The Epidemiology of Facial Pain

J.S.H.A. Koopman

The work presented in this thesis was conducted at the Department of Medical Informatics in collaboration with the Pain Treatment Center, both of the Erasmus MC, Erasmus University Medical Center, Rotterdam.

Most of the studies within this PhD thesis were performed within DALI for PAIN, a national program that focuses on neuropathic paincare optimalisation. DALI for PAIN is an initiative of Pfizer. This project is supported by an unrestricted grant from Pfizer.

The contributions of the participating general practitioners in the IPCI project are greatly acknowledged.

Financial support for printing this thesis was kindly provided by the Erasmus University and the department of Medical Informatics – Integrated Primary Care Information (IPCI) project – of the Erasmus MC, Erasmus University Medical Center, Rotterdam.

Design and production by: H. van Gemert
Cover image: The Scream, Edvard Munch, © Edvard Munch, the Munch Museum, the Munch-Ellingsen Group c/o Pictoright Amsterdam 2010.
This is an expressionist painting by the Norwegian artist Edvard Munch, depicting an agonized figure against a blood red sky. It has become recognised as the actual mental image of the existential angst of civilised man. In the subject of facial pain, it reflects, in my opinion, a patient with facial pain fearing an exacerbation.

The Epidemiology of Facial Pain

De epidemiologie van aangezichtspijn

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 19 mei 2010 om 15.30 uur

door

Josèph Stephanus Hugo Arthuro Koopman

Geboren te Bergen (NH)

Promotiecommissie

Promotoren:	Prof.dr. M.C.J.M. Sturkenboom Prof.dr. F.J.P.M. Huygen
Overige leden:	Prof.dr. A. de Laat Prof.dr. J.J.A. Mooij Prof.dr. J. Klein
Copromotoren:	Dr. J.P. Dieleman

Contents

Chapter 1

General introduction

Assuming that the average age of the readership of this thesis is 35 years, and that 49% is male, given the number of theses printed (n=500) and the average life expectancy (78 years for men, 82.3 years for women), nine [95% confidence interval (95% CI): 8 - 10] readers (1.8%) will get a form of facial pain as studied in this thesis. [1, 2]

Despite its low frequency the severity and debilitating nature of certain facial pain conditions is an important motivator for scientific research in this field. [3-5]
Facial pain comprises many different disease entities, which differ in aetiology, presentation, severity, frequency of occurrence and natural course of disease. In this thesis, we studied eight different forms of facial pain, including trigeminal neuralgia, postherpetic neuralgia in the facial area, cluster headache, occipital neuralgia with referred facial pain, local facial neuralgias, persistent idiopathic facial pain, glossopharyngeal neuralgia and paroxysmal hemicrania. These diseases share some clinical features and are often considered together in the differential diagnosis of a general practitioner. Facial pain conditions can be divided into primary (idiopathic) and secondary (symptomatic) facial pain based on the disease aetiology. [6-13] While the aetiology of primary forms is largely unknown, secondary forms can be due to tumors, infarctions, arterio-venous malformations, multiple sclerosis and many other diseases. [6-13]

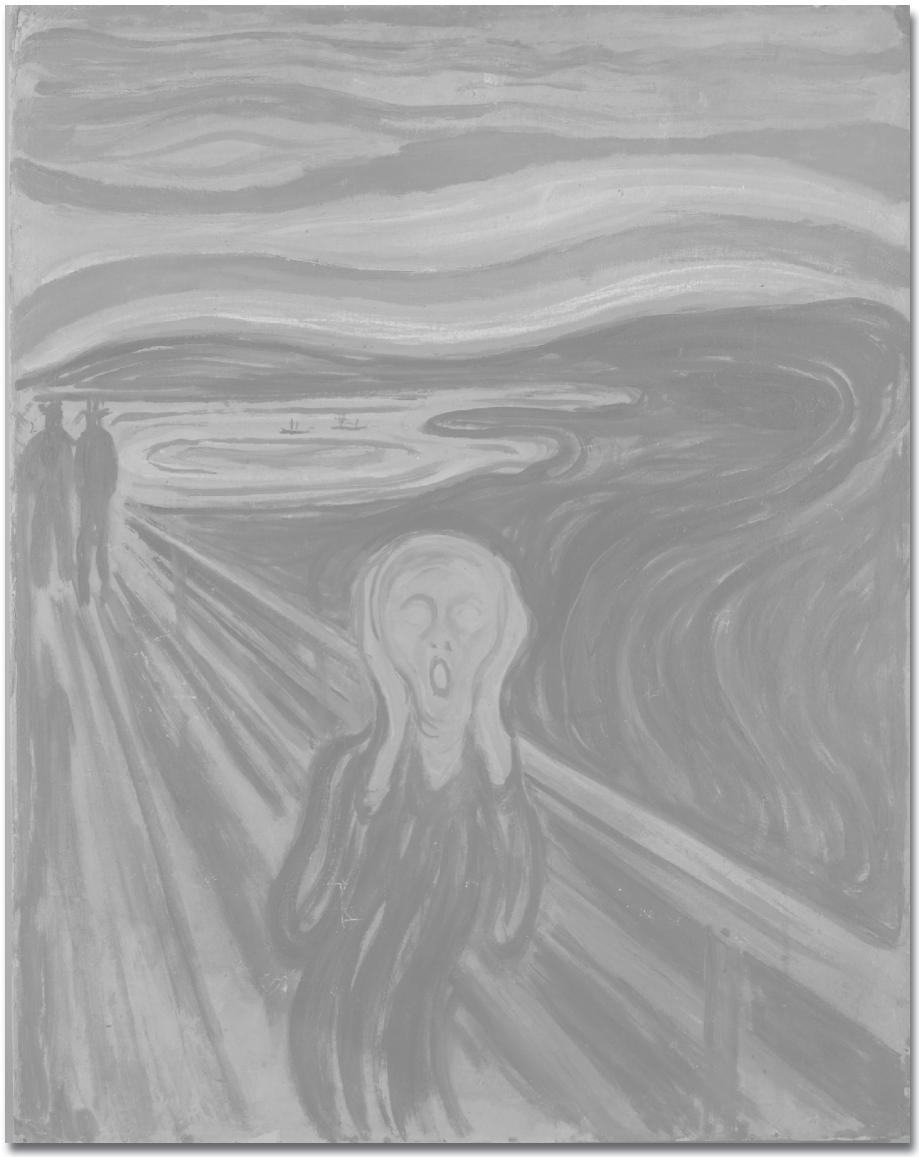
Two of the most frequent forms of facial pain are trigeminal neuralgia and cluster headache. [2]
Trigeminal neuralgia is a severe form of facial pain presenting mostly with unilateral, stabbing, paroxysmal pain in one or more branches of the fifth cranial nerve (trigeminal nerve). [14] Cluster headache is also a unilateral, paroxysmal pain in the first branch of the fifth cranial nerve. [14] It may be accompanied with ipsilateral lacrimation, conjunctival injection, photophobia, nasal stuffiness and / or rhinorrhea. [14]
Until now, research into facial pain is scanty and often limited to a secondary or tertiary care setting. Recent publications reported a higher incidence of trigeminal neuralgia in primary care compared to secondary care. [15-17] This finding suggests that not every patient with facial pain is referred to secondary care. Patients treated in primary care might differ substantially from patients treated in secondary and tertiary care. Reports on patients treated in secondary or tertiary care might not be representative for all patients with facial pain. The lack of recent epidemiological data from primary care and the need for more accurate and comprehensive knowledge about the frequency, aetiology and risk factors, and treatment of facial pain conditions motivated the studies included in this thesis.

Aims and outline of this thesis
In this thesis we aimed to gather epidemiological data on the incidence, risk factors and treatment of eight different forms of facial pain.
In chapter two we describe the incidence rate by age, calendar year, sex and season for trigeminal neuralgia, postherpetic neuralgia in the facial area, cluster headache, occipital neuralgia with referred facial pain, local facial neuralgias, persistent idiopathic facial pain, glossopharyngeal neuralgia and paroxysmal hemicrania.
To study possible aetiological mechanisms we evaluated both known and unknown risk factors for the development of trigeminal neuralgia and cluster headache (chapter 3). Since trigeminal neuralgia and cluster headache may present as relapsing diseases, we also studied risk factors for exacerbation (chapter 3).

Chapter 4 focuses on treatment patterns and treatment outcomes. We described healthcare use and the diagnostic work-up of patients with facial pain. Furthermore, we analyzed drug utilization patterns in general practice including type of drug prescribed, dosage regimen, type of prescriber, treatment delay and failure rates. If patients are refractory to pharmacological treatment, invasive intervention may be considered. In chapter 4 we studied the three most commonly used invasive procedures for trigeminal neuralgia, including percutaneous radiofrequency thermocoagulation, partial sensory rhizotomy and microvascular decompression. To be able to better predict treatment success, we modelled possible predictors of failure of pharmacological treatment in patients with trigeminal neuralgia and cluster headache. Knowledge about predictors for treatment failure or success may facilitate the development of tailor-made medicine which should lead to an improvement of outcome, fewer adverse events and better patient satisfaction. The meaning an limitations of the studies are discussed in chapter 5 of this thesis and recommendations are made for future research.

Chapter 2

Incidence



2.1

Incidence of facial pain in the general population

Published in: Pain. 2009 Dec 15;147(1-3):122-7.

Joseph SHA Koopman, MD [1], Jeanne P Dieleman, PhD [1], Frank. J Huygen, PhD [2], Marissa de Mos, PhD [1], Carola GM Martin, MD [2], Miriam CJM Sturkenboom, PhD [1,3]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: Facial pain has a considerable impact on quality of life. Accurate incidence estimates in the general population are scanty. The aim was therefore to estimate the incidence rate (IR) of trigeminal neuralgia (TGN), postherpetic neuralgia (PHN), cluster headache (CH), occipital neuralgia (ON) with referred facial pain, local facial neuralgia (LoN), atypical facial pain (AFP), glossopharyngeal neuralgia (GPN) and paroxysmal hemicrania (PH) in the Netherlands.
Methods: In the population-based Integrated Primary Care Information (IPCI) medical record database potential facial pain cases were identified from codes and narratives. Two medical doctors reviewed medical records, questionnaires from general practitioners and specialist letters using criteria of the International Association for the Study of Pain. A pain specialist arbitrated if necessary and a random sample of all cases was evaluated by a neurologist. The date of onset was defined as date of first specific symptoms. The IR was calculated per 100,000 person years.
Results: 362 incident cases were ascertained. The overall IR [95% confidence interval] was 38.7 [34.9 - 42.9]. It was more common among women compared to men. Trigeminal neuralgia and cluster headache were the most common forms among the studied diseases. Paroxysmal hemicrania and glossopharyngeal neuralgia were among the rarer syndromes. The IR increased with age for all diseases except CH and ON, peaking in the 4^{th} and 7^{th} decade respectively.
Conclusions: Postherpetic neuralgia, CH and LoN were more common in men than women. From this we can conclude that facial pain is relatively rare, although more common than estimated previously based on hospital data.

Introduction

Facial pain is a rare but severe condition affecting the facial area which can have a considerable impact on the quality of life. [3-5] Two of the most severe and debilitating facial pain conditions are trigeminal neuralgia and cluster headache. Facial pain may either be primary (idiopathic) or secondary to diseases such as tumors, multiple sclerosis and cerebrovascular infarctions. [8, 11-13, 18, 19]
Due to lack of objective diagnostic tools, diagnosis and classification of facial pain is made on clinical judgment using criteria of the International Association for the Study of Pain (IASP) or the criteria of the International Headache Society (IHS). [20, 21] Establishing the correct diagnosis and differentiating between types of facial pain is complicated because different types of facial pain share signs and symptoms and are often considered together in the differential diagnoses at first presentation. The precise underlying pathophysiological mechanisms are not yet completely understood, which further complicates diagnosis. Diseases often considered together in the differential diagnosis of a general practitioner include trigeminal neuralgia, cluster headache, postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, glossopharyngeal neuralgia, local facial neuralgias, glossopharyngeal neuralgia and atypical facial pain. Because of the apparent difficulty of the general practitioner (GP) to differentiate these diseases and based on our clinical judgment, we decided to study them together.
Little is known about the exact incidence of these forms of facial pain in the general population. Recent investigations in general practitioner (GP)-databases showed a considerably higher incidence rate of trigeminal neuralgia compared to estimations from hospital data in the early nineties (26.8 to 28.9 per 100,000 person years (PY) versus 4.7 per 100,000 persons). [15, 16, 22, 23] However, the recent studies relied on diagnosis codes in electronic patient records without additional external confirmation and might therefore have included false positive cases. More accurate population-based incidence estimates are important to better understand the risk of developing the disease. The aim of this study was to investigate the incidence rate and patterns of different types of facial pain in the Netherlands.

Methods

The study was conducted in the Integrated Primary Care Information (IPCI)-database, a GP research database with electronic patient records of more than one million patients throughout the Netherlands. The source population of the IPCI database is representative of the general Dutch population regarding age and sex and has been proven valid for pharmacoepidemiological research. [24, 25] In the Dutch health care system, everyone is registered with one GP who acts as gatekeeper for, and receiver of information from secondary care. [26]
Electronic records contain anonymous and coded information on patient demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC)-codes) and free text narratives, referrals, clinical findings, laboratory assessments, drug prescriptions and hospitalizations. [27] Summaries of hospital discharge letters or additional information from medical specialists are entered as narratives and hard copies can be requested from the GP. To maximize completeness of electronic data, GPs participating in the IPCI-project are requested not to use additional paper-based records. The system complies with European Union guidelines on the use of medical data for research. The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03).

Source population

The source population comprised of persons with at least one year of valid history in the IPCI-database and contributing person time to the database during the study period (January 1996–September 2006). One year of valid history meant that a practice had been contributing data to the IPCI-database for at least one year and that the person had been registered with the GP for at least one year. The one year run-in period was required to have sufficient background information on all subjects and to exclude existing (prevalent) studied facial pain syndromes. Follow-up started at the beginning of the study period or on the date that one year of valid history was available, whichever date was latest. Follow-up ended upon transferring out of practice, date of last data supply by the GP, first occurrence of facial pain, death or end of the study period, whichever came first. Since additional data collection was required for validation of diagnoses, we excluded practices from the source population that could not be contacted for additional data collection. In addition, we excluded non-responding practices and patients with a diagnosis of facial pain prior to the start of follow-up (prevalent cases) from the source population.

Identification and validation of cases

Among facial pain conditions we included trigeminal neuralgia, cluster headache, postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, local facial neuralgias, glossopharyngeal neuralgia and atypical facial pain as facial pain conditions. Local facial neuralgias comprised of individual neuralgias of divisions of the trigeminal nerve such as nervus infra- or supra-orbital neuralgia. Although cluster headache and paroxysmal hemicrania are classified as trigemino-autonomic cephalalgia (TAC), they can be considered facial pain because of the possible involvement of the first trigeminal branch. [21] The case definitions were obtained from the IASP criteria since the amount of detail of our database did not allow the application of the IHS criteria. [21]

Potential cases were identified from computerized records by free text searches while taking into account diagnoses, symptoms, specific treatments, abbreviations, lay terms and spelling errors for each different type of facial pain. This was a broad, sensitive search to minimize false negative findings. We relied on a three step approach for case ascertainment. Firstly, in order to exclude false positive records and to assess the index date (date of first symptoms), all potential cases were manually evaluated by a medical doctor (JK) by reviewing the complete electronic medical records according to IASP criteria. [21] A case was defined as ‘probable’ if either a specialist had diagnosed the disease or if a patient had two or more well documented episodes in the GP-records. A case was defined as ‘possible’ if there was only one episode with a GP-diagnosis or if specific symptoms were mentioned in the patient records. A case was defined as ‘no case’ if symptoms were not specific or if the diagnosis was only mentioned as part of a differential diagnosis and no further details suggesting the facial pain condition were found in the record subsequently. Furthermore, if a more likely alternative diagnosis was present (e.g. complaints related to the cervical facet joint, C2 root, ophthalmic conditions, oto-rhino-laryngical conditions, dental status or temporomandibular joint related pains) a case was defined as no-case. All ‘probable’ cases were evaluated by a second medical doctor (MM) and discrepancies were arbitrated by a pain specialist (FH).

Secondly, for ’possible’ cases additional information was requested from the GP. This was achieved using a questionnaire, in which the criteria of the IASP were specified for each specific facial pain condition. [21] The GP was asked to confirm or reject the diagnosis while taking into account the IASP criteria and send anonymized specialist letters if available. IASP criteria were used rather than the IHS criteria to ensure consistency with criteria used in the beginning of the case validation process. All completed questionnaires and specialist letters were independently evaluated by two medical doctors (JK, MM). Based on the medical record and the GP questionnaire the ‘possible’

cases were classified as 'probable' or 'no case'. Patients with missing questionnaires were evaluated by two medical doctors (JK, MM) using all available patient data. Discrepancies were arbitrated by a pain specialist (FH).
Thirdly, to further ensure validity of diagnoses, a random sample of 250 patients of all initial 'probable' and 'possible' cases from step 1 was reviewed by a neurologist with ample experience in pain treatment (CM). In case of disagreement, a case was discussed between JK and CM until agreement was reached. Non-responding practices were excluded from the source population and could neither contribute cases nor person years to the analyses. Prevalent cases were identified in all three steps by carefully reading the entire patient materials. Date of first symptoms as mentioned in patient records and prior use of drugs for pain treatment were taken into account in this assessment.
At the end of the three case validation steps each potential case was classified as either 'case' or 'no case'. If multiple facial pain conditions occurred in a patient, the first confirmed condition was considered yielding mutually exclusive groups of facial pain. Concordance was estimated by means of observer agreement.

Analyses
Incidence rates were calculated by dividing the total number of incident cases of each disease by the total number of person years at risk in the study population. Incidence rates were calculated per type of facial pain and stratified by sex, age category and calendar year. The incidence rate per calendar year was weighted by taking a three year moving average to avoid fluctuations due to small numbers. This means that the incidence rate of one year is the average of the previous, present and next year. To investigate seasonal influences, incidence rates were also calculated by dividing the number of cases occurring in winter (21 Dec -20 March), spring (21 March – 20 June), summer (21 June – 20 Sept) and fall (21 Sept – 20 Dec) by the total accumulated person time in each season. Ninety-five percent confidence intervals (95% CI) were calculated using a Poisson distribution. [28]

Results

Case description
In the source population of 479,949 (1,898,417 PY) patients in the IPCI-database who had at least one year of valid history, 1466 potential cases were identified (appendix A). Of these, 319 were considered 'no case' after the first validation step and 742 were considered incident (180 'probable', 562 'possible'). For 481 'possible' cases additional information was provided by the GP (response rate 86%). GPs confirmed 247 patients as an incident case of facial pain, 34 were confirmed but prevalent cases of facial pain and 200 were denied as case. After additional validation steps and exclusion of prevalent cases, 368 confirmed possible and probable incident cases of facial pain remained. After validation of the random sample (250 patients) by an experienced neurologist, six further cases were excluded (4 probable, 2 possible), leaving 362 incident cases. These cases consisted of 78 possible cases of trigeminal neuralgia, 16 cases of postherpetic neuralgia in the facial area, 94 possible cases of cluster headache, 15 cases of occipital neuralgia with referred facial pain, 26 possible cases of local facial neuralgias, 14 cases of atypical facial pain, 1 case of glossopharyngeal neuralgia and 2 cases of paroxysmal hemicrania. The reduction of identified records from the automatic search via manual and external validation to our final case set is displayed in the appendix A.
The false positive rate after the first validation step (manual validation of electronic patient records without additional information from GP) was estimated to be 42.0% (266 prevalent or non cases out of 634 potential incident cases from responding practices). The positive predictive value was 57.6%

Table 1: Sex and age distribution of patients with facial pain

Diagnosis*	Cases (%)	Male (%)	Mean age at diagnosis in years, (SD)
Trigeminal neuralgia	118 (32.6)	34 (28.8)	51.5 (17.6)
Postherpetic neuralgia	36 (9.9)	19 (52.8)	68.0 (17.7)
Occipital neuralgia	30 (8.3)	13 (43.3)	54.1 (16.2)
Local neuralgia	17 (4.7)	10 (58.8)	45.2 (15.7)
Glossopharyngeal neuralgia	2 (0.6)	1 (50.0)	54.0 (5.7)
Cluster headache	117 (32.3)	71 (60.7)	41.7 (13.4)
Atypical facial pain	41 (11.3)	10 (24.4)	45.4 (19.6)
Paroxysmal hemicrania	1 (0.3)	0 (0)	24.0 (0)
Total facial pain	**362 (100)**	**158 (43.6)**	**49.1 (18.0)**

SD: Standard deviation
* Mutually exclusive groups

(362/(362+266)). The positive predictive value was 57.3% for trigeminal neuralgia, 83.7% for postherpetic neuralgia in the facial area, 49.4% for cluster headache, 61.2% for occipital neuralgia with referred facial pain, 26.6% for local facial neuralgias, 66.7% for glossopharyngeal neuralgia and 50.0% for paroxysmal hemicrania. Atypical facial pain was initially underreported and yielded more cases after completing the validation process. The observed investigator agreement in the second step was 83% while the observed agreement in the third step was 78%.
The 362 incident cases comprised 118 cases of trigeminal neuralgia, 36 cases of postherpetic neuralgia in the facial area, 117 cases of cluster headache, 30 cases of occipital neuralgia with referred facial pain, 17 cases of local facial neuralgias, 41 cases of atypical facial pain, two cases of glossopharyngeal neuralgia and one case of paroxysmal hemicrania. Overall, 44% of the cases were men, varying between 0% and 61% across the different diagnoses (Table 1). The average age at diagnosis was 49.1 years, ranging between 24.0 and 68.0 years (Table 1).

Incidence rates
After excluding non-responding practices from the source population, the total accumulated person time was 934,716 years for 193,838 persons (average 4.8 years per person). The overall incidence rate of facial pain was 38.7 [95% CI: 34.9 - 42.9] per 100,000 PY. Cluster headache and trigeminal neuralgia were the most frequent types of facial pain with an incidence rate of 12.5 [95% CI: 10.4 - 14.9] and 12.6 per 100,000 PY [95% CI: 10.5 - 15.1] respectively (Table 2 and 3). Before external validation, the incidence rate of trigeminal neuralgia was 21.7 per 100,000 PY [95% CI: 18.9 - 24.9]. For non-responding (and thus non-validated) practices this was 26.1 [23.0 - 29.5], indicating a small difference between excluded and included practices. Disease specific incidence rates were 3.9 [95% CI: 2.7 - 5.3] for postherpetic neuralgia in the facial area, 3.2 [95% CI: 2.2 - 4.5] for occipital neuralgia with referred facial pain, 1.8 [95% CI: 1.1 - 2.8] for local facial neuralgias, 0.2 [95% CI: 0.0 - 0.7] for glossopharyngeal neuralgia, 4.4 [95% CI: 3.2 - 5.9] for atypical facial pain and 0.1 [95% CI: 0.0 - 0.5] per 100,000 PY for paroxysmal hemicrania.
The incidence rates increased with age for all types of facial pain, except for cluster headache and occipital neuralgia with referred facial pain (Table 2). Cluster headache showed a peak incidence in the 4th decade for men and in the 5th decade for women after which it declined. Occipital neuralgia with referred facial pain had a peak incidence rate in the 7th decade for women (Table 2).

Table 2: Age specific incidence rates of facial pain in the general population

Diagnosis:	TGN	PHN	ON	LoN	GPN	CH	AFP	PH
<18:	0.5 [0.0-2.4]	0.0 [0.0-1.3]	0.0 [0.0-1.3]	0.0 [0.0-1.3]	0.0 [0.0-1.3]	1.6 [0.4-4.1]	2.1 [0.7-4.9]	0.0 [0.0-1.3]
18-29:	6.8 [3.5-12.0]	1.4 [0.3-4.3]	0.7 [0.1-3.2]	1.4 [0.3-4.3]	0.0 [0.0-1.7]	12.2 [7.5-18.8]	2.0 [0.6-5.4]	0.7 [0.1-3.2]
30-39:	16.5 [10.9-24.0]	0.7 [0.1-3.1]	5.3 [2.5-10.0]	3.3 [1.3-7.2]	0.0 [0.0-1.6]	25.1 [18.0-34.1]	7.3 [3.9-12.6]	0.0 [0.0-1.6]
40-49:	16.3 [10.7-23.9]	2.0 [0.6-5.5]	1.4 [0.3-4.4]	2.0 [0.6-5.5]	0.0 [0.0-1.7]	19.7 [13.5-28.0]	4.1 [1.7-8.4]	0.0 [0.0-1.7]
50-59:	17.6 [11.3-26.2]	2.4 [0.7-6.4]	5.6 [2.5-11.0]	2.4 [0.7-6.4]	1.6 [0.3-5.1]	12.8 [7.6-20.3]	6.4 [3.0-12.1]	0.0 [0.0-2.0]
60-69:	14.6 [7.9-24.7]	8.5 [3.8-16.7]	9.7 [4.6-18.3]	4.9 [1.6-11.5]	0.0 [0.0-3.0]	10.9 [5.4-19.9]	3.6 [1.0-9.7]	0.0 [0.0-3.0]
70-79:	25.6 [14.9-41.1]	11.9 [5.3-23.4]	3.4 [0.7-10.9]	0.0 [0.0-4.2]	0.0 [0.0-4.2]	5.1 [1.4-13.6]	6.8 [2.3-16.2]	0.0 [0.0-4.2]
≥80:	30.6 [15.1-55.8]	44.2 [24.7-73.4]	6.8 [1.4-21.8]	0.0 [0.0-8.4]	0.0 [0.0-8.4]	3.4 [0.3-15.8]	6.8 [1.4-21.8]	0.0 [0.0-8.4]
Total:	12.6 [10.5-15.1]	3.9 [2.7-5.3]	3.2 [2.2-4.5]	1.8 [1.1-2.8]	0.2 [0.0-0.7]	12.5 [10.4-14.9]	4.4 [3.2-5.9]	0.1 [0.0-0.5]

TGN: Trigeminal neuralgia; PHN: Postherpetic neuralgia; ON: Occipital neuralgia; LoN: Local facial neuralgia; GPN: Glossopharyngeal neuralgia; CH: Cluster headache; AFP: Atypical facial pain; PH: Paroxysmal hemicrania

The overall incidence rate was lower in men than in women (34.1 [95% CI: 29.1 - 39.7] versus 43.3 per 100,000 PY [95% CI: 37.7 - 49.6]). The sex difference was, however, not consistent across all specific types of facial pain. Female predominance was observed in trigeminal neuralgia and atypical facial pain and was present but not significant in occipital neuralgia with referred facial pain and paroxysmal hemicrania, based on overlapping confidence intervals. In cluster headache, postherpetic neuralgia in the facial area and local facial neuralgias, a trend towards male predominance could be seen (Table 3).

Time trends

All types of facial pain showed a stable incidence rate over time, except for cluster headache and trigeminal neuralgia where the incidence decreased from 13.6 in 1997 [95% CI: 5.2 - 29.8] to 10.4 [95% CI: 4.9 - 19.6] (cluster headache) and from 16.3 [95% CI: 6.8 - 33.6] to 11.1 per 100,000 PY [95% CI: 5.3 - 20.5] (trigeminal neuralgia) (Figure 1a).

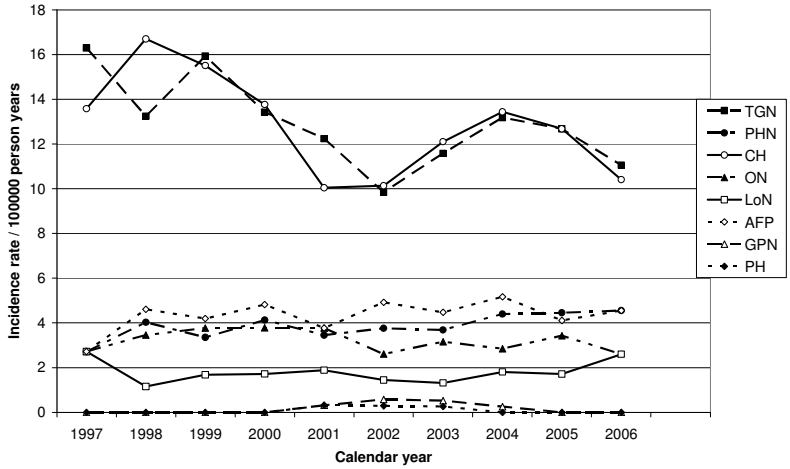
Seasonal time trend analysis showed an increasing incidence of trigeminal neuralgia between spring and winter time (Figure 1b). Cluster headache had a markedly but not significant decreased incidence rate during the summer. For the other diseases, the incidence did not demonstrate a clear seasonal pattern.

Table 3: Sex specific incidence rates of facial pain in the general population

Diagnosis	**Men**	**Women**	**Total:**
Trigeminal Neuralgia	7.3 [5.2-10.1]	17.8 [14.3-22.0]	12.6 [10.5-15.1]
Post-herpetic Neuralgia	4.1 [2.5-6.3]	3.6 [2.2-5.6]	3.9 [2.7-5.3]
Occipital Neuralgia	2.8 [1.6-4.7]	3.6 [2.2-5.6]	3.2 [2.2-4.5]
Local Neuralgia	2.2 [1.1-3.8]	1.5 [0.7-2.9]	1.8 [1.1-2.8]
Glossopharyngeal Neuralgia	0.2 [0.0-1.0]	0.2 [0.0-1.0]	0.2 [0.0-0.7]
Cluster Headache	15.3 [12.1-19.2]	9.8 [7.2-12.9]	12.5 [10.4-14.9]
Atypical Facial Pain	2.2 [1.1-3.8]	6.6 [4.6-9.2]	4.4 [3.2-5.9]
Paroxysmal Hemicrania	0.0 [0.0-0.5]	0.2 [0.0-1.0]	0.1 [0.0-0.5]
Total:	**34.1 [29.1-39.7]**	**43.3 [37.7-49.6]**	**38.7 [34.9-42.9]**

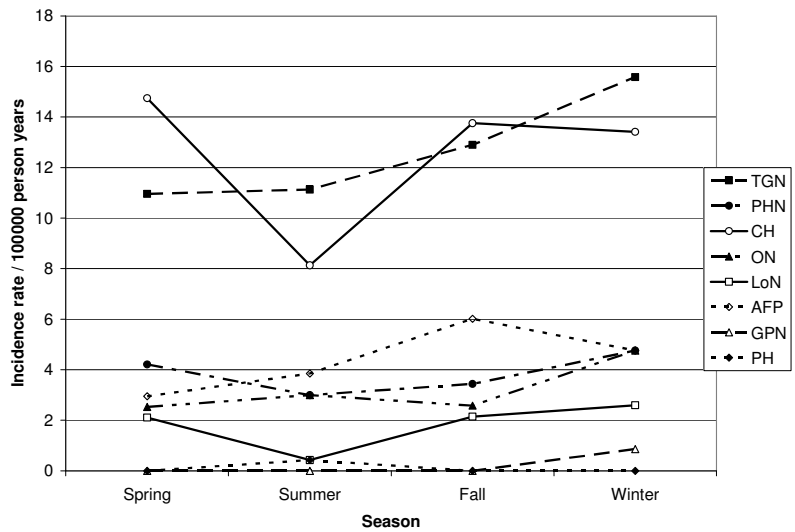
Between brackets: 95% confidence interval

Figure 1a: Incidence rate of facial pain per calendar year



TGN: Trigeminal neuralgia; PHN: Postherpetic neuralgia; ON: Occipital neuralgia; LoN: Local facial neuralgia; GPN: Glossopharyngeal neuralgia; CH: Cluster headache; AFP: Atypical facial pain; PH: Paroxysmal hemicrania; IR: incidence rate per 100,000 person years; 95% CI: 95% confidence interval

Figure 1b: Incidence rate of facial by season



TGN: Trigeminal neuralgia; PHN: Postherpetic neuralgia; ON: Occipital neuralgia; LoN: Local facial neuralgia; GPN: Glossopharyngeal neuralgia; CH: Cluster headache; AFP: Atypical facial pain; PH: Paroxysmal hemicrania; IR: incidence rate per 100,000 person years; 95% CI: 95% confidence interval

Discussion

In this study, we found an overall incidence rate of facial pain of 38.7 per 100,000 PY, which is ten times lower than the incidence of for example ischemic stroke in the Netherlands. [29] Cluster headache and trigeminal neuralgia were the most common types of facial pain each occurring in more than 12 persons per 100,000 PY. Age was an important risk factor for facial pain, whereas gender altered the risk in trigeminal neuralgia, atypical facial pain and CH, each to a different extent and direction.

Literature on the incidence of facial pain is scanty and mainly concerns trigeminal neuralgia. Previous studies that were conducted in the seventies reported an incidence of ~4,5 per 100,000 persons for trigeminal neuralgia based on hospital data. [22, 30] More recently, incidence rates of 28.9 to 26,8 per 100,000 PY were reported from the IPCI database and the General Practice Research Database. [15, 16, 23] Since not all patients are referred to a hospital by the GP, the estimates based on GP-databases may be considered a more reliable estimate and will be higher than rates based on hospital admissions. However, if rates are based on GP diagnoses without further validation (such as previous studies), the substantial false positive rate will lead to overestimation of the incidence. In our study we tried to reduce the false positive rate by extensive review of the patients. In the present study, we found a much lower incidence of 12.7 per 100,000 PY, which is a result of the stricter case definition, validation and removal of false positively identified cases. The previous studies based their estimates on an electronic medical record review without additional GP confirmation. We reported an incidence rate of 21.7 per 100,000 PY before external validation, which is close to the previously reported estimates from GP databases presented in other primary care studies without external validation. [15, 16, 23] As can be seen in appendix A, many potential cases turned out to be false positive cases after validation with the GP. This indicates a high percentage of misclassification in automatic screening of medical records for cases and illustrates the importance of cross-validation with the full medical record, certainly from a research perspective. The low predictive value may also be indicative of the difficulty of correctly diagnosing these forms of facial pain during a single GP visit. The incidence of glossopharyngeal neuralgia was previously reported to be 0.7 per 100,000 persons based on hospital data, whereas we here report an incidence rate of 0.2 per 100,000 PY [95%CI: 0.0 - 0.7]. [22, 31] The incidence of cluster headache (12.5 per 100,000 PY) is slightly higher than the previously reported 9.8 per 100,000 persons which was based on hospital data in Minnesota. [32] This difference can be explained by the fact that not all patients may be referred to secondary care. Researchers from the Mayo Clinic reported a decrease in incidence from 9.8 per 100,000 persons in 1979-1981 to 2.07 in 1989-1990. [32] In our data, a small but non-significant decrease in incidence rate of cluster headache was observed from 13.6 in 1997 to 10.4 in 2007. One previous study explained the drop in incidence rate of cluster headache by a better differentiation between different forms of facial pain at the end of the study period. [32] This explanation will, however, not be fully applicable to our study since all patients were evaluated retrospectively taking into account the current IASP criteria. Nevertheless, diagnostic skills of the GP may have evolved over time, either by more experience or better training. The (non-significant) decrease in the incidence rate of trigeminal neuralgia, although not described in literature before, might have the same explanation. For postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, local facial neuralgias of the face, atypical facial pain and paroxysmal hemicrania, no reports on incidence rates are available in literature.

The seasonal trend we described for cluster headache, exhibiting a lower rate during summer, is something that has been described before. [33] The incidence has been reported to decrease after clock resetting for daylight saving time in april and october. [34] Although this finding concerned the number of attacks per day rather than the onset, the same mechanism might play a role in onset and re-

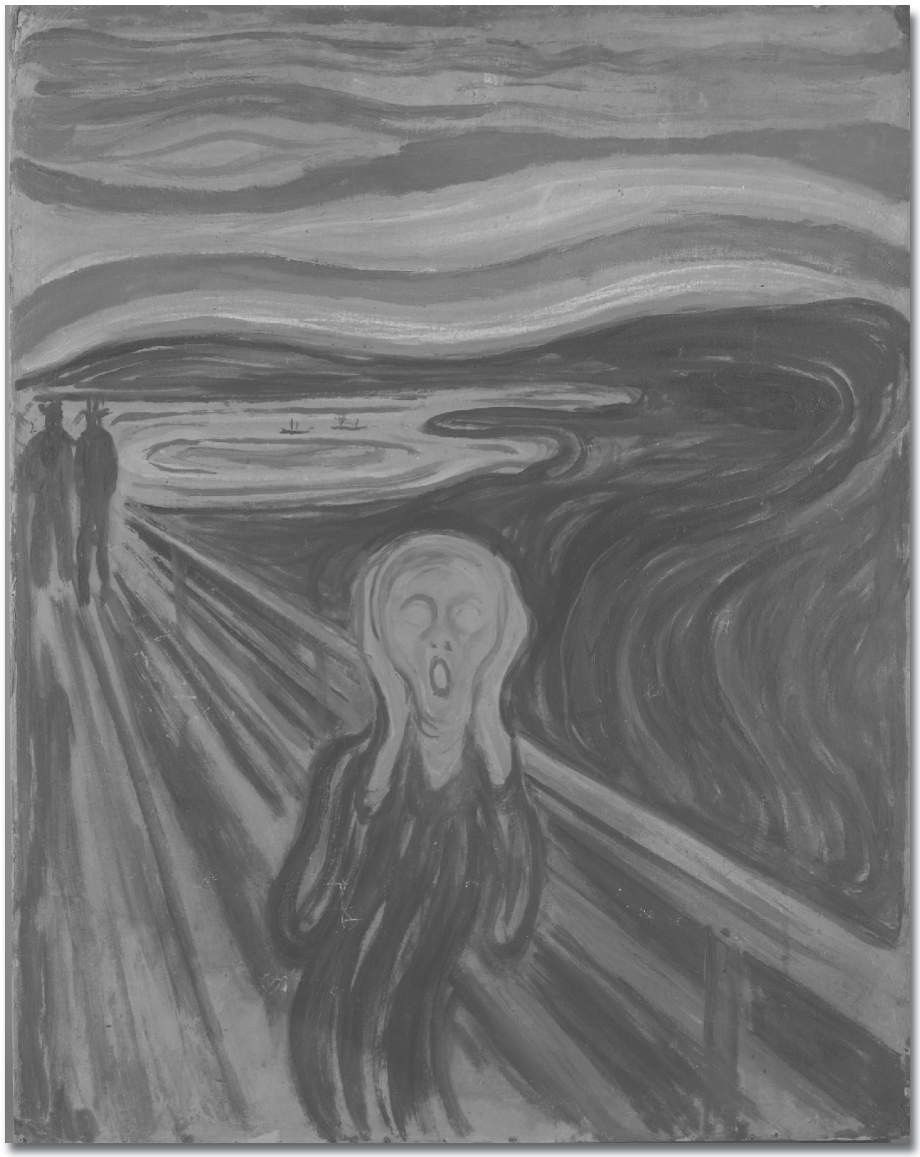
currence. [34] These findings suggest involvement of the suprachiasmatic nucleus in the hypothalamic grey area. [33] For trigeminal neuralgia we observed a linear but non significant increase in incidence from spring towards winter time. Such a seasonal trend has not been described in literature for trigeminal neuralgia so far and we cannot explain the mechanism by which this might occur. In view of the lack of statistical significance the observed seasonal trends may be spurious.

Being an observational study relying on retrospective analysis of electronic patient records, misclassification of the outcome is our main concern. False positive misclassification would lead to an overestimation of the incidence rate while the opposite also holds. To minimize the effect of false positive misclassification we employed a strict case definition and an extensive case ascertainment process in which we requested additional GP confirmation for patients for whom the electronic patient records were inconclusive. In our case definition we assumed that the patients classified as 'probable' based on the electronic patient record (first validation step) were true positive cases. We did not request additional information from the GP for these patients because of cost considerations. However, all cases were reviewed by two medical doctors who had to agree on the diagnosis. During this process, additional information requested from the GP was used to further evaluate the possible cases. The GP usually has more background information and additional information on the course of disease. Considering the false positive cases that were excluded during the case ascertainment process, the positive predictive value of the diagnosis based on review of electronic patient records was 57.6%. To further ensure validity of cases, a random sample (250 patients) of all probable and possible cases was evaluated by a neurologist. There was substantial agreement between the neurologist and previous case review (observer agreement 78%). [35] False negative misclassification might be a problem leading to a potential underestimation of the incidence rate. We tried to minimize this by using a broad, sensitive search algorithm including common symptoms, specific treatments and spelling errors. As can be seen in appendix A, the amount of identified records was extensive (111,810). We believe that our extensive search strategy and case validation procedure has reduced the number of false positive cases accurately without increasing the number of false negative cases. Therefore the presented incidence rates should be close to the actual incidence in the general population and better than previous estimates that did not apply extensive validation. Another limitation may be the types of facial pain conditions selected for this study. This selection was based on our clinical judgment and the place of these syndromes in the differential diagnosis of a GP. As a result this study describes several well known facial pain syndromes while leaving out others such as burning mouth syndrome and hemicrania continua. It would have been stronger if we had made a choice based on pathophysiology; however the unclear aetiology of almost all studied diseases makes any classification arbitrary.

In conclusion, we report the incidence of eight forms of facial pain using the Integrated Primary Care Information (IPCI) database. Facial pain is a rare condition occurring in the general population at a rate of 38.7 per 100,000 PY. Trigeminal neuralgia and cluster headache were the most common forms of facial pain studied.

Chapter 3

Aetiology



3.1

Risk factors for development and exacerbation of trigeminal neuralgia

Submitted

JSHA Koopman, MD [1], Jeanne P Dieleman, PhD [1], Frank. J Huygen, PhD [2], Miriam CJM Sturkenboom, PhD [1, 3]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: Trigeminal neuralgia is a severe form of facial pain with a paroxysmal disease course. To identify risk factor for first occurrence and exacerbations we performed a case-control and case-crossover study in a general practice research database.
Methods: Patients with trigeminal neuralgia were identified in the Integrated Primary Care Information-database with electronic medical records. We matched cases to up to ten random controls by sex, age and general practitioner's (GP) practice. Known risk factors and broad disease categories were evaluated as risk factors for first occurrence of trigeminal neuralgia. To evaluate risk factors for exacerbations we performed a case-crossover study in trigeminal neuralgia cases who had at least one exacerbation (n=34). We evaluated weather conditions, solstices, daylight saving time and treatment regimes as time-varying risk factors (triggers).
Results: We identified 114 cases with idiopathic trigeminal neuralgia and we matched them to 1032 controls. Hypertension was associated with the onset of trigeminal neuralgia (OR: 1.63; [95% CI: 1.02 - 2.60]). Furthermore, diseases of the lipid and glucose metabolism, benign neoplasm and mixed infections were associated with onset of trigeminal neuralgia. By using the case crossover design we could not identify time-varying triggers for exacerbations of trigeminal neuralgia.
Conclusions: We showed that hypertension and other comorbid conditions are associated with onset of trigeminal neuralgia. No triggers for exacerbation of trigeminal neuralgia could be identified in this dataset.

Introduction

Trigeminal neuralgia is a rare but severe form of facial pain with an estimated incidence rate of 12.6 per 100,000 person years. [2] It is a paroxysmal pain presenting with sudden, stabbing pain in one or more branches of the fifth cranial nerve. [14] Most patients who present with trigeminal neuralgia (71%) have more than one exacerbation. [36] Although the exact aetiology of primary trigeminal neuralgia is unknown, it is hypothesized to be due to neurovascular compression at the root entry zone. [37, 38] Occasionally trigeminal neuralgia develops secondary to tumors, infarctions, multiple sclerosis etc. [39] Some risk factors have been identified including hypertension, race, religion, a previous history of surgery and smoking. [17, 22, 40] Most of these findings arise from an epidemiological study that was conducted in the early eighties in a secondary care setting. [40] Attacks can be triggered by heat, cold, eating or a tactile stimulus of certain areas. [36] Identification of risk factors and triggers for development of trigeminal neuralgia and subsequent exacerbations is important to develop primary and secondary prevention strategies.
To identify risk factors for first occurrence and first exacerbation of trigeminal neuralgia, we performed a matched case-control and case-crossover study in a general practice research database

Methods

Source population
Data for this study were derived from the Integrated Primary Care Information (IPCI)-database, a longitudinal observational database, containing data from computer based medical records of general practitioners (GPs) throughout the Netherlands. In the Netherlands a GP acts as the gatekeeper for and receiver of information from secondary care. The database contains anonymized records of over one million patients in 141 practices throughout the Netherlands. The source population has a similar age and sex distribution as the general Dutch population. Participating GPs do not keep paper records to maximize completeness of the database. The records contain coded information on patient demographics, symptoms and diagnoses (coded using the International Classification for Primary Care (ICPC)-codes) as well as free text. [27, 41] It includes referrals, clinical findings, laboratory assessments, drug prescriptions with anatomical, therapeutical and chemical codes (ATC-code) as defined by the World Health Organization (WHO), dose, duration and primary ICPC-coded indication and hospitalizations. [42] Summaries of the hospital discharge letters and information from specialists are entered in a free text format and hard copies can be provided on request. The IPCI-database has been proven valid for pharmacoepidemiological research. [24, 25] The system complies with European Union guidelines on the use of medical data for research. The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03). The source population comprised of persons with at least one year of valid history in the IPCI-database and contributing person time to the database during the study period (January 1996–September 2006). The one year history period was required to have sufficient and valid background information on each study subject.

