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Predictors of severe pain in a cohort of 5271 individuals with self-reported neuropathic pain

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ABSTRACT

The influence of pain descriptors and mechanical hypersensitivity on pain severity in neuropathic pain has not been well researched and is poorly understood. The aim of this study was to determine the relationship between pain severity and other factors describing chronic neuropathic pain in a large cohort of patients with self-reported neuropathic pain potentially recruited as subjects for a Phase IIa study. A questionnaire specific to the study parameters covering demographics and pain characteristics was sent to potential participants. Overall, 9185 questionnaires were returned from potential subjects who self-reported neuropathic pain. Adjusted odds ratios with 95% confidence intervals were used as a measure of association. These were estimated by unconditional logistic regression. Pain descriptors in the questionnaire were: burning, shooting, shocking, and aching. The presence of self-reported allodynia and hyperalgesia was strongly indicative of both moderate and severe pain, with a significant interaction of both factors in moderate and severe pain. Having 3 or 4 pain descriptors was also strongly indicative of both moderate and severe pain. Female gender, age, and history of serious mental disorders were found to be weaker indicators of both moderate and severe pain. Given the large and varied population with many neuropathic pain diagnoses in the study, the findings are not likely to be merely chance, but are likely to reflect important relationships between pain severity and other factors in those who suffer from chronic neuropathic pain.

1. Introduction

There is much interest in describing phenotypes associated with severe chronic pain, and neuropathic pain (NP) in particular, both in animal models and in humans [2,18,19,21]. This began many years ago [20] but has gained more interest and accrued more data in the last few years. Isolating the many factors and relating phenotypes to pain mechanisms is the model for providing personalized medicine that is the aim of clinicians, the pharmaceutical industry, and regulators [6]. Of particular interest to the pharmaceutical industry is the introduction of new compounds with a finite mechanism of action focused on specific phenotypes tested in Proof of Principle and Proof of Mechanism studies in animal models. Identifying similar phenotypes in humans by using a combination of symptoms, quantitative sensory testing, and genetic markers appears to be the way to succeed with new compounds with a finite mechanism of action [10,17,18,22]. Forward-and-back translation among animals, healthy human volunteers, and humans with a specific set of painful symptoms and signs would offer the best approach to link a positive signal to a compound with a restricted mechanism of action.

This was the approach used by AstraZeneca (AZ) to test a new compound in a population of subjects with chronic neuropathic pain. Subjects for the study were to be selected from a cohort of volunteers who self-reported both NP and mechanical hypersensitivity (MH). MH was identified in the questionnaire used as "pain from light touch" (allodynia) and/or "increased response to a painful stimulus" (hyperalgesia). AZ employed Acurian (Horsham, PA, USA), a company with a large database of potential study subjects for medical research (http://www.acurian.com) to help in the recruiting process. The search used a carefully constructed questionnaire to identify potential subjects (Appendix A – questionnaire). The analysis presented in this article was based on subsequent more complete data obtained from Acurian on the total population used for the recruitment process to attempt to identify phenotypes based on responses to the questionnaire. This article reports data from the analysis of symptoms in potential subjects self-reporting NP and the relationship of these symptoms with

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demographics, self-reported MH, and selected comorbidities (eg., major mental disorders, cardiovascular disease) and pain severity using multiple logistic regression models to estimate odds ratios (ORs) as a measure of association.

2. Methods

2.1. Study population

This population came from a group of subjects reporting having chronic disease who responded to either an online or a mailed questionnaire sent by Acurian as part of a recruitment plan for a Phase IIa clinical study in NP with MH conducted by AZ. Acurian is a provider of patient recruitment and retention solutions and recently announced that its recruitment database contains over 65 million subject records, or approximately 49% of the 133 million of the US population thought to have chronic disease. To locate potential participants for the AZ study, Acurian mailed a letter to 753,031 people in their database who reported chronic pain and who lived within 30 miles of a site to be used in the Phase IIa study. Acurian supplemented this recruitment with further strategies including e-mail and other social media to generate volunteers. All advertisements and letters mailed for the trial invited individuals who experienced "a painful tingling, burning, shooting, or stabbing feeling in your body, or pain from light touch or pressure" (wording in the contact material) to be screened for inclusion in the study.

