studies, both from the pharmacological industry and independent of industry, are not reported in the pain literature. The negative studies which are not reported do not enter into the cumulative statistical analyses of effect

in most reviews of the Cochrane type [34]. Recently, some Cochrane reviews have been modified to include them [35]. And then there is the discussion of statistical bias in how data are manipulated [36].

4.5 Low health-related quality of life predicts poor outcome of drug treatment

An alternative explanation for the failure of treatment in RELIEF may relate to a finding by Otto et al. [37]. They analyzed three studies and compared treatment response to SF-36 scales and found a correlation between responders and higher scale scores (better mental and physical health generally) on SF-36. The RELIEF subjects had similar SF-36 scores to the pooled data in the Otto et al. study and RELIEF had a high number of non-responders with low scores as predicted by the SF-36 results in the Otto et al. paper. Similarly, two recent studies showed that patients with peripheral neuropathy who are "catastrophizers" are less responsive to first line pharmacotherapy [38, 39]. There was no evaluation of catastrophizing in the RELIEF population but it is possible that a part of the population studied were catastrophizers.

4.6 Conclusions and implications

In conclusion, the current study supports that patients with neuropathic pain continue to receive inadequate treatment for their pain. The reasons for this may include inadequate use of appropriate first line agents for neuropathic pain as well as a poor response to appropriate agents when they are used.

There is a need for more effective medications for neuropathic pain as well as non-pharmacological treatments [40, 41].

There is a need for broader education regarding approved guidelines so that primary care can move from the use of medications not included in treatment guidelines, i.e. COX inhibitors, to more effective medications. The COX inhibitors, besides being ineffective, may also have serious side effects from the cardiovascular (myocardial infarction and stroke) and gastrointestinal (painless, bleeding ulcers) systems [42].

There is also a need for general access to ALL data on new medications, both positive and negative, so that those who read the pain literature have an unbiased perspective on the effectiveness and safety of new drugs for neuropathic pain. Both patients and doctors are disappointed when the proclaimed highly effective therapies do not measure up in the real world. Clearly, there is a very real need for better medications for neuropathic pain [43].

And, lastly, there is a need for improved clinical trial protocols that can demonstrate more accurately the clinical effects of existing and new medications proposed for the treatment of neuropathic pain. This problem has been addressed by the US Food and Drug Administration who have been instrumental in organizing the Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) group to increase the assay sensitivity and efficiency of analgesic clinical trials [44, 45]. Hopefully, in the future, better clinical studies can indicate appropriate therapies for patients of different phenotypes that present with various neuropathic pain diagnoses.

Authors' statements

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Conflict of interest: Rolf Karlsten and Lena Ring were fully employed by AstraZeneca and Stephen Butler was a consultant for AstraZeneca during the RELIEF study. Daniel EEK was and is still an employee of AstraZeneca.

Informed consent: Obtained.

Ethical approval: The protocol was approved by local ethics committees.

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