Case selection
Case selection and validation was part of a larger project on facial pain, details of which have been described elsewhere. [2] In brief, potential cases of facial pain were identified using a broad and sensitive free text search in the computerized records followed by a three step approach for case ascertainment. Firstly, in order to exclude false positive records and to assess the index date (date of first symptoms), all potential cases were manually evaluated by a medical doctor (JK) using the

complete electronic medical records and criteria of the International Association for the Study of Pain (IASP). [21] They were classified as trigeminal neuralgia, cluster headache, postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, local facial neuralgia, persistent idiopathic facial pain, glossopharyngeal neuralgia or paroxysmal hemicrania. Potential cases were divided into 'probable', 'possible' or 'improbable' depending on the number of episodes, mentioned symptoms and specialist confirmation. Improbable cases were excluded as a case. Secondly, additional information was requested from the GP for all 'possible' cases. This was achieved using a questionnaire, in which criteria from the IASP were mentioned per facial pain condition. [21] The GP was asked to confirm or reject the diagnosis. If specialist letters were present, anonymized hard copies were requested. All case information (including returned questionnaires) of all 'probable' and 'possible' cases was independently evaluated by two medical doctors. Discrepancies were arbitrated by a pain specialist (FH). Thirdly, to further ensure validity of the diagnosis, a random sample of 250 patients of all initial cases from step one was reviewed by a neurologist with ample experience in pain treatment. In case of disagreement, a case was discussed until agreement was reached. At the end of the case validation each subject was classified as either 'case' or 'no case'. Cases with a date of diagnosis before study entry (prevalent cases) were excluded from the source population. In addition, we excluded non-responding practices. For the present study we included only patients who were classified as trigeminal neuralgia. The index-date (start) was set at the date of first symptoms of trigeminal neuralgia. Cases with a secondary form of trigeminal neuralgia (p.e. tumors) were excluded from the study cohort.

Case-control study

For each new case of trigeminal neuralgia we randomly selected up to ten controls from the source population, matched on GP-practice, gender, age and calendar time (controls received the same index date as the case). As possible risk factors we investigated hypertension and smoking, which have been described as risk factors for trigeminal neuralgia before. [17, 22, 40] Hypertension was extracted from the electronic records based on ICPC-codes and elevated average blood pressure values in the year before the index date (i.e. systolic >140 mmHg or diastolic >90 mmHg). Smoking and alcohol abuse were extracted from the electronic records based on a free text search and ICPC-codes. As additional potential risk factor in the analysis we considered comorbidity (derived manually from the full electronic medical records). Comorbidity was categorized as described before for complex regional pain syndrome into mutually exclusive disease categories based on underlying aetiological pathways into anatomical, degenerative, metabolic, neoplasmatic, infectious, inflammatory, psychological and traumatic disease (appendix B). [43] Diseases were categorized into categories independently by two medical doctors. Acute and episodic diseases were only assumed present if they occurred in the year before the index date, whereas chronic diseases were accepted any time before the index date. Disease categories that were associated with the onset of trigeminal neuralgia in the univariate analysis were further divided into subgroups and individual diseases (appendix B).

Case-crossover study

To study risk factors for exacerbations of trigeminal neuralgia subsequent to the first diagnosis, we applied a case-crossover design using only patients with trigeminal neuralgia who experienced an exacerbation to avoid for confounding by stable factors. Exacerbations were defined as a specifically recorded exacerbation or start of a new drug therapy specifically for pain treatment. The index date was set at the date of first symptoms of an exacerbation which was assessed upon manual review of the full electronic medical record. Only the first exacerbation was included in the analysis. Up to four three month control periods were defined based on the duration between the onset of

trigeminal neuralgia and the first exacerbation, the three months just prior to the exacerbation date were considered the 'case' risk window. To ensure that patients had at least one control period, we excluded exacerbations which occurred less than six months after the first diagnosis of trigeminal neuralgia. Risk factors were present in a control or case period if the date of occurrence fell within the respective three month risk window. Binomial risk factors included vaccinations, infections, asthma exacerbations, changes in pain medication (stop or switch), type of pain treatment received and switch of anti-hypertensive drugs. Furthermore we evaluated daylight saving time (i.e. date of changing to summer time or winter time during three month) or solstices (i.e. the date that the earth axis is most tilted towards (summer) or away from (winter) the sun, resulting in the longest and shortest day respectively) as binomial risk factors. Weather conditions including a maximum, minimum and average temperature (°C), air humidity (%) and air pressure (millibars) during the three month period (provided by the Royal Netherlands Meteorological Institute (KNMI)) were analyzed as continuous factors. [44] As weather changes may trigger exacerbations we also considered the direction (increase or decrease) of change in temperature, humidity and pressure during the three month period.

Statistical Data analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression. Factors were included in the multivariable analysis if they were univariately associated with a $P < 0.05$. Statistical significance was assumed for two-sided p-values < 0.05. All statistical analyses were conducted using SPSS software version 15.0 (SPSS inc, Chicago, III).

Results

The source population for this study comprised 479,949 (1,898,417 PY) subjects from the IPCI-database who had at least one year of valid history in the database. Within this population 118 incident cases of trigeminal neuralgia were identified. Four cases with secondary trigeminal neuralgia were excluded leaving 114 patients for analysis.

Risk factors for first development of trigeminal neuralgia

The 114 remaining cases were matched to 1032 controls by sex, age, GP practice and calendar time. The minimum number of controls per case was one. Cases had an average age of 51.3 years (standard deviation (SD) 17.9) and were mostly female (71%) (Table 1). Hypertension was univariately associated with the development of trigeminal neuralgia (OR: 1.63; [95% CI: 1.02 - 2.60]) (Table 1). Based on data from the medical records, smoking was not associated with trigeminal neuralgia. Metabolic diseases, neoplasm and infectious diseases were associated with an increased risk of trigeminal neuralgia development (Table 1). More specifically, these associations were confined to diseases of the lipid and glucose mechanism, benign neoplasm and mixed infections. As most diseases occurred infrequently we could not validly estimate odds ratios for individual diseases. Diabetes mellitus type II and hypercholesterolemia were the most frequently occurring diseases of the lipid and glucose metabolism diseases followed by angina pectoris and other cardiovascular diseases. Benign naevi and myomas were the most common benign tumors. Bronchitis, upper airway tract infections, otitis externa and sinusitis were the most frequent infectious diseases. The study was not powered to demonstrate significant associations for the individual diseases (Table 1).

Table 1: Risk factors for first occurrence

	Cases	Controls	Univariable OR [95% CI]	Multivariable OR [95% CI]
N	114	1032		
Age (SD)	51.3 (17.9)	49.5 (17.0)	Matched	Matched
Male gender	33 (29%)	288 (28%)	Matched	Matched
Known risk factors				
Smoking	19 (17%)	115 (11%)	1.64 [0.94; 2.87]	
Alcohol abuse	0 (0%)	3 (0%)	NA	
Hypertension	63 (55%)	467 (45%)	1.63 [1.02; 2.60]	1.48 [0.91; 2.40]
Disease categories				
Anatomical	14 (12%)	83 (8%)	1.55 [0.83; 2.90]	
Degenerative	15 (13%)	96 (9%)	1.20 [0.63; 2.29]	
Metabolic	**22 (19%)**	**95 (9%)**	**2.28 [1.30; 4.02]**	
Lipid and Glucose Metabolism	**19 (17%)**	**71 (7%)**	**2.55 [1.40; 4.66]**	**2.23 [1.20; 4.13]**
Excesses or Deficiencies	2 (2%)	13 (1%)	NA	
Intoxications	0 (0%)	2 (0%)	NA	
Other	2 (2%)	13 (1%)	NA	
Neoplasmatic	**21 (18%)**	**105 (10%)**	**1.76 [1.01; 3.07]**	
Benign	**16 (14%)**	**69 (7%)**	**1.97 [1.08; 3.60]**	**1.85 [0.98; 3.47]**
Malignant	6 (5%)	39 (4%)	1.15 [0.43; 3.06]	
Infectious	**45 (39%)**	**282 (27%)**	**1.73 [1.15; 2.60]**	
Commonly Bacterial	10 (9%)	83 (8%)	1.05 [0.53; 2.10]	
Commonly Viral	9 (8%)	63 (6%)	1.37 [0.65; 2.89]	

Risk factors for exacerbation of previous trigeminal neuralgia

Of all 114 cases with primary trigeminal neuralgia, 34 patients experienced at least one exacerbation during follow-up, of whom 25 (73.5%) had six months of follow-up and were included in the case-crossover analysis. This group was on average 53.0 years old (SD: 18.2) and mostly female (56%). Almost no case received a vaccination or suffered from an asthma exacerbation their case or control risk windows (Table 2). Infections were associated with a 6-fold increased risk of exacerbations, but do to lack of power this was not significant from a statistical perspective. Daylight saving time, solstices, weather conditions and type of pain medication were not associated with exacerbations of trigeminal neuralgia.

Discussion

In this study we identified several risk factors for first occurrence of trigeminal neuralgia. In addition to hypertension, lipid and glucose metabolism disorders, benign neoplasm and infections were associated with developing trigeminal neuralgia. With the limited power available no statistically significant triggers or risk factors for subsequent exacerbations could be identified, although the point estimates suggest an effect of infections (OR=6-) and increased in air humidity (OR=2.78).
Previous studies reported a 2-fold increased risk of developing trigeminal neuralgia with hypertension. [17, 22] Our point estimate (OR: 1.63 [95% CI: 1.02 - 2.60]) is completely in line with this finding. Smoking was previously reported to be protective for the development of trigeminal neuralgia (OR for non smoking: 1.69; [95% CI: 1.22 - 2.34]). [40] We found the opposite, namely an increased risk associated with smoking (OR: 1.64; [95% CI: 0.94 - 2.87]) although this did not reach statistical significance. The previous report however used patients with cervical osteoarthritis or a ruptured cervical disc as control group. Although no definite association between smoking and osteoarthritis has been found, several reports suggest an association (negatively as well as positively). [45-48] Furthermore, smoking is strongly associated with disc degeneration. [49] If smoking is positively associated with the disease of patients chosen as control group, a negative association between trigeminal neuralgia and smoking may be erroneously found. In our study non-differential

Table 2: Risk factors for exacerbation of trigeminal neuralgia (case-crossover design)

Risk factors*	Cases	Control periods	OR [95% CI]
N	25	90	NA
Age (SD)	53 (18.2)	51.9 (17.8)	NA
Male gender	11 (44%)	43 (48%)	NA
Vaccination	2 (8%)	1 (4%)	NA
Infection	3 (12%)	4 (4%)	6.00 [0.60; 60.44]
Astma exacerbation	0 (0%)	2 (2%)	NA
Daylight saving time (winter)	7 (28%)	22 (24%)	1.24 [0.50; 3.07]
Daylight saving time (summer)	9 (36%)	22 (24%)	1.53 [0.65; 3.58]
Solstice winter	7 (28%)	24 (27%)	0.99 [0.40; 2.44]
Solstice summer	6 (24%)	21 (23%)	1.09 [0.42; 2.81]
Definite stop of pain medication	0 (0%)	3 (3%)	NA
Switch in pain medication	0 (0%)	4 (4%)	NA
Treatment received	8 (32%)	31 (34%)	0.89 [0.26; 3.08]
Stop in anti-hypertensives	1 (4%)	2 (2%)	1.19 [0.09; 14.86]
Temperature (°C)#			
Maximum temperature	25.8 (6.4)	25.1 (6.7)	1.02 [0.96; 1.08]
Minimum temperature	-3.8 (5.1)	-3.1 (5.1)	0.98 [0.90; 1.07]
Average temperature	10.1 (5)	10.4 (4.7)	0.99 [0.91; 1.08]
Increase in temperature	14 (56%)	54 (60%)	0.80 [0.34; 1.88]
Humidity			
Maximum humidity	98.9 (0.3)	98.9 (0.3)	1.39 [0.27; 7.22]
Minimum humidity	32.9 (8.9)	35.3 (10.1)	0.98 [0.94; 1.02]
Average humidity	81.2 (4.8)	82.5 (4.8)	0.96 [0.88; 1.04]
Increase in humidity	4 (16%)	6 (7%)	2.78 [0.73; 10.51]
Pressure			
Maximum pressure	1036 (4.1)	1035 (4.4)	1.04 [0.95; 1.14]
Minimum pressure	988.5 (8.2)	988.7 (7.5)	1.00 [0.94; 1.06]
Average pressure	1015.7 (2.5)	1015.3 (2.3)	1.08 [0.88; 1.33]
Increase in pressure	13 (52%)	49 (54%)	0.95 [0.37; 2.41]

* assessed during three month period before the index date
\# national figures obtained from Royal Netherlands Meteorological Institute (KNMI) in the Netherlands
NA: not assessable (if less than three cases or controls exposed)

misclassification of smoking might have occurred since we applied an automated search algorithm to extract smoking status. This may have diluted the effect of smoking towards the null. Other previously reported risk factors, including being a non-Jew (OR of 2.86), being non-tonsillectomized (OR of 1.88), being native American (OR of 1.78) and non drinking (OR of 1.22) could not be evaluated in our database. [40]

The association between trigeminal neuralgia, diseases of the lipid and glucose metabolism, benign neoplasm and infectious diseases have not been described in literature before. Primary (idiopathic) trigeminal neuralgia is hypothesized to be caused by compression of the trigeminal nerve at the root entry zone by an aberrant blood vessel (neurovascular contact). This may lead to local demyelinisation provoking development of spontaneous action potentials. [50-54] Action potentials can reflect at locations with a higher thickness, such as demyelinated locations causing resonation of the large αβ-fibers (sensitive fibres). The dorsal root reflex can then activate the αδ-fibers (pain fibres) if enough presynaptic discharge takes place. [55]

Diabetes mellitus type 2 can cause chronic inflammatory demyelinating polyneuropathy. [56-60] This process might cause central demyelinisation and thus play a role in the aetiology of trigeminal neuralgia. If idiopathic trigeminal neuralgia is indeed caused by neurovascular contact due to sacking of cerebral arteries, one could argue that cardiovascular diseases such as atherosclerosis will speed up this process. The association between benign tumors and trigeminal neuralgia is less clear. Given that trigeminal neuralgia can be secondary to benign cerebral tumors this association might reflect missed secondary forms of trigeminal neuralgia. Since we defined the index date of trigeminal neuralgia as the date of first symptoms and assessed the presence of comorbidity before the index date, it is unlikely that tumors were discovered during the diagnostic work-up for trigeminal neuralgia. Recently, the role of neuropeptides, more specifically substance P, in trigeminal neuralgia has been highlighted. [61, 62] Benign prostatic hyperplasia has been associated with elevated plasma levels of neuropeptides including substance P. [63] Although a definite conclusion is preliminary it might be an alternative hypothesis. The association we found between infections and trigeminal neuralgia might have the same aetiology. No risk factors for exacerbations have been reported in the literature although attacks may be triggered by heat or cold. [36] In our study no significant risk factors for exacerbation could be identified. Among the various meteorological factors studied (temperature, humidity and air pressure) only humidity increase was associated with a non-significant three-fold exacerbation risk increase. Vaccinations and asthma exacerbations might trigger an inflammatory response possibly leading to an increased exacerbation rate. These factors could not be evaluated due to a low prevalence in our study. We did observe a 6-fold exacerbation risk increase following infections, but the prevalence of infections was too low to reach statistical significance. Changes in preventive pain medication may affect exacerbation risk but they could not be evaluated due to low numbers. There are several alternative reasons why we could not find any significant trigger for exacerbations apart from absence of a true association. Firstly, misclassification of risk factors. Although weather conditions were very accurately measured by the Royal Netherlands Meteorological Institute, they are national averages and may not adequately represent the individual circumstances. [64] Vaccinations, asthma exacerbations and infections were manually assessed to ensure maximum validity. Any remaining misclassification might result from under recording by the GP and is likely to be non-differential which may explain lack of effect. Despite the above mentioned limitations, our findings may provide some direction into the search of the aetiology of trigeminal neuralgia, especially since very little data is actually available. Our results may point to a potential role of neuropeptides and demyelinization in the pathophysiology of trigeminal neuralgia.

3.2

Risk factors for development and exacerbation of cluster headache

Submitted

JSHA Koopman, MD [1], Frank. J Huygen, PhD [2], Jeanne P Dieleman, PhD [1], Miriam CJM Sturkenboom, PhD [1, 3]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: Cluster headache is a severe form of facial pain with a paroxysmal disease course. To identify risk factor for first occurrence and exacerbations we performed a case-control and case-crossover study in a general practice database.
Methods: Patients with cluster headache were identified in the Integrated Primary Care Information-database with electronic GP records using an extensive validation procedure. We matched cases to up to ten random controls by sex, age and GP practice. Known risk factors and broad disease categories were evaluated as risk factors for first occurrence. To evaluate risk factors for exacerbations we performed a case-crossover study in cluster headache cases undergoing at least one exacerbation. We evaluated weather conditions, solstices, daylight saving time, treatment regimes and oral contraceptive use as risk factors.
Results: We identified 115 cases with idiopathic cluster headache and we matched them to 1123 controls. Smoking was significantly associated with onset of cluster headache (OR: 2.93; [95% CI: 1.71 - 5.00]). Furthermore, diseases of the internal organs, of the musculoskeletal tract, mycoses, mixed infections, allergies, menstrual cycle and climacterium related disorders were significantly associated with first occurrence of cluster headache. We could not identify any risk factors for exacerbations of cluster headache.
Conclusions: We confirmed that smoking is a risk factor for cluster headache and we identified several potential new risk factors. The power of the study was too limited to identify risk factors for exacerbation of cluster headache.

Introduction

Cluster headache (CH) is a rare but severe type of paroxysmal headache presenting with severe, unilateral pain in the orbito-temporal region accompanied with autonomic symptoms such as lacrimation, nasal stuffiness, rhinorrhea, miosis, ptosis or scleral injection. [65] In some patients, cluster headache is secondary to other diseases such as aneurysms, arteriovenous malformations, subarachnoid cysts and dissection of the internal carotid artery. [13, 66-76] In most patients however no precipitating cause can be found. Although the exact pathway of (primary) cluster headache is unknown, neurovascular disorders in the hypothalamus are presumed to play a major role. [65, 77] Several factors have been reported to be associated with either the development of cluster headache or with exacerbations, including head trauma, smoking and alcohol consumption. [78-87] Hypertension has been suggested as a risk factor for development of severe headache but its risk for development of cluster headache has not yet been investigated. [88] Furthermore, there is a male predominance which could point at hormonal influence, but on the other hand, in females, menstrual cycle, oral contraceptive use, menopause and hormone replacement therapy have never been shown to influence the attack rate. Genetic susceptibility in cluster headache patients has also been suggested. [85, 89-91] Finally, there are some indications that daylight changes such as solstices and daylight saving time can trigger cluster headache attacks. [34] Most of the currently available studies include populations recruited from secondary care clinics. These patients may differ from those treated in primary care settings regarding characteristics severity and exacerbation frequency. [86] Valid risk estimates for development and exacerbation of cluster headache based on primary care data may help improving treatment strategies. To evaluate known risk factors for first development and to identify new risk factors we performed a population based matched case-control study using a general practitioner (GP) database. For identification and quantification of risk factors for exacerbations we performed a case-crossover study.

Methods

Source population

Data for this study were derived from the Integrated Primary Care Information (IPCI)-database, a longitudinal observational database, containing data from computer based patient records of general practitioners (GPs) throughout the Netherlands. In the Netherlands a GP acts as the gatekeeper for and receiver of information from secondary care. The database contains anonymized records of more than one million patients in 141 practices throughout the Netherlands. The source population has a similar age and sex distribution as the general Dutch population. Participating GPs do not keep paper records to maximize completeness of the database. The records contain coded information on patient demographics, symptoms and diagnoses (coded using the International Classification for Primary Care (ICPC)-codes) as well as free text. [27, 41] It includes referrals, clinical findings, laboratory assessments, drug prescriptions with anatomical, therapeutic and chemical codes (ATC-code) as defined by the World Health Organization (WHO), dose, duration and primary ICPC-coded indication and hospitalizations. [42] Summaries of the hospital discharge letters and information from specialists are entered in a free text format and hard copies can be provided on request. The IPCI-database has been proven valid for pharmacoepidemiological research. [24, 25] The system complies with European Union guidelines on the use of medical data for research. The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03). The source population comprised of persons with at least one year of valid history in the IPCI-database and contributing person time to the database during the study period (January 1996–September 2006). The one year history period was required to have sufficient background information on each study subject.

Case ascertainment

Case selection and validation was part of a larger project on facial pain, details of which have been described elsewhere. [2] In brief, potential cases of facial pain were identified using a broad and sensitive free text search in the computerized records followed by a three step approach for case ascertainment. Firstly, in order to exclude false positive records and to assess the index date (date of first symptoms), all potential cases were manually evaluated by a medical doctor (JK) using the complete electronic medical records and criteria of the International Association for the Study of Pain (IASP). [21] They were classified as trigeminal neuralgia, cluster headache, postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, local facial neuralgia, persistent idiopathic facial pain, glossopharyngeal neuralgia or paroxysmal hemicrania. Potential cases were divided into 'probable', 'possible' or 'improbable' depending on the number of episodes, mentioned symptoms and specialist confirmation. Improbable cases were excluded as a case. Secondly, additional information was requested from the GP for all 'possible' cases. This was achieved using a questionnaire, in which criteria from the IASP were mentioned per facial pain condition. [21] The GP was asked to confirm or reject the diagnosis. If specialist letters were present, anonymized hard copies were requested. All case information (including returned questionnaires) of all 'probable' and 'possible' cases was independently evaluated by two medical doctors. Discrepancies were arbitrated by a pain specialist (FH). Thirdly, to further ensure validity of the diagnosis, a random sample of 250 patients of all initial cases from step one was reviewed by a neurologist with ample experience in pain treatment. In case of disagreement, a case was discussed until agreement was reached. At the end of the case validation each case was classified as either 'case' or 'no case'. Cases with a date of diagnosis before study entry (prevalent cases) were excluded from the source population. In addition, we excluded non-responding practices. For the present study we included only patients who were classified as cluster headache. The index-date was set at the date of first symptoms of cluster headache. Furthermore, cases with a secondary form of cluster headache (p.e. multiple sclerosis) were excluded from the study cohort.

Case-control study

For each case we randomly selected up to ten controls from the source population, matched on GP-practice, sex, age and calendar time (controls received the same index date as the case). As possible risk factors we included specific risk factors of interest including head trauma, hypertension, alcohol consumption, smoking, oral contraceptive and hormonal replacement therapy use. [83, 88] Hypertension was based on ICPC-codes and average blood pressure values in the year preceding the index date. An average blood pressure higher than 140 (systolic) or 90 (diastolic) was considered as hypertension. Smoking was assessed from free text search in the medical record and ICPC-codes. Oral contraceptive use and use of hormone replacement therapy were evaluated together and based on ATC-codes in the prescription records. Furthermore we evaluated several broad disease categories as possible new risk factors for first occurrence of cluster headache. Disease categories were based on underlying aetiological mechanisms and included an anatomical, degenerative, metabolic, neoplasmatic, infectious, inflammatory, psychological and traumatic disease category (see appendix B). [43] Occurrence of chronic diseases was assessed using the entire medical history prior to the index date. Acute diseases were assessed in the year prior to index date. Firstly, the overall diseases categories were used. Disease categories which were statistically significant associated were further examined in subgroups (appendix B). These subgroups in turn were, if associated with first occurrence, divided in individual diseases.

Case-crossover study
To study risk factors for exacerbations of cluster headache subsequent to the first diagnosis, we applied a case-crossover design using only patients with cluster headache who experienced an exacerbation to avoid for confounding by stable factors. Exacerbations were defined as a specifically recorded exacerbation or start of a new drug therapy specifically for pain treatment. The index date was set at the date of first symptoms of an exacerbation which were assessed upon manual review of the full electronic medical record. Only the first exacerbation was included in the analysis. Up to four three month control periods were defined based on the duration between the onset of cluster headache and the first exacerbation, the three months just prior to the exacerbation date were considered the 'case' risk window. To ensure that patients had at least one control period, we excluded exacerbations which occurred less than six months after the first diagnosis of cluster headache. Risk factors were present in a control or case period if the date of occurrence fell within the respective three month risk window. Binomial risk factors included vaccinations, infections, asthma exacerbations, changes in pain medication (stop or switch), type of pain treatment received and switch of anti-hypertensive drugs. Furthermore we evaluated daylight saving time (i.e. date of changing to summer time or winter time during three month) or solstices (i.e. the date that the earth axis is most tilted towards (summer) or away from (winter) the sun, resulting in the longest and shortest day respectively) as binomial risk factors. Weather conditions including a maximum, minimum and average temperature (°C), air humidity (%) and air pressure (millibars) during the three month period (provided by the Royal Netherlands Meteorological Institute (KNMI)) were analyzed as continuous factors. [44] As weather changes may trigger exacerbations we also considered the direction (increase or decrease) of change in temperature, humidity and pressure during the three month period.

Statistical Data analysis
Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using conditional logistic regression. Factors were included in the multivariable analysis if they were univariately associated with a $P < 0.05$. Statistical significance was assumed for two-sided p-values < 0.05. All statistical analyses were conducted using SPSS software version 15.0 (SPSS inc, Chicago, III).

Results

The source population for this study contained 479,949 (1,898,417 PY) subjects from the IPCI-database who had at least one year of valid history in the database. Within this population 117 incident cases of cluster headache were identified. Two cases with secondary cluster headache were excluded leaving 115 cases for analysis.

Risk factors for development of cluster headache
The 115 cases of cluster headache were matched to 1123 controls by sex, age, GP practice and calendar time. The minimum number of controls per case was five. Cases had an average age of 41.7 years (standard deviation (SD) 13.4) and were mostly male (61%) (Table 1).
Of the specifically evaluated risk factors (head trauma, smoking, alcohol consumption and hypertension) only smoking was associated with cluster headache occurrence (OR: 2.93; [95% CI: 1.71 - 5.00]) (Table 1). Regarding the larger disease categories; anatomical diseases, infections, inflammatory diseases and hormonal diseases were associated with the development of cluster headache. More specifically, anatomical diseases of internal organs and the locomotoric tract, mycoses, mixed infectious diseases, allergies, menstrual cycle related diseases and climacterium related diseases were significantly associated with first cluster headache occurrence (Table 1). Most diseases oc-

Table 1: Risk factors for first occurrence

	Cases	Controls	Univariable OR [95% CI]	Multivariable OR [95% CI]
N	115	1123		
Age (SD)	41.7 (13.4)	41.2 (12.9)	Matched	Matched
Male gender	70 (61%)	686 (61%)	Matched	Matched
Known risk factors				
Smoking	**24 (21%)**	**106 (9%)**	**2.93 [1.71; 5.00]**	**2.65 [1.52; 4.62]**
Alcohol	0 (0%)	4 (0%)	NA	
Hypertension	47 (41%)	380 (34%)	1.43 [0.92; 2.23]	
Head trauma	6 (5%)	31 (3%)	1.93 [0.78; 4.77]	
Disease categories				
Anatomical	**17 (15%)**	**64 (6%)**	**3.03 [1.67; 5.50]**	
Internal Organs	**8 (7%)**	**18 (2%)**	**4.86 [2.01; 11.73]**	**4.80 [1.83; 12.64]**
Neurological Tract	4 (3%)	14 (1%)	2.91 [0.94; 8.97]	
Locomotoric Tract	**4 (3%)**	**9 (1%)**	**4.69 [1.35; 16.26]**	**3.84 [1.06; 13.96]**
Vascular Tract	1 (1%)	21 (2%)	0.45 [0.06; 3.35]	
Other	0 (0%)	3 (0%)	NA	
Degenerative	4 (3%)	41 (4%)	0.91 [0.32; 2.61]	
Metabolic	9 (8%)	64 (6%)	1.40 [0.65; 3.01]	
Neoplasmatic	6 (5%)	77 (7%)	0.70 [0.30; 1.67]	
Infectious	**45 (39%)**	**275 (24%)**	**1.96 [1.32; 2.93]**	
Commonly Bacterial	12 (10%)	75 (7%)	1.58 [0.83; 3]	
Commonly Viral	9 (8%)	64 (6%)	1.42 [0.68; 2.96]	
Mycoses	**12 (10%)**	**63 (6%)**	**1.99 [1.03; 3.81]**	**1.60 [0.79; 3.22]**
Several Types of Microorganisms Possible	**23 (20%)**	**116 (10%)**	**2.19 [1.33; 3.60]**	**1.65 [0.96; 2.83]**
Other	0 (0%)	1 (0%)	NA	
Inflammatory	**32 (28%)**	**192 (17%)**	**1.88 [1.21; 2.93]**	
Hypersensitivity	**26 (23%)**	**129 (11%)**	**2.25 [1.39; 3.63]**	
Auto-immune	4 (3%)	22 (2%)	1.80 [0.61; 5.33]	
Asthma	4 (3%)	26 (2%)	1.47 [0.50; 4.33]	
Allergy	**13 (11%)**	**50 (4%)**	**2.87 [1.48; 5.59]**	**2.15 [1.05; 4.43]**
Eczema	7 (6%)	37 (3%)	1.92 [0.82; 4.51]	
Locomotoric Tract	8 (7%)	56 (5%)	1.46 [0.65; 3.26]	
Other	5 (4%)	19 (2%)	2.58 [0.95; 7.04]	
Hormonal	**9 (8%)**	**32 (3%)**	**3.05 [1.37; 6.78]**	
Sex Hormones	**7 (6%)**	**23 (2%)**	**3.40 [1.35; 8.59]**	
Menstrual Cycle Related	**5 (4%)**	**18 (2%)**	**3.15 [1.07; 9.30]**	**2.98 [0.97; 9.14]**
Climacterium Related	**3 (3%)**	**5 (0%)**	**5.54 [1.32; 23.3]**	**3.96 [0.75; 20.86]**
Other	0 (0%)	0 (0%)	NA	
Thyroid Hormones	1 (1%)	7 (1%)	NA	
Other	1 (1%)	1 (0%)	NA	
Psychological	12 (10%)	84 (7%)	1.45 [0.75; 2.79]	
Traumatic	10 (9%)	84 (7%)	1.18 [0.60; 2.34]	
Oral contraceptives / hormone replacement therapy	23 (20%)	240 (21%)	0.87 [0.45; 1.67]	

curred infrequently. We therefore did not calculate odds ratios for individual diseases. Among these broad disease categories, gastro-esophageal reflux disease (4 cases, 4 controls) and urolithiasis (2 cases, 6 controls) were the most common diseases of the internal organs followed by diaphragmatic hernias (2 cases, 3 controls). Cervicobrachial syndrome (4 cases, 9 controls) was the most frequent locomotoric tract disease. The most common mycoses were dermatomycoses (4 cases, 12 controls), tinea pedis (4 cases, 17 controls), candida (1 case, 13 controls) and onychomycoses (1 case, 11 controls). Bronchitis (1 case, 18 controls), upper airway tract infections (1 case, 22 controls), otitis externa (4 cases, 15 controls), otitis media (1 case, 12 controls) and sinusitis (10 cases, 27 controls) were the most frequent infectious diseases. Allergic diseases consisted mainly of allergic rhinitis (8 cases, 31 controls) and allergic conjunctivitis (5 cases, 5 controls). Metro- or menorrhagie contributed mainly (2 cases, 10 controls) to menstrual cycle related diseases. Atrophic vaginitis (3 controls), climacterial symptoms (1 case, 2 controls) and osteoporosis (2 cases) contributed equally to climacterium related diseases. The multivariable analyses are shown in table 1. Although some factors do not retain statistical significance, the trend is retained.

Table 2: Risk factors for exacerbations

	Case periods	Control periods	OR [95% CI]
N	29	87	NA
Age (SD)		40.5 (12.8)	NA
Male gender		17 (59%)	NA
Vaccin	0 (0%)	1 (3%)	NA
Infection	1 (3%)	4 (5%)	NA
Astma exacerbation	0 (0%)	0 (0%)	NA
Daylight saving time (winter)	7 (24%)	22 (25%)	1.06 [0.43; 2.63]
Daylight saving time (summer)	9 (31%)	20 (23%)	1.34 [0.57; 3.11]
Solstice winter	9 (31%)	21 (24%)	1.28 [0.56; 2.95]
Solstice summer	9 (31%)	22 (25%)	1.20 [0.53; 2.73]
Definite stop of pain medication	1 (3%)	0 (0%)	NA
Switch in pain medication	0 (0%)	2 (2%)	NA
Treatment received	29 (100%)	87 (100%)	NA
Stop in anti-hypertensives	0 (0%)	3 (3%)	NA
Temperature			
Maximum temperature	25.3 (7)	25.6 (6.8)	1.00 [0.95; 1.05]
Minimum temperature	-3.2 (5.2)	-3 (5.1)	1.00 [0.93; 1.08]
Average temperature	10.3 (4.7)	10.7 (4.8)	0.99 [0.92; 1.08]
Increase in temperature	15 (52%)	49 (56%)	0.72 [0.31; 1.67]
Humidity			
Maximum humidity	99 (0.2)	99 (0.2)	1.09 [0.11; 10.77]
Minimum humidity	35.4 (11.2)	35.1 (10.8)	1.00 [0.97; 1.04]
Average humidity	82.8 (5.2)	82.5 (5.1)	1.01 [0.94; 1.09]
Increase in humidity	3 (10%)	12 (14%)	0.74 [0.19; 2.87]
Pressure			
Maximum pressure	1034 (4.5)	1034.8 (5.1)	0.96 [0.88; 1.05]
Minimum pressure	986.7 (7.2)	988.2 (7.9)	0.98 [0.93; 1.04]
Average pressure	1014.8 (2.7)	1015 (3)	0.96 [0.83; 1.11]
Increase in pressure	13 (45%)	48 (55%)	0.69 [0.30; 1.60]
Oral contraceptives / hormone replacement therapy	2 (7%)	6 (7%)	0,78 [0,1; 5,85]

* assessed during three month period before the index date
# national figures obtained from Royal Netherlands Meteorological Institute (KNMI) in the Netherlands
NA: not assessable (if less than three cases or controls exposed)

Risk factors for exacerbation

Of all 115 cases with primary cluster headache, 47 underwent at least one exacerbation during follow-up. Twenty-nine had at least six months of follow-up and were included in the case-crossover analysis. This group was 40.5 years old (SD: 12.7) on the date of first exacerbation and mostly male (59%). Almost no one received a vaccination or suffered from an infection or asthma exacerbation during follow-up (Table 2). There were no differences between case and control periods regarding daylight saving time and solstices. Characteristics of received pain medication as well as weather conditions did not differ between case and control periods. Overall, no predictors for exacerbations could be identified.

Discussion

In our study we found an association between smoking and development of cluster headache . Hypertension was not associated with cluster headache. We could not evaluate the influence of alcohol consumption as risk factor due to the low exposure prevalence. Despite the low prevalence of

smokers in our study (i.e. 21% versus 80-97% in others) we confirmed the presence of an almost three-fold increased risk of cluster headache in smokers [83, 86, 87] Most other studies included patients seen in secondary care, and their study population might not be comparable to ours. Patients seen in secondary care could be more severe patients with a higher percentage of smokers. Also these studies used questionnaires to study the prevalence of smoking. This might lead to recall bias and thus selective over- or underreporting. Since our data is collected independently of the research question, recall bias is of no major concern. A plausible explanation for the effect of smoking on cluster headache might be the influence on the cerebrovascular blood flow [33, 92] Another possible factor playing a role in smoking is a reduced level of melatonin, which is reduced in smokers and cluster headache patients. [33, 93] Hypertension has been associated with severe headache but an association with cluster headache has not been shown yet. [88] In this study we could not demonstrate an association between cluster headache and hypertension, which brings further support to the fact that it is not associated.
In a more hypothesis generating approach, that requires confirmation, we found possible new risk factors for cluster headache occurrence, including diseases of the internal organs or locomotoric tracts, mycoses, mixed type infections, allergies and menstrual cycle or climacterium related diseases. The association with these diseases may point at a role for neuropeptides in the aetiology of cluster headache. Substance P, calcitonin gene related peptide and neurokinase play an important role in the activation of the cerebral blood vessels and dura mater. [33] Substance P and other neuropeptides are mentioned in the pathogenesis of gastro-esophageal reflux disease and atopic dermatitis. [94-96] In addition, the association of smoking and irregular menstrual cycle with cluster headache suggests a role for melatonin in the pathophysiology of cluster headache. An association between irregular menstrual cycle and reduced melatonin levels was shown in a Japanese study. Both were identified as a risk factor for cluster headache in our study. [33, 97]
Previously, we demonstrated a decreasing incidence of cluster headache during the summer. [2] This might be due to weather conditions such as temperature, humidity or air pressure. These weather conditions may be associated with the onset of cluster headache which we could not further verify due to matching on calendar time, but they were not associated with an increased exacerbation frequency. None of the other investigated factors was significantly associated with an increased exacerbation rate, however, this might be due to lack of power only. Apart from power, there are several other reasons why we may not have been able to find risk factors for exacerbations of cluster headache. Firstly, the risk factors we evaluated might simply be unrelated to the exacerbation risk. Secondly, there could be misclassification of risk factors. The extent of this is probably minimal for weather conditions since these are very accurately measured by the Royal Netherlands Meteorological Institute. [64] Nevertheless, national averages may not adequately represent individual local circumstances. Vaccinations, asthma exacerbations and infections are manually validated to ensure maximum validity.

Besides the above mentioned limitations regarding the case crossover study on exacerbation triggers there are some others to be discussed for the risk factors of cluster headache onset. As we used observational data our main concern is misclassification of covariates (exposures) and disease. Misclassification of the outcome was minimized by an extensive validation process following a broad sensitive search algorithm. Misclassification of covariates is of a larger concern. Hypertension, smoking and chronic alcohol consumption were automatically assessed. Smoking and chronic alcohol consumption might be underestimated due to under recording by GPs.
Despite the described limitations, we identified some potential new risk factors for first occurrence of cluster headache. These associations, however, must be further studied in future research.

3.3

Cluster headache and head trauma: A Dutch population-based study

Submitted

JSHA Koopman, MD [1], Apinya Kunthonluxamee, MD [1,2,3], Jeanne P Dieleman, PhD [1], Frank. J Huygen, PhD [4], Miriam CJM Sturkenboom, PhD [1, 5]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Anaesthesia, Pra Nangklao Hospital , Ministry of Public Health, Nonthaburi, Thailand
[3] Dept. of Neurosurgery, Phyathai2 Hospital, Phyathai Bangkok, Thailand
[4] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[5] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: There remains controversy regarding head trauma and cluster headache (CH).
Methods: We performed a case-control study using the IPCI database to clarify the association. Incident cases were matched to ten controls by age, sex, GP and index date. Patients with a history of eye/brain surgery, cervical spine surgery or mastoidectomy were excluded. Head trauma was manually assessed and included trauma details. Multivariate conditional logistic regression was used for analyses.
Results: 117 cases were identified and matched to 1143 controls. Head trauma was present in 5% of cluster headache patients and in 3% of controls. The median latency period between head trauma and CH was 2.83 years. The ORadj was 1.93 (95%CI 0.78 - 4.75). Recent head trauma (< 2.83 years) revealed a 3.5-fold increased risk [95% CI: 1.25 - 9.96].
Conclusions: We were unable to show an association between head trauma and cluster headache but showed a 3.5-fold risk increase of CH with recent head trauma.

Introduction

Cluster headache (CH) is a rare but severe type of headache which has a prevalence varying from 59 to 279 per 100,000 and an incidence rate of 12.5 per 100,000 person years (PY). [2, 98] Most patients present with severe, unilateral pain in the orbito-temporal region accompanied with autonomic symptoms such as lacrimation, nasal stuffiness, rhinorrhea, meiosis, ptosis or scleral injection. [65] Neurovascular disorders in the hypothalamus are postulated to play a major role in the development of cluster headache. [65, 77] The exact pathway, however, is not known. [65, 77] Many factors are reported to be associated with cluster headache such as arterial dissection of the internal carotid artery, enucleation, removal of a subarachnoid cyst and smoking. [73, 75, 76, 82] Furthermore, there is a male predominance and possibly a genetic susceptibility. [85, 89] Alcohol use, and in women, menstrual cycle, oral contraceptives, pregnancy and menopause were found to trigger attacks in some although the effect of female hormones was smaller in cluster headache patients compared to migraine patients. [86, 91, 99]

Several studies addressed the risk of cluster headache after head trauma. [78-81] Two case-control studies reported a significant association between head trauma and cluster headache with a reported history of head trauma in 36% of cases versus 17% of controls. [82, 83] The latent period ranged between 6.4 and 12.7 years but longer latency periods have been described. [79, 83] Although these findings are consistent, controversy remains regarding the relation between head trauma and cluster headache. [84] The findings might be (partly) explained by behavioral or lifestyle characteristics such as alcohol and coffee consumption or cigarette smoking making cluster headache patients more prone to also have experienced head trauma. [84] Furthermore, the reported long latency periods and the usually minor traumata preceding the cluster headache occurrence make head trauma seem an implausible explanation for cluster headache. [84] To further elucidate and quantify the association between cluster headache and head trauma, we performed a population based matched case-control study using a general practitioner (GP) database.

Methods

Data for this study were derived from the Integrated Primary Care Information (IPCI)-database, a longitudinal observational database, containing data from computer based medical records of general practitioners (GPs) throughout the Netherlands. In the Netherlands a GP acts as the gatekeeper for and receiver of information from secondary care. The database contains anonymized records of more than 1 million patients in 141 practices throughout the Netherlands. The source population has a similar age and sex distribution as the general Dutch population. Participating GPs do not keep paper records to maximize completeness of the database. The records contain coded information on patient demographics, symptoms and diagnoses (coded using the International Classification for Primary Care (ICPC)-codes) as well as free text. [27, 41] It includes referrals, clinical findings, laboratory assessments, drug prescriptions with anatomical, therapeutical and chemical codes (ATC-code) as defined by the World Health Organization (WHO), dose, duration and primary ICPC-coded indication and hospitalizations. [42] Summaries of the hospital discharge letters and information from specialists are entered in a free text format and hard copies can be provided on request. The IPCI-database has been proven valid for pharmaco-epidemiological research. [24, 25] The system complies with European Union guidelines on the use of medical data for research. The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03).

Cases and controls

The source population comprised of persons with at least one year of valid history in the IPCI-database and contributing person time to the database during the study period (January 1996–September 2006). The one year history period was required to have sufficient background information on each study subject. Case selection and validation was part of a larger project facial pain, details of which have been described elsewhere. [2] In brief, potential cases of facial pain were identified using a broad and sensitive free text search in the computerized records followed by a three step approach for case ascertainment. Firstly, in order to exclude false positive records and to assess the index date (date of first symptoms), all potential cases were manually evaluated by a medical doctor (JK) using the complete electronic medical records and criteria of the International Association for the Study of Pain (IASP). [21] They were classified as trigeminal neuralgia, cluster headache, postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, local facial neuralgia, persistent idiopathic facial pain, glossopharyngeal neuralgia or paroxysmal hemicrania. Potential cases were divided into 'probable', 'possible' or 'improbable' depending on the number of episodes, mentioned symptoms and specialist confirmation. Improbable cases were excluded as a case. Secondly, additional information was requested from the GP for all 'possible' cases. This was achieved using a questionnaire, in which criteria from the IASP were mentioned per facial pain condition. [21] The GP was asked to confirm or reject the diagnosis. If specialist letters were present, anonymized hard copies were requested. All case information (including returned questionnaires) of all 'probable' and 'possible' cases was independently evaluated by two medical doctors. Discrepancies were arbitrated by a pain specialist (FH). Thirdly, to further ensure validity of the diagnosis, a random sample of 250 patients of all initial cases from step one was reviewed by a neurologist with ample experience in pain treatment. In case of disagreement, a case was discussed until agreement was reached. At the end of the case validation each case was classified as either 'case' or 'no case'. For the present study we included patients who were classified as cluster headache. The index-date was set at the date of first symptoms of cluster headache. Cases with a date of diagnosis before study entry (prevalent cases) were excluded from the source population. In addition, we excluded non-responding practices. To avoid influence of obvious known risk factors for cluster headache we also excluded from the source population subjects with mastoidectomy, brain surgery, eye surgery or cervical spine surgery from the source population. For each case we randomly selected up to ten controls from the source population, matched on GP-practice, gender, age and calendar time (controls received the same index date as the case).