Subsequently, interested individuals were asked to complete an extensive questionnaire used for describing their pain and also giving information on age, pain descriptors (burning, shooting, aching, shocking, and "other"), presence or absence of MH symptoms, pain duration, pain severity, cause of pain, history of serious mental disorders (depression, bipolar disorder, schizophrenia, anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder), and cardiovascular disease, among others. This was a population with a variety of NP diagnoses but with some concomitant nonneuropathic diagnoses such as fibromyalgia syndrome and myofascial pain syndrome (Table 1).

2.2. Analysis

The descriptive analysis including age categories, pain descriptors, and presence and frequency of pain scores was done for the 9185 subjects who self-reported NP on the questionnaire, and an article on this complete analysis has been submitted for publication. There were 6233 subjects (67.9%) with full data, but several were excluded because of their diagnoses (spinal cord injury, myofascial pain syndrome, Type I complex regional pain syndrome, stroke, trigeminal neuralgia, and fibromyalgia), and this study is based primarily on 5271 subjects. A list of the diagnoses and frequencies is shown in Table 1. These exclusions were used in an effort to minimize bias by including subjects with a high probability of having a peripheral source for NP. Crude OR estimates of the full 9185, including those with missing data, were done and show results similar to those presented here. This is supportive of the contention that the group presented here is not a biased subset due to exclusion of those with missing data.

Age was calculated from August 2010 at study start and divided into 3 categories: 18–39, 40–59, and 60–80 years. Pain was classified as Mild (numeric rating scale [NRS] 1-3), Moderate (NRS 4-6), and Severe (NRS 7-10). The means and SDs for continuous variables and frequencies for categorical variables were calculated and presented by gender.

Unconditional multiple logistic regression models were used to calculate ORs and 95% confidence intervals (CI) for pain severity associated with age, gender, self-reported MH (including allodynia and hyperalgesia), pain descriptors, duration of pain, and the presence of serious mental disorders. The software used for the computations was LOGISTIC by Statistical Analysis Systems SAS/STAT software, Release 8.02 (SAS Institute, Cary, NC, USA). The analysis was to identify possible predictors of severe pain and moderate pain compared to mild pain in this population. This analysis included the 5271 subjects with probable peripheral NP based on their diagnosis and who had no missing data (Table 1). Both crude and adjusted ORs were calculated, but only the adjusted ORs are presented for simplicity because the estimates were approximately the same.

2.3. Ethics approval

Because all information in the database was "de-identified" by Acurian, no ethics approval was needed. See "De-identified information" at the end of the article.

3. Results

OR estimates that were calculated compared the relationship between severe pain (NRS 7-10) and mild pain, and between moderate pain (NRS 4-6) and mild pain (NRS 0-3).

Table 1
Self-reported cause of neuropathic pain among all, after excluding missing and certain pain diagnoses.

Self-reported cause of NP	Among all NP (n = 9185)		Missing excluded (n = 6233)		Final data[a] (n = 5271)	
	n	%	n	%	n	%
Diabetic peripheral neuropathy	813	8.9	204	3.3	142	2.7
Post traumatic neuropathy	3718	41.5	2399	38.5	2049	38.9
Post herpetic neuropathy	293	3.2	177	2.8	131	2.5
Lumbosacral radiculopathy	2794	30.4	1681	27.0	1427	27.1
Meralgia paresthetica	643	7.0	325	5.2	257	4.9
Myofascial pain syndrome	659	7.2	50	0.8	0	0.0
Other NP	2327	25.3	1391	22.3	1095	20.8
Nondiabetic polyneuropathy	1512	16.5	868	13.9	703	13.3
Spinal cord injury	766	8.3	70	1.1	0	0.0
Stroke	147	1.6	28	0.4	0	0.0
Trigeminal neuralgia	171	1.9	25	0.4	0	0.0
Type I complex regional pain syndrome	312	3.4	25	0.4	0	0.0
Type II complex regional pain syndrome	132	1.4	41	0.7	25	0.5
Unknown (nerve pain)	1578	17.2	1349	21.6	1198	22.7
Other	1217	13.2	896	14.4	671	12.7
Fibromyalgia	947	10.3	862	13.8	0	0.0

[a] Final data (excluding spinal cord injury, myofascial pain syndrome, type I complex regional pain syndrome, stroke, trigeminal neuralgia, and fibromyalgia from analysis).