Exposure and confounders

The primary exposure of interest was a history of head trauma as mentioned in the patient records. Head trauma was defined as any trauma to the supracervical area. Type of trauma (fall, traffic accident or blunt trauma) and clinical aspect such as contusion, loss of consciousness and post traumatic deficit (amnesia, visual deficit, concentration problems, lethargia or whiplash) were manually assessed. The investigator assessing exposure was blinded for the case status. The time to occurrence of cluster headache was defined as the time lapse between head trauma and index date. To evaluate the exposure window, we classified time lapse as below and above the median of cases and controls together. The prevalence on the index date of smoking, alcohol abuse, cerebro- and cardiovascular disease (stroke, transient ischemic attack, heart failure, ischemic heart disease, acute myocardial infarction, angina pectoris or peripheral artery disease), atrial fibrillation / flutter, heart failure, hypertension (i.e. diagnosis of hypertension), diabetes mellitus (i.e. diagnosis of diabetes mellitus or prescription of drugs used in diabetes (ATC-code A10)), hypercholesterolemia (i.e. diagnosis of hypercholesterolemia and/or the use of lipid modifying treatment (ATC-code C10)) and oral contraceptive use (including hormonal replacement therapy use and contraceptive use) were as-

sessed automatically from the medical journal by free text search for lay terms, ICPC-codes, medical abbreviations and ATC-codes. [41, 42]

Statistical Data analysis

Means were compared using a student's T-test, proportions by chi-square statistics. We used Mann-Whitney U for comparison of time lapse between head trauma and occurrence of cluster headache in cases and controls. The association between cluster headache and head trauma was analyzed using a conditional logistic regression analysis with absence of head trauma as the reference exposure category. Potential confounders were included into the final analysis if they were associated with cluster headache ($p \leq 0.05$) and if they changed the crude point estimate of the association between head trauma and cluster headache by 10%. We explored the effect of duration by adding duration as a dichotomous variable based on the overall median of cases and controls. To evaluate effect modification by age and gender, we repeated the analysis stratified for gender and age (below and over median). An adjusted odds ratio (OR) and 95% confidence intervals (95% CI) was derived from the final model. Point estimates were only calculated if there were more than three exposed cases. All statistical analyses were conducted using SPSS software version 15.0 (SPSS inc, Chicago, III). Statistical significance was accepted at a p-value equal to or below 0.05.

Results

The source population for this study comprised 479,949 (1,898,417 PY) subjects from the IPCI-database who had at least one year of valid history in the database. Within this population 117 incident cases of cluster headache were identified and matched to 1143 controls by sex, age, GP practice and calendar time. Cases had an average age of 41.6 years (standard deviation (SD) 13.3) and were mostly male (61%) (Table 1). Smoking and hypercholesterolemia were significantly more common in cases compared to controls ($p<0.05$). Cases slightly more often had cardiovascular disease than controls, but this was borderline statistically significant ($p=0.052$). The prevalence of diabetes mellitus, alcohol abuse, oral contraceptive use and hypertension did not differ significantly between cases and controls ($p>0.05$).

A history of head trauma preceding the index date was more common in cases (5%) than in controls (3%), but this difference was not statistically significant ($p=0.14$) (Table 2). Traffic accidents were the main cause. The median duration from head trauma until the index date (date of cluster headache in cases) was 1.57 years (inter quartile range (IQR): 0.99 – 3.08) in cases and 3.09 years (IQR: 1.61 – 5.09) in controls ($p=0.15$). Overall, it was 2.83 years (IQR): 1.37 – 4.52). In controls, the time lapse between head trauma and cluster headache ranged between 66 days to 38 years and in cases between 58 days and 4.6 years. The majority of head trauma was without contusion (99%) and loss of consciousness (99%). A minority of patients had post traumatic deficits (1%) most commonly consisting of amnesia (Table 2). The crude analyses showed a statistically non-significant association between head trauma and cluster headache (ORmatched: 1.93; [95% CI: 0.78 - 4.75], $p=0.15$) (Table 2). Numbers did not allow for analysis of associations between individual aspects of head trauma (contusion or loss of consciousness, deficit etc) and cluster headache. Analysis of head trauma with different categories of time lapse until cluster headache (latency period) did yield different odds ratios for the separate categories. Head trauma occurring before the median latency period (2.83 years) was statistically significant associated with cluster headache (ORmatched: 3.53; [95% CI: 1.25 - 9.96]) (Table 2).

Table 1: Baseline characteristics of the study population

	Cases	Controls	OR [95% CI]	P-value
Total	117	1137		
Age (SD) *	41.6 (13.3)	41.1 (12.8)	Matched	Matched
Below 37 years (%)	49 (42%)	472 (42%)		
Above 37 years (%)	68 (58%)	665 (58%)		
Male Sex (%) *	71 (61%)	694 (61%)	Matched	Matched
Comorbidity				
Diabetes Mellitus (%)	6 (5%)	30 (3%)	2.03 [0.79; 5.2]	0.12
Ischemic Cerebro-cardiovascular Disease (%) **	8 (7%)	48 (4%)	1.64 [0.73; 3.68]	0.23
Heart Failure (%)	**3 (3%)**	**3 (0.3%)**	**10.36 [1.7; 62.93]**	**0.01**
Atrial fibrillation / flutter (%)	3 (3%)	11 (1%)	2.71 [0.71; 10.4]	0.15
Hypertension (%)	10 (9%)	57 (5%)	1.79 [0.83; 3.88]	0.11
Hypercholesterolaemia (%)	**20 (17%)**	**121 (11%)**	**1.89 [1.06; 3.36]**	**0.04**
Smoking (%)	**37 (32%)**	**195 (17%)**	**2.42 [1.55; 3.78]**	**<0.01**
Alcohol abuse (%)	0 (0%)	4 (0.4%)	0.04 [0.00; 140523.38]	0.52
OC use (%)	24 (21%)	245 (22%)	0.9 [0.47; 1.72]	0.80

*Age and sex are matching factors thus showing similar distributions.
** Includes stroke, transient ischemic attack, ischemic heart disease, acute myocardial infarction, angina and peripheral artery disease.
SD: standard deviation, OR: odds ratio, CI: confidence interval, OC: oral contraceptives and hormone replacement therapy

Adding smoking, hypercholesterolemia and heart failure to the model did not change the point estimates (Table 2). Stratification for age below and above 37 (median age) suggested effect modification between age and head trauma in the risk of cluster headache. People aged under 37 had a higher risk for cluster headache after head trauma (ORadj: 3.09; [95% CI: 0.98 - 9.77] vs ORadj: 1.01; [95% CI: 0.22 - 4.71]) although the difference was not statistically significant. Stratification for gender showed that the association was slightly but non-significantly stronger in men as compared to women (ORadj: 2.16; [95% CI: 0.67 - 6.95] vs ORadj: 1.64; [95% CI: 0.32 - 8.46]).

Discussion

In this study, we did not find a statistically significant association between cluster headache and head trauma, although the risk of cluster headache tended to be increased with head trauma (ORadj: 1.92; [95% CI: 0.77 - 4.82]). Only smoking, hypercholesterolemia and heart failure were statistically significant associated with the development of cluster headache but did not affect the point estimate for head trauma. The lag time between head trauma and first occurrence of cluster headache was not statistically different between cases and controls but the variation was smaller in cases (58 days to 4.6 years) than in controls (66 days to 38 years). Recent head trauma (< 2.83 years) was significantly associated with a 3.5-fold increased risk for cluster headache. Furthermore, patients younger than 37 years seemed to have a higher risk compared to older patients. This might reflect a different or more severe head trauma in younger patients or a different mechanism of action.
Although the exact pathway underlying cluster headache remains unknown, head trauma may play a role by causing damage to relevant neurovascular structures. [33, 79] Literature describing the association between head trauma and cluster headache consists of several case reports and case-control studies. [78-83] A case control study performed in Italy revealed that head trauma was significantly associated with cluster headache (OR: 2.50; [95% CI: 1.28 - 4.88]). [82] Whereas more objective ex-

Table 2: Head trauma and the risk of cluster headache

	Cases (n=117)	Controls (n=1137)	OR * (95% CI)	OR adjusted * ^ (95% CI)
Head trauma (%)	6 (5%)	31 (3%)	1.93 [0.78; 4.75]	1.92 [0.77; 4.82]
Fall (%)	1 (1%)	12 (1%)	NA	NA
Traffic accident (%)	4 (3%)	16 (1%)	2.44 [0.81; 7.39]	2.63 [0.85; 8.14]
Blunt trauma (%)	0 (0%)	2 (0.2%)	NA	NA
Median duration until Cluster headache in years (IQR): *	1.57 (2.08)	3.09 (3.47)		
0-2.83 years	5 (83%)	14 (46%)	**3.53 [1.25; 9.96]**	**3.26 [1.13; 9.43]**
>=2.84 years	1 (17%)	17 (54%)	NA	NA
0-1.37 years	2 (33%)	7 (23%)	NA	NA
>=1.37 years	4 (67%)	24 (77%)	1.67 [0.56; 4.94]	1.68 [0.56; 5.07]
Clinical aspect: #, +				
No serious aspect reported (%)	4 (67%)	22 (73%)	1.82 [0.62; 5.35]	1.65 [0.55; 4.97]
Contusion (%)	2 (33%)	8 (26%)	NA	NA
Loss of consciousness (%)	0 (0%)	1 (3%)	NA	NA
Post traumatic deficit: #				
Non reported (%)	4 (67%)	22 (7%)	1.83 [0.62; 5.39]	1.89 [0.63; 5.65]
Amnesia (%)	1 (17%)	5 (16%)	NA	NA
Visual deficit (%)	1 (17%)	0 (0%)	NA	NA
Concentration problems (%)	0 (0%)	1 (3%)	NA	NA
Whiplash (%)	0 (0%)	2 (6%)	NA	NA
Lethargia (%)	0 (0%)	0 (0%)	NA	NA

1 missing / unknown
* 'no head trauma' as reference category; median duration calculated in total population
^ Adjusted for smoking, hypercholesterolemia and heart failure
+ One patient had both a contusion as well as loss of consciousness
The characteristics of head traumata and the duration until occurrence of cluster headache are displayed. Post traumatic deficits are also displayed.
OR: odds ratio, CI: Confidence interval, IQR: Interquartile range, NA: not assessable; there are not enough cases to calculate an association.

posure such as previous head trauma with loss of consciousness was not significantly associated with cluster headache (OR: 1.57; [95% CI: 0.63 - 4.00]) which could point at differential misclassification of head trauma without loss of consciousness. [82] Alternatively, there could be a lack of power. A major difference between this study and ours is that the prevalence of head trauma in our study population is much lower (3-5% versus 16-36%). [83] In our study there may be underreporting of head trauma because patients may omit reporting it and GPs may omit registering it. The Italian study on the other hand, may have over reporting of head trauma because of a wider definition of head trauma. Furthermore, since exposure in these studies was assessed retrospectively using questionnaires this might lead to information bias and selective misclassification of exposure. In our study all cases of head trauma were registered by the GP before the first symptoms of cluster headache occurred. Our exposure is thus less likely to be biased. The duration until cluster headache in literature ranged from 2 to 30 years which is comparable to our findings. [79] We explored the effect of longer latency periods between head trauma and cluster headache and found that head trauma with a latency periods longer than 2.83 years were not associated with cluster headache. Head trauma with a latency period of less than 2.83 years was associated.

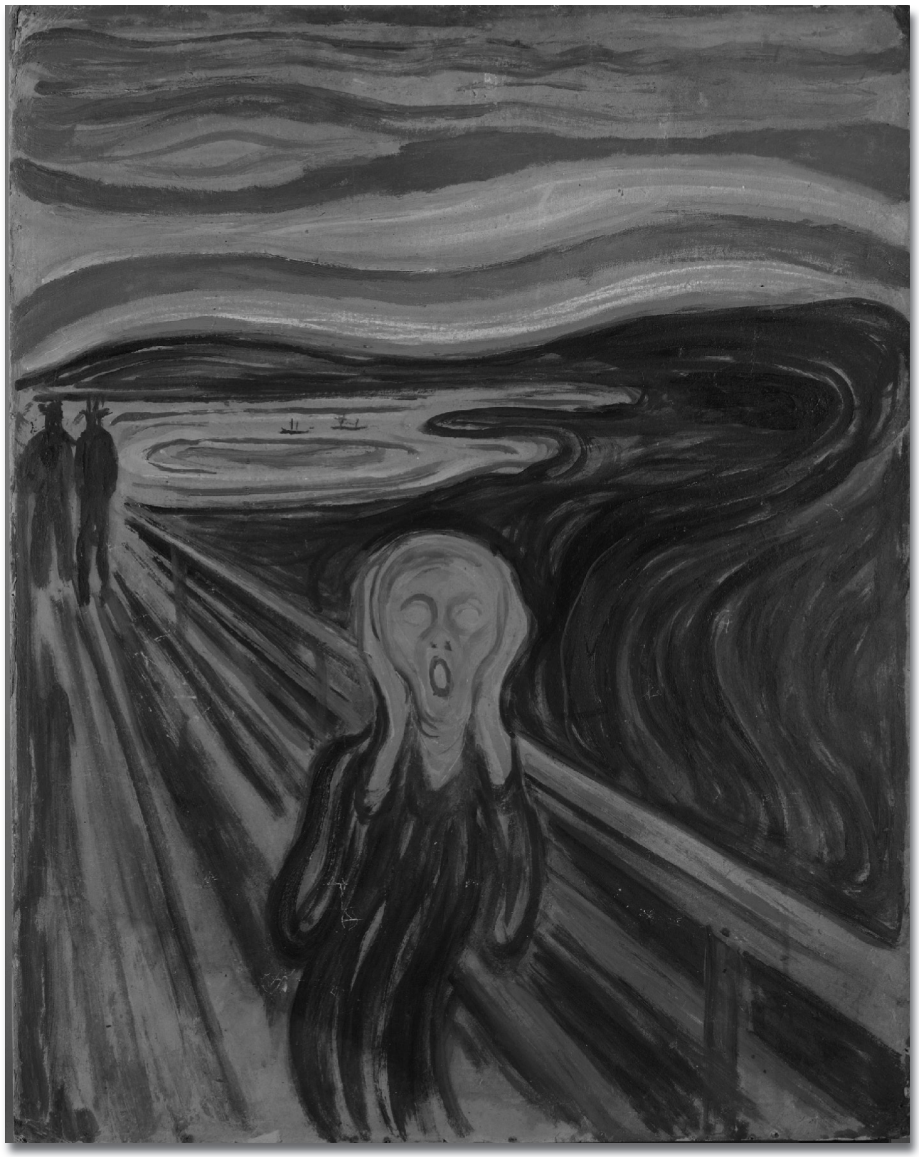
In the literature debate remains regarding the association between head trauma and cluster headache and the influence by life style factors or information bias. [79, 84] Social lifestyle such as smoking and alcohol consumption or coffee drinking are associated with cluster headache. [100] Up to 90% of cluster headache patients are smokers or former smokers and 90% are drinkers. [83] Furthermore, 84.9% of cluster headache patients were current or past drinkers while alcohol use could trigger attacks in 80% of patients. [99] We also found smoking to be more common among cases (32%) compared to controls (17%). Social lifestyle factors confounding the association between head trauma and cluster headache may also explain the higher incidence of cluster headache in men who are possibly more prone to head trauma due to more risky behavior. [2]

There might be several reasons why we could not show an association between head trauma and cluster headache. Since we performed an observational study, residual confounding may be an issue. Information bias is an important source of spurious associations, especially misclassification of outcome, exposure and confounders. To minimize false negative and false positive misclassification of the outcome, we performed a broad, sensitive search including ICPC-codes, lay terms, specific treatment and symptoms which were manually validated while blinded for exposure. Manual validation of exposure blinded for case status was done to avoid (differential) misclassification of exposure. Despite this, there might be a considerable underestimation of head trauma in our study. This is illustrated by our much lower prevalence of head trauma compared to previous studies (36% vs. 5%). [83] This difference might, in part, be explained by different exposure measurements (questionnaires vs. electronic patient records). Cases sent directly to the emergency department might be missed if no communication is sent to the general practitioner or if the communication is not digitally available. This underestimation is probably non-differential among case status, as it occurred before occurrence of cluster headache. It will therefore lead to an underestimation of the effect. Our measurement of confounders was done automatically. This might also have led to underestimation of confounder status although standardized search algorithms were used to minimize this. The effect of this on the point estimate depends on the relation of the confounder with exposure and outcome and might lead to either an underestimation or overestimation of the association. Given the prospective nature of the database and the fact that general practitioners record data irrespectively of the research question, recall bias is not an issue in our study as is selection bias. Probably the main cause of concern in our study is the lack of power. The low number of exposed cases may explain the statistically non-significant elevated risk of cluster headache after head trauma in this study. This is partly due to the low prevalence of head trauma.

Despite these limitations we report an epidemiologically sound study revealing no statistically significant association between head trauma and cluster headache. This might be caused by lack of power and underestimation of exposure. An alternative hypothesis might be that there is no association between cluster headache and head trauma. We did, however, find an 3.5-fold increased risk for cluster headache in patients with a recent head trauma. This might be due to (selective) underreporting of head trauma occurring longer ago. It might also indicate subacute mechanisms underlying the relationship between head trauma and cluster headache. Future research on this subject should thus focus on recent head trauma and should have an objective definition of head trauma.

Chapter 4

Treatment



4.1

Pharmacological treatment of neuropathic facial pain in the Dutch general population

Published in: Journal of Pain. 2010 Mar;11(3):264-72

Joseph SHA Koopman, MD [1], Frank. J Huygen, PhD [2], Jeanne P Dieleman, PhD [1], Marissa de Mos, PhD [3], Miriam CJM Sturkenboom, PhD [1, 4]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Anesthesiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[4] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: Few drugs are registered for treatment of neuropathic facial pain (NFP) and not much is known about treatment choices for NFP in daily practice.
Methods: Patients with NFP were identified in the Integrated Primary Care Information-database with longitudinal electronic general practitioner (GP) records. We described prescription patterns of pain medication following first symptoms. Off-label, off-guideline use, failure and reasons for failure were assessed. Failure was defined as treatment switch, exacerbation, adverse event or invasive treatment for NFP.
Results: Of 203 NFP cases, 160 (79%) received pharmacological pain treatment. Most patients (90%) were initially treated by a GP with anti-epileptic drugs (55%) or NSAIDs (16%) as monotherapy. The median treatment delay was 0 days (range 0-2478 days). Adverse events were experienced by 16 (10%) of patients. Sixty-two percent of first prescriptions were in adherence to guidelines and 59% were considered on-label while 34% of prescriptions were both off-label and off-guideline. Of the first therapy, 38% failed within three months. The median duration until failure was 251 days.
Conclusions: General practitioners usually are the first to treat NFP. They usually prescribe drugs licensed for NFP and according to guidelines, but the extent of off-label use is substantial. Initial treatment often failed within a short period after starting therapy.

Introduction

Neuropathic facial pain represents a group of neuropathic conditions which affect the facial area. Though relatively rare, the nature of the pain and its location cause a considerable impact on the quality of life and the daily functioning. Each year, 21.7 out of 100,000 persons are newly diagnosed with one of these diseases according to recent data. [101]

The most common type of neuropathic facial pain is trigeminal neuralgia, which presents with paroxysmal, unilateral facial pain in one or more branches of the fifth cranial nerve. Other forms include postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, local facial neuralgias and glossopharyngeal neuralgia. It is generally assumed that all forms of neuropathic facial pain share a common aetiology involving demyelinisation of cranial nerves in the root entry zone. However the cause of this demyelinisation may differ between the different types of neuralgias. [37, 102-105]

Many different pharmacological strategies have a proven efficacy but studies evaluating effectiveness in real clinical practice are scanty. The European Federation of Neurological Societies (EFNS) has developed guidelines for the pharmacological treatments of trigeminal neuralgia and postherpetic neuralgia. [106] For trigeminal neuralgia the guidelines recommend carbamazepine (level A level of evidence (LOE)) but also oxcarbazepine (level B LOE) and even baclofen and lamotrigine (level C LOE). [106] For postherpetic neuralgia they recommend tricyclic antidepressants, gabapentine, pregabalin and opioids (level A LOE). [106] Capsaicin, tramadol, topical lidocaine and valproate have a lower efficacy or are less well evaluated (level B LOE). [106] In the Netherlands only carbamazepine is officially registered for trigeminal neuralgia. Gabapentine is registered for peripheral neuralgia which might include postherpetic neuralgia in the facial area and local facial neuralgias. [107] Pregabalin is registered for peripheral and central neuropathic pain which covers all forms of neuropathic facial pain. [107] The discrepancy between guideline recommendation and formal indication may affect the treatment approach in real life practice.

Drug utilization studies evaluating real life pharmacological treatment patterns of neuropathic facial pain are scarce. The extent of off-label and off-guideline drug use in the treatment of these painful conditions has not been quantified to date. The aim of this study was to investigate drug prescription patterns in patients with trigeminal neuralgia, postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, local facial neuralgias and glossopharyngeal neuralgia in a primary care setting. Additionally, we quantified the extent of off-label and off-guideline treatment as well as treatment failure.

Methods

Setting

The study was conducted within the Integrated Primary Care Information (IPCI) database, a general practitioners (GP) research database with longitudinal electronic patient records of more than one million patients throughout the Netherlands. The patient population is representative of the general Dutch population regarding age and sex. In the Dutch health care system, everyone is registered with a GP who acts as gatekeeper for medical care. Information from secondary care is collected in the patient records of the GP. [26] Electronic records contain anonymous and coded information on patient demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC-codes) and free text terminology), referrals, clinical findings, laboratory assessments, drug prescriptions and hospitalizations. [27] Summaries of hospital discharge letters and additional information from medical specialists are entered in a free text format and hard copies

can be requested. Information on drug prescriptions comprised amount, strength, ICPC-coded indication, prescribed daily dose and Anatomical Therapeutic Chemical (ATC) classification code. [42] To maximize completeness of electronic data, GPs participating in the IPCI project are not allowed to use additional paper-based records. The system complies with European Union guidelines on the use of medical data for research and has been proven valid for pharmacoepidemiological research. [24, 25] The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03).

Source population

The source population comprised all persons contributing person time to the database during the study period (January 1996–September 2006) with at least one year of valid history in the IPCI database. Since extra data collection was required for the validation of diagnoses, we excluded practices from the source population that could not be contacted for data collection. In addition, we excluded non-responding practices. Follow-up started at the beginning of the study period or the date that one year of valid history was available and ended upon transferring out of practice, date of last data supply by the GP, death or end of the study period, whichever came first.

Cohort definition

This study was conducted in a cohort of patients with incident neuropathic facial pain, which is part of a larger project on facial pain in general. The overall study cohort for the project included all persons from the source population who were newly diagnosed with facial pain according to the criteria of the International Association for the Study of Pain (IASP). [14] Facial pain was identified from the computerized records by a sensitive search on codes and free text comprising specialist reported diagnoses and synonyms / abbreviations. Identification was followed by a three step approach for case ascertainment. Firstly, in order to exclude false positive records and to label the probability and type of diagnosis, all potential cases were manually reviewed by a medical doctor (JK) using the complete electronic medical records. Facial pain was classified as 'probable' if diagnosed by a specialist or if more than one episode of typical symptoms was recorded in the records, and as 'possible' if only one episode was recorded or specific symptoms were mentioned in the patient records. Patients for whom no typical symptoms or specialist diagnosis were recorded were classified as 'no case'. Secondly, GPs were requested to confirm the presence and type of facial pain of all 'possible' cases. In addition, they were asked to send the anonymized hard copies of all specialist letters regarding this diagnosis. All returned information was independently evaluated by two medical doctors (JK, MM) to classify cases as 'probable' or 'no case'. Discrepancies were arbitrated by a pain specialist (FH). Thirdly, to further ensure the validity of the diagnosis, a random sample of 250 patients of all initial 'probable' and 'possible' cases (742) from step one was reviewed by a neurologist with ample experience in pain treatment. In case of disagreement with the previous classification, a case was discussed. Agreement was reached in all discussed cases.

At the end of the case validation process each potential case was classified as either 'case' or 'no case' by type of facial pain. The index date was set at the date of first symptoms of facial pain. If multiple facial pain conditions occurred in a patient only the first was considered, yielding mutually exclusive groups of facial pain. Patients having a diagnosis of facial pain before the start of follow-up (prevalent cases) were excluded in order to retain a cohort of incident (newly diagnosed) patients. Within the cohort we made a distinction between neuropathic facial pain and other facial pain, because of fundamental differences in treatment approaches. For the present analysis we excluded all patients with vascular facial pain resulting in a cohort of patients with incident neuropathic facial pain.

Treatment

Drug prescribing patterns were evaluated using the electronic prescription records from the IPCI database and using full specialist letters requested from the GPs. As study drugs we included paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, anti-epileptics, anti-migraine drugs, anti-depressants, benzodiazepines, calcium-antagonists, clonidin and oxygen. The electronic prescription records were manually evaluated to assess whether a drug was prescribed for an episode of neuropathic facial pain. If no indication for drug prescription was recorded in free-text and no indication code was entered by the GP, the first indication for prescribing the drug was used for subsequent prescriptions until otherwise mentioned. If the drug was started before the index date, the drug was considered not to be prescribed for facial pain. If a prescription started after the index date and no indication could be found, it was considered as prescribed for facial pain to avoid false negative misclassification.

Legend durations were calculated by dividing the total number of prescribed tablets by the prescribed daily number of tablets to be taken. Drugs were assumed to be concomitant if they were prescribed on the same day. Episodes of use were defined as periods of continuous drug (based on full ATC-codes) use with gaps of 30 days or less. To evaluate whether the definition of the gap influenced failure parameters we conducted several sensitivity analyses in which the gap width was varied between 15 and 60 days.

Dosage regimens were classified as titration, fixed or as needed based on the prescribed regimens. The prescribed daily dosage (PDD) was expressed as the number of defined daily dosages (DDD) as defined by the World Health Organisation (WHO) taken per day. [108, 109] If no dosage regimen was recorded and no regimen was available from follow-up treatment prescribed by the GP, the PDD was calculated based on the prescribed total amount and the prescribed duration. If the prescribed duration was missing, the average dosage regimen for the same drug and prescriber (GP or specific specialist) were imputed. If this was not available, average dosage regimens were imputed not considering prescriber. Remaining empty variable were filled using guidelines and DDD. The total PDD for concomitant medications was calculated as the sum of the individual PDDs. For combination products, (e.g. paracetamol with codeine), the DDD of the main component was used (e.g. paracetamol).

Outcome parameters

Various outcome parameters were considered comprising: patient demographics, the average number of study drug prescriptions and treatment episodes per patient, proportion of treated patients and patients in follow-up, treatment delay between index date and first study drug, type of prescriber (GP or specialist), guideline adherence, on- and off-label treatment, type of pain medication, treatment regimen, failure of first therapy, reported adverse events and treatment switches during the first episode. On- or off-label use was evaluated using the summary of product characteristics (SPC) from the Medicines Evaluation Board in the Netherlands. [107] Drugs were considered on-label for a certain diagnosis if that diagnosis was specifically mentioned as an indication in the SPC or if a drug had a broader indication for pain (i.e. ‘severe pain’ or ‘chronic pain’). All other use was classified as off-label. For trigeminal neuralgia and glossopharyngeal this meant that carbamazepine, pregabalin and gabapentin were classified as on-label. For postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain and local facial neuralgias pregabalin and gabapentin were considered as on-label.

Adherence to guidelines was assessed by making use of the EFNS guidelines on treatment of trigeminal neuralgia and postherpetic neuralgia. [106] There is no EFNS guideline available for local facial neuralgias, occipital neuralgia with referred facial pain and glossopharyngeal neuralgia. As a result

guideline adherence for these subtypes was not assessed. Furthermore, these diseases were censored while calculating percentage of patients treated with on-guideline drugs.
Failure was classified through the following outcomes:
a) Specific reason stated in the records (invasive pain treatment, adverse events leading to cessation of therapy, exacerbations, suicide or dose adjustment (excluding titration regimens)).
b) No specific reason stated in the records (drug switch without mentioned cause).
Failures were attributed to the drug if it occurred during its legend duration or within the carryover period of 30 days. The date of failure was defined as the date of starting the new episode (in case of switch) or the date of recorded event, whichever came first. Sensitivity analyses were performed with a carryover period of 15, 45 and 60 days. Only failure of the first treatment episode was considered. In this analysis follow-up was right censored upon the end of the treatment episode plus 30 days (carryover period).

Analyses
Standard descriptive statistics were used to describe utilization patterns (percentages, means and medians). Median time until first treatment was calculated as the total accumulated number of days between the index date and date of first treatment divided by the number of persons receiving treatment during follow-up. Comparisons in treatment delays were tested using the Mann-Whitney U-test. Within treated persons, median time till first failure and absolute risk of failure at three months was assessed by a Kaplan-Meier analysis. In these analyses the start of follow-up was defined as the date of first treatment start. All statistical analyses were conducted using SPSS 15.0 (SPSS inc, Chicago, III).

Results

The source population comprised 479,949 persons who contributed 1,898,417 person years of total follow-up. We identified 203 incident patients with neuropathic facial pain of who 118 suffered from trigeminal neuralgia, 36 from postherpetic neuralgia in the facial area, 30 from occipital neuralgia with referred facial pain, 17 from local facial neuralgias and two from glossopharyngeal neuralgia. The mean follow-up after disease onset was 3.39 years (SD 0.18) and accumulated to a total of 688.5 person years. Patients were on average 54.3 years old (SD 18.3) at first diagnosis of neuropathic facial pain and 77 (37.9%) were male (Table 1).

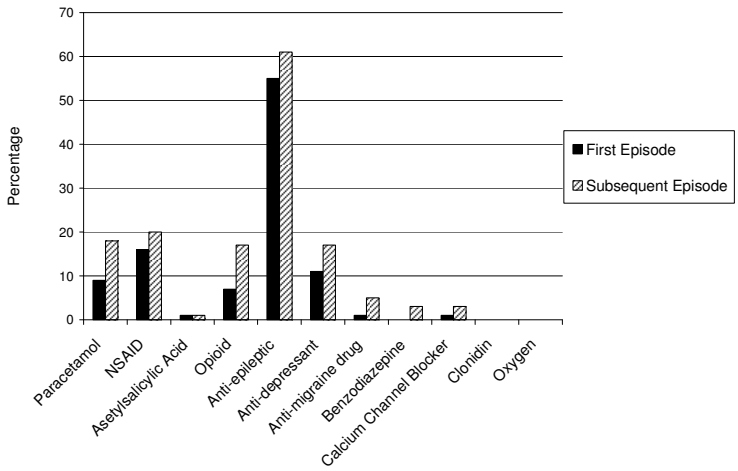
First line pharmacological treatment
During the follow-up 160 out of 203 (79%) patients with neuropathic facial pain were treated with some kind of pharmacological pain treatment, 86% of patients with trigeminal neuralgia, 78% of patients with postherpetic neuralgia in the facial area, 67% of patients with occipital neuralgia with referred facial pain, 47% of patients with local facial neuralgia and 100% of patients with patients with glossopharyngeal neuralgia.
The median delay till first treatment was 0 days (ranging 0 to 2478 days). The median treatment delay was much longer for patients with glossopharyngeal neuralgia (315 days) than for patients with postherpetic neuralgia in the facial area (0 days), although this was not statistically significant ($p=0.12$). Most patients were treated by a general practitioner (90%), the remaining part mostly by a neurologist (6%), usually with a single drug treatment (Table 1). The distribution was equal for men and women ($p > 0.05$).

Table 1: Patient and treatment characteristics and prescriber

	Neuropathic facial pain		Trigeminal Neuralgia		Postherpetic Neuralgia		Occipital Neuralgia		Local Neuralgias		Glossopharyngeal Neuralgia	
	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent episodes
Number	203		118		36		30		17		2	
Mean age (SD)	54.3 (18.3)		51.5 (17.6)		68.0 (17.7)		54.1 (16.2)		45.2 (15.7)		54.0 (5.7)	
Male sex (%)	77 (37.9%)		34 (28.8%)		19 (52.8%)		13 (43.3%)		10 (58.8%)		1 (50.0%)	
Mean number treated (SD)												
No of episodes	2.6 (3.5)		3.5 (4.0)		3.6 (3.8)		2.5 (2.2)		1.9 (1.1)		2.5 (0.7)	
1 episode	160 (79%)		102 (86%)		28 (78%)		20 (67%)		8 (47%)		2 (100%)	
2 episodes	96 (47%)		62 (53%)		18 (50%)		10 (33%)		4 (24%)		2 (100%)	
>2 episodes	59 (29%)		36 (31%)		14 (39%)		6 (20%)		2 (12%)		1 (50%)	
Number of drugs used												
Single drug	150 (94%)	77 (80%)	99 (97%)	47 (76%)	21 (75%)	14 (78%)	20 (100%)	10 (100%)	8 (100%)	4 (100%)	2 (100%)	2 (100%)
Two Drugs Combined	10 (6%)	18 (19%)	3 (3%)	14 (23%)	7 (25%)	4 (22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Three Drugs Combined	0 (0%)	1 (1%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prescriber												
General Practitioner	144 (90%)	92 (96%)	90 (88%)	59 (95%)	28 (100%)	18 (100%)	19 (95%)	10 (100%)	6 (75%)	4 (100%)	1 (50%)	1 (50%)
Anesthesiologist	1 (1%)	4 (4%)	1 (1%)	1 (2%)	0 (0%)	2 (11%)	0 (0%)	0 (0%)	0 (0%)	1 (75%)	0 (0%)	0 (0%)
Neurologist	10 (6%)	15 (16%)	8 (8%)	12 (19%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (13%)	0 (0%)	1 (50%)	2 (100%)
Other Specialist	5 (3%)	1 (1%)	3 (3%)	0 (0%)	0 (0%)	1 (6%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

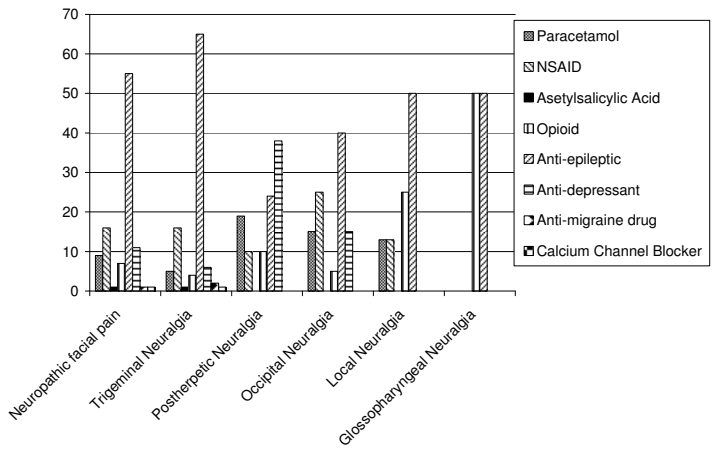
The stated numbers are number of patients meaning that, for example, 18 patients have been treated with a combination of drugs during subsequent treatment. SD = standard deviation

Figure 1: Drug use in neuropathic facial pain



Drug usage of different drugs in first and subsequent treatment episodes.
NSAID = non-steroidal anti-inflammatory drug

Figure 2: Drug usage of different drugs per disease during first treatment episode



NSAID = non-steroidal anti-inflammatory drug

Type of drugs

Anti-epileptic drugs were by far the most frequently prescribed drug for the first treatment of neuropathic facial pain (55% of patients) followed by NSAIDs (16%) (Figure 1). This distribution was observed for trigeminal and occipital neuralgia with referred facial pain but not for other types of facial neuropathic pain. Patients with postherpetic neuralgia in the facial area received mostly antidepressant (38%) and anti-epileptic drugs (24%) as first prescription (Figure 2). Patients with local or glossopharyngeal neuralgia received mostly anti-epileptic drugs or opioids as first prescription. No statistically significant differences in first line therapy were observed between sexes ($P > 0.05$). Subsequent use of anti-migraine drugs or calcium-antagonist was more common in men ($p \leq 0.05$). In total, 42 of all treatment episodes in a total of 28 people contained a combination of two drugs and two contained a combination of three drugs. The most common combination was an opioid with an anti-epileptic drug (14%), followed by an opioid or paracetamol with an anti-depressant drug (both 10%). Drugs were mostly prescribed in a fixed regimen (Table 2). Combination therapy and dosage regimen did not differ between men and women ($p > 0.05$). As needed prescribing was most common with conventional analgesics such as paracetamol (28%) and NSAIDs (23%). Titration to a fixed regimen occurred with anti-epileptics and anti-depressants. Anti-migraine drugs and opioids were rarely used but if used they were prescribed 'as needed'.

Off label/off guideline

Regarding guidelines, 61% of patients were first treated with a level A LOE drug. Fifty-nine percent received a drug with a labelled indication (42% narrow +17% broad) (Table 2). Together, 55 (34%) of patients received initial treatment with an off-label and off-guideline drug. Subsequent treatment episodes included level A LOE drugs in 58% of cases. Adherence to guidelines or registration labels did not differ between men and women for both the first and subsequent treatment ($p > 0.05$).

Treatment persistence /failure

The neuropathic facial pain patients received a total of 745 study drug prescriptions for facial pain with an average of 4.1 prescriptions (SD 6.3) per patient, 96 patients (47%) had gaps between prescriptions or failed and therefore had multiple treatment episodes during follow-up (Table 1). The average number of different treatment episodes was 2.6 (SD 3.5). The median duration of the first treatment episode was 20 days (inter-quartile range (IQR): 12-47 days). Initially a high proportion of patients received treatment however the proportion persisting on treatment stabilized to approximately 20% of patients after 6 months (Figure 3).

One hundred and four out of 160 treated patients successfully completed the first treatment episode or continued this treatment uneventfully within the first year after starting therapy. First treatment of neuropathic facial pain failed in 57 patients out of 160, of who 38 failed because of unspecified reasons and 19 because of specified reasons (adverse events, exacerbation, invasive treatment or dose adjustment). Failure rates and Kaplan Meier analysis are displayed in table 3 and figure 4. The median duration till first failure was 251 days overall (IQR: 20-353 days). Sensitivity analyses with varying carryover periods showed a range of 50-60 cases failing treatment overall with similar distributions for each individual type of neuropathic facial pain. Patients mostly switched to anti-epileptic agents or a combination of drugs (Table 4).

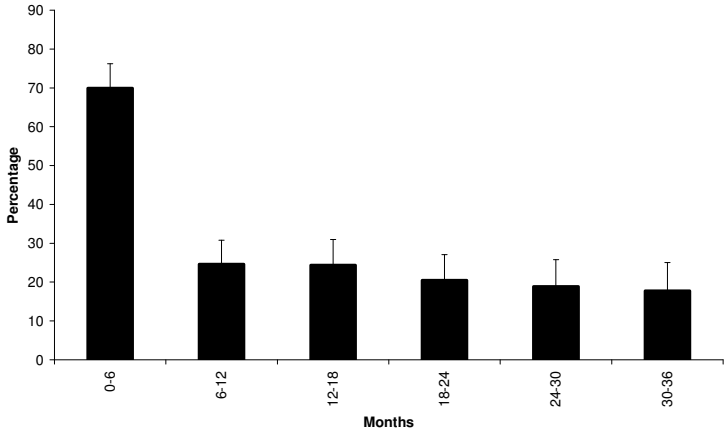
Adverse events occurred in 16 of first treatment episodes (10%) leading to a treatment switch in 9 patients (56%) (Table 2). In total 31 adverse events were recorded, including mostly central nervous system adverse events such as dizziness (2), hallucinations (3), headaches (1) or drowsiness (4) and gastro-intestinal adverse events such as elevated liver enzymes (2), nausea (1), vomiting (1) and dry mouth (1). There was no significant difference in frequency of treatment failure or the occurrence of adverse events between sexes ($p > 0.05$).

Table 2: Prescriptions classified by labelling status and guideline recommendations

	Neuropathic facial pain		Trigeminal Neuralgia		Postherpetic Neuralgia		Occipital Neuralgia		Local Neuralgias		Glossopharyngeal Neuralgia	
	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes	First Episode	Subsequent Episodes
EFNS guideline followed												
Level A	79 (61%)	56 (70%)	60 (59%)	42 (68%)	19 (68%)	14 (78%)	NA	NA	NA	NA	NA	NA
Level B	0 (0%)	1 (1%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	NA	NA	NA	NA	NA	NA
Level C	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	NA	NA	NA	NA	NA	NA
On-label treatment												
Narrow indication	67 (42%)	46 (48%)	60 (59%)	41 (66%)	4 (14%)	4 (22%)	1 (5%)	0 (0%)	1 (13%)	0 (0%)	1 (50%)	1 (50%)
Broad indication	27 (17%)	36 (38%)	10 (10%)	18 (29%)	9 (32%)	11 (61%)	4 (20%)	4 (40%)	3 (38%)	3 (75%)	1 (50%)	0 (0%)
Off-guideline and off-label	55 (34%)	59 (61%)	31 (30%)	35 (56%)	5 (18%)	10 (56%)	15 (75%)	9 (90%)	4 (50%)	3 (75%)	0 (0%)	2 (100%)
Dosage regimen												
As Needed	17 (11%)	25 (26%)	9 (9%)	16 (26%)	4 (14%)	3 (17%)	3 (15%)	4 (40%)	1 (13%)	2 (50%)	0 (0%)	0 (0%)
Titration Regimen	14 (9%)	26 (27%)	6 (6%)	21 (34%)	5 (18%)	5 (28%)	1 (5%)	0 (0%)	1 (13%)	0 (0%)	1 (50%)	0 (0%)
Fixed Dose	130 (81%)	91 (95%)	87 (85%)	57 (92%)	20 (71%)	18 (100%)	16 (80%)	10 (100%)	6 (75%)	4 (100%)	1 (50%)	2 (100%)
Adverse Events	16 (10%)	12 (13%)	11 (11%)	9 (15%)	1 (4%)	2 (11%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)

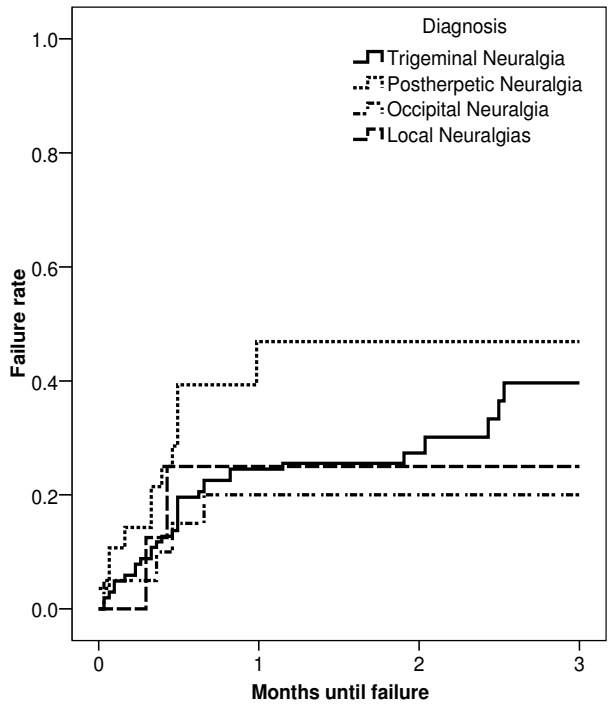
These numbers represent the 'positive' examples meaning that 'level A' = 79 represents 79 people receiving a registered drug as first treatment. Level A, B and C recommendations are assessed using the European Federation of Neurological Societies (EFNS) guidelines. SD = standard deviation. NA indicates absence of a guideline or of an event. Narrow indication means a certain diagnosis is mentioned in the summary of product characteristics. Broad indication means a drug had a broader indication for pain (i.e. 'severe pain' or 'chronic pain'). Fixed Dose indicates no as needed regimen and no titration regimen.

Figure 3: Percentage of people on-treatment during follow-up



The largest percentage of patients receives a prescription during the first six months. After that, the percentage treated drops considerably.

Figure 4: Failure rate



Most failure occurs early during treatment. Glossopharyngeal neuralgia included only two cases and has been left out.

Table 3: Failure of first treatment according to type of facial neuropathic pain

	Neuropathic Facial Pain	Trigeminal Neuralgia	Postherpetic Neuralgia	Occipital Neuralgia	Local Neuralgia	Glossopharyngeal Neuralgia
Failure (overall)	0.38 [0.28 ; 0.47]	0.40 [0.26 ; 0.53]	0.47 [0.28 ; 0.66]	0.20 [0.63 ; 0.97]	0.25 [0.00 ; 0.55]	0.50 [0.00 ; 1.00]
Failure due to unspecified causes	0.23 [0.16 ; 0.30]	0.21 [0.13 ; 0.29]	0.44 [0.25 ; 0.63]	0.05 [0.00 ; 0.15]	0.13 [0.00 ; 0.35]	0.50 [0.00 ; 1.00]
Failure due to specified causes	0.19 [0.09 ; 0.29]	0.24 [0.09 ; 0.38]	0.05 [0.00 ; 0.13]	0.16 [0.00 ; 0.32]	0.14 [0.00 ; 0.31]	NA

The stated numbers are failure rates within three months as derived from Kaplan Meier analysis. The duration until failure is the median in days with the interquartile range between square brackets. NA means such event has not taken place or a percentile has not been reached. A duration until that failure can thus not be calculated. * This includes adverse events, invasive treatment, exacerbations and suicide. # These represent the 25th percentile.

Table 4: Switching behaviour by first drug in patients with neuropathic facial pain who switched (overall)

		Second drug								
		PCM	NSAID	Opioid	Anti-epileptic	Anti-depressant	Anti-migraine	Benzodiazepine	CCB	Combination
First drug	PCM	-	2 (20%)	1 (10%)	3 (30%)	2 (20%)	-	-	-	2 (20%)
	NSAID	1 (14%)	-	2 (29%)	3 (43%)	-	1 (14%)	-	-	-
	Opioid	-	-	-	4 (100%)	-	-	-	-	-
	Anti-epileptic	1 (8%)	2 (15%)	1 (8%)	5 (38%)	1 (8%)	-	-	-	3 (23%)
	Anti-depressant	1 (25%)	-	-	2 (50%)	-	-	-	1 (25%)	-
	Anti-migraine	-	-	-	1 (50%)	1 (50%)	-	-	-	-
	CCB	-	-	-	1 (100%)	-	-	-	-	-
	Combination	3 (27%)	-	2 (18%)	2 (18%)	1 (9%)	-	1 (9%)	-	2 (18%)
	Total	6 (12%)	4 (8%)	6 (12%)	21 (40%)	5 (10%)	1 (2%)	1 (2%)	1 (2%)	7 (13%)

The first and second drug is shown for people failing and thus switching drug prescriptions. People switching within a category (p.e. anti-migraine switching to anti-migraine) indicates intraclass switching to a different drug. PCM = paracetamol, NSAID = non-steroidal anti-inflammatory drug, CCB = calcium channel blocker

Discussion

This study showed that neuropathic facial pain was often treated at short notice using either anti-epileptic drugs or NSAIDs, mostly by a general practitioner. The three months failure rate terms of switching, necessity to increase dose or necessity to stop because of reported adverse events was almost 40%. Almost 60% of prescriptions were labeled for the indication and 62% were in line with recommendations from the EFNS guidelines. One third (34%) of treatment was off-label and off-guideline. Most treatment was given during the first six months after which the number of treated patients dropped considerably. The reduction in treatment can be explained by the natural history of, for example, trigeminal and glossopharyngeal neuralgia with patients having prolonged painfree remissions for months to years. [17, 31, 110] Furthermore it could be caused by lack of effectiveness or side effects. Although it seems alarming that paracetamol and NSAIDs add up to 25% of first treatment regimens this might be due to initial misclassification of the diagnosis or latency period between onset of symptoms and definite diagnosis. On the other hand we cannot exclude the inappropriate use of medication because of lack of education or unfamiliarity with the treatment guidelines. By defining the index date as date of first symptoms instead of as date of first diagnosis, possible false negative misclassification of drug exposure is prevented with little chance of introducing false positive misclassification. [111-113] For our definition of on- and off-label, we considered drugs prescribed for central and peripheral neuropathic pain to be on-label for all studied diseases since these can be classified as central or peripheral. Drugs with 'severe pain' or 'chronic pain' listed as indication can be considered drugs for chronic pain syndromes but not specifically registered for neuropathic pain. These are therefore defined as having a broad indication. It is as of yet unclear whether being off-label or off-guideline is a prognostic factor for failure.

The results of our study on prescription behavior are comparable to previous reports although literature is not available for all types of facial pain. One previous study performed in the United Kingdom showed that the mean duration of treatment was 49.1 (Sd 84.7) days for trigeminal neuralgia and 47.3 (SD 93.4) days for postherpetic neuralgia. [16] In the UK carbamazepine was the drug of choice for trigeminal neuralgia (in line with our results) and coproxamol was the drug of choice (24.9%) in postherpetic neuralgia. [16]

A study surveying the impact of chronic pain in general on quality of life also reported similar treatment patterns. [114] Of all chronic pain patients, 2% were currently treated by a pain management specialist while one-third did not receive treatment anymore. Two-thirds were taking prescription drugs, 44% NSAIDs, 28% opioids and 18% paracetamol. [114] Management was inadequate in 40%. [114] These findings are in agreement with our results although they do not specifically concern neuropathic facial pain.

Two more recent papers reported that postherpetic neuralgia was most often treated with amitriptyline while anti-epileptics were less used.[23, 115] Our results show a slightly higher use of anti-epileptic drugs (24%) and a lower use of anti-depressants (38%). Similarly for trigeminal neuralgia we showed a higher amount of first treatments with anti-epileptics (65% vs. 55.3%) and lower percentages treated with paracetamol (5% vs. 11.3%) and amitriptyline (6% vs. 26.1%). [23]

Our study possibly has some limitations. As we used observational data our main concern is false positive and false negative misclassification of the diagnosis, outcome and the exposure. The lower incidence rate of trigeminal neuralgia in our study as compared to other studies might indicate an underestimation of the incidence rate in our study. [15, 23] To ensure maximum sensitivity and thereby avoid false negative misclassification we performed a very broad search. To maximize specificity and thereby avoid false positive misclassification we performed an extensive manual validation. Nevertheless our incidence rate might be an underestimation. This could have led to an overestimation of drug usage, adverse events and failure since patients requiring drug treatment, experi-

encing adverse events and failure of therapy are most likely to be seen by a GP and thus be identified by our search algorithm. Misclassification of exposure might occur due to over-the-counter use of paracetamol and NSAIDs leading to an underestimation of its use. Similarly, since we based our exposure date on a GP database we might miss specialist prescriptions. To ensure maximum completeness of our data, manual review of specialist letters (electronic and hard copy) was performed. The extent of omitting specialist prescriptions is probably minimal since GPs usually take responsibility for repeat prescriptions. The uncommon use of combination therapy might likewise be an underestimation of the actual use since most combinations are prescribed by specialists. In addition, we may have missed adverse events and exacerbations which were not reported by the patient or GP leading to an underestimation of our reporting of adverse events and to a possible underestimation of the failure rate. To compensate for this, we considered any switch in treatment regimen as failure of treatment assuming a switch to be due to adverse events or loss of effectiveness. Cost considerations played a minor role since all drugs studied are reimbursed in the Netherlands. Misclassification of the treatment outcome due to errors in assessing legend durations was further minimized by taking a 30 day carryover effect. After 30 days a drug was considered to be prescribed for a new exacerbation of the disease rather than a failure of treatment. Although this 30 day period is chosen arbitrarily, sensitivity analyses were performed with a 15, 45 and 60 day period showing minor chances.

This study showed that the extent of off-label treatment in neuropathic facial pain conditions is substantial but less than 50%. Patients are treated rapidly, mostly by a GP, but treatment failure occurs rapidly as well. Prescriptions that are both off-label and off-guideline occur in 34% of the first treatment episodes. Whether or not this is a prognostic factor for failure has to be determined in further studies. Reasons for off-label and off-guideline prescriptions are, although not yet clarified, of possible interest and may direct future action towards improving the effectiveness of treatment of neuropathic facial pain.

4.2

Predictors of carbamazepine treatment failure in trigeminal neuralgia

Submitted

Joseph SHA Koopman, MD [1], Jeanne P Dieleman, PhD [1], Frank. J Huygen, PhD [2], Ewout W. Steyerberg, PhD [3], Miriam CJM Sturkenboom, PhD [1,4]

Abstract

Background: Trigeminal neuralgia (TN) is a severe form of facial pain for which carbamazepine is the first choice of treatment. Carbamazepine treatment is known to fail in 1 of 3 patients. We aimed to identify predictors for failure of first carbamazepine treatment in patients with trigeminal neuralgia.
Methods: Patients with validated incident TN were identified in the Integrated Primary Care Information (IPCI)-database. TN patients were included in the analysis upon first start of carbamazepine treatment. Failure was defined as a change in treatment regimen, adverse event, surgical procedure or TN exacerbation. Age, sex, daily dose, treatment regimen, primary or symptomatic TN, delay until carbamazepine treatment, prior use of pain treatment, prescriber, alcohol abuse, smoking and comorbidity were evaluated as predictors. Predictors were analyzed using Cox regression analyses with penalized maximum likelihood model estimation. Model performance was expressed using a concordance (c) statistic.
Results: Out of 118 incident cases with TN, 76 (64%) received carbamazepine treatment (67% females. The median age was 47.5 years. The one month cumulative failure risk was 20%. Specialist prescriber, symptomatic TN, and alcohol abuse could not be evaluated due to a low prevalence. In a multivariable model, a higher dose and a long treatment delay were significant predictors of failure. The c-statistic was 0.61 [95% CI: 0.47 - 0.74] reflecting poor ability to predict failure.
Conclusions: Although we identified several predictors of the carbamazepine treatment failure, failure in individual patients cannot be predicted. Further studies are needed to identify stronger predictors for treatment failure.

Introduction

Trigeminal neuralgia is a severe form of paroxysmal facial pain presenting in one or more divisions of the fifth cranial nerve. [20] It is a rare disease with an incidence rate of 12.6 per 100.000 person years but known as seriously debilitating. [2] It can be either primary or secondary (symptomatic) to other causes such as multiple sclerosis and tumors. Although surgical interventions exist, the primary treatment is pharmacologically. [116] Recent guidelines advise carbamazepine (level A level of evidence (LOE)) and oxcarbazepine (level B LOE) as primary treatment with lamotrigine or baclofen as less well proven alternatives. [116] Only carbamazepine is specifically registered for trigeminal neuralgia in the Netherlands. [107] Other commonly used drugs for neuropathic pain such as pregabalin, gabapentin and tricyclic antidepressants have an unknown efficacy although they are frequently used in clinical practice. [101, 116] Pregabalin and gabapentin are registered for central and peripheral neuropathic pain which includes trigeminal neuralgia in the Netherlands. [107] A recent drug utilization study showed that most patients are primarily treated with anti-epileptics in the primary care setting. [101] Clinical experience and review of clinical data however revealed a high failure rate. [101] Given the seriousness of the condition, patients would benefit from an a priori estimation of the probability of treatment success. If predictors could be identified for treatment failure, this could be a first step towards more tailor-made medicine and prevention of unnecessary adverse events. Until today, predictors for failure of carbamazepine treatment in trigeminal neuralgia have not been identified.
In this hypothesis-generating study, we aimed to identify predictors for failure of first carbamazepine treatment for trigeminal neuralgia using an electronic general practitioners database.

Methods

Setting
The study was conducted within the Integrated Primary Care Information (IPCI) database, a general practitioners (GP) research database with longitudinal electronic patient records of over one million patients throughout the Netherlands. The patient population is representative of the general Dutch population regarding age and sex. In the Dutch health care system, everyone is registered with a GP who acts as gatekeeper for medical care. Information from secondary care is recorded in the patient records of the GP. [26] Electronic records contain anonymous and coded information on patient demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC-codes) and free text terminology), referrals, clinical findings, laboratory assessments, drug prescriptions and hospitalizations. [27] Summaries of hospital discharge letters and additional information from medical specialists are entered in a free text format and hard copies can be requested. Information on drug prescription comprises amount, strength, ICPC-coded indication, prescribed daily dose and Anatomical Therapeutic Chemical (ATC) classification code. [42] To maximize completeness of electronic data, GPs participating in the IPCI project do not use additional paper-based records. The system complies with European Union guidelines on the use of medical data for research and has been proven valid for pharmacoepidemiological research. [24] The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03).

Source population
The source population comprised all persons contributing person time to the IPCI database during the study period (January 1996–September 2006) and with at least one year of valid history in the database. Since extra data collection was required for the validation of diagnoses, we excluded

practices from the source population that could not be contacted for additional data collection. In addition, we excluded non-responding practices. Follow-up started at the beginning of the study period or the date that one year of valid history was available and ended upon transferring out of practice, date of last data supply by the GP, death or end of the study period, whichever came first.

Study population

Within the source population we identified all patients with an incident diagnosis of trigeminal neuralgia, as part of a wider project on facial pain using criteria of the International Association for the Study of Pain (IASP). [2, 14] Case validation is prescribed in detail elsewhere. [2] In brief, facial pain was identified from the computerized records by a sensitive search followed by a three step approach for case ascertainment. Firstly, all potential cases were manually reviewed by a medical doctor (JK) using the complete electronic medical records. Facial pain was classified as 'probable' if diagnosed by a specialist or if more than one episode of typical symptoms was recorded in the records and as 'possible' if only one episode was recorded or specific symptoms were mentioned in the patient records. Patients for whom no typical symptoms or specialist diagnosis were recorded were classified as 'no case'. Secondly, GPs were requested to confirm the presence and type of facial pain of all 'possible' cases. In addition, they were asked to send the anonymized hard copies of all specialist letters regarding this diagnosis. All returned information was independently evaluated by two medical doctors to classify cases as 'probable' or 'no case'. Thirdly, to further ensure the validity of the diagnosis, a random sample of 250 patients of all initial 'probable' and 'possible' cases (n=742) from step one was reviewed by a neurologist with ample experience in pain treatment. At the end of the case validation process each potential case was classified as either 'case' or 'no case' by type of facial pain. The index date was set at the date of first symptoms of facial pain. If multiple facial pain conditions occurred in a patient only the first was considered, yielding mutually exclusive groups of facial pain. Patients having a diagnosis of facial pain before the start of follow-up (prevalent cases) were excluded in order to retain a cohort of incident (newly diagnosed) patients. For this study we only selected patients with incident trigeminal neuralgia who were treated with carbamazepine. Follow-up started on the date of first carbamazepine prescription and ended upon treatment failure, end of first carbamazepine treatment episode (including a 30 day carryover period) or end of follow-up, whichever was earliest. Carbamazepine was chosen since it is the only drug with a level A recommendation of the American Association of Neurologists and the European Federation of Neurological Societies. [116]

Treatment

Ascertainment of carbamazepine prescribing patterns is described in detail elsewhere. [101] In brief, we manually evaluated study drugs using the electronic prescription records from the IPCI database and using full specialist letters available in the free text of the database or requested from the GPs. We manually ascertained strength, dosing regimen, titration regimen, as-needed prescription and indication of use. Legend durations were calculated by dividing the total number of prescribed tablets by the prescribed daily number of tablets to be taken. Episodes of use were defined as periods of continuous drug (based on full ATC-codes) use with gaps of 30 days or less.

Outcome

The primary outcome was treatment failure, defined as invasive pain treatment, adverse events leading to cessation or switch of treatment, exacerbations, suicide or drug switch without mentioned cause or dose adjustment (excluding titration regimes).

Treatment failure was attributed to the drug if it occurred during its legend duration or within the carryover period of 30 days. The date of failure was defined as the date of starting a new treatment

episode (in case of switch) or the date of recorded event, whichever came first. Only failure of the first treatment episode with carbamazepine was considered. For calculation of the one month failure risk, follow-up was additionally right censored upon one month after start of treatment.

Predictors

Various predictors for failure were considered, including sex, age, comorbidity, smoking, alcohol abuse, prescriber, primary or symptomatic trigeminal neuralgia, dosage and treatment regimen during the first episode of carbamazepine treatment. Furthermore, we considered as predictor for failure the delay between the date of first symptoms (index date) and start of first carbamazepine treatment and treatment naivety (i.e. naive if carbamazepine treatment was the first pain treatment received for trigeminal neuralgia). We classified comorbidity according to the number of unique ATC-codes prescribed in the year preceding (not including) the date of first symptoms (i.e. comorbidity index). This score is used as a proxy for illness using drug prescription data instead of clinical diagnoses. Predictors were assessed using automated search algorithms (alcohol abuse, smoking, comorbidity index and treatment delay) or manual validation (prescriber, dosage and treatment regime). Dosage regimens were classified as flexible (titration regimen or as-needed) or fixed (exact regimen). The dosage was defined as the dosage taken per day expressed as the prescribed daily dosage (PDD) divided by the defined daily dosages (DDD), as set by the World Health Organisation (WHO), yielding a PDD / DDD-ratio. [42] The DDD for carbamazepine is 1000 milligram per day for the main indication (anti-epileptic). Age, treatment delay, the PDD / DDD-ratio and comorbidity index were entered as continuous variables after checking for non-linearity. Non-linearity was checked by adding a quadratic term in a univariate Cox proportional hazards model. [117] Categorization might have led to a loss of power and residual confounding. [118]

Analyses

Standard descriptive statistics were used to describe baseline characteristics (percentages, means and medians) with standard deviation (SD; for means) and interquartile range (IQR; for medians). The one month failure risk was derived from Kaplan-Meier analysis in which duration till failure was right censored at three months.

The association of predictors with the outcome was analyzed using a Cox proportional hazards model. Hazard ratios (HR) and adjusted hazard ratios (HRadj) were reported with 95% confidence intervals (95% CI). The hazard ratio of age was reported per ten year band, treatment delay per week, the PDD / DDD-ratio per decimal and the comorbidity index per whole point (i.e. additional ATC-code). To be considered for the multivariable analyses, variables had to have a reasonable spread (at least 5% prevalence). A penalized maximum likelihood model was used to deal with possible overfitting. [119] We used an absolute ("Lasso") and quadratic ("Ridge") penalty to simultaneously select and shrink the coefficients and reduce potential overfitting. [120] This method has been described before as a solution to a large number of evaluated predictors compared to the number of events or cases. [121] By applying the proper penalties, which can be selected by maximizing the penalized likelihood of the model, coefficients of individual prognostic factors are reduced towards zero. Any variables with a coefficient of zero (after penalizing) were dropped out of the model. Since the penalized model does not return standard errors we did not provide 95% CI for factors in the final model but only their HR. Predictors of failure from this model were used as penalized maximum likelihood HRs (HRpml). Model performance was tested using the concordance statistic (c-statistic) with 95% CI which is equivalent to the area under the curve (AUC) for binary outcomes. [122] Statistical analyses were conducted using SPSS 15.0 (SPSS inc, Chicago, III) and R (version 2.7.12) using the packages Penalized and Design. [123]

Results

The source population comprised 479,949 persons who contributed 1,898,417 person years of total follow-up. We identified 118 incident patients with trigeminal neuralgia. The mean follow-up after disease onset was 4.21 years (SD: 2.67). In total, 76 patients with trigeminal neuralgia used carbamazepine. Patients were on average 50 years old (SD: 18) at first diagnosis of trigeminal neuralgia and 25 (33%) were male (Table 1). Three people had secondary trigeminal neuralgia.
The median delay was 0.9 weeks (IQR: 0.0 – 10.8 weeks) until the first treatment with carbamazepine. Patients failing treatment had a significantly longer treatment delay than patients not failing their first carbamazepine treatment ($p = 0.02$). Carbamazepine was mostly initiated by a GP (86%) and as fixed dosage regimes (87%). Dosages were usually lower than the DDD as defined by the WHO for treatment of epilepsy (PDD / DDD-ratio 0.3, IQR 0.2-0.4), but it did not differ significantly between people failing and not failing treatment ($p = 0.47$). People were, on average, healthy with a median comorbidity index of 2.0 (IQR: 1.0-7.0). Patients failing were equally healthy as non-failing patients as proxied by the comorbidity index ($p = 0.17$). Most patients received carbamazepine as first treatment (78%) while a minority received it subsequent to other treatment (22%). Failure risk was equal for treatment naïve and treatment experience patients. The one month failure risk was 20% [95% CI: 10% - 30%] (Table 1). Failure occurred after a median duration of 25.0 days (IQR: 12.0-70.0 days).
Alcohol abuse, primary or symptomatic trigeminal neuralgia and prescriber could not be evaluated because of too little spread (prevalence <5%). Univariately, longer delay (weeks) till first carbamazepine treatment (HR: 1.01; [95% CI: 1.00 - 1.01]) and a higher PDD / DDD – ratio (HR: 1.3; [95% CI: 1.0 - 1.7]) were associated with failure ($p < 0.05$). In the multivariate Cox proportional hazard model, delay till first carbamazepine treatment (HRadj: 1.01; [95% CI: 1.00 - 1.01]) was significantly associated with treatment failure (Table 1). PDD / DDD ratio was no longer statistically significant but the point estimate remained stable.

Penalized model
After shrinkage using the penalized model, two variables were retained: delay until carbamazepine treatment and PDD / DDD-ratio. Longer delay until carbamazepine treatment (HRpml: 1.01) and higher PDD / DDD – ratio (HRpml: 1.16) were associated with an increased risk of failure. Since the penalized model does not provide standard errors we cannot report 95% CIs around the HRpml. Overall, the c-statistic of the final model was 0.61 [95% CI: 0.47 - 0.74], which is poor. [117]

Discussion

In this study we identified several predictors for failure of the first carbamazepine treatment for trigeminal neuralgia. In a penalized multivariable model we found longer delay until carbamazepine treatment and a higher daily dosage to be most predictive of the risk of failure of carbamazepine treatment. Overall, the model with these two variables performed poorly with a c-statistic of 0.61. [117]
The finding that a higher dosage leads to increased failure might seem contra-intuitively but this may be explained by confounding by severity. More severe trigeminal neuralgia might be treated with higher dosages and have a higher a priori failure risk. Alternatively, the increased risk may be caused by an increased risk of adverse effects at higher dosages.
The one month failure rate was 20% which is in line with the 70 to 89% success rate of carbamazepine for treatment of trigeminal neuralgia reported elsewhere. [124] Other studies had however

Table 1: Baseline characteristics of patients with incidence trigeminal neuralgia, and absolute and relative carbamazepine treatment failure risk

Characteristic	n	Events	1-month risk (95% CI)	Univariable HR	Multivariable HR
Sex					
Male	25	8	0.1 [0.0; 0.2]	Ref	Ref
Female	51	15	0.2 [0.1; 0.3]	0.8 [0.3; 2.0]	0.9 [0.3; 2.4]
Age* [#]	47.5 (36.0 - 63.8)	56.0 (37.0 - 64.0)		1.0 [0.8; 1.2]	1.0 [0.7; 1.3]
Prescriber					
General practitioner	65	19	0.2 [0.1; 0.3]	Ref	Ref
Anaesthesiologist	1	0	NA	NA	NA
Neurologist	9	4	0.2 [0.0; 0.5]	NA	NA
Other	1	0	NA	NA	NA
Dosage regimen					
Flexible	10	5	0.3 [0.0; 0.6]	Ref	Ref
Fixed	66	18	0.2 [0.1; 0.3]	0.4 [0.2; 1.2]	0.4 [0.1; 1.2]
Alcohol abuse					
No	76	23	1.0 [0.9; 1.1]	NA	NA
Yes	0	0	NA	NA	NA
Smoking					
No	58	17	0.2 [0.1; 0.3]	Ref	Ref
Yes	18	6	0.2 [0.0; 0.3]	0.7 [0.3; 2.0]	0.8 [0.2; 2.6]
Treatment Delay (weeks)*	0.9 (0.0 - 10.8)	7.7 (0.0 - 59.0)	-	**1.01 [1.00; 1.01]**	**1.01 [1.00; 1.01]**
PDD / DDD – ratio* [%]	0.3 (0.2 - 0.4)	0.3 (0.2 - 0.4)		**1.3 [1.0; 1.7]**	1.3 [0.9; 1.8]
Unique ATC-codes* [&]	2.0 (1.0 - 7.0)	3.0 (2.0 - 8.0)		1.00 [0.89; 1.13]	1.0 [0.9; 1.1]
Treatment naive					
Yes	59	16	0.2 [0.1; 0.2]	Ref	Ref
No	17	7	0.3 [0.1; 0.5]	1.9 [0.7; 4.7]	1.2 [0.4; 3.5]
Total	76	23	0.2 [0.1; 0.3]	-	-

This table displays the total number of treated patients per baseline characteristic (n) and the number of failures per category (events). Also. the one month failure risks (from Kaplan-Meier analysis) are displayed and the univariate and multivariate hazards ratios.

* Age. treatment delay until first carbamazepine treatment. the PDD / DDD-ratio and the number of unique ATC-codes in the year preceding the index date are entered as a continuous variable. The median is displayed with the interquartile range between brackets in total (n) and cases (events).

[#] The HR of age displayed is per ten years.

[%] The HR of the PDD / DDD-ratio displayed is per tenth of a point.

[&] The HR of the number of unique ATC-codes is per point.

PDD / DDD – ratio: prescribed daily dosage (PDD) divided by the defined daily dosage (DDD). The DDD indicates a standardized dose as defined by the World Health Organization.

95% CI: 95% confidence intervals.

HR: hazard ratio as derived from a cox proportional hazard model.

NA: not assessable. It usually indicates there are not enough cases to do a calculation.

a longer follow-up and therefore probably have a much lower failure rate at one month than our study. The difference in failure rate can have several explanations. For one, patients in our study received a median dosage of 300 mg compared to up to 2400 mg in clinical trials. [124] Furthermore, there were methodological issues such as the lack of a washout period and allowing of concurrent interventions. [125-127] Also, since these studies were randomized clinical trials the patient population might have been more homogenous and more closely supervised than in our study. All these issues lead to incomparable results. To our knowledge, no reports exist regarding the identification of predictors of failure of carbamazepine treatment for trigeminal neuralgia in routine clinical practice. Some studies report predictors for carbamazepine failure in epilepsy patients but most of the predictors in that setting are not applicable to our situation. [128]

Our study has several limitations. As we used observational data our main concern is misclassification of the exposure and outcome. False negative misclassification of carbamazepine use might occur because we miss some specialist prescriptions. To ensure maximum completeness of our data, manual review of specialist letters (electronic and hard copy) was performed. The extent of omitting specialist prescriptions is probably minimal since GPs usually take responsibility for repeat prescriptions. In addition, we may have missed adverse events and exacerbations which were not reported by the patient or GP leading to an underestimation of our reporting of adverse events and to a possible underestimation of the failure rate. To compensate for this, we considered any switch in treatment regimen within 30 days of cessation of the last prescription as failure of treatment assuming a switch to be due to adverse events or lack of effectiveness. This is an assumption which may not fully compensate for the underestimation of treatment failure or which may even lead to an overestimation of the outcome. Misclassification of our predictors is another limitation. There is probably no or little misclassification of sex, age, prescriber, dosage and treatment regimen, treatment delay and treatment naivety. Since comorbidity is ascertained based on drug use our study probably underestimates the presence of comorbidity although this is likely to be non-differential. The presence of smoking, alcohol abuse and primary or symptomatic trigeminal neuralgia might be severely underestimated in our study. False negative misclassification of these predictors will most likely lead to an underestimation of their effect and residual confounding. This might cause certain factors to drop out of our model while they might be important predictors for treatment failure. The main limitation of this study is the small sample size. This leads to optimistic estimations of model performance and limited power for selection of important predictors. Using a p-value of 0.05 for predictor selection would have been too strict. We therefore used a penalized model to shrink the coefficients and reduce the optimism of the model and performed bootstrapping for validation.

Despite these limitations, this study tried to identify potential predictors for failure of first carbamazepine treatment for trigeminal neuralgia. Given the hypothesis generating nature of this study and the poor predictability of our model, no clinical judgment can yet be made based on our results. Further studies should be performed in a larger dataset to identify stronger predictors and ideally include severity at baseline in addition to dose and dosing regimen. Building of a clinical prediction model might enable tailor made medicine and avert the trial and error approach in daily practice.

4.3

Pharmacological treatment of cluster headache in the general population

Submitted

Joseph SHA Koopman, MD [1], Ewout W. Steyerberg, PhD [2], Frank. J Huygen, PhD [3], Jeanne P Dieleman, PhD [1], Marissa de Mos, PhD [4], Miriam CJM Sturkenboom, PhD [1, 5]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Public Health, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[4] Dept. of Anesthesiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[5] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: Few drugs are registered for treatment cluster headache (CH) and not much is known about treatment choices in daily practice. We evaluated treatment patterns, treatment failure, off-label, off-guideline use and predictors for treatment failure.
Methods: Cases were identified in the population-based Integrated Primary Care Information-database. First and ever prescription of pain medication following index date were assessed in terms of off-label and off-guideline use. Treatment failure was defined as switching of pain medication, exacerbation of cluster headache, recorded adverse events and referral for invasive treatment. Predictors of failure were evaluated in first time users of sumatriptan, oxygen or zolmitriptan. Age, sex, dose, treatment regimen, treatment delay until treatment, prior use of pain treatment, prescriber, alcohol abuse, smoking and comorbidity were evaluated. Predictors were analyzed using Cox regression analyses with penalized maximum likelihood estimation.
Results: Of the 117 confirmed incident cases of CH, 105 (90%) received pharmacological pain treatment. Most of these patients (95%) were initially treated by a GP with anti-migraine drugs (49%) or NSAIDs (17%) as monotherapy. Fifty-five percent of first prescriptions were in adherence to guidelines and 15% were considered on-label treatment while 34% of prescriptions were both off-label and off-guideline. Based on type of first therapy, 31% [95% CI: 15% - 47%] failed within one month. We identified 60 first time users of sumatriptan, oxygen or zolmitriptan. Dosage regimen (strength and fixed dose), comorbidity, treatment delay, drug prescribed and age were statistically significant predictors.
Conclusions: General practitioners usually are the first to treat cluster headache. They regularly choose drugs not licensed for this indication. A considerable percentage of these treatments failed within the first month of treatment. We identified several predictors for treatment failure. Further studies may consider these predictors to identify patients at increased risk of treatment failure.

Introduction

Cluster headache is a chronic facial pain syndrome which has a serious impact on the quality of life. [5] Each year, 12.5 out of 100,000 persons are newly diagnosed with this disease. [2] Cluster headache is considered to be a trigeminal-autonomal cephalalgia (TAC) which represents a distinct group of facial pains together with paroxysmal hemicrania and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). [65] Although cluster headache is a cephalalgia, it can be considered as a form of facial pain given the involvement of the first branch of the trigeminal nerve. [14]

The recommended drugs of the European Federation of Neurological Societies (EFNS) are often not in agreement with the limited registered pharmacological treatment options for cluster headache. [107, 129] For instance, in the Netherlands subcutaneous sumatriptan is the only drug registered for acute treatment of cluster headache and methysergide is the only drug registered for prophylaxis. [107] The EFNS guidelines recommends not only sumatriptan but also oxygen and zolmitriptan for the treatment of cluster headache attacks and verapamil or steroids for the prevention of relapses (all level A level of evidence (LOE)). [129] Methysergide is only recommended at a level B. [129] The discordance between drug licensing and treatment guidelines is likely to lead to extensive off-label treatment for cluster headache. The extent of off-label use and the consequences in the general population are not known. In fact, there is very limited insight in the use and effects of pharmacological treatment for cluster headache in general practice.

Treatment is only successful in a 60-75% of patients being treated with oxygen or sumatriptan. [65] Given the severity of cluster headache, it is important to identify patients at a higher risk for failure. Identifying predictors for treatment failure can help to develop tailor-made treatment approaches thereby minimizing the risk of adverse events and delay till effective treatment. Smoking, alcohol intake, age, nausea, vomiting and restlessness have been reported to influence treatment response of various drugs in the treatment of cluster headache. [85, 87, 130, 131]

To provide more data on drug utilization patterns and to identify new predictors of first sumatriptan, oxygen or zolmitriptan treatment we performed a cohort study using the population-based Integrated Primary Care Information (IPCI) database in the Netherlands.

Methods

Setting

The study was conducted within the Integrated Primary Care Information (IPCI) database, a general practitioners (GP) research database with longitudinal electronic medical records of currently more than one million patients throughout the Netherlands (total population 17 million). The patient population is representative of the general Dutch population regarding age and sex. In the Dutch health care system, everyone is registered with a GP who acts as gatekeeper for medical care. Information from secondary care is collected as narratives in the patient records of the GP. [26]

Electronic medical records contain anonymous and coded information on patient demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC-codes) and free text terminology), referrals, clinical findings, laboratory assessments, drug prescriptions and hospitalizations. [27] Summaries of hospital discharge letters and additional information from medical specialists are entered in a free text format and hard copies can be requested. Information on drug prescription comprises amount, strength, ICPC-coded indication, prescribed daily dose and Anatomical Therapeutic Chemical (ATC) classification code. [42] To maximize completeness of electronic data, GPs participating in the IPCI project are not allowed to use additional paper-based

records. The system complies with European Union guidelines on the use of medical data for research and has been proven valid for pharmacoepidemiological research. [24, 25] The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03).

Source population
The source population for the study comprised of all persons contributing person time to the IPCI database during the study period (January 1996-September 2006) with at least one year of valid history in the database. Since extra data collection was required for the validation of the cluster headache diagnoses, we excluded all practices from the source population that could not be contacted for additional data collection. In addition, we excluded non-responding practices. Follow-up started at the beginning of the study period or the date that one year of valid history was available and ended upon transferring out of practice, date of last data supply by the GP, death or end of the study period, whichever came first.

Cohort definition
This study was conducted in a cohort of patients with incident cluster headache, which is part of a larger project in which we study the epidemiology of facial pain in general. [2] The overall study cohort for the project included all persons from the source population who were newly diagnosed with facial pain according to the criteria of the International Association for the Study of Pain (IASP). [14] Cases were identified from the computerized records by a sensitive search on codes and free text comprising specialist reported diagnoses. Identification was followed by a three step approach for case ascertainment. Firstly, the electronic medical records of all potential cases were manually reviewed by a medical doctor (JK). Cases were classified as 'probable' if diagnosed by a specialist or if more than one episode of typical symptoms was recorded in the records, and as 'possible' if only one episode was recorded or specific symptoms were mentioned in the patient records. Patients for whom no typical symptoms or specialist diagnosis were recorded were classified as 'no case'. Secondly, GPs were requested to confirm the presence and type of facial pain of all 'possible' cases and to send the anonymized hard copies of all specialist letters regarding this diagnosis. The information was independently evaluated by two medical doctors (JK, MM) to classify cases as 'probable' or 'no case'. Discrepancies were arbitrated by a pain specialist (FH). Thirdly, to further ensure the validity of the diagnosis, a random sample of 250 patients of all initial 'probable' and 'possible' cases (742) from step one was reviewed by a neurologist with ample experience in pain treatment. In case of disagreement with the previous classification, a case was discussed.
To identify possible predictors of treatment failure we only studied patients with incident cluster headache who were treated with sumatriptan, oxygen or zolmitriptan, which are the level-of-evidence (LOE) A drugs for acute treatment of abortion of cluster headache attacks according to the guidelines of the European Federation of Neurological Societies. [129] These are mutually exclusive groups meaning only the first treatment episode with one of the above mentioned drugs is analyzed. Follow-up for this cohort started on the date of first drug prescription and ended upon treatment failure, end of treatment or end of follow-up, whichever was earliest.

Treatment
Drug prescribing patterns were evaluated using both the electronic prescription records from the IPCI database and the medical specialist letters that were requested from the GPs. As study drugs we included paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, anti-epileptics, anti-migraine drugs (triptans and ergots), anti-depressants, benzodiazepines, calcium-antagonists, clonidin and oxygen. Indications were obtained from linked or written indications and follow-up indications if available. If the drug was started before the index date, the drug was not considered to

be prescribed for cluster headache. If a prescription started after the index date and no indication could be found, it was considered as probably prescribed for cluster headache to avoid underreporting of prescription rates.
Legend durations were calculated by dividing the total number of prescribed tablets by the prescribed daily number of tablets to be taken. Drugs were assumed to be used concomitantly if they were prescribed on the same day. Episodes of use were defined as periods of continuous drug (based on full ATC-codes) use with refill gaps of 30 days or less. To evaluate as to whether the definition of the gap width influenced failure parameters we conducted several sensitivity analyses in which the gap width was varied between 15 and 60 days.
Dosage regimens were classified as titration, fixed or as needed based on the prescribed regimens of the index and subsequent prescriptions. The prescribed daily dosage (PDD) was expressed as the number of defined daily dosages (DDD) as defined by the World Health Organisation (WHO) taken per day (PDD / DDD-ratio). [42]

Outcome parameters
The primary outcome of interest of this study was the drug utilization patterns in cluster headache patients' first starting treatment. Parameters comprised: proportion of treated patients, the number of study drug prescriptions and treatment episodes per patient, treatment delay, type of prescriber (GP or specialist), type of pain medication, treatment regimen, labelling status, adherence to the EFNS guideline and treatment switches. Labelling status was evaluated using the summary of product characteristics (SPC) from the Medicines Evaluation Board in the Netherlands. [107] Drugs were considered on-label if cluster headache was specifically mentioned or if a drug had a broader indication for pain (i.e. 'severe pain' or 'chronic pain'). All other use was classified as off-label. The secondary outcome was failure of first line treatment defined as:
a) Failure mentioned in the electronic record (e.g. requirement of invasive pain treatment, adverse events leading to cessation of therapy, exacerbations of pain, suicide or dose adjustment (excluding titration regimens)).
b) No specific reason stated in the records but a switch to another type of pain treatment.
Failure was attributed to the drug if one of these events occurred during the legend duration or within the carryover period of 30 days.

Predictors
Various predictors for failure were considered, including sex, age, comorbidity, smoking, alcohol abuse, prescriber, dosage and treatment regimen during the first episode of use. Furthermore, we considered treatment delay between date of first symptoms (index date) and first level A LOE treatment and treatment naivety (i.e. naïve means that there was no previous treatment) for cluster headache. We classified comorbidity according to the number of unique prescriptions on ATC-7 level in the year preceding the index date. This score is a proxy for comorbidity using drug prescription data instead of clinical diagnoses with zero indicating absence of comorbidity. Predictors were abstracted from the electronic patient records using automated search algorithms (alcohol abuse, smoking, comorbidity and treatment delay) and by manual validation (prescriber, dosage and treatment regimen). Dosage regimens were classified as flexible (titration regimen or as-needed) or fixed (exact regimen). The dosage was defined as the PDD / DDD-ratio.

Analyses
Standard descriptive statistics were used to describe utilization patters (percentages, means and medians). Median time until first treatment was calculated as the total accumulated number of days between the index date and date of first treatment divided by the number of persons receiving treatment

during follow-up. Treatment delay and treatment failure risk were estimated using Kaplan Meier analysis and the Mann-Whitney U-test. The association of predictors with the outcome was analyzed by applying a Cox proportional hazards model. Hazard ratios (HR) and adjusted hazard ratios (HRadj) were reported with 95% confidence intervals (95% CI). Age, treatment delay (in weeks), the PDD / DDD-ratio and chronic disease score were entered as continuous variables after checking for absence of non-linearity. Non-linearity was checked by adding a quadratic term in a univariate Cox proportional hazards model. Dichotomizing might have led to a loss of power and residual confounding. [118] The hazard ratio of age was reported per ten year band, treatment delay per week, the PDD / DDD-ratio per decimal point and the number of unique ATC-codes per whole point. To be considered for the multivariable analyses, variables had to have a reasonable spread (at least 3 positive events). A penalized maximum likelihood model was used to deal with possible overfitting. [117, 119] We used an absolute ("Lasso") and quadratic ("Ridge") penalty to simultaneously select and shrink the coefficients and reduce potential overfitting. [120] This method has been described before as a solution to the presence of a large number of evaluated predictors compared to the number of patients with the outcome. [121] By applying the proper penalties, which can be selected by maximizing the penalized likelihood of the model, coefficients of individual prognostic factors are reduced towards zero. Any variables with a coefficient of zero (after penalizing) were dropped out of the model. Since the penalized model does not return standard errors we did not provide 95% CI for factors in the final model but only their hazard ratios. Predictors of failure from this model were expressed as penalized maximum likelihood hazard ratios (HRpml). Model performance was tested using the concordance statistic (c-statistic) with 95% CI which is equivalent to the area under the curve (AUC) for binary outcomes. [122] Statistical analyses were conducted using SPSS 15.0 (SPSS inc, Chicago, III) and R (version 2.7.12) using the packages Penalized and Design. [123]

Results

The source population comprised 479,949 eligible persons who contributed 1,898,417 person years of follow-up. We identified 117 patients with incident cluster headache. The mean follow-up after disease onset was 3.48 years (SD 0.23) and accumulated to a total of 406.6 person years. Patients were on average 41.7 years old (SD 13.4) at first diagnosis and 71 (61%) were male (Table 1).

First line pharmacological treatment
During the follow-up 105 out of 117 (90%) patients with cluster headache were pharmacologically treated. The median delay till first treatment was 0 days (range 0 to 2107 days). Most patients were treated by a general practitioner (95%), the remaining part mostly by a neurologist (4%). Patients were usually treated with a single drug (Table 1).

Type of drugs
Anti-migraine drugs were the most frequently prescribed drugs for the first treatment of cluster headache (49% of patients) followed by NSAIDs (17%) (Figure 1). In the studied patient a total of 665 medication prescriptions were made, 61 of these contained a combination of two drugs and three contained a combination of three drugs. The most common combination was an anti-migraine drug with a calcium channel blocker (61%), followed by an anti-migraine drug with either an NSAID or an anti-epileptic drug (both 7%). As needed prescribing was most common with conventional analgesics such as paracetamol (16%) and anti-migraine drugs (71%). Titration to a fixed regimen occurred with anti-epileptics and calcium channel blockers. Oxygen was rarely used but if used it was prescribed 'as needed'.

Table 1: Patient and treatment characteristics

	Cluster Headache	
	First Episode	Second Episode
Number	117	
Mean age (SD)	41.7 (13.4)	
Male sex (%)	71 (61%)	
Number treated		
No of episodes	4.8 (6.2)	
1 episode	105 (90%)	
2 episodes	69 (59%)	
>2 episodes	53 (45%)	
Number of drugs used		
Single drug	94 (90%)	59 (86%)
Two Drugs Combined	11 (10%)	9 (13%)
Three Drugs Combined	0 (0%)	1 (1%)
Prescriber		
General Practitioner	100 (95%)	60 (87%)
Neurologist	4 (4%)	9 (13%)
Other Specialist	1 (1%)	0 (0%)
EFNS guideline followed		
Level A*	57 (54%)	35 (51%)
Level B*	1 (1%)	4 (6%)
On-label treatment		
Narrow indication	4 (4%)	6 (9%)
Broad indication	12 (11%)	6 (9%)
Dosage regimen		
PRN	48 (46%)	31 (45%)
Titration Regimen	3 (3%)	3 (4%)
Fixed Dose	54 (51%)	35 (51%)
Off-guideline and off-label	36 (34%)	24 (35%)
Adverse events	1 (1%)	2 (3%)

The stated numbers are number of patients meaning that, for example, 10 patients have been treated with any combination of drugs during their second treatment episode. SD = standard deviation.
* This reflects the level-of-evidence for a drug as recommended by the guidelines of the European Federation for Neurological Societies.

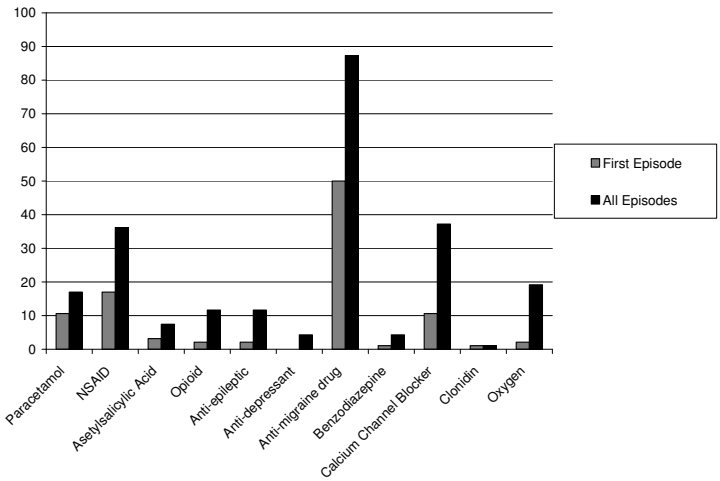
Off label / off guideline

Regarding guidelines, 54% of patients were first treated with a level A LOE drug. Fifteen percent received a drug with a labelled indication (4% according to narrow definitions, 11% if broad definitions were applied) (Table 1). Together, 36 (34%) of patients received initial treatment with an off-label and off-guideline drug. Second treatment episodes were slightly worse with 51% including a level A drug.

Treatment persistence / failure

The cluster headache patients received a total of 665 prescriptions of drugs (501 episodes) included in this study with an average of 6.3 (SD 8.8) per patient. Sixty-nine patients (59%) had multiple treatment episodes during follow-up (Table 1) with an average number of 4.8 (SD 6.2). The median duration of the first treatment episode was 10 days (inter-quartile range (IQR): 5.0 – 15.0). After six months the proportion remaining on treatment stabilized to approximately 30% of patients (Figure 2).
First treatment of cluster headache failed in 34 patients out of 105, 28 because of unspecified reasons (i.e. as approximated by treatment switch) and 6 because of specified reasons (adverse events,

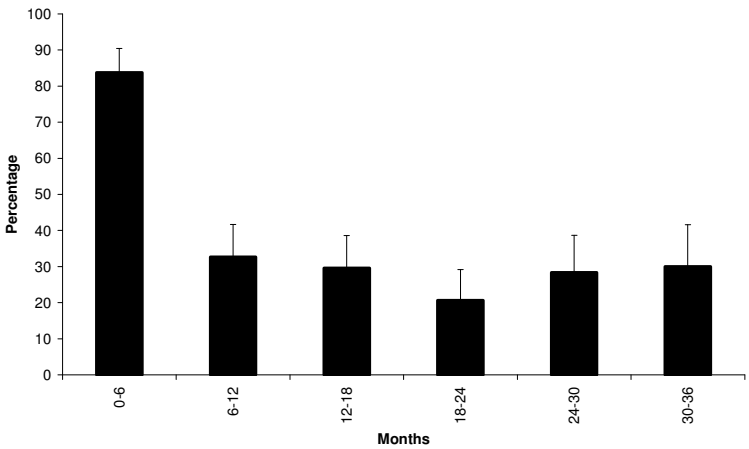
Figure 1: First and total type of drug prescribed



NSAID = non-steroidal anti-inflammatory drug

exacerbation, invasive treatment or dose adjustment). The one month failure rate of treated patients was 31% [95% confidence interval (95% CI): 15% - 47%], 27% [95% CI: 18% - 36%] for switching and 5% [95% CI: 0; 10%] for failure due to specific causes (Figure 3). Reported adverse events leading to a treatment switch occurred once (1%) (Table 2). In total six adverse events were recorded, including gastro-intestinal adverse events such as weight gain (n=1), restless legs (n=1), unspecified (n=2), oedema (n=1) and dizziness (n=1).
Sensitivity analyses with varying carryover periods showed a range of 31-37 cases failing treatment overall. Patients mostly switched to anti-migraine drugs or a combination of drugs (Table 2).

Figure 2: Percentage of people on-treatment during follow-up



Predictors

During the study period, 60 (51%) used either oxygen (n=5, 8%), sumatriptan (n=54, 90%) or zolmitriptan (n=1, 2%) as single drug treatment. The median treatment delay was 0.9 weeks (IQR: 0.0-17.9 weeks) until the first treatment (Table 3). Treatment was mostly initiated by a GP (n=56, 93%) and as a flexible dosage regimen (n=48, 60%). Doses were usually lower than the DDD as defined by the WHO (PDD / DDD-ratio 0.6, SD 0.2-2.0). Patients used a median number of unique ATC-codes of 3.0 (IQR: 2.0-6.0). Most treatment was given as the first cluster headache treatment (66%) while only 33% was subsequent to another treatment for cluster headache.

Alcohol abuse and prescriber could not be evaluated because of too little spread. Univariately, treatment with a fixed dosage regimen (HR: 0.2; [95% CI: 0.0 - 0.6]) was associated with failure. If all variables were included in a cox proportional hazard model the number of unique ATC-codes was associated too (HRadj: 1.4; [95% CI: 1.1 - 1.7]) (Table 3). After shrinkage using the penalized model, six variables were retained namely age, fixed dosage regimen, treatment delay, the PDD / DDD - ratio, the number of unique ATC-codes and treatment naivety for other pain treatments for cluster headache. The number of unique ATC-codes (HRpml: 1.21) and being treatment experienced for other pain treatments (HRpml: 1.25) were associated with an increased risk of failure. Older age (HRpml: 0.88 per 10 year increase), receiving a fixed dose regimen (HRpml: 0.45), longer treatment delay (HRpml: 0.999 per week delay) and a higher PDD / DDD – ratio (HRpml: 0.98 per 0.1 increase) were associated with a reduced risk of treatment failure. Overall, the c-statistic of the final model was 0.72 [95% CI: 0.60 - 0.83].

Figure 3: Failure rate of first treatment

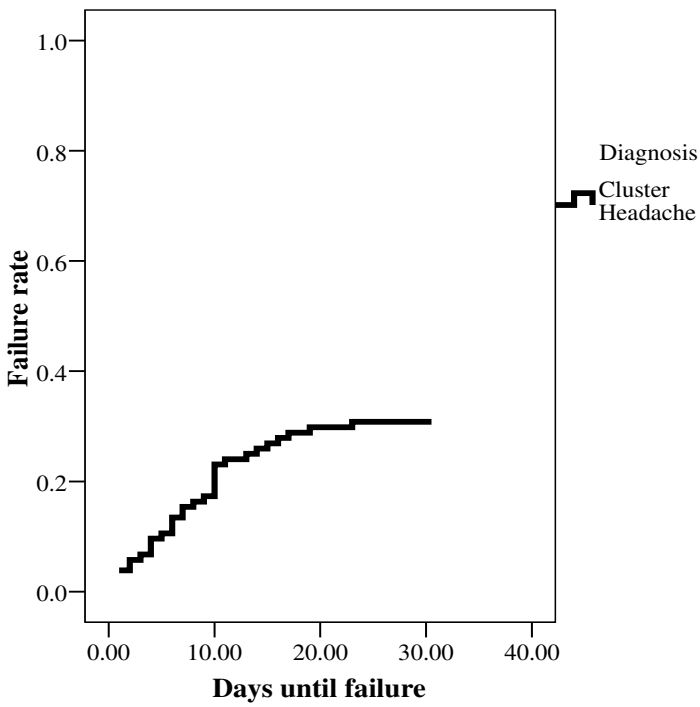


Table 2: Switching patterns in patients who switched the first treatment to another type of drug or combination

			Second drug						
		Starting	NSAID	Opioid	Anti-epileptic	Anti-depressant	Anti-migraine	CCB	Combination
First drug	PCM	10 (100%)	-	-	1 (10%)	-	1 (10%)	-	-
	NSAID	16 (100%)	-	-	-	1 (6%)	2 (13%)	-	2 (13%)
	Asetylsalicylic Acid	3 (100%)	-	-	-	-	1 (33%)	-	-
	Opioid	2 (100%)	-	-	-	-	2 (100%)	-	-
	Anti-epileptic	2 (100%)	-	-	-	-	1 (50%)	-	-
	Anti-migraine	47 (100%)	3 (6%)	1 (2%)	-	-	-	1 (2%)	5 (11%)
	Benzodiazepine	1 (100%)	-	-	-	-	1 (100%)	-	-
	CCB	10 (100%)	-	1 (10%)	-	-	-	-	1 (10%)
	Oxygen	2 (100%)	-	-	-	-	1 (50%)	-	-
	Clonidin	1 (100%)	-	-	-	-	-	-	-
	Combination	11 (100%)	-	-	1 (9%)	-	2 (18%)	-	-
	Total	105 (100%)	3 (3%)	4 (4%)	2 (2%)	1 (1%)	11 (10%)	1 (1%)	8 (8%)

Anti-migraine drugs are both triptans as well as ergots. PCM = paracetamol, NSAID = non-steroidal anti-inflammatory drug, ASA = acetylsalicylic acid, CCB = calcium channel blocker

Table 3: Baseline characteristics, risks and hazard ratios

Characteristic	n	Events	one month risk (95% CI)	Univariate HR	Multivariate HR
Sex					
Male	38	14	0.32 [0.17; 0.46]	Ref	Ref
Female	22	7	0.33 [0.13; 0.53]	0.8 [0.3; 2.1]	1.1 [0.3; 3.3]
Age* [#]	39.5 (32.3 - 50.0)	36.0 (30.5 - 53.5)		1.0 [0.7; 1.4]	0.7 [0.4; 1.1]
Prescriber					
General practitioner	56	19	0.30 [0.18; 0.42]	NA	NA
Anaesthesiologist	0	0	NA	NA	NA
Neurologist	4	2	0.67 [0.13; 1.00]	NA	NA
Other	0	0	NA	NA	NA
Dosage regimen					
Flexible	48	20	0.38 [0.24; 0.52]	Ref	Ref
Fixed	12	1	0.08 [0.00; 0.24]	**0.2 [0.0; 0.6]**	**0.1 [0.0; 0.8]**
Alcohol abuse					
No	60	21	1.00 [0.88; 1.12]	NA	NA
Yes	0	0	NA	NA	NA
Smoking					
No	43	13	0.26 [0.13; 0.40]	Ref	Ref
Yes	17	8	0.47 [0.23; 0.71]	1.7 [0.7; 4.2]	0.7 [0.2; 2.0]
Treatment Delay (weeks) *	0.9 (0.0 – 17.9)	2.0 (0.0 - 29.7)		1.00 [0.99; 1.01]	1.0 [0.98; 1.01]
PDD / DDD - ratio* [%]	0.6 (0.2 - 2.0)	0.2 (0.1 - 1.5)		0.99 [0.96; 1.02]	0.99 [0.96; 1.02]
Chronic Disease Score* [&]	3.0 (2.0 - 6.0)	4.0 (1.5 - 8.0)		1.13 [0.99; 1.29]	**1.4 [1.1; 1.7]**
Treatment naive					
Yes	40	11	0.28 [0.14; 0.42]	Ref	Ref
No	20	10	0.40 [0.18; 0.62]	1.8 [0.8; 4.3]	1.6 [0.5; 5.0]
Total	69	22	0.32 [0.20; 0.44]		

This table displays the total number of treated patients per baseline characteristic (n) and the number of failures per category (events). Also, the one month failure risks (from Kaplan-Meier analysis) are displayed and the univariate and multivariable hazards ratios.

* Age, treatment delay until first level A recommended treatment, the PDD / DDD-ratio and the number of unique ATC-codes in the year preceding the index date are entered as a continuous variable. The median is displayed with the interquartile range between brackets in total (n) and cases (events).

[#] The HR of age displayed is per ten years.

[%] The HR of the PDD / DDD-ratio displayed is per tenth of a point.

[&] The HR of the number of unique ATC-codes is per point.

** Mutually exclusive treatment groups

PDD / DDD – ratio: prescribed daily dosage (PDD) divided by the defined daily dosage (DDD). The DDD indicates a standardized dose as defined by the World Health Organization.

95% CI: 95% confidence intervals.

HR: hazard ratio as derived from a cox proportional hazard model.

NA: not assessable. It usually indicates there are not enough cases to do a calculation.

Discussion

This study showed that cluster headache is often treated instantly and for a short duration using either anti-migraine drugs or NSAIDs prescribed by a general practitioner. Although most drugs were off-label a considerable part was used according to the EFNS guidelines. Only 33% of patients had treatment for over six months. This might be explained by the natural history of cluster headache with patients having painfree remissions for months to years. [132] First line treatment failure was common and occurred early in treatment, mostly because patients needed a switch of their medication. We found a younger age, flexible dose regimen, a shorter treatment delay, a lower PDD / DDD-ratio, a higher comorbidity score and being treatment experienced to be associated with failure. Overall, our model with these six variables performed satisfactory with a c-statistic (= AUC) of 0.72. [117] The higher risk in non-naive patients may be explained by the fact that these patients

failed on previous treatment which may point at a higher a priori risk of failure. Patients receiving a fixed dose might have a less severe form of cluster headache with a lower a priori failure risk. Alternatively, a fixed dose itself might be more effective due to more stable blood levels. Similarly, shorter treatment delay may point at a severe form of cluster headache with a higher a priori risk of treatment failure. The lower failure risk in older people might have several explanations. Firstly, patients presenting with cluster headache at a higher age might generally have a less severe form of cluster headache. Secondly, given their age and the natural course of cluster headache, older people might have a lower risk of exacerbations. Thirdly, given a lower renal and hepatic function, older patients might have higher plasma levels of prescribed drugs thus potentially leading to a lower failure rate. Patients with a higher comorbidity score might be at a higher failure risk due to the complexity of the circumstances (i.e. drug-drug interactions). In our study, smoking was not associated with an increased risk of treatment failure.

Drug utilization studies in chronic pain syndromes in a primary care setting are rare. A recent survey under medical doctors found that 3% of neurologists prescribed gabapentine (GBP) for cluster headache. [133] Analgetics were mostly used for a registered indication and in only 5% for scientifically unjustified off-label indications. [133] In contrast, we found 34% of first treatment episodes and 35% of second treatment episodes to be with off-label and off-guideline drugs. This difference can be caused by a different patient population and a different on-label definition. We required the diagnosis or either 'chronic pain' or 'severe pain' to be explicitly mentioned in the SPC. If the mention of 'pain' is considered as indication for all types of pain, most analgesics will be on-label.

Another study performed in Canada assessed drug utilization and effectiveness in pain patients retrospectively using questionnaires. [134] One third of patients with episodic cluster headache had used anti-migraine drugs or oxygen. [134] Our study did not evaluate as to whether treatment was used prophylactic or acute, but it showed a low rate of oxygen use compared to the use of calcium channel blockers and anti-migraine drugs. The difference with our study might reflect a selection bias or different entry criteria in the Canadian study. Finally, we defined the start of follow-up as the date of first symptoms rather than the date of diagnosis. As a consequence, the prescribed treatment as observed in our study could partly reflect treatment during diagnostic work up. This could explain the high rate of off-label and off-guideline drug prescription as well as the high failure rate.

Several studies have evaluated predictors for treatment failure in either migraine or cluster headache. Smoking is associated with the development of cluster headache and might thus be associated with exacerbations leading to more failure among smokers. [82] A previous study however found smoking to be unrelated to triptan or oxygen treatment failure, which is in line with our study. [130] Alcohol was found to be a trigger for exacerbations of cluster headache. [85-87] This could, however, not be confirmed in patients using triptans or oxygen. [130] Unfortunately, we could not evaluate alcohol consumption as predictor of treatment failure due to low numbers of exposed patients. Other factors such as the presence of autonomic features, the form of cluster headache and the absence of aura could not be evaluated in our study. While age was not a factor of relevance in topiramate treatment, older age was reported before to be predictive of triptan treatment failure in migraine patients, but not in cluster headache patients. [130, 135, 136] We found age to have a positive influence on success of therapy (HRpml: 0.88). Given our small dataset and the absence of confidence intervals after shrinkage, no definite conclusion can be drawn regarding comparability of these findings. Although one study in migraine found males to be more at risk for failure, the difference was minor (OR 1.27; [95% CI: 1.10 - 1.50]). [136] Sex had no influence on failure in our final model, confirming findings of a study about response to triptan and oxygen treatment in cluster headache patients and topiramate response in migraine patients. [130, 135]

Our study possibly has some limitations. As we used observational data our main concern is false positive and false negative misclassification of the disease, outcome and the exposure. We aimed to limit the extent of false negative misclassification of cluster headache by performing a broad, sensitive search algorithm including common symptoms, specific treatments and spelling errors. Misclassification of the exposure might occur due to over-the-counter use of paracetamol and NSAIDs leading to an underestimation of its use. Similarly, since we based our exposure data on a GP database we might miss specialist prescriptions. To ensure maximum completeness of our data, manual review of specialist letters (electronic and hard copy) was performed. Furthermore, since the GPs usually take responsibility for repeat prescription the omission of specialist prescriptions was probably minimal. In addition, we may have missed adverse events and exacerbations which were not reported by the patient or GP leading to an underestimation of our reporting of adverse events and to a possible underestimation of the failure rate. To compensate for this, we considered any switch in treatment regimen as failure of treatment assuming a switch to be due to adverse events or loss of effectiveness. Cost considerations played a minor role since all drugs studied are reimbursed in the Netherlands. Misclassification of the treatment outcome was further minimized by taking a 30 day carryover effect. After 30 days a new prescription was considered to be prescribed for a new exacerbation of the disease rather than a failure of treatment. Although this 30 day period is chosen arbitrarily, sensitivity analyses were performed with a 15, 45 and 60 day period showing minor changes. There is no or little misclassification of sex, age, prescriber, dosage and treatment regimen, treatment delay and treatment naivety. Since comorbidity was based on drug use our study probably underestimated the presence of comorbidity although the misclassification this is likely to be non-differential. The presence of smoking and alcohol abuse is probably severely underestimated in our study. False negative misclassification of these predictors will most likely lead to an underestimation of the effect. This might cause certain factors to drop out of our model while they in fact are important predictors for treatment failure. The main limitation of this study is the small sample size. This leads to optimistic estimates of model performance and limited power for selection of important predictors. Using a p-value of 0.05 for predictor selection would have been too strict. [121] We therefore used a penalized model to shrink the coefficients and reduce the optimism of the model and performed bootstrapping for validation.

This study showed that the extent of off-label treatment in cluster headache in the Netherlands is more than 80% whereas 55% is in agreement with the EFNS guidelines. One third of patients were first treated with an off-guideline and off-label drug which might explain the high and rapid failure rate (42%). Furthermore, this study represents a first step towards identifying potential predictors for treatment failure of first sumatriptan, oxygen or zolmitriptan treatment for cluster headache. Given the hypothesis generating nature of this study, no clinical judgment can yet be made based on our results. The findings can be used to base further research on. Our findings should be replicated preferably in a larger dataset and ideally include severity at baseline and presence of autonomic features in addition to dose and dosing regimen.

4.4

Pharmacological treatment of persistent idiopathic facial pain in the general population

Submitted

Joseph SHA Koopman, MD [1], Frank. J Huygen, PhD [2], Jeanne P Dieleman, PhD [1], Marissa de Mos, PhD [3], Miriam CJM Sturkenboom, PhD [1, 4]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Anesthesiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[4] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: Few drugs are registered for treatment of persistent idiopathic facial pain (PIFP) and little is known about treatment choices for PIFP in daily practice. We therefore studied treatment patterns, treatment failure, off-label and off-guideline use for PIFP.
Methods: PIFP cases were newly identified patients in the population-based Integrated Primary Care Information-database containing electronic general practitioner (GP) records. All cases were extensively validated to ensure the presence, type and onset of PIFP. Prescriptions of pain medication following the index date were evaluated by disease and prescriber. Furthermore, off-label use of pain medication was assessed. Treatment failure included switching of drugs, visits for exacerbations of PIFP, reported adverse events or a referral for invasive treatment.
Results: Of 41 confirmed PIFP cases, 31 (76%) received pharmacological pain treatment. Most (90%) were initially treated by a GP with anti-epileptic drugs (29%) or NSAIDs (21%) as monotherapy. Seventy-one percent of pain medication was considered off-label PIFP. Of first line treatment 27% [95% CI: 11.2 - 43.4] failed within one month.
Conclusions: First line PIFP treatment is most often started by the GP, but often with drugs not licensed for PIFP, one quarter of first line treatment failed.

Introduction

Persistent idiopathic facial pain (PIFP), also referred to as atypical facial pain, is a rare chronic pain syndrome affecting the facial area with a serious impact on the quality of life. [2] The pathophysiology of PIFP is unclear but thought to be of neuropathic origin. [137] There are no guidelines for treatment of PIFP and no drugs are currently registered for this specific indication in the Netherlands. Not much is known about the actual treatment of PIFP in primary care. Therefore we investigated drug prescription patterns in patients with PIFP in the general population by using the population-based Integrated Primary Care Information (IPCI) database in the Netherlands. This study was part of a larger study into facial pain conditions.

Methods

In brief, the study was conducted within the Integrated Primary Care Information (IPCI) database, an anonymized population-based medical record database currently capturing data from more than 500 GPs and more than one million patients. Details of the source population and cohort definition are described in detail elsewhere. [2]
Since this study was retrospective and based on medical records we used the criteria of the International Association for the Study of Pain (IASP) to classify PIFP cases. Detailed information on case validation has been described before. [2, 14] The index date was the date of first symptoms and represented the start of follow-up.
Drug prescribing patterns were manually evaluated using the electronic prescription records from the IPCI database and using full specialist letters requested from the GPs. As study drugs for pain treatment we included paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), acetyl-salicylic acid, opioids, anti-epileptics, anti-migraine drugs (triptans and ergots), anti-depressants, benzodiazepines, calcium-antagonists, clonidin and oxygen. Episodes of use were defined as periods of continuous drug (based on full Anatomical Therapeutic and Chemical (ATC)-codes) use with gaps of 30 days or less. [42]

Outcome parameters
Various outcome parameters were considered including treatment persistence (number of treated patients divided by the number of patients in follow-up during each consecutive six months period), treatment delay, type of prescriber and off-label use. Drugs were considered on-label for a certain diagnosis if that diagnosis was specifically mentioned as an indication in the summary product characteristic (SPC). Since no drugs are specifically registered for PIFP in the Netherlands we defined on-label drugs as drugs with a broader indication for pain (i.e. ‘severe pain’ or ‘chronic pain’). On-label drugs included: carbasalate calcium, fentanyl, pregabalin, gabapentin, paracetamol (with or without codeine), tramadol or rofecoxib. All other use was classified as off-label. In addition we described the type of pain medication, treatment regimen and failure of first therapy.
Treatment failure was defined as referral for invasive pain treatment, adverse events leading to cessation of treatment, exacerbations of facial pain, suicide or dose adjustment (excluding titration regimens)) (i.e. specified failure). Switching to another drug for pain treatment without reporting of any of the aforementioned events was considered as unspecified treatment failure. Failures were attributed to the drug if one of these events occurred during the legend duration or within the carryover period of 30 days. The date of failure was defined as the date of starting the new episode (within the carryover period) or the date of recorded event, whichever came first. Only failure of

the first treatment episode was considered. In this analysis follow-up was right censored upon the end of the treatment episode with 30 days carryover.
Standard descriptive statistics were used to describe utilization patters (percentages, means and medians). All statistical analyses were conducted using SPSS 15.0 (SPSS inc, Chicago, III).

Results

After completing the thorough review process, 41 out of 361 incident cases of facial pain were classified as PIFP. [2]

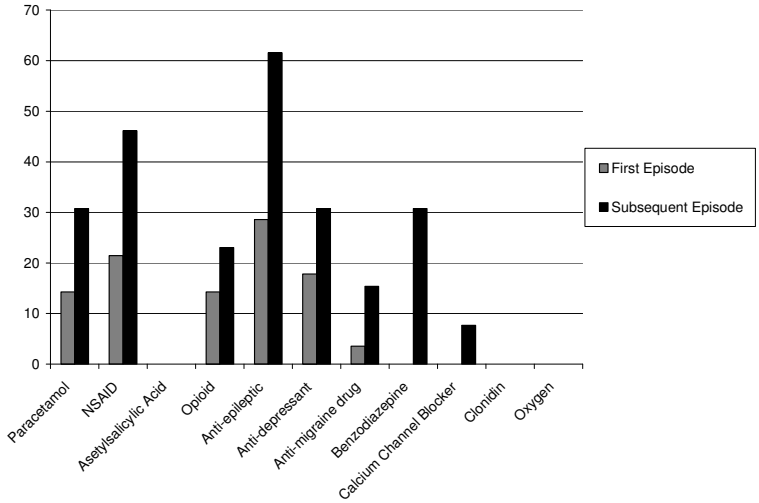
First line pharmacological treatment
During follow-up 31 out of 41 (76%) PIFP patients were pharmacologically treated by a general practitioner (90%) after a median delay of 15 days (Table 1). Anti-epileptic drugs and NSAIDs were the most frequently prescribed drugs for the first line treatment (29% and 21% of patients respectively) (Figure 1).

Treatment persistence / failure
In the first six month-period, 63% of patients were treated with one of the study drugs; after six months the proportion remaining on treatment stabilized to approximately 32% (Figure 2).
First treatment failed in eight out of 31 treated patients within a month, seven because of switch for unspecified reasons and one because of recorded lack-of-effectiveness. The one month failure rate was 27% [95% confidence interval: 11.2 - 43.4] (Figure 3).

Table 1 Characteristics of patients with persistent idiopathic facial pain and their treatment

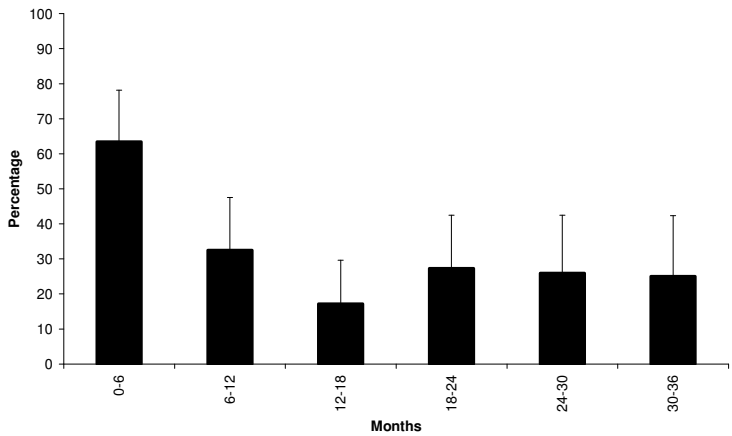
	Atypical Facial Pain
Number of patients	41
Mean age (SD)	45.4 (19.6)
Male sex (%)	10 (24%)
Number of treatment episodes	
Average number of episodes	4.6 (7.2)
At least 1 episode	31 (76%)
2 or more episodes	17 (41%)
Number of drugs used	
Single drug	28 (90%)
Two drugs combined	3 (10%)
Three or more drugs combined	0 (0%)
Prescriber first treatment episode	
General practitioner	28 (90%)
Anesthesiologist	1 (3%)
Neurologist	2 (7%)
Dosage regimen first treatment episode	
As needed	8 (26%)
Titration regimen	1 (3%)
Fixed dose	22 (71%)

Figure 1: First and subsequent type of drug prescribed in patients with persistent idiopathic facial pain



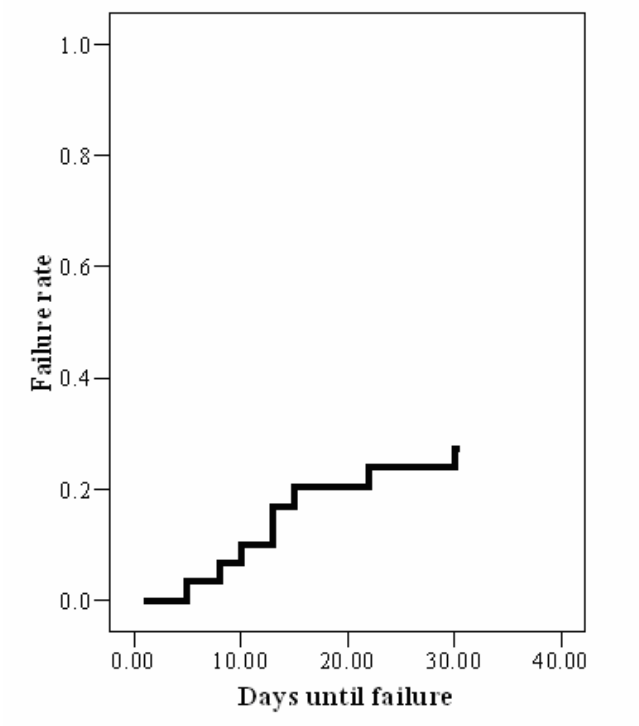
The Y-axis shows the percentage of patients with the number of patients with persistent idiopathic facial pain treated with a single drug (n=28 for first episode, n=13 for subsequent episodes) as the denominator. Persons can contribute to more than one subsequent episode.
NSAID = non-steroidal anti-inflammatory drug

Figure 2: Percentage of people on treatment for persistent idiopathic facial pain during follow-up



This figure displays the percentage of patients receiving at least one prescription in each six month period with the number of patients in follow-up in the denominator (at least one day in concerned period) during consecutive six months periods. Six month periods start on the date of first symptoms (t=0). Error bars represent upper 95% confidence intervals.

Figure 3: One month failure rate of first treatment episode (n=31)



Discussion

This study reported treatment patterns for persistent idiopathic facial pain in a primary care setting. The pattern of use was directed towards treatment of neuropathic facial pain since anti-epileptic drugs were relatively frequently used. Treatment was mostly initiated by the general practitioner, was mostly off-label and given for a short period of time.

Drug utilization studies in chronic pain syndromes in a primary care setting are rare and to our knowledge no information is available on treatment patterns of idiopathic facial pain in particular. A study performed in a primary care setting in the UK in patients with neuropathic pain in general reported that 46-66% of all patients were treated at first diagnosis, usually with one drug. [16] Antidepressants were given in 30% of the cases, anti-epileptics and opioids in 20%. [16] Our finding that 20% of patients received anti-epileptics and 15% opioids is in line with these results. A study surveying the impact of chronic pain in general also reported slightly different treatment patterns. [114] Two-thirds of chronic pain patients were taking prescription drugs, 44% NSAIDs, 28% opioids and 18% paracetamol. [114] In our PIFP patients we observed a smaller percentage of use of NSAID and opioid use. This difference can be explained by the fact that PIFP may be considered of neuropathic origin, which impacts on treatment choices (e.g. anti-epileptics). We previously reported drug utilization patterns in patients with neuropathic facial pain, mainly consisting of trigeminal neuralgia. [101] The study on neuropathic facial pain showed that anti-epileptics were frequently used (55%) while opioids were used less frequently (7%). [101] The percentage of patients treated with NSAIDs in neuropathic facial pain was comparable to that of PIFP (16%). [101]

The strengths of this study are the extensive case validation process, the availability of information from general practice and specialists and the possibility to follow patients over time. Limitations are potential misclassification of disease which was limited due to extensive validation, and misclassification of exposure. Misclassification of the exposure might occur due to over-the-counter use of paracetamol and NSAIDs leading to an underestimation of its use. In addition, we may have missed adverse events and exacerbations which were not reported by the patient or GP leading to an underestimation of our reporting of adverse events and to a possible underestimation of the failure rate. To compensate for this, we considered any switch in treatment regimen as failure of treatment assuming a switch to be due to adverse events or loss of effectiveness.

This study showed that persistent idiopathic facial pain is mostly treated by the GP with anti-epileptic drugs, similar to neuropathic pain syndromes. Failure rates were limited and mostly caused by treatment switching. Whether or not anti-epileptics are efficacious in treating PIFP requires further research.

4.5

Burden of disease and resource use in facial pain

Submitted

Joseph SHA Koopman, MD [1], Frank. J Huygen, PhD [2], Jeanne P Dieleman, PhD [1], Miriam CJM Sturkenboom, PhD [1,3]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Background: Some forms of facial pain are rare but severe. There is a lack of data on healthcare consumption and diagnostic work-up of these rare forms. We studied healthcare consumption and diagnostic work-up of trigeminal neuralgia (TN), postherpetic neuralgia (PN) in the facial area, cluster headache (CH), occipital neuralgia with referred facial pain (ON), local facial neuralgias (LN), persistent idiopathic facial pain (PIFP), glossopharyngeal neuralgia (GN) and paroxysmal hemicrania (PH).
Methods: Patients with facial pain were identified in the Integrated Primary Care Information-database with electronic GP records using an extensive validation procedure. All electronic records were manually evaluated for secondary causes, GP and specialist visits, diagnostic delay, delay until first referral, (time until first) investigations performed and (invasive) treatment. Specialists included dentists, physiotherapists and psychologists.
Results: We identified 362 cases of facial pain (118 TN, 36 PN, 117 CH, 30 ON, 17 LN, 2 GN, 1 PH). Only 6 (2%) patients had a secondary form. The median diagnostic delay was 0 days with the GP diagnosing 77% of cases. Of all cases, 98% visited a GP for their pain, the median number of visits was three. During the first visit pharmacological treatment was initiated in almost all patients, only half of all patients was referred to a specialist with a median time until referral of 14.5 days. One third underwent some form of additional investigation. These investigations concerned X-rays or laboratory tests.
Conclusions: Most patients are seen and treated in primary care, there should be a shift of focus on treatment and research from secondary care to primary care.

Introduction

Severe non-traumatic facial pain conditions include trigeminal neuralgia, postherpetic neuralgia in the facial area, cluster headache, occipital neuralgia with referred pain, local facial neuralgias, persistent idiopathic facial pain (atypical facial pain), glossopharyngeal neuralgia and paroxysmal hemicrania. These conditions often come together in the differential diagnosis of a general practitioner (GP) as they share common clinical features. The overall frequency of these forms of facial pain in the general population is low but the impact on quality of life is high. [2-5] Available studies on cluster headache showed a large diagnostic delay of up to 6.6 years from first symptoms and specialist care in 70% of cases with many receiving dental or phsyical threapy. [5, 138] The aetiology of these forms can be either primary (idiopathic) or secondary (symptomatic) to diseases such as multiple sclerosis (MS), tumors and infarctions. [6-13] Based on hospital data it was estimated that 10-15% of all trigeminal neuralgia cases are secondary to other diseases. [36] However, the proportion of secondary facial pain in primary care is at present unknown. Being a debilitating disease which is difficult to diagnose the burden on health care consumption per facial pain is probably high.
Information on diagnostic work-up and resource consumption of facial pain conditions are sparse. The available data are often based on information from secondary or tertiary care centers possibly representing only a special part of the patient population. [5, 114, 138-140] Moreover, all reported studies relied on questionnaires or interviews of patients which may have suffered from recall bias. Accurate primary care data about healthcare consumption may help to get a better view on the impact and burden of disease. We therefore studied the diagnostic work-up and healthcare consumption of facial pain patient by performing a cohort study in a general practice research database.

Methods

The study was conducted in the Integrated Primary Care Information (IPCI)-database, a GP research database with electronic patient records of more than one million patients throughout the Netherlands. The source population of the IPCI database is representative for the general Dutch population regarding age and sex and has been proven valid for pharmacoepidemiological research. [24, 25] In the Dutch healthcare system, everyone is registered with one GP who acts as gatekeeper for, and receiver of information from secondary care. [26]
Electronic records contain coded (anonymized) information on patient demographics, symptoms and diagnoses (using the International Classification for Primary Care (ICPC)-codes) and free text narratives, referrals, clinical findings, laboratory assessments, drug prescriptions and hospitalizations [27]. Summaries of hospital discharge letters or additional information from medical specialists are entered as narratives and hard copies can be requested from the GP. To maximize completeness of electronic data, GPs participating in the IPCI-project are requested not to use additional paper-based records. The system complies with European Union guidelines on the use of medical data for research. The scientific and ethical advisory board of the IPCI project approved this study (project number 07/03).

Source population
The source population comprised of persons with at least one year of valid history in the IPCI-database and contributing person time to the database during the study period (January 1996–September 2006). One year of valid history meant that a practice had been contributing data to the IPCI-database for at least one year and that the person had been registered with the GP for at least one year. The one year run-in period was required to have sufficient background information on all

subjects and to exclude existing (prevalent) facial pain. Follow-up started at the beginning of the study period or on the date that one year of valid history was available, whichever date was latest. Follow-up ended upon transferring out of practice, date of last data supply by the GP, death or end of the study period, whichever came first. Since additional data collection was required for validation of diagnoses, we excluded practices from the source population that could not be contacted for additional data collection. In addition, we excluded non-responding practices and patients with a diagnosis of facial pain prior to the start of follow-up (prevalent cases) from the source population. The study population comprised all incident cases of facial pain. Facial pain included trigeminal neuralgia, postherpetic neuralgia in the facial area, cluster headache, occipital neuralgia with referred facial pain, local facial neuralgias, persistent idiopathic facial pain, glossopharyngeal neuralgia and paroxysmal hemicrania.

Identification and validation of cases

Case selection and validation has been described elsewhere. [2] In brief, potential cases of facial pain were identified using a broad and sensitive free text search in the computerized records followed by a three step approach for case ascertainment. Firstly, in order to exclude false positive records and to assess the index date (date of first symptoms), all potential cases were manually evaluated by a medical doctor (JK) using the complete electronic medical records and applying the criteria of the International Society for the Study of Pain (IASP). [21] Potential cases were divided into 'probable', 'possible' or 'improbable' depending on the number of disease episodes, mentioned symptoms and specialist confirmation. Improbable cases were excluded as a case. Secondly, additional information was requested from the GP for all 'possible' cases. This was achieved using a questionnaire in which criteria from the IASP were mentioned per type of facial pain. [21] The GP was asked to confirm or reject the diagnosis. If specialist letters were present, anonymized hard copies were requested. All case information (including returned questionnaires) of all 'probable' and 'possible' cases was independently evaluated by two medical doctors. Discrepancies were arbitrated by a pain specialist (FH). Thirdly, to further ensure validity of the diagnosis, a random sample of 250 patients of all initial cases from step one was reviewed by a neurologist with ample experience in pain treatment. In case of disagreement, a case was discussed until agreement was reached. At the end of the case validation each case was classified as either 'case' or 'no case'. The index-date was set at the date of first symptoms of facial pain. Incident cases of facial pain were included in the study population. Follow-up started on the index date. Since there is controversy in literature regarding the definition of postherpetic neuralgia in the facial area, we have chosen to set the index date at date of first herpes zoster symptoms.

Outcome parameters

Diagnostic work up

As part of diagnostic work-up we assessed the diagnostic investigation delay (i.e. time lapse between first symptoms and first investigation), and treatment delay (i.e. time lapse between diagnosis and first symptoms). As diagnostic investigations we included computed tomography (CT)-scans, magnetic resonance imaging (MRI)-scans, laboratory investigations and X-rays.

Health care consumption

Healthcare consumption included the number of GP visits pertaining to facial pain, actions taken by the GP (treatment initiation, switch or continuation of treatment or referral), specialist referrals and treatment given. Referrals could be to any specialist including dentists, physiotherapists and psychologists. Treatment was categorized as invasive (i.e. surgery), drugs and non-invasive treatment

(i.e. dentist, physiotherapy). Treatment given by a dentist was always considered to be non-invasive treatment (including tooth removal).
All outcome measures were validated by manual review of the full medical records and all other available information like specialist letters and questionnaires which were obtained from the GPs.

Analyses
Standard descriptive statistics were used to describe various outcome measures (percentages, means and medians) with standard deviations (SD) or interquartile ranges (IQR), whichever was applicable. The diagnostic delay, the delay between index date and date of first diagnostic investigation (investigation delay) and between index date and date of first treatment (treatment delay) were calculated as the median number of days between index date and the applicable date (date of first diagnosis, of first investigation or of first treatment). Investigation and treatment delay were calculated within people undergoing an investigation or any form of treatment. All statistical analyses were conducted using SPSS 15.0 (SPSS inc, Chicago, III).

Results

In the source population of 479,949 (1,898,417 PY) patients in the IPCI-database who had at least one year of valid history, 362 incident cases with facial pain were identified. Of these, 118 cases had trigeminal neuralgia, 36 had postherpetic neuralgia in the facial area, 117 had cluster headache, 30 had occipital neuralgia with referred facial pain, 17 had local facial neuralgias, 41 had persistent idiopathic facial pain, two had glossopharyngeal neuralgia and one had paroxysmal hemicrania. The average follow-up time after the index date was 3.4 years (SD 2.5). The mean age at diagnosis was 49.1 years (SD: 18.0) and 158 (44%) were male (Table 1).

Diagnostic work-up
The diagnosis was made by a GP in 77% of all cases followed by neurologists diagnosing 16% of all cases. The two cases of glossopharyngeal neuralgia were exclusively diagnosed by a neurologist, the one case of paroxysmal hemicrania by a GP (Figure 1). Overall, the median diagnostic delay was 0.0 days (IQR: 0.0 – 43.5). The diagnostic delay was longest for patients with glossopharyngeal neuralgia (median: 323.0 days) and lowest for patients with postherpetic neuralgia in the facial area (median: 0.0; IQR: 0.0 – 0.0). Of all 362 patients, one third (n = 120) underwent investigations as part of the diagnostic work-up. First investigations mostly included an X-ray (n = 47) or laboratory tests (n = 36). In total, 54 X-rays were performed, 49 laboratory investigations, 19 CT-scans and 37 MRI-scans (Figure 2).
Most patients had a primary form of facial pain. Only six (2%) patients had secondary facial pain (TGN:4, CH: 2) due to multiple sclerosis (n=4), Sjogrens disease (n=1) and meningioma (n=1). Most secondary causes were already known at date of first symptoms of facial pain.

Healthcare consumption:
Of all 362 cases, 355 (98%) visited a GP with a median number of facial pain related visits of 3.0 (IQR: 1.0 – 6.0) during follow-up after the date of first symptoms (Table 1). During first GP visits pharmacological treatment was initiated in the majority of cases (n = 248, 70%) (Table 1). Subsequent visits usually led to either a change or a prolongation of the prescription (n = 76, 30% and n = 75, 29% respectively).

Table 1: Baseline characteristics and actions taken by the general practitioner

		Diagnosis								
Action taken		TGN	PHN	CH	ON	LN	PIFP	GPN	PH	Total
	N total	118 (33%)	36 (10%)	117 (32%)	30 (8%)	17 (5%)	41 (11%)	2 (1%)	1 (0%)	362 (100%)
	Mean age (SD)	51.5 (17.6)	68.0 (17.7)	41.7 (13.4)	54.1 (16.2)	45.2 (15.7)	45.4 (19.6)	54.0 (5.7)	24.0 (0)	49.1 (18.0)
	Male sex (%)	34 (29%)	19 (53%)	71 (61%)	13 (43%)	10 (59%)	10 (24%)	1 (50%)	0 (0%)	158 (44%)
	Total visits	3.0 (1.0 - 7.0)	4.0 (3.0 - 6.0)	3.0 (1.0 - 7.0)	2.0 (1.0 - 4.0)	1.0 (1.0 - 3.0)	3.0 (2.0 - 6.0)	4.5 (3.0 -)		3.0 (1.0 - 6.0)
	N of first GP visits *	115 (97%)	35 (97%)	115 (98%)	30 (100%)	16 (94%)	41 (100%)	2 (100%)	1 (100%)	355 (98%)
	N of second GP visits *	86 (73%)	33 (92%)	78 (67%)	16 (53%)	8 (47%)	34 (83%)	2 (100%)	0 (0%)	257 (71%)
	Diagnostic delay #	0.0 (0.0 - 37.8)	0.0 (0.0 - 0.0)	0.0 (0.0 - 61.5)	0.0 (0.0 - 32.5)	0.0 (0.0 - 100.5)	12.0 (0.0 - 264.0)	323.0 (16.0 -)	0	0.0 (0.0 - 43.5)
	Time till first investigation #	55.0 (1.0 - 128.0)	-	68.0 (1.0 - 213.0)	148.5 (11.3 - 577.5)	1.0 (0.0 -)	37.0 (8.0 - 358.0)	-	-	52.0 (1.0 - 160.0)
	Time till first treatment #	0.0 (0.0 - 29.3)	18.0 (10.0 - 32.8)	0.0 (0.0 - 13.0)	0.0 (0.0 - 10.0)	8.0 (0.0 - 37.8)	16.0 (1.5 - 101.3)	315.0 (0.0 -)	0	0.0 (0.0 - 26.8)
No action taken	First visit * &	35 (30%)	6 (17%)	24 (21%)	11 (37%)	8 (50%)	13 (32%)	1 (50%)	0 (0%)	98 (28%)
	Second visit * &	18 (21%)	4 (12%)	14 (18%)	4 (25%)	3 (38%)	11 (32%)	0 (0%)	NA	53 (21%)
Treatment initialized	First visit * &	75 (65%)	29 (83%)	90 (78%)	18 (60%)	7 (44%)	27 (66%)	1 (50%)	1 (100%)	248 (70%)
	Second visit * &	20 (23%)	4 (12%)	13 (17%)	3 (19%)	0 (0%)	5 (15%)	0 (0%)	NA	45 (18%)
Treatment continuation	First visit * &	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Second visit * &	25 (29%)	9 (27%)	23 (29%)	7 (44%)	2 (25%)	8 (24%)	1 (50%)	NA	75 (29%)
Treatment switch	First visit * &	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Second visit * &	22 (26%)	16 (48%)	25 (32%)	2 (13%)	3 (38%)	7 (21%)	1 (50%)	NA	76 (30%)
Diagnostic	First visit * &	4 (3%)	0 (0%)	1 (1%)	1 (3%)	1 (6%)	1 (2%)	0 (0%)	0 (0%)	8 (2%)
	Second visit * &	1 (1%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	3 (9%)	0 (0%)	NA	7 (3%)

Number of patients visiting a general practitioner (GP) divided per action taken by the GP for first and second visits.

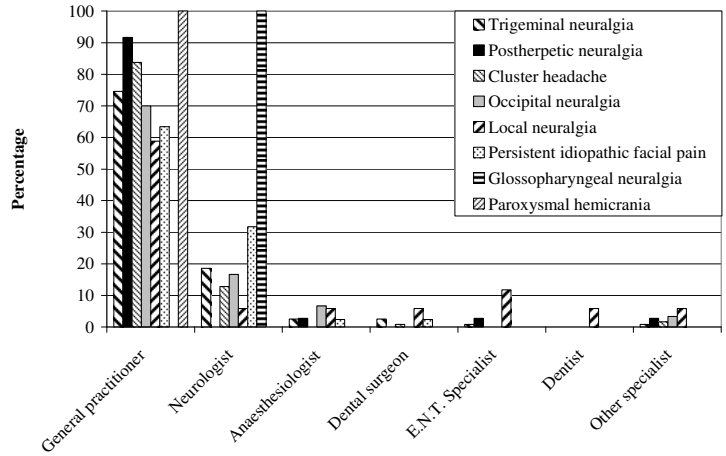
* Between brackets are the percentages as percentage of all people visiting a GP (first or second visit, whichever is applicable).

This is the median number of days between the index date and the date of diagnosis, first treatment of first investigation. Between brackets is the interquartile range.

& Mutually exclusive groups.

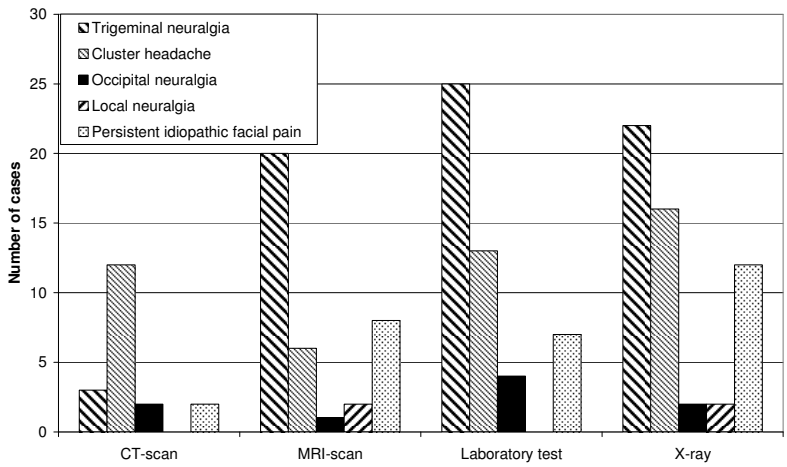
TGN: trigeminal neuralgia, PHN: postherpetic neuralgia, CH: cluster headache, ON: occipital neuralgia, LN: local facial neuralgias, PIFP: persistent idiopathic facial pain, GPN: glossopharyngeal neuralgia, PH: paroxysmal hemicrania.

Figure 1: Diagnosing physician



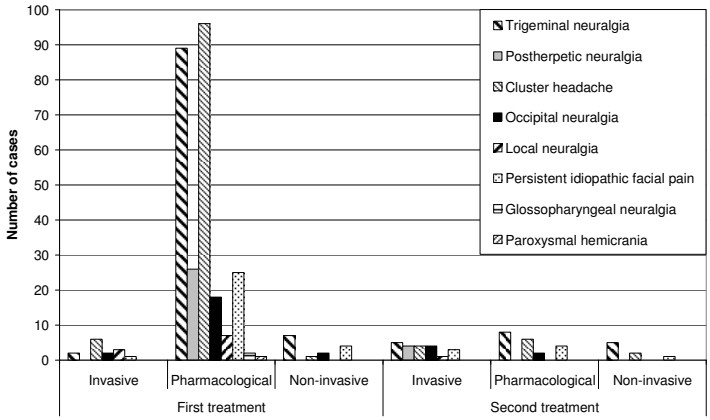
The figure displays the percentage of cases per specialist who diagnosed the disease and per disease. The general practitioner diagnosed most of the cases except for persistent idiopathic facial pain and glossopharyngeal neuralgia. E.N.T. Specialist: ear, nose and throat specialist.

Figure 2: Total investigations performed



The total number of investigation per disease is presented here divided by type of test performed. For postherpetic neuralgia, glossopharyngeal neuralgia and paroxysmal hemicrania there were no investigations performed.
CT-scan = computed tomography scan; mri-scan = magnetic resonance imaging scan

Figure 3: First and second form of treatment initialized



The first and second form of treatment initialized per disease is presented here. Many people undergo only one treatment, mostly pharmacologically. Non-invasive treatment includes dental interventions, physiotherapist interventions, homeopathy and gamma-knife.

Glossopharyngeal neuralgia had the longest treatment delay (median: 315.0 days; IQR: 0.0 -) of all diseases (Table 1). Pharmacotherapy was given to 297 patients at any time after diagnosis (82%). Besides glossopharyngeal neuralgia and paroxysmal hemicrania, of which all patients were treated, cluster headache patients were most frequently treated pharmacologically (90%) followed by trigeminal neuralgia patients (86%). Patients with trigeminal neuralgia were mostly treated with anti-epileptics (55%), patients with cluster headache with anti-migraine drugs (41%) (Figure 3).
In total, 182 (50%) of all patients visited a specialist, a dentist, physiotherapists or psychologists for facial pain. If only first referrals to medical specialists were studied, 135 (37%) patients were referred (Table 2). If all referrals during follow-up were taken into account, 160 (44%) patients were seen in secondary care at some point in time during follow-up. People were referred to a specialist a median of 1.0 (IQR: 0.0 – 2.0) time. The median time until first referral was 14.5 (IQR: 0.0 – 87.8) days (Table 2).
Overall, 26 (7%) patients with a form of facial pain received non-invasive treatment. Dental extraction and other dental therapies were performed in ten cases (3%). Most dental extractions (n = 6, 5% of cases) were performed in patients with trigeminal neuralgia. Physiotherapeutic interventions were used in nine cases (2%). In persistent idiopathic facial pain, a disease known for the many dental extractions performed, only one extraction was performed (2% of cases).
Only 37 patients (10%) received a form of invasive therapy. Local anesthetics (n = 13, 4%) were mostly given followed by percutaneous radiofrequency thermocoagulation of either ganglion of Gasser (n = 7, 2%) or the sphenopalatinum ganglion (n = 1, 0.3%). Of all studied forms of facial pain, patients with local facial neuralgias were most frequently treated invasively (24%); exclusively with local anaesthetics. Patients with trigeminal neuralgia were treated invasively in eight (7%) cases mainly with percutaneous radiofrequency thermocoagulation (n = 4, 3%). Similarly, only ten (9%) cluster headache patients were treated invasively, mostly with local anaesthesia (n = 6, 60%). Patients usually did not receive more than one form of treatment (Figure 3).

Table 2: Specialist referrals

Specialist		Diagnosis TGN	PHN	CH	ON	LN	PIFP	GPN	PH	Total
	N total	118	36	117	30	17	41	2	1	362
	N referred	62 (53%)	15 (42%)	52 (44%)	19 (63%)	10 (59%)	22 (54%)	2 (100%)	0 (0%)	182 (50%)
	Different specialists visited #	1.0 (0.0 - 2.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)	1.0 (0.0 - 1.0)	1.0 (0.0 - 1.0)	1.0 (0.0 - 2.0)			1.0 (0.0 - 1.0)
	Total specialist visits #	1.0 (0.0 - 2.0)	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.5)	1.0 (0.0 - 1.3)	1.0 (0.0 - 1.5)	1.0 (0.0 - 3.0)	2.0 (1.0 -)		1.0 (0.0 - 2.0)
	Time till referral *	12.0 (0.0 - 107.8)	2.0 (0.0 - 27.0)	23.5 (3.3 - 258.5)	1.0 (0.0 - 11.0)	6.0 (0.0 - 135.3)	33.0 (2.3 - 90.0)	323.0 (16.0 -)		14.5 (0.0 - 87.8)
Neurologist	As first specialist	23 (37%)	0 (0%)	33 (63%)	5 (26%)	1 (10%)	10 (45%)	2 (100%)	0 (0%)	74 (41%)
	As second specialist	15 (24%)	1 (7%)	3 (6%)	1 (5%)	1 (10%)	6 (27%)	0 (0%)	0 (0%)	27 (15%)
Anaesthesiologist	As first specialist	2 (3%)	3 (20%)	1 (2%)	2 (11%)	1 (10%)	1 (5%)	0 (0%)	0 (0%)	10 (5%)
	As second specialist	4 (6%)	3 (20%)	1 (2%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9 (5%)
Dental surgeon	As first specialist	4 (6%)	0 (0%)	1 (2%)	0 (0%)	1 (10%)	3 (14%)	0 (0%)	0 (0%)	9 (5%)
	As second specialist	4 (6%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)	2 (9%)	0 (0%)	0 (0%)	8 (4%)
E.N.T. Specialist	As first specialist	8 (13%)	1 (7%)	4 (8%)	1 (5%)	4 (40%)	1 (5%)	0 (0%)	0 (0%)	19 (10%)
	As second specialist	2 (3%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)	2 (9%)	0 (0%)	0 (0%)	6 (3%)
Dentist	As first specialist	15 (24%)	0 (0%)	7 (13%)	0 (0%)	1 (10%)	3 (14%)	0 (0%)	0 (0%)	26 (14%)
	As second specialist	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Phsyiotherapist	As first specialist	4 (6%)	0 (0%)	2 (4%)	10 (53%)	0 (0%)	2 (9%)	0 (0%)	0 (0%)	18 (10%)
	As second specialist	4 (6%)	0 (0%)	3 (6%)	4 (21%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (6%)
Other specialist	As first specialist	5 (8%)	11 (73%)	4 (8%)	1 (5%)	2 (20%)	2 (9%)	0 (0%)	0 (0%)	25 (14%)
	As second specialist	1 (2%)	2 (13%)	1 (2%)	0 (0%)	1 (10%)	2 (9%)	0 (0%)	0 (0%)	7 (4%)

Specialist referrals per disease and per specialist, first as well as second referrals. Between brackets are the percentages as percentage of all people referred to a specialist.
* Median delay between index date and date of diagnosis in days.
# Medians with interquartile range are presented.
TGN: trigeminal neuralgia, PHN: postherpetic neuralgia, CH: cluster headache, ON: occipital neuralgia, LN: local facial neuralgias, PIFP: persistent idiopathic facial pain, GPN: glossopharyngeal neuralgia, PH: paroxysmal hemicrania.

Discussion

This study showed that diagnostic workup was usually quick with 75% being performed within 44 days. Diagnosis was most quickly made by a GP without using additional investigations. Most patients had a form of primary facial pain. A GP was visited a median number of three times. This frequently lead to treatment initiation (first visit) or treatment prolongation or switch (subsequent visits). A minority was referred to secondary care. Treatment was mostly initiated immediately and pharmacologically. The main findings of our study include extensive data on healthcare consumption and diagnostic work-up of eight forms of facial pain, namely trigeminal neuralgia, cluster headache, postherpetic neuralgia in the facial area, occipital neuralgia with referred facial pain, glossopharyngeal neuralgia, local facial neuralgias, glossopharyngeal neuralgia or persistent idiopathic facial pain. Most people are treated in primary care and only half is ever referred to a specialist, dentist, physiotherapist or psychologist.

Literature regarding the burden of disease and health care use of facial pain is scanty and mostly concerns trigeminal neuralgia and cluster headache. Secondary trigeminal neuralgia has been reported in 10-20% of trigeminal neuralgia. [36, 111, 141-146] A pooled analysis yielded an estimate of 15% [95% CI: 11% - 20%]. [147] This differs substantially from our finding of secondary causes in 3%. This discrepancy may be explained by the different settings. Previous reports studied a secondary care population which cannot be generalized to a primary care setting. [12, 141-146] Alternatively, our numbers might be an underestimation since not all patients underwent additional investigations.

Forty-three percent of cluster headache patients visiting their GP in the last year. [5] The same percentage visited a specialist in the last year and 1.2% underwent a hospital admission. [5] In other studies, the average delay between start of symptoms and diagnosis in cluster headache has been reported to be 2.6 - 6.6 years. [138, 139] Furthermore, 5-13% of patients underwent a form of surgery related to cluster headache and 58% underwent a form of non-medical treatment (physical therapy, acupuncture, etc). [5, 138, 139] Additional investigations were done in 58-75% undergoing either a CT-scan or MRI-scan. [138, 139] The proportion referred to a specialist was 70% with 42% visiting a dentist. [5, 138] We reported the diagnostic delay to be zero days, 8.5% received a form of invasive treatment and 15% undergoing a CT- or MRI-scan. Furthermore, patients visited their GP a median of three times during the course of their disease which agrees well. However, we did find a lower numbers for specialist referrals (50% total) and neurologist as diagnosing specialist (16%). Only 3% underwent non-invasive treatment either as first or as second treatment. There are some possible explanations for this difference. Firstly, it might be a difference in study design and data sources (internet questionnaires vs electronic GP records). Questionnaires may be subject to recall bias and patient recruitment through a website may cause selection bias. Recall bias might have led to a differential misclassification of the outcome since more severe patients might remember their procedures more accurately and might have undergone more procedures. Selection bias might have led to inclusion of more (or less) severe patients since these are more likely to participate and these patients might differ substantially from patients in primary care. We might underestimate the number of paramedical visits because these might not be documented by a GP, although we performed a manual free text search. Furthermore, time trends may explain differences. A decrease in mean time to diagnosis from 12 years (before 1950) to 2.6 years (1990-1999) was reported. [138]

A large multicountry study in Europe about the impact of chronic pain showed 60% of patients to visit their doctor for their pain 2-9 times in the last six months. [114] Only 2% were currently treated by a pain management specialist. [114] 66% used non-medical treatments such as massage (30%), physical therapy (21%) or acupuncture (13%). [114]

Regarding trigeminal neuralgia, a study about the burden of disease in primary care reported that 78% of trigeminal neuralgia patients visited their physician at least once during the past four weeks. [148] Almost half (45%) even visited their GP two or more times while 53% were evaluated by a pain specialist. [148] Almost one-third (30.5%) received physical therapy. [148] This is comparable to our finding that 50% visits a specialist.
Our study possibly has some limitations besides the ones already mentioned above. To ensure a complete case series we performed a broad and sensitive search algorithm followed by extensive validation including revisions by a neurologist to ensure the validity of a diagnosis. Nevertheless, since accurate description of symptoms was sometimes lacking, there might be some misclassification of the index date and diagnostic delay, and misclassification of facial pain. To minimize misclassification of facial pain we employed an extensive validation process including GP confirmation and double review of electronic patient records. Furthermore, given the nature of our database, we rely on the accuracy of GP registration. Assuming GPs have an under registration of investigations and treatment performed and depend on specialist communication / letters, we may underestimate the number of procedures and investigations performed. To minimize this, we manually evaluated specialist letters and GP questionnaires in which GPs were asked to supply us with investigations performed. Since only half the patients are referred to a specialist and 37 patients underwent either a CT- or MRI-scan, we might severely underestimate the number of patients with secondary facial pain. On the other hand, one might question the validity of this underestimation since most people apparently do not suffer severe adverse effects from missed underlying diseases.

Despite the above mentioned limitations we think our report offers a valuable contribution with sound epidemiological data on healthcare consumption and diagnostic work-up of eight rare forms of facial pain. We can conclude that many patients are primarily treated by a GP without being referred to secondary case and without undergoing additional investigations. Given our low percentage of secondary trigeminal neuralgia, additional investigations might not be required to exclude secondary causes although further investigations are needed to give a definitive answer.

4.6

A nation-wide study of three invasive treatments for trigeminal neuralgia

Submitted

Joseph SHA Koopman, MD [1], Laura M de Vries [3, 4], Jeanne P Dieleman, PhD [1], Frank. J Huygen, PhD [2], Bruno HCh Stricker, PhD [1, 3, 4], Miriam CJM Sturkenboom, PhD [1, 3]

[1] Dept. of Medical Informatics, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[2] Dept. of Pain Treatment, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[3] Dept. of Epidemiology, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands
[4] Dept. of Pharmaceutical Affairs and Medical Technology, Health Care Inspectorate, The Hague, the Netherlands

Abstract

Background: Invasive procedures for treatment of trigeminal neuralgia (TGN) consist namely of percutaneous radiofrequency thermocoagulation (PRT), partial sensory rhizotomy (PSR) and microvascular decompression (MVD).
Methods: We described the frequency of use, patient characteristics and evaluated treatment failure. For this we used a nationwide discharge registry from the Netherlands. Each patient undergoing a PRT, PSR or MVD between 1-1-2002 and 31-12-2004 and without a procedure in the year prior were included. Primary outcome was readmission for repeat procedures for TGN or known complications within one year. Comparability of patient populations was assessed through propensity scores based on hospital, age, sex and comorbidity. Conditional logistic regression matched on propensity score was used to calculate relative risks (RR) with 95% confidence intervals (95% CI) for repeat procedures or complications.
Results: During our study period, 672 patients with TGN underwent PRT, 39 underwent PSR and 87 underwent MVD. Hospital was the predominant determinant of the type of procedure while age, sex and comorbidity were weak predictors. The RR for repeat procedures for PSR was 0.21 [95% CI: 0.07 - 0.65] and the RR of MVD 0.13 [95% CI: 0.05 - 0.35]. For complications, the RR of PSR was 5.36 [95% CI: 1.46 - 19.64] and of MVD 4.40 [95% CI: 1.44 - 13.42]. Sex, urbanization and comorbidity did not influence prognosis but hospital and surgical volume did.
Conclusions: MVD and PSR are associated with a lower risk of undergoing a repeat procedure compared to PRT. However, MVD and PSR seem to be more prone to complications requiring readmission in hospital.

Introduction

Trigeminal neuralgia is a severe form of facial pain presenting with paroxysmal, unilateral pain in one or more branches of the fifth cranial nerve. [36] It has an estimated annual incidence of 12.6 per 100,000 person years. [2] It can be either idiopathic or secondary to diseases such as tumors, infarction and multiple sclerosis. [12, 149-152] Idiopathic trigeminal neuralgia is currently hypothesized to be caused by neurovascular contact between an aberrant vein or artery and the fifth cranial nerve at the root entry zone. [39] The three most common invasive modalities for the treatment of idiopathic trigeminal neuralgia are microvascular decompression, partial sensory rhizotomy and percutaneous radiofrequency thermocoagulation. During microvascular decompression a teflon patch is placed between the nerve and vascular structure using an open brain surgical approach. [153] Partial sensory rhizotomy and percutaneous radiofrequency thermocoagulation are both destructive techniques aiming to destroy a part of Gasserians ganglion by respectively a neurosurgical or a minimal invasive röntgen-guided approach. [154, 155]

Partial sensory rhizotomy is sometimes used as an alternative for microvascular decompression if arterial contact cannot be found, but it is also an open neurosurgical procedure with risks comparable to those of microvascular decompression. [155] A literature study describing long term outcomes of individual treatment modalities indicate that microvascular decompression has a better effectiveness than percutaneous radiofrequency thermocoagulation, but also a higher rate of adverse events. [156] Studies included in this review concerned mainly cohort studies of individual procedures with more than five years of follow-up. These studies, however, have not been performed in one data source and therefore do not allow for a direct comparison of procedures. To our knowledge no randomized clinical trials have been performed.

At present the frequency of use of the individual invasive treatment modalities for trigeminal neuralgia in daily practice is not known and comparisons of the safety and effectiveness of the different treatment modalities on a population-based scale are lacking. Direct comparisons between the treatment modalities using one data source have not been reported. Furthermore, reports on prognostic factors for the success rate of individual treatment modalities remain contradictory. [157] In order to describe the frequency of use of microvascular decompression, partial sensory rhizotomy and percutaneous radiofrequency thermocoagulation and to compare the complication and failure rate of these modalities on a nationwide scale, we performed a cohort study using a database with hospital discharge diagnoses with complete coverage of the population in the Netherlands.

Methods

Source population

Data were retrieved from a nationwide electronic database with hospital discharge records, that covers admissions in nearly all general and university medical centers in the Netherlands (Landelijke Medische Registratie). The database includes, among others, demographics, date of admission and discharge, main intervention (coded), medical specialism (coded) and the main and secondary diagnoses at discharge, based on the ICD-9-CM coding system. [158] Characteristics of hospitalizations are recorded by medical specialists or residents and coded by professional code clerks on the basis of hospital discharge letters. For every admission, one discharge/main diagnosis (mandatory), and up to nine secondary diagnoses (optional) are registered. This is done similarly for interventions. The coding is independent of reimbursement of hospital or specialist. Patients and hospitals are anonymized to allow for secondary use and processing of the data. All diagnoses are submitted in the same format, mostly electronically. The database used for this study comprised

data from 1 January 2001 up to and including 31 December 2005. More recent data are not available due to a change in the registration system in the Netherlands, which has resulted in incompleteness of the registry after 2005.

Cohort definition
For incidence rate calculations, the study base comprised the entire population of the Netherlands during the study period between 1 January 2002 and 31 December 2004. For all other analyses we generated a cohort of patients admitted for microvascular decompression (ICD-9 codes: 5-014.0), partial sensory rhizotomy (intervention code (ICD-9 codes): 5-014.1, 5-014.2) or percutaneous radiofrequency thermocoagulation (ICD-9 codes: 5-043.2) all with trigeminal neuralgia as main diagnosis during the study period. Patients who had one of the procedures in the year prior to study entry were excluded from the cohort. Each cohort member was followed until the earliest of one of the following events: admission for a complication, repeat procedure (any of the three studied) or end of a one year follow-up period, whichever came first.

Outcome definition
The primary outcome parameters in this study were frequency of use, plus complications and treatment failure leading to hospital readmission within one year of the initial admission. Complications included hospitalizations for hearing loss, dysaesthesia, persistent neurological deficit, death, cerebrospinal fluid leakage, facial hypaesthesia, meningitis, ataxia, heamatoma, infarctions, pulmonary embolisms, herpes labialis, vertigo, tinnitus, an- or hypacusis, facial spasms, trochlear and acoustic palsy, facial paresis, severe brain damage, keratitis, sensory loss, corneal hypaesthesia, arteriovenous fistula, bleeding, loss of sight, corneal anesthesia, facial asymmetry and all ICD-9 codes specifically specifying complications of procedures (appendix C). [153, 155, 156, 159-165] Complications were identified based on the ICD-9 codes of the main or secondary diagnoses. Treatment failure was defined as a readmission for one of the studied procedures for treatment of trigeminal neuralgia or for other reasons (e.g. pharmacological treatment) with trigeminal neuralgia mentioned as primary or secondary diagnosis. The index date for complications and failure was the date of hospital admission.
In addition to readmission rates for first complication or repeat procedure, we examined the duration of hospital stay of the initial procedure (index hospitalization) and in-hospital mortality of the index hospitalization as secondary outcomes. To evaluate complications and treatment failure after discharge, patients were linked by patient number (same hospital) and gender, date of birth and postal code (other hospitals).

Covariates
We considered the patient related (age, sex, urbanization level, comorbidity, specialism performing the procedure) and hospital related variables (surgical procedure volume per hospital, type of hospital) as potential confounders and prognostic factors. These factors might be related to treatment choice and outcome based on either clinical judgment or literature. The year prior to the index hospitalization was used to assess the presence of comorbidity (leading to hospital admission) on the basis of discharge diagnoses during that year. Comorbidity was categorized according to the Charlson comorbidity index adapted for ICD-9 CM. [166, 167] During the study period, there were 105 hospitals in the Netherlands, of which eight were university medical centers. To compare the experience with a specific procedure between hospitals we classified the surgical volume (i.e. number of procedures performed) for each procedure in each hospital into quintiles. Quintiles were based on the distribution of surgical volumes in the population. A surgical volume category of one meant that the hospital belonged to the 20% hospitals with the lowest surgical volume in a certain procedure (in-

cluding zero procedures). A score of five meant that the hospital belonged to the group of 20% hospitals with the highest surgical volume. The scores related to the three different procedures were then added together in one overall score ranging from 3 to 15, under the assumption that all types of procedures add to the experience of hospitals and surgeons. [153] Urbanization of the home address was evaluated using postal code data from Statistics Netherlands. [1] Very urban indicated more than 2500 houses per squared kilometer. Moderately urban is between 1500 and 2500, normal between 1000 and 1500, moderately rural between 500 and 1000 and very rural below 500 houses per squared kilometer.

Analysis

For each treatment modality we calculated the incidence rate by dividing the number of procedures by the total Dutch population for that year according to Statistics Netherlands. [1]

Failure and complication risks were calculated for each type of intervention at 1 month, 1-2 months, 2-3 months and 3-12 months after the initial hospitalization by Kaplan-Meier analysis. Rates of failure and complication were calculated by dividing the number of readmissions by the total number of person years (patients could count multiple times). 95% Confidence intervals (95% CI) were calculated based on a binomial distribution.

To study whether we could compare outcomes between treatment groups we calculated propensity scores for each procedure with percutaneous radiofrequency thermocoagulation as reference category. [168] Overlapping propensity scores of different procedures would indicate comparable treatment groups allowing for calculation of relative risks for complications and repeat procedures. Propensity scores were calculated for each procedure separately. The following variables were included in the model: the Charlson comorbidity score, sex, age and the type of treating hospital using logistical regression analysis. The final propensity score included all of these covariates for all procedures. Since we expected the treating hospital to be a very large predictor for type of procedure, we calculated a second propensity score model including age, sex and chronic disease score. Conditional logistic regression with matching on propensity score (including age, sex and comorbidity within bins of 0.1) was used to yield relative risks (RR) for partial sensory rhizotomy and microvascular decompression. Percutaneous radiofrequency thermocoagulation was taken as reference category. A Cox proportional hazards model was used to analyze prognostic factors for treatment failure.

A sensitivity analysis was performed including only specific complications described in literature (all of the above except the ICD-9 codes specifically specifying complications of procedures). [153, 155, 156, 159-165] Furthermore, to ensure complications were due to the index hospitalization and not due to other interventions after the index hospitalization a sensitivity analysis was performed in patients without hospitalizations between the index hospitalization and the first complication. Further sensitivity analyses included only patients operated in 2004 and taking into account only complications and readmissions stated as primary discharge diagnosis (not as additional diagnoses). Hospitalization data only provide information on in-hospital death and death may impact on the failure rates. Therefore we conducted a survival analysis with imputed survival data to take into account deaths occurring during follow-up. Survival data was imputed using the age and gender specific mortality data of the general Dutch population from 2003 as provided by Statistics Netherlands (CBS). [1] Imputation of survival data was done using R (version 2.7.12). [123] Five possible dates of death were imputed based on age and gender. The Kaplan Meier analyses were redone using this imputed survival data. In compliance with the method of multiple imputations the rates and the standard errors were averaged. [169] All statistical analyses were conducted in SPSS 15.0 (SPSS inc, Chicago, III).

Table 1: Baseline characteristics

	Percutaneous Radiofrequency Thermocoagulation	Partial sensory rhizotomy	Microvascular decompression	Total	P-value #
N	672	39	87	798	-
Incidence rate / 1.000.000 persons per year [95% CI]	13.8 [12.8; 14.9]	0.8 [0.6; 1.1]	1.8 [1.4; 2.2]	16.4 [15.3; 17.6]	
Average age (SD)	67.3 (12.9)	58.0 (14.0)	57.8 (13.0)	65.8 (13.4)	<0.01
Male sex (%)	288 (42.8%)	15 (38.5%)	43 (49.4%)	346 (43.4%)	0.42
Mean duration of first Admission (SD)	1.52 (1.52)	10.44 (6.55)	7.59 (2.55)	2.62 (3.38)	<0.01
Urbanization					0.01
Very urban	107 (16.2%)	9 (23.1%)	10 (11.8%)	126 (16.0%)	
Moderately urban	148 (22.4%)	14 (35.9%)	13 (15.3%)	175 (22.3%)	
Normal	122 (18.4%)	10 (25.6%)	16 (18.8%)	148 (18.8%)	
Moderately rural	150 (22.7%)	6 (15.4%)	22 (25.9%)	178 (22.6%)	
Very rural	135 (20.4%)	0 (0.0%)	24 (28.2%)	159 (20.2%)	
Comorbidity index*					0,64
0 (%)	640 (95.2%)	39 (100.0%)	85 (97.7%)	764 (95.7%)	
1 (%)	21 (3.1%)	0 (0.0%)	1 (1.1%)	22 (2.8%)	
2 (%)	4 (0.6%)	0 (0.0%)	1 (1.1%)	5 (0.6%)	
3 (%)	7 (1.0%)	0 (0.0%)	0 (0.0%)	7 (0.9%)	
Type of specialist					<0.01
Neurosurgeon (%)	70 (10.4%)	39 (100.0%)	86 (98.9%)	195 (24.4%)	
Anesthesiologist (%)	601 (89.4%)	0 (0.0%)	0 (0.0%	601 (75.3%)	
Other (%)	1 (0.2%)	0 (0.0%)	1 (1.1%)	2 (0.2%)	
Type of hospital					<0.01
General (%)	653 (97.2%)	12 (30.8%)	37 (42.5%)	702 (88.0%)	
Academic (%)	19 (2.8%)	27 (69.2%)	50 (57.5%)	96 (12.0%)	

Between square brackets, the 95% confidence interval is given. # chi-square analysis for categorical analysis, t-test for continuous variables

*The comorbidity index is based on the Charlson comorbidity score.

Results

Incidence

Between 1 January 2002 and 31 December 2004, 87 microvascular decompressions, 39 partial sensory rhizotomies and 672 percutaneous radiofrequency thermocoagulations were performed. The incidence rate of the three studied invasive procedures for trigeminal neuralgia in the Dutch population was 16.4 per million persons per year [95% CI: 15.3 - 17.6] (Table 1). The rates were highest between the age of 70 and 79 for all procedures and the rate remained more or less stable over calendar time (Figure 1a + b).

Baseline characteristics

Patients undergoing an intervention for trigeminal neuralgia during the study period were on average 65.8 years of age (standard deviation (SD): 13.4) and a minority was male (43%) (Table 1). Patients were generally healthy with a mean Charlson comorbidity index of zero. The average number of procedures performed per hospital per year was 5.54 (SD: 8.94). Percutaneous radiofrequency thermocoagulation was the most widely applied procedure with a high average relative surgical volume level compared to that of partial sensory rhizotomy and microvascular decompression (1.17, 0.44 and 0.31 procedures per hospital respectively). Finally, patients undergoing percutaneous radiofrequency thermocoagulation were on average older and had a shorter hospital stay than patients admitted for the other procedures. There were large differences in hospital and physician characteristics between the three procedures (Table 1).

Complications / therapeutic failure

In total, 33.8% of patients were readmitted for a repeat procedure (2.4%) or a complication (31.6%) within one year following the initial procedure (Table 2). The one year readmission risk derived from Kaplan-Meier analysis was 34% [95% CI: 30 - 37%] for all procedures together. The one year readmission risk was lowest with microvascular decompression (9%; [95% CI: 3% - 15%]) and highest for percutaneous radiofrequency thermocoagulation (38%; [95% CI: 34% - 42%]) (Table 2 & Figure 2).

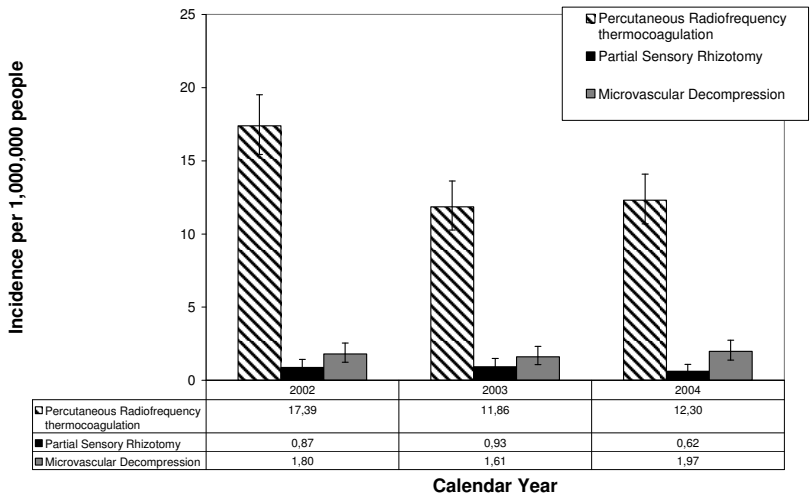
Most complications occurred within the first month (31.6%) after the initial procedure. The risk of complications was lowest for percutaneous radiofrequency thermocoagulation (2% versus 8% and 6%). The majority of complications were unspecific procedure complication codes (61%). Specified complications included Bell's palsy (11%), infections (5%), anaphylactic shock (6%), hemiplegia (6%), aspiration (6%), hematoma (6%) and respiratory complications (6%). Most repeat procedures took place between the third and ninth month (36.5%) after the initial procedure.

A propensity score model based on hospital, age, sex and comorbidity could accurately predict which treatment was given (Figure 3a) (c-statistic 0.99). There was, however, poor overlap. If hospital was excluded from the propensity score the model performed worse (c-statistic 0.70) but there was considerable overlap showing that actually the hospital was important for the decision which treatment to perform and not so much the patient (Figure 3b). After matching on propensity score (not considering hospital), the relative risk of partial sensory rhizotomy for readmission (both complications or repeat procedures) was 0.40 [95% CI: 0.18 - 0.90], 5.36 [95% CI: 1.46 - 19.64] for complications and 0.21 [95% CI: 0.07 - 0.65] for repeat procedures. Microvascular decompression had a relative risk of 0.25 [95% CI: 0.12 - 0.52] for total readmission, 4.40 [95% CI: 1.44 - 13.42] for complications and 0.13 [95% CI: 0.05 - 0.35] for undergoing a repeat procedure. Most people undergoing a percutaneous radiofrequency thermocoagulation underwent a percutaneous radiofrequency thermocoagulation as repeat procedure while most people undergoing a partial sensory rhizotomy underwent this procedure again as repeat procedure. In contrast, after microvascular

Figure 1a: Incidence of individual treatments

The figure displays the incidence per 1,000,000 people per age category in the Netherlands. Treatments are applied more in older people, which is to be expected since the incidence of trigeminal neuralgia increases with age. Neurovascular treatment is not used after the age of 80.

Figure 1b: Incidence rate per calendar year



	2002	2003	2004
Percutaneous Radiofrequency thermocoagulation	17,39	11,86	12,30
Partial Sensory Rhizotomy	0,87	0,93	0,62
Microvascular Decompression	1,80	1,61	1,97

The y-error bars display the 95% confidence interval. The incidence rate of most treatment modalities is more or less stable over time.

Table 2: Characteristics of readmissions following initial procedure for trigeminal neuralgia

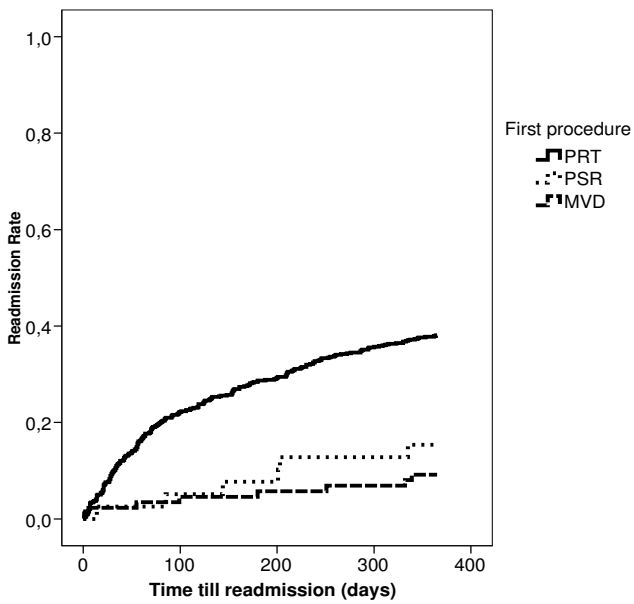
	Percutaneous Radiofrequency Thermocoagulation	Partial Sensory Rhizotomy	Microvascular Decompression	Total
Readmission total (%)	256 (100%)	6 (100%)	8 (100%)	270 (100%)
Complication (%)	11 (4.3%)	3 (50.0%)	5 (62.5%)	19 (7.0%)
Repeat procedure (%)	245 (95.7%)	3 (50.0)	4 (37.5%)^	252 (93.0%)^
Repeat procedure				
Percutaneous Radiofrequency Thermocoagulation (%)	196 (80.0%)	0 (0.0%)	2 (50.0%)	198 (78.6%)
Partial Sensory Rhizotomy (%)	2 (0.8%)	2 (66.7%)	1 (25.0%)	5 (2.0%)
Microvascular Decompression (%)	6 (2.4%)	0 (0.0%)	1 (25.0%)	7 (2.8%)
Other or unspecified (%)*	41 (16.7%)	1 (33.3%)	0 (0.0%)	42 (16.7%)
One year readmission risk #	38 [34; 42]	15 [4; 27]	9 [3; 15]	34 [30; 37]
One year complication risk #	2 [1; 3]	8 [0; 16]	6 [1; 11]	3 [2; 4]
One year risk for repeat procedure #	37 [33; 41]	8 [0; 17]	5 [0; 9]	32 [29; 35]

This table displays the prevalence and type of readmission within one year according to type of initial procedure for trigeminal neuralgia.
* Admission for trigeminal neuralgia without a specific intervention listed. A reason for readmission without intervention can be drug treatment.
^ There is one patient admitted for both a repeat procedure and a complication.
# Calculated by using Kaplan-Meier analysis with days from discharge until readmission as follow-up time. Between square brackets are the 95% confidence intervals. SD = standard deviation.

decompression most people had a percutaneous radiofrequency thermocoagulation as second procedure (Table 2).
Sensitivity analyses considering only patients operated in 2004, or only healthy patients (Charlson comorbidity index of zero), or only in literature specified complications, or only main diagnoses or using imputed survival data showed that the results and conclusions did not materially change ($p>0.05$).
Concerning our secondary outcomes; the admission duration of the index hospitalization was 2.62 days (SD: 3.38). No patients died during hospital stay [95% CI: 0.0% - 0.4%].

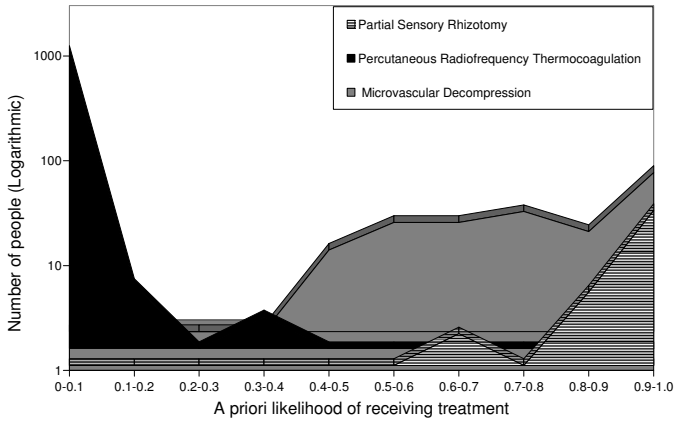
Prognostic factors
Sex, age, comorbidity, surgical volume, urbanization and hospital (aggregated) were evaluated as prognostic factors for treatment failure. Cox regression analysis, stratified by the type of first procedure showed surgical volume and type of hospital to be associated with failure (Table 3). Only the second and fifth group of surgical volume were associated with an increased risk of failure (OR: 1.54; [95% CI: 1.10 - 2.16]) and 1.53 [95% CI: 1.07 - 2.20] respectively). However, no clear volume-success relationship (i.e. dose-effect) could be shown. Being treated in a general hospital was associated with an increased risk of failure (OR: 4.81; [95% CI: 2.47 - 9.34]) compared to being treated in a university hospital.

Figure 2: Survival curve



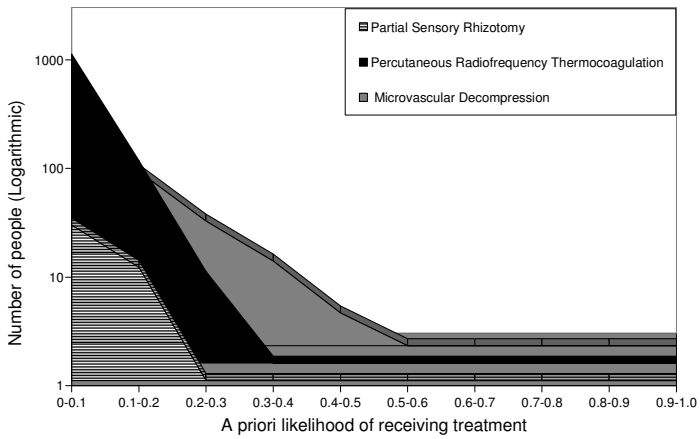
Of the three studied treatment modalities, the percutaneous radiofrequency thermocoagulation had the highest risk of readmission. PRT: percutaneous radiofrequency thermocoagulation PSR: partial sensory rhizotomy MVD: microvascular decompression.

Figure 3a: Propensity scores including treatment hospital



The propensity scores of partial sensory rhizotomy and microvascular decompression are shown with percutaneous radiofrequency thermocoagulation as reference category. Treating hospital, age, sex and the Charlson comorbidity were entered in the propensity score model. There is little overlap in the propensity scores of the different treatment modalities. This means that we can accurately predict treatment received.

Figure 3b: Propensity scores excluding hospital



The same is shown as in figure 3a except we only included age, sex and Charlson comorbidity index. Although we can not predict treatment given there is overlap between the different treatment modalities. This shows that the hospital patients are referred to mainly determined the chosen procedure and not patient characteristics like age, sex and comorbidity. This enables a direct comparison of treatment modalities.

Table 3: Prognostic factors

	Percutaneous radiofrequency thermocoagulation	Partial sensory rhizotomy	Microvascular decompression	Total
Age	0.92 [0.72; 1.18]	1.30 [0.24; 7.08]	7.18 [0.88; 58.39]	1.01 [0.79; 1.28]
Sex	1.01 [1.00; 1.02]	0.96 [0.00; 1.02]	1.00 [0.95; 1.05]	**1.01 [1; 1.02]**
Comorbidity index				
0	Ref	NA	Ref	Ref
1	1.21 [0.62; 2.36]	NA	0.05 [0.00; ∞]	1.33 [0.68; 2.58]
2	**4.19 [1.34; 13.12]**	NA	0.05 [0.00; ∞]	2.92 [0.94; 9.13]
3	0.73 [0.18; 2.92]	NA	NA	0.85 [0.21; 3.4]
Hospital				
University	Ref	Ref	Ref	Ref
General	**4.56 [1.13; 18.32]**	0.03 [0; 32.85]	**10.35 [1.27; 84.12]**	**4.81 [2.47; 9.34]**
Surgical volume				
1	Ref	NA	Ref	Ref
2	**1.49 [1.06; 2.08]**	Ref	98257.15 [0.00; ∞]	**1.54 [1.1; 2.16]**
3	0.76 [0.33; 1.78]	0.85 [0.05; 13.68]	86540.31 [0.00; ∞]	0.8 [0.38; 1.68]
4	0.94 [0.60; 1.48]	NA	NA	0.99 [0.63; 1.56]
5	**1.50 [1.04; 2.15]**	1.42 [0.15; 13.64]	NA	**1.53 [1.07; 2.2]**
6	0.49 [0.23; 1.02]	0.19 [0.01; 3.05]	15163.02 [0.00; ∞]	0.29 [0.17; 0.52]
Urbanization				
Very urban	Ref	Ref	Ref	Ref
Moderately urban	0.97 [0.66; 1.44]	0.59 [0.08; 4.20]	0.70 [0.10; 4.99]	0.94 [0.64; 1.36]
Normal	0.84 [0.55; 1.29]	0.43 [0.04; 4.80]	0.86 [0.14; 5.16]	0.82 [0.54; 1.22]
Moderately rural	0.88 [0.59; 1.31]	0.68 [0.06; 7.55]	0.20 [0.02; 2.19]	0.82 [0.56; 1.2]
Very rural	0.89 [0.59; 1.33]	NA	0.00 [0.00; ∞]	0.8 [0.54; 1.19]

In bold are the statistically significant predictors of treatment failure. Ref is reference category, NA is not assessable (no cases in that group).

Discussion

This study showed that percutaneous radiofrequency thermocoagulation was the most frequently applied invasive procedure for trigeminal neuralgia with 13.8 procedures per 1 million person years per calendar year. The rate of invasive procedures did not materially change over time. Given an estimated prevalence of trigeminal neuralgia in the Netherlands of 1600 per 1 million persons approximately 1% of persons with trigeminal neuralgia undergo a first invasive procedure each year. [170] The type of procedures performed were strongly hospital, age and specialist dependent. Partial sensory rhizotomy and microvascular decompression were more likely to be carried out in specialized centers than percutaneous radiofrequency thermocoagulation. Percutaneous radiofrequency thermocoagulation was mostly performed by anesthesiologists while partial sensory rhizotomy and microvascular decompression were almost exclusively carried out by neurosurgeons. Microvascular decompression had the lowest relative risk for readmission (either complications or repeat procedures), mainly because of a lower risk for repeat procedures. Microvascular decompression had, however, a higher complication risk compared to percutaneous radiofrequency thermocoagulation. Readmission was not associated with sex, urbanization and comorbidity, which is in line with previous reports. [171] It was, however, positively associated with surgical volume (low and high) and receiving treatment in a general hospital. Our finding that younger patients more frequently underwent microvascular decompression is in line with current practice. [172] This is presumably due to the allegedly longer effect of microvascular decompression and presence of comorbidity in older patients which makes it difficult to conduct that intervention. [172]

Percutaneous radiofrequency thermocoagulation showed the lowest absolute complication rate but the highest failure rate which is in line with recent reviews. [156, 157, 164, 173, 174] One study compared microvascular decompression to percutaneous radiofrequency thermocoagulation and reported an

equal effect but a lower long-term complication rate for microvascular decompression. [175] Our study shows a difference in effect, but this may be because we only assessed serious complications requiring a readmission, which do not represent the total range of adverse events. Assuming that neurosurgical interventions have a higher percentage of adverse events requiring hospitalization, this will lead to a selective underestimation favoring percutaneous radiofrequency thermocoagulation. The high failure rate of percutaneous radiofrequency thermocoagulation might have several reasons. Compared to microvascular decompression which is usually performed by experienced neurosurgeons, percutaneous radiofrequency thermocoagulation is also performed by less experienced doctors. Furthermore, to avoid anesthesia dolorosa, doctors will be careful to apply too much coagulation. They prefer to conduct the operation in two stages instead of risking adverse events. The low complication rate of percutaneous radiofrequency thermocoagulation is especially noteworthy since it is more often performed in high risk (older) patients.

Limitations

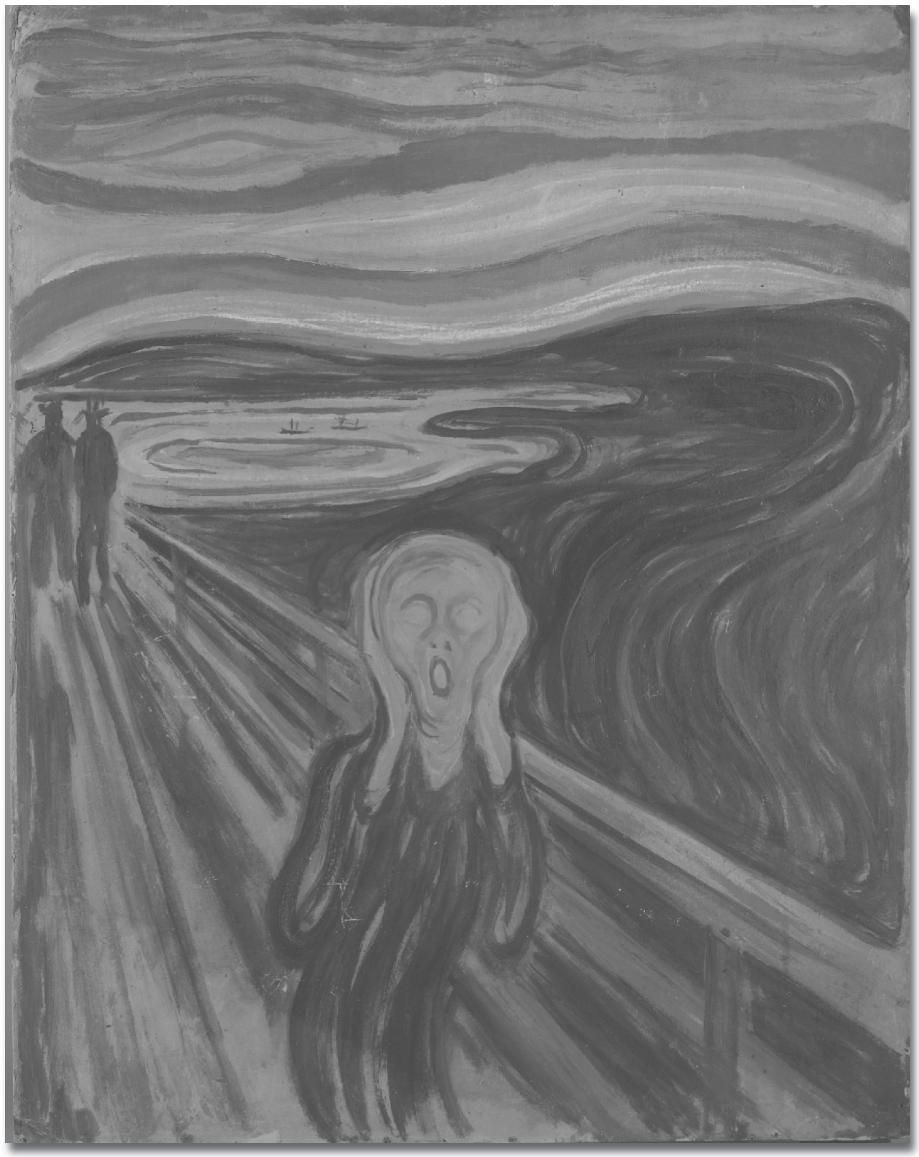
Being an observational study using a hospital registry we have to consider the influence of potential misclassification and confounding. There are several sources of misclassification. Firstly, the failure rate may be an underestimation, since not every failure requires readmission as some recurrences may be treated conservatively. Our study did not focus on failure that could be addressed in an outpatient setting. Secondly, admission for complications after the intervention may have been the result of other hospitalizations during follow-up, this issue was explored by exclusion of patients with other hospitalization during follow-up. This did not change the results substantially. Thirdly, since the database only captures in-hospital deaths and not the outpatient deaths, people dying the year after readmission are lost to follow-up and cannot count in the numerator which may lead to an underestimation of risks. Due to differences in age, this is less likely to happen for microvascular decompression and more for the other interventions. People undergoing a MVD are younger and thus less likely to die out of the hospital. To minimize this bias, we imputed age and gender specific survival data from the general Dutch population, the relative risk estimated did not change substantially.

The fourth limitation of our study is the low number of prognostic variables and the lack of specific prognostic factors such as disease severity. Previous destructive surgery, a known risk factor for an unfavorable outcome of microvascular decompression and partial sensory rhizotomy, could not be considered in our analyses since we only had one year of history available. [153, 155] Patients undergoing a destructive procedure in that year were excluded from the analysis to minimize possible confounding. To further limit residual confounding due to the fact that we had limited prior history data we performed a sensitivity analysis amongst people undergoing a procedure in 2004, for these persons we had three years of prior history, the results in these patients were consistent with the main analysis showing that residual confounding due to a short availability of information is limited. Finally, known prognostic factors such as having a clear-cut and marked vascular compression at surgery, type of vessel compressing, duration of complaints, involvement of all three branches and postoperative pain relief could not be evaluated given the nature of our database. [155, 164, 171, 176, 177]

Despite its limitations the results of our study are unique in that they capture a large nationwide study sample which provides a comprehensive overview of the application of invasive procedures for trigeminal neuralgia in daily practice. The study further gives a valid estimate of the absolute and relative risks (complications requiring admission) and effectiveness (readmission for repeat procedure) of individual surgical procedures in patients with trigeminal neuralgia. Previous reports showing a higher success rate of microvascular decompression compared to percutaneous radiofrequency rhizotomy have now been confirmed in a single data source. Finally, we have shown that the choice for a certain treatment modality is, at least in the Netherlands, largely institutionalized practice and not based on a nationwide consensus.

Chapter 5

General discussion



In this thesis we present several studies on the occurrence and disease course of facial pain. Facial pain refers to a group of painful conditions affecting the face. Among the rarest and most severe types of facial pain are trigeminal neuralgia, postherpetic neuralgia in the facial area, cluster headache, occipital neuralgia with referred facial pain, local facial neuralgias, persistent idiopathic facial pain, glossopharyngeal neuralgia and paroxysmal hemicrania. Facial pain can be caused by many different diseases or occur without direct cause. The aetiology varies across different types of facial pain and is mostly unknown.
Available epidemiological data on facial pain conditions mostly concern secondary care facial pain patients. In this thesis we studied incidence rates (chapter two), aetiology and risk factors (chapter three) and treatment (chapter four) using data from a population based general practitioners' database.

Main findings

Incidence rate of facial pain
We estimated the incidence of facial pain to be 38.7 per 100.000 person years [95% CI: 34.9 - 42.9]. [2] Trigeminal neuralgia and cluster headache were the most frequently occurring types with incidence rates of 12.6 and 12.5 per 100.000 person years. Glossopharyngeal neuralgia and paroxysmal hemicrania were the least frequent. [2] Studies based on hospital data estimated incidence rates of 4.7 cases of trigeminal neuralgia per 100.000 persons per year. [17] On the other hand studies using less well validated primary care data reported an incidence rate of trigeminal neuralgia of 26.8 – 28.9 per 100.000 person years. [15, 16] While our incidence rates were obtained from general practice data, we employed a more rigorous validation process including general practitioner verification and double review. The false positive rate of the initial diagnosis after initial validation turned out to be around 40%. This high rate may have several explanations. Firstly, the clinical presentation of some of these facial pain syndromes might mimic other diseases such as sinusitis. This complicates the differentiation between different forms of facial pain at first presentation. Secondly, revision of the diagnosis of, for example, trigeminal neuralgia and cluster headache occurs especially if the paroxysmal nature of facial pain cannot be confirmed in subsequent clinic visits. [14, 36] The results of our study and its discrepancies with previous incidence rate estimates suggest that not all patients with facial pain are referred to secondary care and that there is substantial over recording of facial pain diagnoses in primary care medical records. Hence, we argue that the most accurate incidence rate estimates for facial pain conditions result from population based primary care databases with a thorough facial pain case ascertainment process.

Aetiology and risk factors
To learn more about the aetiology of facial pain and in search of (modifiable) risk factors we studied risk factors for the most common types of facial pain (trigeminal neuralgia and cluster headache) in our facial pain cohort.

Cluster headache
We confirmed the previously suggested association between smoking and cluster headache. [83] While head trauma was reported as a risk factor for cluster headache in some studies and not in others, our study suggests that a possible association is confined to only recent head trauma (eg. less than 3 years ago). [79, 84] In line with previous research hypertension was not associated with cluster headache. [88] We did, however, show that anatomical diseases of internal organs and the locomotoric tract, mycoses, mixed infectious diseases, allergies, menstrual cycle related diseases and climacterium related

diseases were significantly associated with first cluster headache occurrence. These findings may shed further light on the underlying pathophysiological pathway for cluster headache. They support the hypothesis that complex trigemino-vascular and cranial parasympathic pathways are involved in the development of cluster headache. [33] In this hypothesis, stimulation of the trigeminal ganglion results in cerebral vasodilatation by activating afferent trigeminal branches and by stimulating parasympathic outflow. The latter is also accomplished by a functional reflex between the caudalic nerve (trigemino-vascular system) and the superior salivatory nucleus (cranial parasympathic system). [33] Activation of the trigemino-vascular system will lead to pain in the first branch of the trigeminal nerve while activation of the parasympathic system will lead to symptoms of lacrimation or decreased nasal passage as seen in cluster headache and paroxysmal hemicrania. [33] In addition, involvement of the hypothalamus has been suggested. [33] This could explain the association between cluster headache and the longest and shortest day of the year as well as the association with menstrual cycle related diseases as we observed in our study. [33] The influence of menstrual cycle related disease may also be mediated through lower melatonin levels, which have been implemented in the aetiology of cluster headache risk previously. [33, 97] Finally, it has been hypothesized that substance P, calcitonin gene related peptide and neurokinin A play an important role in the aetiology of cluster headache. [33, 96, 178] This could be an explanation for the higher risk of cluster headache with mycoses and infections that we observed in our study. [94, 95] Although the role of neuropeptides in cluster headache and in the different disease categories that were associated with cluster headache in our study has not been fully clarified, our data support this as a possible mechanism.

Trigeminal neuralgia

In our study we confirmed the previous finding that hypertension is associated with trigeminal neuralgia. [17, 22] At variance with a previous study reporting a protective effect of smoking, smoking was not a risk factor in our study which supports our impression that the previous study was subject to selection bias. [40] Their selected control category might have been related to smoking leading to a change in point estimate. New information provided by our study is the association between diseases of the lipid and glucose mechanism, benign neoplasm and mixed infections with first trigeminal neuralgia occurrence. Although the associations between these disease groups and trigeminal neuralgia remain to be substantiated and further elucidated, they provide further anchors for a theory regarding the aetiology underlying idiopathic trigeminal neuralgia. Idiopathic trigeminal neuralgia is believed to be the consequence of compression of the trigeminal nerve at the root entry zone near the brainstem by an aberrant blood vessel (neurovascular contact), which leads to local demyelinisation and spontaneous action potentials. [50-54] Many things about this theory, however, remain unclear including the exposure prevalence of this neurovascular contact. [35-42] Disorders in the lipid and glucose mechanism, which include cardiovascular diseases such as atherosclerosis and diabetes mellitus type 2, may exert their effect on trigeminal neuralgia by arterial sacking thereby increasing the risk of neurovascular contact. Central demyelinisation caused by diabetes mellitus type 2 might be an explanation for the association between diabetes mellitus 2 and trigeminal neuralgia. [56-60]

Apart from neurovascular contact, other factors have been implicated in the development of trigeminal neuralgia. Recently, the role of neuropeptides, more specifically substance P, in trigeminal neuralgia has been put forward. [61, 62] Since benign prostatic hyperplasia and infections have been associated with elevated plasma levels of neuropeptides including substance P, these conditions might possibly be associated with trigeminal neuralgia through this pathway. [63]

Risk factors for exacerbation

Both cluster headache and trigeminal neuralgia are diseases that may exacerbate. Better insight into the risk factors for exacerbations of cluster headache and trigeminal neuralgia may help to develop better secondary prevention strategies.

Previous studies have suggested an influence of alcohol, solstices, daylight saving time and weather conditions. [34, 36, 83] None of these factors was associated with exacerbations of cluster headache of trigeminal neuralgia in our study. Oral contraceptives and hormone replacement therapy did not influence the exacerbation risk in our study which confirmed previous findings. [85, 91] A major shortcoming of our analyses was the number of exacerbations which may explain the lack of statistical power to confirm associations.

Management of facial pain

The diagnosis of facial pain was made by the general practitioner in more than 75% of the cases. The diagnostic process was usually short (median 0 days) and involved additional investigations in only one third. In total, 50% of all patients were (eventually) referred to secondary care.

Available literature suggests a longer diagnostic delay and a higher proportion of additional investigations performed. [5, 114, 138-140] Most available literature on this subject however was derived from secondary or tertiary care populations or was obtained using internet questionnaires. [5, 114, 138-140] The results are therefore difficult to generalize. These patient populations probably represent more severely ill patients and represent almost 50% of our patient population since the other half was not referred. Data from questionnaire studies may not be representative of the entire patient population. Since we used electronic patient records from primary care physicians containing a well defined population and data gathered irrespective of the research question our study does not suffer from selection bias.

Treatment of facial pain

Pharmacotherapy was given to 82% of all facial pain patients, 7% received a form of non-invasive, non-pharmacological treatment and 10% received a form of invasive treatment. Anti-epileptic drugs were most commonly used for neuropathic facial pain while anti-migraine drugs were mostly used for cluster headache. Paracetamol and NSAIDs were frequently used in the treatment of both neuropathic facial pain and cluster headache. This may account for the high treatment failure rate observed in the first treatment episode (30% for cluster headache and 38% for neuropathic facial pain). Persistent idiopathic facial pain, a disease with a badly understood aetiology, was mostly treated with anti-epileptic drugs and NSAIDs. Only few drugs are registered in the Netherlands for the specific diseases we studied. [107] Even the recommended drugs in the clinical treatment guidelines often are not licensed for the indication. [106, 107, 129] Our studies showed that 34% of cluster headache and trigeminal neuralgia patients received drugs that were both off-label and off-guideline, indicating a gap between available treatment options and treatment needs.

Since treatment failure is a significant problem in the treatment of facial pain, even for recommended drugs, we studied predictors for failure of the first level A recommended drugs for trigeminal neuralgia (carbamazepine) and cluster headache (sumatriptan, zolmitriptan and oxygen). For trigeminal neuralgia, treatment delay and the carbamazepine dose were predictors for carbamazepine treatment failure. In cluster headache, comorbidity, previous pain treatment, age, a fixed dose regimen, treatment delay and the prescribed dose were associated with failure of sumatriptan, oxygen or zolmitriptan treatment (level A drugs).

The major limitation of these prognostic studies is the small sample size and poor model performance (c-statistics of 0.6 - 0.7). The prediction models provide however a first step towards more evidence on the determinants of failure. If confirmed in the future it may aid in tailored treatment.

If pharmacological treatment fails, patients with trigeminal neuralgia can be invasively treated using percutaneous radiofrequency thermocoagulation, partial sensory rhizotomy and microvascular decompression. We identified 672 patients in the Landelijke Medische Registratie database undergoing a percutaneous radiofrequency thermocoagulation, 39 patients undergoing a partial sensory rhizotomy and 87 patients undergoing a microvascular decompression. Using percutaneous radiofrequency thermocoagulation as reference category, partial sensory rhizotomy had a relative risk of 0.21 [95% CI: 0.07 - 0.65] for a repeat procedure (within one year) and 5.36 [95% CI: 1.46 - 19.64] for a complication. Microvascular decompression had a relative risk of 0.13 [95% CI: 0.05 - 0.35] for repeat procedures and 4.40 [95% CI: 1.44 - 13.42] for complications.

Methodological considerations

Setting
Most data used for this thesis came from the Integrated Primary Care Information (IPCI) database which contains anonymized medical records of over one million general practitioner patients. The database is representative for the Dutch population regarding age and sex. General practitioners act as gatekeepers for secondary care in the Netherlands. [26] As such, their records can be considered to hold most relevant medical information about a patient. No paper records are being kept by a general practitioner participating in the project except specialist letters which were requested during the validation process. Given the rarity of the studied diseases, using a large database ensured a considerable dataset for most analyses. Yet, the sample size occasionally was too small to draw reliable conclusions. Since data in the IPCI database was collected prospectively and irrespective of the research question, no selection bias is present.

Study population
All cases with facial pain were identified in the IPCI database. Controls, when applicable, were drawn at random from the entire source population. Since we used routine electronic patient records, we focused on an extensive validation process for our cases of facial pain. Since not all cases might have been recognized by the general practitioner and since we were interested in the date of first symptoms, we performed a broad and sensitive search on clinical symptoms, specific treatments, diagnoses and diagnosis codes. To be as specific as possible as to not overestimate the incidence we manually evaluated against the criteria of the International Association for the Study of Pain (IASP). [14] Cases were subsequently classified as ‘probable’ (specialist confirmation, two or more well defined episodes), ‘possible’ (one well defined episode) or ‘improbable’ (none of the before mentioned). For all possible cases a questionnaire was sent to the general practitioners to confirm the diagnosis according to the criteria of the IASP. [14] All case material (electronic patient records and questionnaires) were evaluated independently by two medical doctors. A random sample (n=250) was evaluated by a neurologist. This extensive case ascertainment process ensured a maximum sensitivity and specificity.

Confounders, covariates and predictors
Misclassification of exposure and covariates may cause residual confounding and spurious estimates. We used both automated search and manual validation of confounders, covariates and predictors. For efficiency reasons we chose to automatically assess covariates for which previously validated search algorithms were available and which are registered consistently by general practitioners: hypertension, diabetes mellitus, concomitant drug use, patient demographics (age, sex), smoking and alcohol abuse.

For evaluation of less commonly used covariates or suspected inconsistency of registration between different general practitioners we performed manual validation using the entire electronic patient record. Although one could argue that probable cases had less information since no questionnaires were sent to the general practitioners in the validation process, these patients usually had specialist summaries in their electronic records.

Landelijke medische registratie (LMR)
For our study on three commonly used invasive procedures for trigeminal neuralgia we used the national morbidity register (LMR). This database contains discharge diagnoses and admission details of almost all Dutch hospitals. Discharge diagnoses and procedures are coded by trained personnel in the hospital. In this database, we identified all patients undergoing a partial sensory rhizotomy, microvascular decompression or percutaneous radiofrequency thermocoagulation for trigeminal neuralgia. We looked at the relative risk for a hospitalization for repeat procedure for trigeminal neuralgia (any of the three) or complication within one year. Our main concern in this study was misclassification of the outcome (since minor complications will not be captured) although this is probably non-differential for the different procedures. Non-differential misclassification of the outcome might lead to an underestimation of the effect. Furthermore, since we only have data on hospitalizations, we could not evaluate the risk of minor complications and exacerbations not requiring hospitalization. Since the complications of microvascular decompression and partial sensory rhizotomy might be more severe than those of percutaneous radiofrequency rhizotomy misclassification might lead to an overestimation of the risk for complications of microvascular decompression and partial sensory rhizotomy.

Conclusions from this thesis

In this thesis we provided a population based estimate of the incidence rate of facial pain. In addition, we described the diagnostic work-up, health care use, drug utilization patterns, predictors of treatment failure and risk factors for first occurrence and exacerbations. The higher incidence rate compared to hospital data and the lower incidence compared to less stringently validated primary care data emphasized the need to use study populations recruited from primary care settings but to ensure proper case validation. The same applies to the assessment of the diagnostic delay, which was shorter than previously suggested based on hospital data. [5, 138] Treatment failure is a frequent and significant problem. We identified several possible predictors for treatment failure which need further substantiation in larger datasets.
Furthermore, we identified several new risk factors for first occurrence of cluster headache and trigeminal neuralgia. Based on these new risk factors we support the previously postulated hypothesis of a neuropeptide mediated aetiology for both cluster headache and trigeminal neuralgia. Given the hypothesis generating nature of this study, however, more research is needed to confirm these associations and to identify a possible pathway.

Recommendations for further research

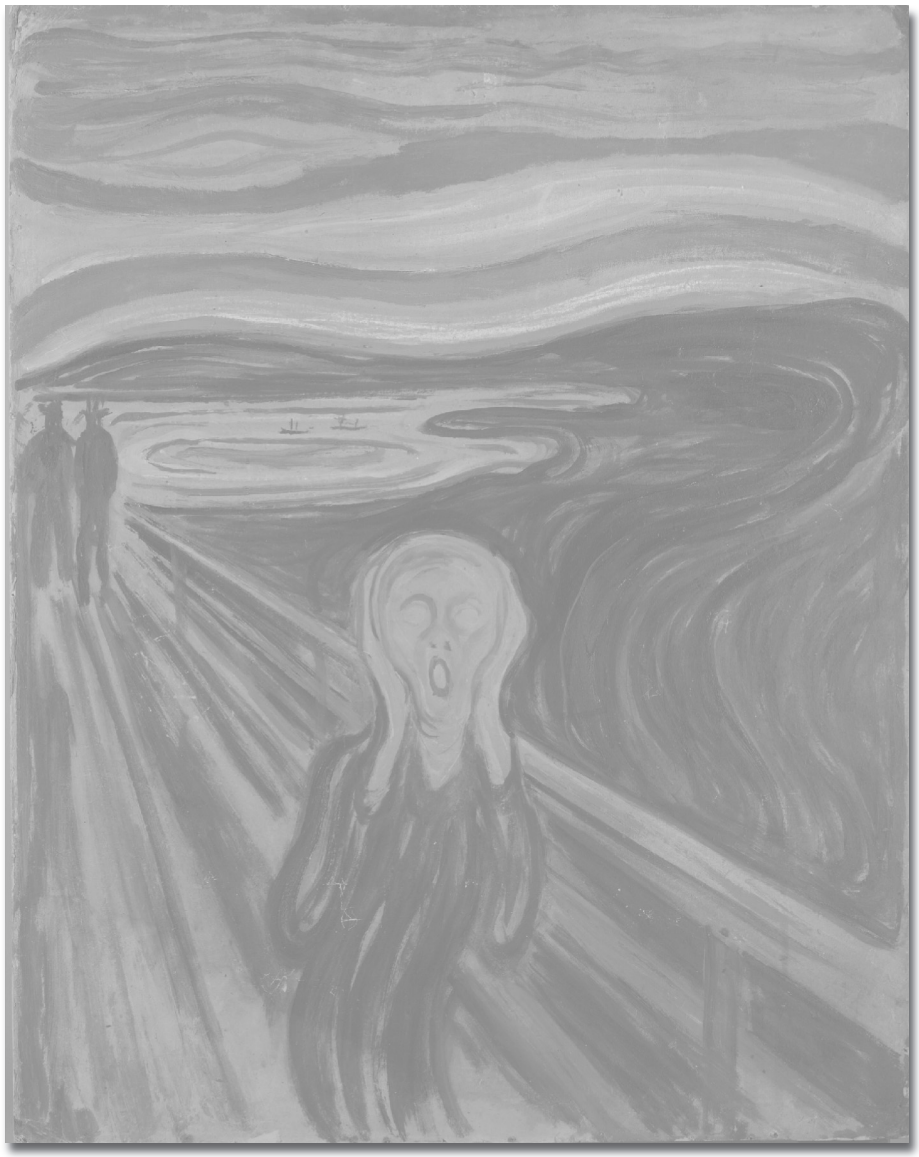
The studies in this thesis may help to give direction to further research in the field of facial pain. Our research is the first to provide information on incidence rates, patient management and treatment failure based on a primary care population and profound case validation.

Replication of our studies in other primary care datasets would strengthen the conclusions. In addition, the findings on risk factors for trigeminal neuralgia and cluster headache need substantiation in a larger population. More detailed information on individual diseases rather than groups of diseases could give a better insight into the underlying pathophysiological mechanisms. Moreover, treatable risk factors may provide options for preventive strategies in the treatment of facial pain. Future studies are needed to elucidate the risk factors we identified and to investigate the role of neuropeptides in the aetiology of facial pain.

Although this thesis presents new information on the risk of trigeminal neuralgia and cluster headache, much remains unknown. Regarding trigeminal neuralgia, more research into the role of neurovascular contact is needed before drawing definite conclusions. There are several ways to accurately address this issue. One could be to establish neurovascular contact in incident cases or attacks of trigeminal neuralgia and matched control persons. With the development of more sophisticated computer algorithms of large datasets automatically assessing the presence of neurovascular contact and superior MRI-scanners to detect neurovascular contact, this goal might be reachable.
Given the high proportion of off-label and off-guideline use of treatment for facial pain and the high treatment failure rate, research should focus on developing more effective treatment strategies. For this, properly performed randomized controlled trials comparing frequently used drugs with carbamazepine regarding effectiveness and safety should be performed. Performing these trials will also enable the development of prediction models for failure and adverse events. Identifying patients at high risk for failure will greatly improve treatment and might prevent adverse events.
In this thesis we have shown the need to study facial pain in a primary care setting rather than a secondary or tertiary care setting. Since not everyone is referred to secondary care, results from research performed in a secondary care setting might not be generalizable to primary care patients. Given the low incidence, a large enough source population should be used to identify patients to ensure valid results.

Chapter 6

Summary



Summary

Facial pain is a symptom of many different diseases. The differential diagnosis of some of the rarer forms includes trigeminal neuralgia, postherpetic neuralgia in the facial area, cluster headache, occipital neuralgia with referred facial pain, local facial neuralgias, persistent idiopathic facial pain (atypical facial pain), glossopharyngeal neuralgia and paroxysmal hemicrania. There is a lack of knowledge on the aetiology, natural course, risk factors for development of first occurrence and exacerbations, treatment algorithms and outcome of facial pain. Chapter 1.1 gives a brief introduction in which the aim and background of this thesis is described.

In chapter two a study about the estimation of the incidence of these eight forms of facial pain in the Netherlands is described. Incidence rates are given per age category, gender, calendar year and season. To estimate the incidence rates we used the Integrated Primary Care Information (IPCI) database with electronic medical records of over 140 general practices throughout the Netherlands. We showed that trigeminal neuralgia and cluster headache are the most frequently occurring types of the studies facial pains with an incidence of 12.6 [10.5 – 15.1] and 12.5 [10.4 – 14.9] per 100,000 person years respectively. They were more frequent than previous studies using hospital data suggested but less frequent than suggested by studies using less well validated primary care data.

In chapter three we describe a study in which we evaluated risk factors for occurrence of trigeminal neuralgia and cluster headache. We showed an association between smoking, recent head trauma and cluster headache. Furthermore, we confirmed a previously shown association between hypertension and trigeminal neuralgia. In addition to studying known associations, we also performed a hypothesis generating study to identify new associations. We showed that some disease categories are associated with trigeminal neuralgia and cluster headache. Disorders of the lipid and glucose metabolism, benign neoplasm and mixed infections were related to trigeminal neuralgia. Diseases of the internal organs, locomotoric tract, mycoses, mixed infections, allergies, menstrual cycle related disorders and climacterium related disorders were related to cluster headache. A mechanism was proposed to explain this possible association, namely via neuropeptides. Neuropeptides have previously been associated with trigeminal neuralgia, cluster headache and also with some of the diseases that showed an association. Furthermore, we tried to identify predictors for an exacerbation of cluster headache or trigeminal neuralgia. Although, based on literature, several risk factors were of interest, we were not able to confirm these.

In chapter four we report four descriptive studies on treatment patterns in facial pain. Most patients were treated rapidly after disease onset. The large majority was treated by a general practitioner. Facial pain was usually treated according to guidelines or in line with licensing data. In one third of the cases, a drug was used which was neither registered for the indication nor recommended by guidelines. Remarkably enough, almost one fifth of the first prescriptions included a non-opioid analgesic. This is remarkable because these drugs are, in general, not recommended by guidelines nor registered for the forms of facial pain we studied (with the exception of indomethacin for paroxysmal hemicrania). One third of the first treatment episodes failed within three months. We describe a study in which we evaluated several predictors for carbamazepine treatment failure. Treatment delay, the dosage and comorbidity were associated with treatment failure. In chapter four we also give a description of the diagnostic work-up and health care consumption of facial pain patients. In the majority of cases the diagnosis was made by the general practitioner. Overall, half of all facial pain patients visited some kind of specialist (both medical and paramedical). A minority underwent some form of additional investigation. Most patients were treated pharmacologically, a minority invasively. Invasive procedures used for trigeminal neuralgia include microvascular decompression, partial sensory rhizotomy and percutaneous radiofrequency thermocoagulation. We used the “Landelijke Medische Registratie” database to compare safety and effectiveness of these

three procedures and determined that microvascular decompression and partial sensory rhizotomy had a significantly better effectiveness compared to percutaneous radiofrequency thermocoagulation but a worse safety profile. Hospital volume and type of hospital were prognostic factors for treatment failure.
Chapter five includes a general discussion on our findings and methodological aspects and concludes with suggestions for further research.

Samenvatting

Aangezichtspijn kan veroorzaakt worden door veel verschillende aandoeningen. Als een huisarts denkt aan een zeldzame vorm van aangezichtspijn dan staan er verschillende specifieke syndromen in de differentiaal diagnose. Dit zijn bijvoorbeeld trigeminus neuralgie, postherpetische neuralgie in het gezicht, cluster hoofdpijn, occipitaal neuralgie met uitstralende pijn in het gezicht, persisterende idiopatische aangezichtspijn (voorheen atypische aangezichtspijn), glossopharyngeus neuralgie en paroxysmale hemicranie. Er is een groot gebrek aan kennis over de etiologie, het ziektebeloop, risicofactoren voor het onstaan en exacerberen van de aandoening , behandel algoritmes en voorspellende factoren voor het falen van de therapie.. Hoofdstuk I beschrijft het doel en de indeling van het proefschrift.. In hoofdstuk wordt de geslacht en leeftijds-specifieke incidentie van deze acht vormen van aangezichtspijn in Nederland beschreven. Hiervoor hebben we gebruik gemaakt van de Integrated Primary Care Information (IPCI) database. Deze database bevat de geanonimiseerde, elektronische, medische gegevens van meer dan 140 huisartsenpraktijken door heel Nederland. In deze studie hebben we laten zien dat trigeminus neuralgie en cluster hoofdpijn het meeste voorkomen van de acht door ons bestudeerde vormen van aangezichtspijn met respectievelijk een incidentie van 12,6 [10,5 – 15,1] en 12,5 [10,3 – 14,9] per 100.000 persoonsjaren. Dit was hoger dan verwacht kon worden op basis van getallen die vooral gebaseerd waren op data uit ziekenhuizen maar lager dan verwacht op basis van gegevens uit minder strikt gevalideerde huisartsenstudies.

Risicofactoren voor het ontwikkelen van trigeminus neuralgie en cluster hoofdpijn worden besproken in hoofdstuk 3. We hebben een verband aangetoond tussen roken, een recent hoofdtrauma en cluster hoofdpijn. Ook hebben we de reeds bekende relatie tussen hypertensie en trigeminus neuralgie bevestigd. Daarnaast hebben we ook gepoogd nieuwe associaties te ontdekken middels een explorerende aanpak. Sommige categoriëen van ziektes zijn geassocieerd met trigeminus neuralgie en cluster hoofdpijn. Ziektes die verband houden met het lipide en glucose metabolisme, benigne neoplasmata en gemengde infecties (bacterieel en viraal) waren gerelateerd aan het ontwikkelen van trigeminus neuralgie. Aandoeningen van de interne organen, van de tractus locomotorius, schimmelinfecties, gemengde infecties, allergiëen, aandoeningen van de menstruele cyclus en climacterium gerelateerde aandoeningen waren geassocieerd met de ontwikkeling van cluster hoofdpijn. Mogelijk spelen neuropeptides een rol in deze relaties. Neuropeptides zijn eerder beschreven in de etiologie van cluster hoofdpijn en trigeminus neuralgie en ze zijn in verband gebracht met sommige van de ziektes die gerelateerd waren aan trigeminus neuralgie en cluster hoofdpijn. Ook hebben wij geprobeerd voorspellende factoren voor een exacerbatie van trigeminus neuralgie en cluster hoofdpijn te identificeren. Alhoewel enkele predictoren in de literatuur beschreven zijn, konden wij deze niet bevestigen in onze studies.

Hoofdstuk vier bevat vier beschrijvende studies over de behandeling van aangezichtspijn in de dagelijkse praktijk. De meeste patiënten worden snel na ontwikkeling van de eerste symptomen behandeld en het meestal door de huisarts. De meeste behandelingen waren geregistreerd voor de specifieke pijn indicatie of waren conform de beschikbare richtlijnen voor behandeling. In eenderde van de patiënten werd een medicijn voorgeschreven dat niet geregistreerd was, noch aanbevolen werd in de richtlijnen. Opmerkelijk genoeg werd eenvijfde van de patiënten behandeld met paracetamol of een NSAID. Deze medicijnen worden over het algemeen niet aanbevolen voor de aandoeningen die wij bestudeerden (met uitzondering van indometacine voor paroxysmale hemicranie). Eenderde van de eerste behandelepisodes faalde binnen drie maanden. We hebben onderzocht of falen van behandeling voorspeld kan worden aan het begin van de behandeling en vonden dat het uitstellen van behandeling, de dosis en comorbiditeit geassocieerd waren met therapiefalen. Daarnaast hebben we beschreven hoe het diagnostisch proces verloopt in patiënten met aange-

zichtspijn en hoeveel beslag deze patiënten leggen op de gezondheidszorg. De huisarts stelde de diagnose in de meerderheid van de gevallen. De helft van alle patiënten werd doorverwezen naar een medisch specialist (medisch en paramedisch), slechts een minderheid onderging aanvullende onderzoeken. De meeste mensen werden pharmacologisch behandeld; een minderheid invasief. Microvasculaire decompressie, partiële sensore rhizotomie en percutane radiofrequente thermocoagulatie zijn invasieve procedures die gebruikt worden voor trigeminus neuralgie. Wij hebben de veiligheid en effectiviteit van deze procedures vergeleken in de "Landelijke Medische Registratie". Microvasculaire decompressie en partiële sensore rhizotomie waren effectiever dan percutane radiofrequente thermocoagulatie maar ook onveiliger. Het aantal ingrepen per ziekenhuis en het type ziekenhuis (academisch of perifeer) waren predictoren voor falen van therapie.
Wij sluiten af in hoofdstuk vijf met een algemene discussie van onze bevindingen, methodologische aspecten van onze studies en suggesties voor toekomstig onderzoek.

Chapter 7

PhD portfolio

Research skills:

Statistics and methodology:

2007 – 2009	Master or Science in Clinical Epidemiology, Netherlands Institute for Health Sciences, Erasmus University, Rotterdam
2007-2009	Additional courses on specific statistical methods.

Presentations:

2008	12th World Congress on Pain – The International Association for the Study of Pain; Poster presentation
2008	24th International Conference on Pharmaco-Epidemiology – The International Society for Pharmaco-Epidemiology; Poster presentation
2009	25th International Conference on Pharmaco-Epidemiology – The International Society for Pharmaco-Epidemiology; Poster presentation (2x)

Teaching:

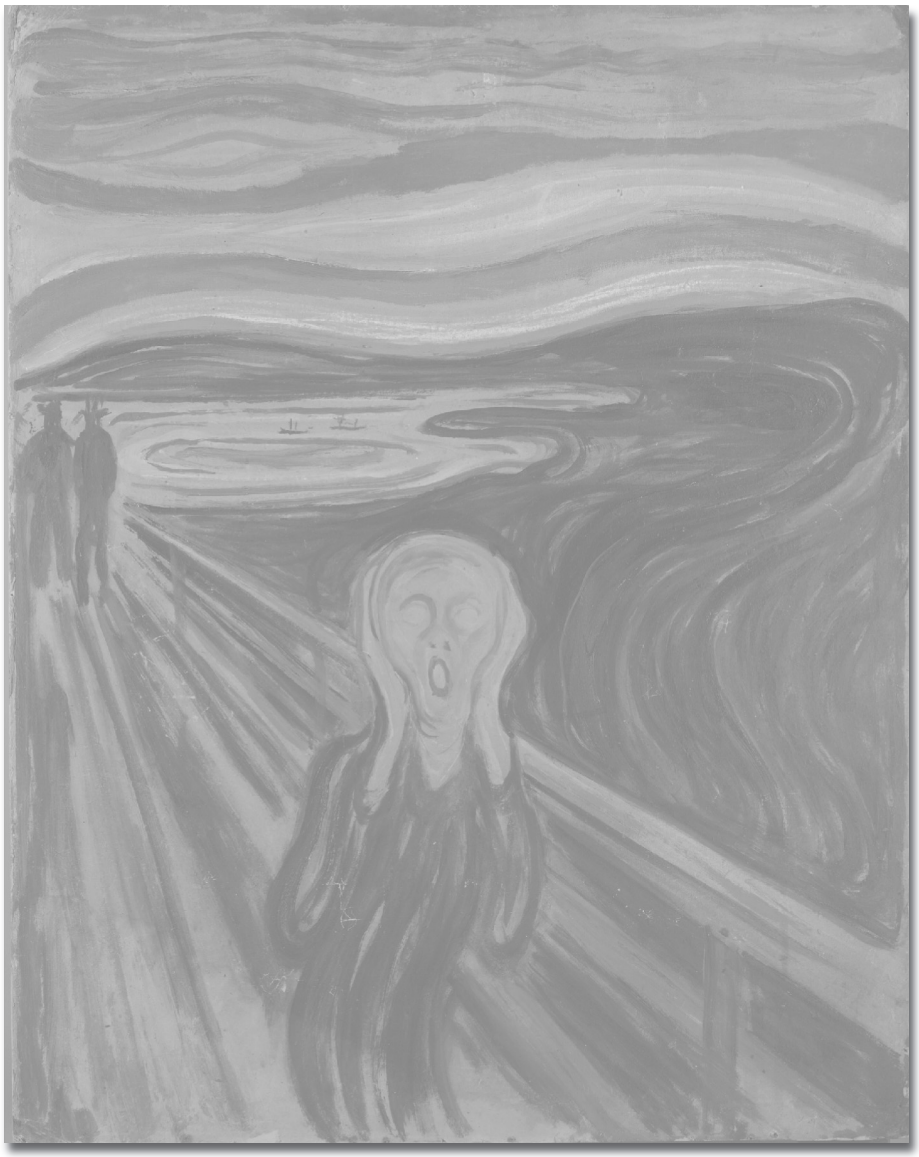
2007-2009	Supervising and teaching medical students, Erasmus MC, Erasmus University Medical Center, Rotterdam, the Netherlands

Other:

2007 – 2009	Organiser of various drinks, lunches and dinners
2007 – 2009	Editing of multiple movies for graduating PhD-students

Chapter 8

References



1. *Dutch statistics*. [cited 2009 01-01-2009]; January 1, 2009]. Available from: http://www.cbs.nl/nl-NL/menu/cijfers/statline/zelf-tabellen-maken/default.htm.
2. Koopman, J.S., et al., *Incidence of facial pain in the general population.* Pain, 2009. **147**(1-3): p. 122-7.
3. Young, M.K., M. Wood, and N. Jean-Noel, *Postherpetic neuralgia in older adults: culture, quality of life, and the use of alternative/complementary therapies.* Holist Nurs Pract, 2007. **21**(3): p. 124-34.
4. Barker, F.G., 2nd, *Quality of life and individual treatment choice in trigeminal neuralgia.* Pain, 2007. **131**(3): p. 234-6.
5. Jensen, R.M., A. Lyngberg, and R.H. Jensen, *Burden of cluster headache.* Cephalalgia, 2007. **27**(6): p. 535-41.
6. Minagar, A. and W.A. Sheremata, *Glossopharyngeal neuralgia and MS.* Neurology, 2000. **54**(6): p. 1368-70.
7. Warren, H.G., A.L. Kotsenas, and L.F. Czervionke, *Trigeminal and concurrent glossopharyngeal neuralgia secondary to lateral medullary infarction.* AJNR Am J Neuroradiol, 2006. **27**(3): p. 705-7.
8. Phuong, H.L., et al., *Glossopharyngeal neuralgia due to an epidermoid tumour in the cerebellopontine angle.* J Clin Neurosci, 2004. **11**(7): p. 758-60.
9. Ballesteros-Del Rio, B., et al., *Occipital (Arnold) neuralgia secondary to greater occipital nerve schwannoma.* Headache, 2003. **43**(7): p. 804-7.
10. Moulin, D.E., K.M. Foley, and G.C. Ebers, *Pain syndromes in multiple sclerosis.* Neurology, 1988. **38**(12): p. 1830-4.
11. Golby, A.J., A. Norbash, and G.D. Silverberg, *Trigeminal neuralgia resulting from infarction of the root entry zone of the trigeminal nerve: case report.* Neurosurgery, 1998. **43**(3): p. 620-2; discussion 622-3.
12. Cheng, T.M., T.L. Cascino, and B.M. Onofrio, *Comprehensive study of diagnosis and treatment of trigeminal neuralgia secondary to tumors.* Neurology, 1993. **43**(11): p. 2298-302.
13. Valenca, M.M., et al., *Cluster headache and intracranial aneurysm.* J Headache Pain, 2007. **8**(5): p. 277-82.
14. *Detailed description of pain syndromes*. 2006 29-04-2008]; April 29, 2008]. Available from: https://www.iasp-pain.org/AM/Template.cfm?section=Classification_of_Chronic_Pain1&template=/MembersOnly.cfm&ContentID=2786.
15. Dieleman, J.P., et al., *Incidence rates and treatment of neuropathic pain conditions in the general population.* Pain, 2008. **137**(3): p. 681-8.
16. Hall, G.C., et al., *Epidemiology and treatment of neuropathic pain: the UK primary care perspective.* Pain, 2006. **122**(1-2): p. 156-62.
17. Katusic, S., et al., *Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984.* Ann Neurol, 1990. **27**(1): p. 89-95.
18. Soustiel, J.F., et al., *Brain-stem trigeminal and auditory evoked potentials in multiple sclerosis: physiological insights.* Electroencephalogr Clin Neurophysiol, 1996. **100**(2): p. 152-7.
19. Cerrato, P., et al., *Occipital neuralgia as isolated symptom of an upper cervical cavernous angioma.* J Neurol, 2002. **249**(10): p. 1464-5.
20. HCSIHS, *The International Classification of Headache Disorders: 2nd edition.* Cephalalgia, 2004. **24 Suppl 1**: p. 9-160.
21. Anonymous. *Detailed description of pain syndromes*. 2006 29-04-2008]; Available from: https://www.iasp-pain.org/AM/Template.cfm?section=Classification_of_Chronic_Pain1&template=/MembersOnly.cfm&ContentID=2786.

22. Katusic, S., et al., *Epidemiology and clinical features of idiopathic trigeminal neuralgia and glossopharyngeal neuralgia: similarities and differences, Rochester, Minnesota, 1945-1984.* Neuroepidemiology, 1991. **10**(5-6): p. 276-81.
23. Hall, G.C., D. Carroll, and H.J. McQuay, *Primary care incidence and treatment of four neuropathic pain conditions: a descriptive study, 2002-2005.* BMC Fam Pract, 2008. **9**: p. 26.
24. Vlug, A.E., et al., *Postmarketing surveillance based on electronic patient records: the IPCI project.* Methods Inf Med, 1999. **38**(4-5): p. 339-44.
25. van der Lei, J., et al., *The introduction of computer-based patient records in The Netherlands.* Ann Intern Med, 1993. **119**(10): p. 1036-41.
26. Schrijvers, A., *Health and health care in the Netherlands: a critical self assessment of Dutch experts in medical and health sciences.* 1997, Utrecht: De Tijdstroom.
27. de Lusignan, S., *Codes, classifications, terminologies and nomenclatures: definition, development and application in practice.* Inform Prim Care, 2005. **13**(1): p. 65-70.
28. Rothman, K.J. *Episheet*. 2007 23-03-2007 24-10-2007]; Available from: http://members.aol.com/krothman/modepi.htm.
29. Havulinna, A.S., et al., *Geographic patterns of incidence of ischemic stroke and acute myocardial infarction in Finland during 1991-2003.* Ann Epidemiol, 2008. **18**(3): p. 206-13.
30. Yoshimasu, F., L.T. Kurland, and L.R. Elveback, *Tic douloureux in Rochester, Minnesota, 1945-1969.* Neurology, 1972. **22**(9): p. 952-6.
31. Katusic, S., et al., *Incidence and clinical features of glossopharyngeal neuralgia, Rochester, Minnesota, 1945-1984.* Neuroepidemiology, 1991. **10**(5-6): p. 266-75.
32. Black, D.F., J.W. Swanson, and P.E. Stang, *Decreasing incidence of cluster headache: a population-based study in Olmsted County, Minnesota.* Headache, 2005. **45**(3): p. 220-3.
33. Dodick, D.W., et al., *Cluster headache.* Cephalalgia, 2000. **20**(9): p. 787-803.
34. Kudrow, L., *The cyclic relationship of natural illumination to cluster period frequency.* Cephalalgia, 1987. **7 Suppl 6**: p. 76-8.
35. Kundel, H.L. and M. Polansky, *Measurement of observer agreement.* Radiology, 2003. **228**(2): p. 303-8.
36. Bennetto, L., N.K. Patel, and G. Fuller, *Trigeminal neuralgia and its management.* Bmj, 2007. **334**(7586): p. 201-5.
37. Bowsher, D., *Trigeminal neuralgia: an anatomically oriented review.* Clin Anat, 1997. **10**(6): p. 409-15.
38. Nurmikko, T.J. and P.R. Eldridge, *Trigeminal neuralgia—pathophysiology, diagnosis and current treatment.* Br J Anaesth, 2001. **87**(1): p. 117-32.
39. Krafft, R.M., *Trigeminal neuralgia.* Am Fam Physician, 2008. **77**(9): p. 1291-6.
40. Rothman, K.J. and R.R. Monson, *Epidemiology of trigeminal neuralgia.* J Chronic Dis, 1973. **26**(1): p. 3-12.
41. Lamberts, H., M. Wood, and I.M. Hofmans-Okkes, *International primary care classifications: the effect of fifteen years of evolution.* Fam Pract, 1992. **9**(3): p. 330-9.
42. World Health Organization (WHO), *Anatomical Therapeutical Chemical Index With Defined Daily Dosages.* Oslo, Norway: WHO Collaborating Center for Drug Statistics Methodology, 2002.
43. de Mos, M., et al., *Medical history and the onset of complex regional pain syndrome (CRPS).* Pain, 2008. **139**(2): p. 458-66.
44. INSTITUTE, R.N.M. 30-09-2009]; Available from: www.knmi.nl.
45. Elloumi, M. and M.H. Kallel, *Which relationship does osteoarthritis share with smoking?* Osteoarthritis Cartilage, 2007. **15**(9): p. 1097-8.

46. Zeng, Q.Y., et al., *Associated risk factors of knee osteoarthritis: a population survey in Taiyuan, China.* Chin Med J (Engl), 2006. **119**(18): p. 1522-7.
47. Wilder, F.V., B.J. Hall, and J.P. Barrett, *Smoking and osteoarthritis: is there an association? The Clearwater Osteoarthritis Study.* Osteoarthritis Cartilage, 2003. **11**(1): p. 29-35.
48. Jones, G., H.M. Cooley, and J.M. Stankovich, *A cross sectional study of the association between sex, smoking, and other lifestyle factors and osteoarthritis of the hand.* J Rheumatol, 2002. **29**(8): p. 1719-24.
49. Kauppila, L.I., *Atherosclerosis and disc degeneration/low-back pain—a systematic review.* Eur J Vasc Endovasc Surg, 2009. **37**(6): p. 661-70.
50. Beaver, D.L., *Electron microscopy of the gasserian ganglion in trigeminal neuralgia.* J Neurosurg, 1967. **26**(1): p. Suppl:138-50.
51. Hilton, D.A., et al., *Pathological findings associated with trigeminal neuralgia caused by vascular compression.* Neurosurgery, 1994. **35**(2): p. 299-303; discussion 303.
52. Kerr, F.W. and R.H. Miller, *The pathology of trigeminal neuralgia. Electron microscopic studies.* Arch Neurol, 1966. **15**(3): p. 308-19.
53. Burchiel, K.J., *Abnormal impulse generation in focally demyelinated trigeminal roots.* J Neurosurg, 1980. **53**(5): p. 674-83.
54. Smith, K.J. and W.I. McDonald, *Spontaneous and evoked electrical discharges from a central demyelinating lesion.* J Neurol Sci, 1982. **55**(1): p. 39-47.
55. Calvin, W.H., J.D. Loeser, and J.F. Howe, *A neurophysiological theory for the pain mechanism of tic douloureux.* Pain, 1977. **3**(2): p. 147-54.
56. Bagai, K., et al., *Electrophysiological patterns of diabetic polyneuropathy.* Electromyogr Clin Neurophysiol, 2008. **48**(3-4): p. 139-45.
57. Gorson, K.C., et al., *Influence of diabetes mellitus on chronic inflammatory demyelinating polyneuropathy.* Muscle Nerve, 2000. **23**(1): p. 37-43.
58. Malik, R.A., *The pathology of human diabetic neuropathy.* Diabetes, 1997. **46 Suppl 2**: p. S50-3.
59. Sharma, K.R., et al., *Demyelinating neuropathy in diabetes mellitus.* Arch Neurol, 2002. **59**(5): p. 758-65.
60. Uncini, A., et al., *Chronic inflammatory demyelinating polyneuropathy in diabetics: motor conductions are important in the differential diagnosis with diabetic polyneuropathy.* Clin Neurophysiol, 1999. **110**(4): p. 705-11.
61. Zhao, Y., X. Jiang, and Y. Liu, *[Observation of vasoactive intestinal polypeptide in patients with trigeminal neuralgia: a 16-cases report].* Hua Xi Kou Qiang Yi Xue Za Zhi, 2002. **20**(1): p. 33-4, 38.
62. Strittmatter, M., et al., *Cerebrospinal fluid neuropeptides and monoaminergic transmitters in patients with trigeminal neuralgia.* Headache, 1997. **37**(4): p. 211-6.
63. Cussenot, O., et al., *Plasma neuroendocrine markers in patients with benign prostatic hyperplasia and prostatic carcinoma.* J Urol, 1996. **155**(4): p. 1340-3.
64. Anonymous. *Weather data*. 30-09-2009]; Available from: www.knmi.nl.
65. May, A., *Cluster headache: pathogenesis, diagnosis, and management.* Lancet, 2005. **366**(9488): p. 843-55.
66. Lai, S.L., et al., *Cluster-like headache from vertebral artery dissection: angiographic evidence of neurovascular activation.* Cephalalgia, 2005. **25**(8): p. 629-32.
67. Cremer, P.D., G.M. Halmagyi, and P.J. Goadsby, *Secondary cluster headache responsive to sumatriptan.* J Neurol Neurosurg Psychiatry, 1995. **59**(6): p. 633-4.
68. Frigerio, S., et al., *Symptomatic cluster headache in internal carotid artery dissection—consider anhidrosis.* Headache, 2003. **43**(8): p. 896-900.

69. Mainardi, F., et al., *Spontaneous carotid artery dissection with cluster-like headache.* Cephalalgia, 2002. **22**(7): p. 557-9.
70. Koenigsberg, A.D., G.D. Solomon, and G. Kosmorsky, *Psuedoaneurysm within the cavernous sinus presenting as cluster headache.* Headache, 1994. **34**(2): p. 111-3.
71. Evers, S., et al., *Cluster headache after orbital exenteration.* Cephalalgia, 1997. **17**(6): p. 680-2.
72. Mani, S. and J. Deeter, *Arteriovenous malformation of the brain presenting as a cluster headache—a case report.* Headache, 1982. **22**(4): p. 184-5.
73. Rahmann, A., I.W. Husstedt, and S. Evers, *Cluster headache after removal of a subarachnoid cyst: a case report.* Headache, 2003. **43**(2): p. 130-1.
74. Rigamonti, A., et al., *Two symptomatic cases of cluster headache associated with internal carotid artery dissection.* Neurol Sci, 2007. **28 Suppl 2**: p. S229-31.
75. Razvi, S.S., et al., *Cluster headache due to internal carotid artery dissection.* J Neurol, 2006. **253**(5): p. 661-3.
76. Soros, P., et al., *Enucleation and development of cluster headache: a retrospective study.* BMC Neurol, 2005. **5**(1): p. 6.
77. Waldenlind, E., *Physiological rhythms in cluster headache.* Ital J Neurol Sci, 1999. **20**(2 Suppl): p. S15-7.
78. Formisano, R., et al., *Cluster-like headache and head injury: case report.* Ital J Neurol Sci, 1990. **11**(3): p. 303-5.
79. Manzoni, G.C., G. Lambru, and P. Torelli, *Head trauma and cluster headache.* Curr Pain Headache Rep, 2006. **10**(2): p. 130-6.
80. Reik, L., Jr., *Cluster headache after head injury.* Headache, 1987. **27**(9): p. 509-10.
81. Turkewitz, L.J., et al., *Cluster headache following head injury: a case report and review of the literature.* Headache, 1992. **32**(10): p. 504-6.
82. *Case-control study on the epidemiology of cluster headache. I: Etiological factors and associated conditions. Italian Cooperative Study Group on the Epidemiology of Cluster Headache (ICECH).* Neuroepidemiology, 1995. **14**(3): p. 123-7.
83. Manzoni, G.C., *Cluster headache and lifestyle: remarks on a population of 374 male patients.* Cephalalgia, 1999. **19**(2): p. 88-94.
84. Walker, R.W., *Cluster headache and head trauma: is there an association?* Curr Pain Headache Rep, 2007. **11**(2): p. 137-40.
85. Bahra, A., A. May, and P.J. Goadsby, *Cluster headache: a prospective clinical study with diagnostic implications.* Neurology, 2002. **58**(3): p. 354-61.
86. Schurks, M., et al., *Cluster headache: clinical presentation, lifestyle features, and medical treatment.* Headache, 2006. **46**(8): p. 1246-54.
87. Levi, R., et al., *Episodic cluster headache. II: High tobacco and alcohol consumption in males.* Headache, 1992. **32**(4): p. 184-7.
88. Cirillo, M., et al., *Headache and cardiovascular risk factors: positive association with hypertension.* Headache, 1999. **39**(6): p. 409-16.
89. El Amrani, M., et al., *Familial cluster headache: a series of 186 index patients.* Headache, 2002. **42**(10): p. 974-7.
90. Rozen, T.D., *Pure menstrual cluster headache.* Headache, 2007. **47**(7): p. 1093-5.
91. van Vliet, J.A., et al., *Cluster headache in women: relation with menstruation, use of oral contraceptives, pregnancy, and menopause.* J Neurol Neurosurg Psychiatry, 2006. **77**(5): p. 690-2.
92. Boms, N., et al., *Effect of Smoking Cessation on Visually Evoked Cerebral Blood Flow Response in Healthy Volunteers.* J Vasc Res, 2009. **47**(3): p. 214-220.

93. Ozguner, F., A. Koyu, and G. Cesur, *Active smoking causes oxidative stress and decreases blood melatonin levels.* Toxicol Ind Health, 2005. **21**(1-2): p. 21-6.
94. Hosokawa, C., S. Takeuchi, and M. Furue, *Severity scores, itch scores and plasma substance P levels in atopic dermatitis treated with standard topical therapy with oral olopatadine hydrochloride.* J Dermatol, 2009. **36**(4): p. 185-90.
95. Salomon, J. and E. Baran, *The role of selected neuropeptides in pathogenesis of atopic dermatitis.* J Eur Acad Dermatol Venereol, 2008. **22**(2): p. 223-8.
96. Yoshida, N., *Inflammation and oxidative stress in gastroesophageal reflux disease.* J Clin Biochem Nutr, 2007. **40**(1): p. 13-23.
97. Miyauchi, F., K. Nanjo, and K. Otsuka, *[Effects of night shift on plasma concentrations of melatonin, LH, FSH and prolactin, and menstrual irregularity].* Sangyo Igaku, 1992. **34**(6): p. 545-50.
98. Torelli, P., E. Beghi, and G.C. Manzoni, *Cluster headache prevalence in the Italian general population.* Neurology, 2005. **64**(3): p. 469-74.
99. Schurks, M. and H.C. Diener, *Cluster headache and lifestyle habits.* Curr Pain Headache Rep, 2008. **12**(2): p. 115-21.
100. Favier, I., J. Haan, and M.D. Ferrari, *Chronic cluster headache: a review.* J Headache Pain, 2005. **6**(1): p. 3-9.
101. Koopman, J.S., et al., *Pharmacological Treatment of Neuropathic Facial Pain in the Dutch General Population.* J Pain, 2009.
102. Fischbach, F., et al., *Vascular compression in glossopharyngeal neuralgia: demonstration by high-resolution MRI at 3 tesla.* Neuroradiology, 2003. **45**(11): p. 810-1.
103. Kost, R.G. and S.E. Straus, *Postherpetic neuralgia—pathogenesis, treatment, and prevention.* N Engl J Med, 1996. **335**(1): p. 32-42.
104. Love, S. and H.B. Coakham, *Trigeminal neuralgia: pathology and pathogenesis.* Brain, 2001. **124**(Pt 12): p. 2347-60.
105. Shimizu, S., et al., *Can proximity of the occipital artery to the greater occipital nerve act as a cause of idiopathic greater occipital neuralgia? An anatomical and histological evaluation of the artery-nerve relationship.* Plast Reconstr Surg, 2007. **119**(7): p. 2029-34; discussion 2035-6.
106. Attal, N., et al., *EFNS guidelines on pharmacological treatment of neuropathic pain.* Eur J Neurol, 2006. **13**(11): p. 1153-69.
107. MEB. *Medicines Data Bank.* 2008 02-07-2008 [cited 2008 04-07-2008]; July 4, 2008]. Available from: http://www.cbg-meb.nl/CBG/nl/people/geneesmiddeleninformatiebank/default.htm.
108. CVZ. *Farmacotherapeutisch Kompas*. 2008 1-4-2008 25-06-2008]; Available from: http://www.fk.cvz.nl/.
109. Anonymous, *ATC and DDD values. Geneva, World Health Organization.* 1996.
110. Rushton, J.G., J.C. Stevens, and R.H. Miller, *Glossopharyngeal (vagoglossopharyngeal) neuralgia: a study of 217 cases.* Arch Neurol, 1981. **38**(4): p. 201-5.
111. De Simone, R., et al., *Cranial neuralgias: from physiopathology to pharmacological treatment.* Neurol Sci, 2008. **29 Suppl 1**: p. S69-78.
112. Post, A.F., P. Narayan, and R.W. Haid, Jr., *Occipital neuralgia secondary to hypermobile posterior arch of atlas. Case report.* J Neurosurg, 2001. **94**(2 Suppl): p. 276-8.
113. Teixeira, M.J., S.R. de Siqueira, and E. Bor-Seng-Shu, *Glossopharyngeal neuralgia: neurosurgical treatment and differential diagnosis.* Acta Neurochir (Wien), 2008. **150**(5): p. 471-5; discussion 475.
114. Breivik, H., et al., *Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment.* Eur J Pain, 2006. **10**(4): p. 287-333.

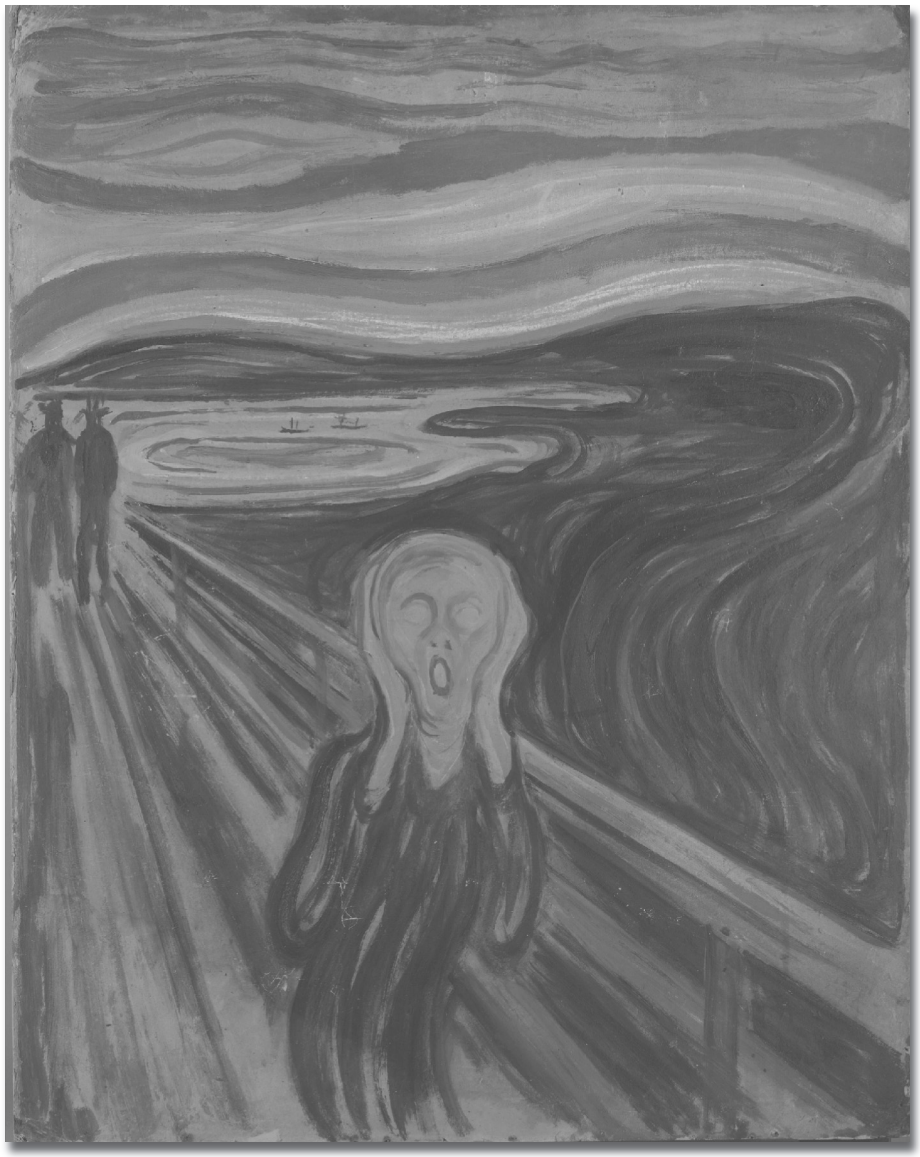
115. Tunsuriyawong, S. and S. Puavilai, *Herpes zoster, clinical course and associated diseases: A 5-year retrospective study at Tamathibodi Hospital.* J Med Assoc Thai, 2005. **88**(5): p. 678-81.
116. Cruccu, G., et al., *AAN-EFNS guidelines on trigeminal neuralgia management.* Eur J Neurol, 2008. **15**(10): p. 1013-28.
117. Steyerberg, E.W., *Clinical Prediction Models*. 1 ed. Statistics for biology and health, ed. M. Gail, et al. 2009, New York: Springer.
118. Royston, P., D.G. Altman, and W. Sauerbrei, *Dichotomizing continuous predictors in multiple regression: a bad idea.* Stat Med, 2006. **25**(1): p. 127-41.
119. Gray, R.J., *Flexible Methods for Analyzing Survival Data Using Splines, With Applications to Breast Cancer Prognosis.* Journal of the American Statistical Association, 1992. **87**(420): p. 942-951.
120. Zou, H. and T. Hastie, *Regularization and variable selection via the elastic net.* Journal of the Royal Statistical Society. Series B (Methodological), 2005. **67**: p. 310-320.
121. Steyerberg, E.W., et al., *Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets.* Stat Med, 2000. **19**(8): p. 1059-79.
122. Harrell, F.E., Jr., et al., *Regression modelling strategies for improved prognostic prediction.* Stat Med, 1984. **3**(2): p. 143-52.
123. R Development Core Team, *R: a language and environment for statistical computing.* . 2008, Vienna: R Foundation for Statistical Computing.
124. Tremont-Lukats, I.W., C. Megeff, and M.M. Backonja, *Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy.* Drugs, 2000. **60**(5): p. 1029-52.
125. Killian, J.M. and G.H. Fromm, *Carbamazepine in the treatment of neuralgia. Use of side effects.* Arch Neurol, 1968. **19**(2): p. 129-36.
126. Nicol, C.F., *A four year double-blind study of tegretol in facial pain.* Headache, 1969. **9**(1): p. 54-7.
127. Rockliff, B.W. and E.H. Davis, *Controlled sequential trials of carbamazepine in trigeminal neuralgia.* Arch Neurol, 1966. **15**(2): p. 129-36.
128. Dlugos, D.J. and R.J. Buono, *Predicting outcome of initial treatment with carbamazepine in childhood focal epilepsy.* Pediatr Neurol, 2004. **30**(5): p. 311-5.
129. May, A., et al., *EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias.* Eur J Neurol, 2006. **13**(10): p. 1066-77.
130. Schurks, M., et al., *Predictors of acute treatment response among patients with cluster headache.* Headache, 2007. **47**(7): p. 1079-84.
131. Tfelt-Hansen, P. and J. Tfelt-Hansen, *Verapamil for cluster headache. Clinical pharmacology and possible mode of action.* Headache, 2009. **49**(1): p. 117-25.
132. *The International Classification of Headache Disorders: 2nd edition.* Cephalalgia, 2004. **24 Suppl 1**: p. 9-160.
133. Caspers, P.W.J., R. Gijsen, and A. Blokstra. *Off-label use of prescription drugs. Transparency required*. 2008 2007 [cited 2008 24-06-2008]; June 24, 2008]. Available from: www.rivm.nl.
134. Riess, C.M., W.J. Becker, and M. Robertson, *Episodic cluster headache in a community: clinical features and treatment.* Can J Neurol Sci, 1998. **25**(2): p. 141-5.
135. Rothrock, J.F., et al., *Predictors of a negative response to topiramate therapy in patients with chronic migraine.* Headache, 2005. **45**(7): p. 932-5.
136. Diener, H.C., et al., *Identification of negative predictors of pain-free response to triptans: analysis of the eletriptan database.* Cephalalgia, 2008. **28**(1): p. 35-40.
137. Forssell, H., et al., *Differences and similarities between atypical facial pain and trigeminal neuropathic pain.* Neurology, 2007. **69**(14): p. 1451-9.

138. Bahra, A. and P.J. Goadsby, *Diagnostic delays and mis-management in cluster headache.* Acta Neurol Scand, 2004. **109**(3): p. 175-9.
139. Klapper, J.A., A. Klapper, and T. Voss, *The misdiagnosis of cluster headache: a nonclinic, population-based, Internet survey.* Headache, 2000. **40**(9): p. 730-5.
140. Van Alboom, E., et al., *Diagnostic and therapeutic trajectory of cluster headache patients in Flanders.* Acta Neurol Belg, 2009. **109**(1): p. 10-7.
141. Dandy, W.E., *Concerning the cause of trigeminal neuralgia.* American Journal of Surgery, 1934. **24**(2): p. 447-455.
142. Cruccu, G., et al., *Diagnostic accuracy of trigeminal reflex testing in trigeminal neuralgia.* Neurology, 2006. **66**(1): p. 139-41.
143. Goh, B.T., C.Y. Poon, and R.H. Peck, *The importance of routine magnetic resonance imaging in trigeminal neuralgia diagnosis.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2001. **92**(4): p. 424-9.
144. Majoie, C.B., et al., *Symptoms and signs related to the trigeminal nerve: diagnostic yield of MR imaging.* Radiology, 1998. **209**(2): p. 557-62.
145. Nomura, T., et al., *Trigeminal neuralgia: differentiation between intracranial mass lesions and ordinary vascular compression as causative lesions.* Neurosurg Rev, 1994. **17**(1): p. 51-7.
146. Sato, J., et al., *Diagnostic significance of carbamazepine and trigger zones in trigeminal neuralgia.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2004. **97**(1): p. 18-22.
147. Gronseth, G., et al., *Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies.* Neurology, 2008. **71**(15): p. 1183-90.
148. Tolle, T., E. Dukes, and A. Sadosky, *Patient burden of trigeminal neuralgia: results from a cross-sectional survey of health state impairment and treatment patterns in six European countries.* Pain Pract, 2006. **6**(3): p. 153-60.
149. Love, S., D.E. Bateman, and L. Hirschowitz, *Bilateral lambda light chain amyloidomas of the trigeminal ganglia, nerves and roots.* Neuropathol Appl Neurobiol, 1997. **23**(6): p. 512-5.
150. Meaney, J.F., et al., *Association between trigeminal neuralgia and multiple sclerosis: role of magnetic resonance imaging.* J Neurol Neurosurg Psychiatry, 1995. **59**(3): p. 253-9.
151. Nakamura, K., T. Yamamoto, and M. Yamashita, *Small medullary infarction presenting as painful trigeminal sensory neuropathy.* J Neurol Neurosurg Psychiatry, 1996. **61**(2): p. 138.
152. Bornemann, A., et al., *Amyloidoma of the gasserian ganglion as a cause of symptomatic neuralgia of the trigeminal nerve: report of three cases.* J Neurol, 1993. **241**(1): p. 10-4.
153. Jannetta, P.J., *Microsurgical management of trigeminal neuralgia.* Arch Neurol, 1985. **42**(8): p. 800.
154. Morley, T.P., *Case against microvascular decompression in the treatment of trigeminal neuralgia.* Arch Neurol, 1985. **42**(8): p. 801-2.
155. Young, J.N. and R.H. Wilkins, *Partial sensory trigeminal rhizotomy at the pons for trigeminal neuralgia.* J Neurosurg, 1993. **79**(5): p. 680-7.
156. Tatli, M., et al., *Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes.* Acta Neurochir (Wien), 2008. **150**(3): p. 243-55.
157. Toda, K., *Operative treatment of trigeminal neuralgia: review of current techniques.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2008. **106**(6): p. 788-805, 805 e1-6.
158. Kupka, K., *International classification of diseases: ninth revision.* WHO Chron, 1978. **32**(6): p. 219-25.

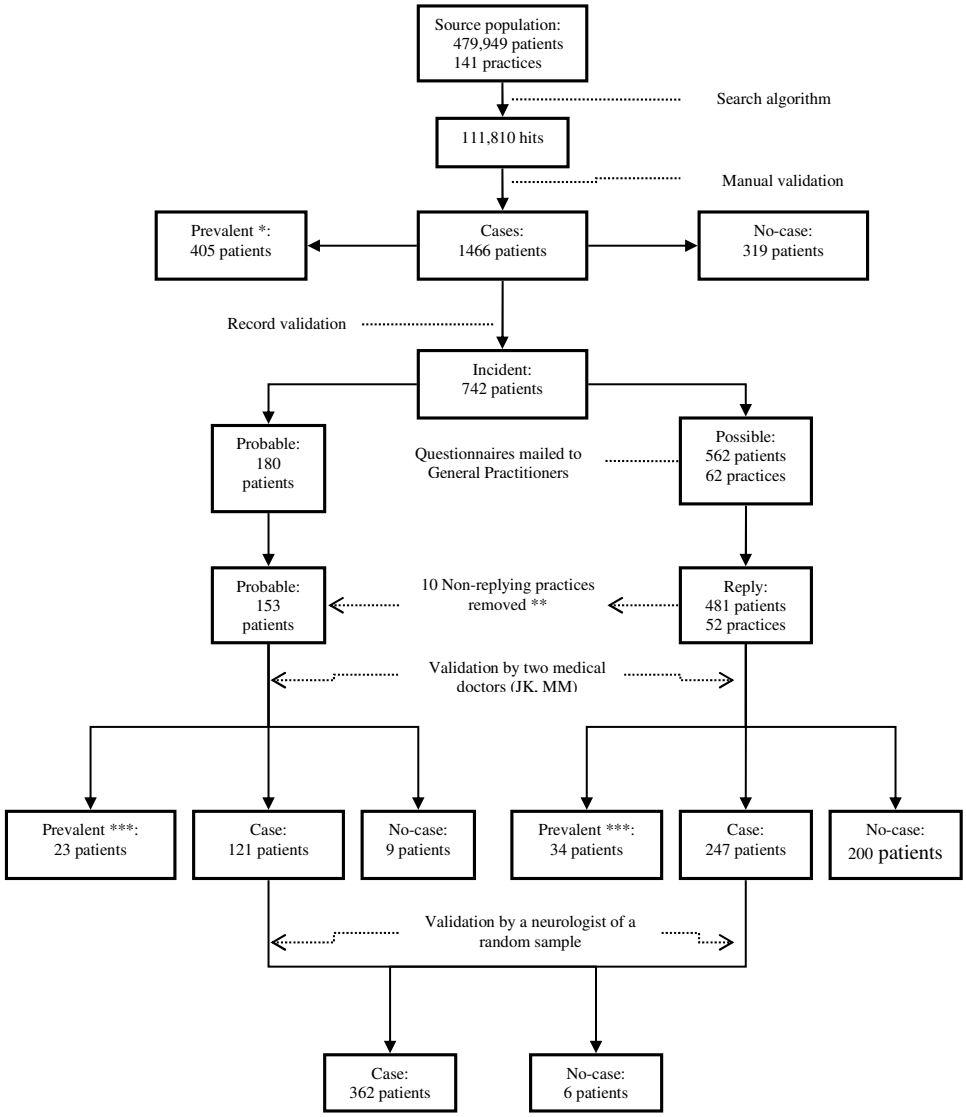
159. Jannetta, P.J., *Neurovascular compression in cranial nerve and systemic disease.* Ann Surg, 1980. **192**(4): p. 518-25.
160. Kolluri, S. and R.C. Heros, *Microvascular decompression for trigeminal neuralgia. A five-year follow-up study.* Surg Neurol, 1984. **22**(3): p. 235-40.
161. Linskey, M.E., H.D. Jho, and P.J. Jannetta, *Microvascular decompression for trigeminal neuralgia caused by vertebrobasilar compression.* J Neurosurg, 1994. **81**(1): p. 1-9.
162. McLaughlin, M.R., et al., *Microvascular decompression of cranial nerves: lessons learned after 4400 operations.* J Neurosurg, 1999. **90**(1): p. 1-8.
163. Sweet, W.H. and J.G. Wepsic, *Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia.* J Neurosurg, 1974. **40**(2): p. 143-56.
164. Tronnier, V.M., et al., *Treatment of idiopathic trigeminal neuralgia: comparison of long-term outcome after radiofrequency rhizotomy and microvascular decompression.* Neurosurgery, 2001. **48**(6): p. 1261-7; discussion 1267-8.
165. Taha, J.M., J.M. Tew, Jr., and C.R. Buncher, *A prospective 15-year follow up of 154 consecutive patients with trigeminal neuralgia treated by percutaneous stereotactic radiofrequency thermal rhizotomy.* J Neurosurg, 1995. **83**(6): p. 989-93.
166. Deyo, R.A., D.C. Cherkin, and M.A. Ciol, *Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases.* J Clin Epidemiol, 1992. **45**(6): p. 613-9.
167. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
168. Rubin, D.B., *Estimating causal effects from large data sets using propensity scores.* Ann Intern Med, 1997. **127**(8 Pt 2): p. 757-63.
169. Rubin, D.B. and N. Schenker, *Multiple imputation in health-care databases: an overview and some applications.* Stat Med, 1991. **10**(4): p. 585-98.
170. Sjaastad, O. and L.S. Bakketeig, *The rare, unilateral headaches. Vaga study of headache epidemiology.* J Headache Pain, 2007. **8**(1): p. 19-27.
171. Sindou, M., et al., *Microvascular decompression for primary trigeminal neuralgia: long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression.* J Neurosurg, 2007. **107**(6): p. 1144-53.
172. Kabatas, S., et al., *Microvascular decompression as a surgical management for trigeminal neuralgia: a critical review of the literature.* Neurol India, 2009. **57**(2): p. 134-8.
173. Broggi, G., P. Ferroli, and A. Franzini, *Treatment strategy for trigeminal neuralgia: a thirty years experience.* Neurol Sci, 2008. **29 Suppl 1**: p. S79-82.
174. Spatz, A.L., J.M. Zakrzewska, and E.J. Kay, *Decision analysis of medical and surgical treatments for trigeminal neuralgia: how patient evaluations of benefits and risks affect the utility of treatment decisions.* Pain, 2007. **131**(3): p. 302-10.
175. Laghmari, M., et al., *Are the destructive neurosurgical techniques as effective as microvascular decompression in the management of trigeminal neuralgia?* Surg Neurol, 2007. **68**(5): p. 505-12.
176. Barker, F.G., 2nd, et al., *The long-term outcome of microvascular decompression for trigeminal neuralgia.* N Engl J Med, 1996. **334**(17): p. 1077-83.
177. Li, S.T., et al., *Trigeminal neuralgia: what are the important factors for good operative outcomes with microvascular decompression.* Surg Neurol, 2004. **62**(5): p. 400-4; discussion 404-5.
178. Aggestrup, S., et al., *Regulatory peptides in the lower esophageal sphincter of man.* Regul Pept, 1985. **10**(2-3): p. 167-78.

Chapter 9

Appendices



Appendix A: Flowchart



Appendix B: Classification of morbidities (by pathogenesis)

Anatomic

Internal Organs
- abdominal hernia
- cardiac valve deformity
- diaphragmatic hernia
- gastro-esophageal reflux disease
- inguinal hernia
- nefrolithiasis
- spermatocèle
- umbilical hernia
- urinary tract reflux
- urogenital adhesions
- urogenital stricture
- urolithiasis
- torsio testis

Neurologic tract
- meralgia paresthetica
- nerve entrapment
- radicular syndrome
- spina bifida occulta
- spinal disc herniation
- carpal tunnel syndrome

Locomotoric tract
- anatomic disorder of any extremity not futher defined
- cervicobrachial syndrome
- cervicogenic vertigo
- dysplasia of the hip

Vascular tract
- hemorrhoids
- hypostatic eczema
- (trombogenic) varices
- venous insufficiency

Other
- atrophy of the maxilla
- deviation of the nasal septum
- incarnated nail
- obstruction of the parotic gland
- obstructive sleep apnea
- phimosis

Degenerative

Internal organs
- diverticulosis
- urogenital prolaps

Neurologic tract
- Alzheimer's dementia
- benign paroxysmal position dependent vertigo
- Parkinson's disease
- psychogeriatric problems

Locomotoric tract
- arthrosis
- chondromalacia
- chondropathy
- costoclavicular compression syndrome
- discopathy
- stenosis of the vertebral column
- tendinosis
- thoracic outlet syndrome
- vertebral weakness
- trigger finger

Vascular tract
- aneurysm of the aorta

Other
- ablatio retinae
- blepharochalazis
- cataract
- retraction of corpus vitreum
- ectropion
- keratoconjunctivitis
- luxation of the lens
- macula degeneration
- mamma involution
- mouches volantes

Metabolic

Lipid and glucose metabolism
- amaneurosis fugax
- angina pectoris
- arterial stenosis
- atherosclerosis
- cerebrovascular accident
- cholelithiasis
- claudicatio intermittens
- cysteinuria
- diabetes mellitus type II
- diabetic nefropathy
- diabetic polyneuropathy
- diabetic retinopathy
- cardiovascular disease
- hepatic steatosis
- hypercholesterolemia
- hyperglycemia
- hypertensive retinopathy
- intracranial bleeding
- lipodystrophia
- transient ischemic attack
- thrombosis of the eye
- xantelasmata

Excesses or deficiencies
- erythropoietic protoporphyria
- folic acid deficiency anemia
- hemochromatosis
- hemoglobinopathy
- hypokalemia
- iron deficiency anemia
- lactose intolerance
- leber opticus atrophy
- Lewy body dementia
- mitochondrial disease
- myositis ossificans
- syndrome of Bartter
- syndrome of Klippel-Trenaunay
- thalassemia
- vitamine B12 deficiency
- vitamine B12 deficiency anemia
- vitamine D deficiency
- vtiamine B1 deficiency
- Willibrand's disease

Intoxications
- alcoholic gastritis
- alcoholic hepatitis intoxication
- Korsakoff's disease
- liver cirrhosis

Other
- acute tubular necrosis
- cardia insufficiency
- decubitus
- disturbed kidney function
- gout
- hyperuricemia
- postoperative delirium

Neoplasm

Benign
- adenoma
- angioma
- benign brain tumor
- benign lung tumor
- benign mamma tumor
- benign nervous system tumor
- benign parotic tumor
- benign prostate hyperplasia
- benign skin tumor
- benign thyroid tumor
- cholesteatoma
- clavus
- cornu cutaneum
- dermatofibroma
- eccrien hidrocytoma
- exostosis
- feochromocytoma
- fibroadenoma
- fibroma
- granuloma
- hemangioma
- histiocytoma
- keloid
- lipoma
- meningeoma
- myoma
- naevus
- neurinoma
- neurofibroma
- osteoma
- papilloma
- polyp
- schwannoma

Malignant
- astrocytoma
- Barret's esophagus
- Bowen's disease
- carcinoma of the bladder
- carcinoma of the colon
- carcinoma of the endometrium
- carcinoma of the kidney
- carcinoma of the lung
- carcinoma of the mamma
- carcinoma of the prostate
- carcinoma of the sinus
- carcinoma of the skin
- cervical dysplasia
- Hodgkin's lymphoma
- keratosis actinica
- leucoplakia
- melanoma
- Non-Hodgkin's lymphoma

Infections

Commonly bacterial
- abces
- acute rheumatic fever
- appendicitis
- axillar dermatitis
- bacterial conjunctivitis
- balantitis
- bartholinitis
- campylobacter infection
- cellulitis
- chlamydia
- cholangitis
- cholecystitis
- cystitis
- diverticulitis
- duodenic ulcer
- dysenteria
- epididymitis
- erysipelas
- erythema nodosum
- erytrasma
- flebitis
- folliculitis
- furuncle
- gardnerella infection
- giardiasis
- gingivitis
- gonorrhea
- helicobacter pylori gastric ulcer
- helicobacter pylori gastritis
- hordeolum/chalazion
- hydradenitis
- impetigo
- Lymes' disease
- orchiitis
- ostemylitis
- parodontitis
- paronychia
- parotitis
- pelvic inflammatory disease
- phlegmon
- prostatitis
- pyelonefritis
- salmonelloses
- scarlet fever
- sexual transmittable disease
- trichomonas infection
- tuberculosis
- urethritis
- urinary tract infection
- urosepsis

Commonly viral
- Bornholm's disease
- condylomata accuminata
- chorioretinitis
- croup
- cytomegalo virus
- hepatitis A
- herpes simplex
- herpes zoster
- Pfeiffer's disease
- post viral fatigue syndrome
- varcella zoster infection

Infections (contin.)

Mycoses
- dermatomycosis
- intertrigo
- onychomycosis
- oral mycosis
- perianal mycosis
- pharyngeal mycosis
- pityriasis
- rosacea
- tinea pedis
- urogenital mycosis
- candida

Several types of microorganisms possible
- adenoiditis
- blepharitis
- bronchitis
- corneitis
- dacryocystitis
- dermatitis not further defined
- endocarditis
- enteritis
- epiglottitis
- gastroenteritis
- upper airway tract infection
- infection not further defined
- infectious conjunctivitis
- infectious rhinitis
- laryngitis
- meibomitis
- meningitis
- otitis externa
- otitis media
- perforation of the tympanum
- pharyngitis
- pneumonia
- respiratory tract infection
- sinusitis
- skin infection not further defined
- stomatitis
- tonsilitis
- tracheitis
- ulcer of the cornea
- ulcer of the ear
- ulcer of the perineum
- vaginitis
- vulvitis

Other
- headlice
- oxyuria
- scabies

Inflammation

Hypersensitivity

*Autoimmune**
- autoimmune hepatitis
- Bechterew's disease
- Behcet's disease
- Chron's disease
- Churg Strauss' disease
- colitis ulcerosa
- crest syndrome
- diabetes mellitus type I
- Graves disease
- lichen ruber planus
- lichen sclerosis et atroficans vulvae
- mixed connective tissue disease
- multiple sclerosis
- myasthenia gravis
- polymyalgia rheumatica
- psoriasis
- psoriatic arthritis
- Quervain's disease
- rheumatic syndrome
- rheumatoid arthritis
- sarcoidosis
- Sjögren' s disease
- Still's disease
- vasculitis
- vitiligo

*Asthma**
- asthma
- chronic aspecific respiratory disorders

*Allergy**
- allergic conjunctivitis
- allergic rhinitis
- allergy not further defined
- angioedema
- broncheal hyperactivity
- urticaria
- allergic vasculitis

eczema
- atopic eczema
- constitutional eczema
- contact eczema
- seborrhoeic eczema

Locomotoric tract
- arthritis
- bursitis
- capsulitis
- costochondritis
- lateral epicondylitis
- medial epicondylitis
- fasciitis plantaris
- synovitis
- tendinitis
- tendosynovitis
- tendovaginitis
- apexitis

Inflammation (contin.)

Other
- asthmatic bronchitis
- chronic bronchitis
- colitis not further defined
- episcleritis
- esophagitis
- fibrosis of the lung
- interstitial pulmonary disorder
- iriits
- lymfadenitis
- lymfadenopathy
- mastitis
- neuritis
- neurodermatitis
- photodermatosis
- proctitis
- scleritis
- sigmoiditis
- thyroiditis
- uveitis
- chronic obstructive pulmonary disease/ emphysema
- keratitis
- duodenitis

verrucae
viral conjunctivitis
undefined viral infection

Hormonal	Psychological factors	Trauma
Sex hormones ***Menstrual Cycle related**** dysmenorhea irregular menstrual cycle metro/menorrhagia polymenorhea premenstrual syndrome senundary amenorhea ***Climacteriu related*** atrophic vaginitis Climacterial symptoms climacterium praecox osteoporosis/ osteopenia* ***Other*** endometriosis hirsutism hypertrichosis Thyroid hormones athyroidism hyperthyroidism hypothyroidism struma Other hyperparathyroidism hyperprolactinaemia hypofyse related problems hypogonadism	Depression* bipolar disorder depression not further defined dysthymic disorder neurotic depression postnatal depression psychotic depression reactive depression Anxiety* anxiety/panic disorder anxious/nervous feelings hyperventilation hypochondria phobia Psychosocial* psychosocial problems Stress* burn out posttraumatic stress syndrome stress Other alcohol abuses anorexia nervosa attention deficit hyperactivity disorder bulimia drug abuse functional polyuria hallucinations impulse regulation disorder catatonia manic disorder medication abuses nervous dermatitis neurasthenia/surmenage neurosis nicotine abuse personality disorder psychiatric problems not further defined psychogenic epilepsy psychosis schizophrenia	Soft tissue ecchymosis fissura ani hematoma rontgen dermatitis syndrome of Mallory Weiss top injury of a finger wound Locomotoric tract frozen shoulder loge syndrome meniscus lesion muscle fascia defect patellofemoral pain syndrome perihumeroscapulair syndrome pseudoarthrosis of the arm pseudoarthrosis of the wrist repetitive strain injury rotator cuff syndrome spoke injury neurological tract commotion cerebri contusion cerebri post spinal headache posttraumatic tinnitus whiplash Other bleeding in the eye cornea erosion corpus alienum at any location orbital bleeding posttraumatic syndrome

Appendix C: ICD-9 Complication

389 Hearing loss
34981 Cerebrospinal fluid rhinorrhea
7820 Disturbance of skin sensation
38861 Cerebrospinal fluid otorrhea
322 Meningitis of unspecified cause
321 Meningitis due to other organisms
320 Bacterial meningitis
047 Meningitis due to enterovirus
7813 Lack of coordination
368 Visual disturbances
998 Other complications of procedures, NEC
997 Complications affecting specified body systems, not elsewhere classified
996 Complications peculiar to certain specified procedures
054 Herpes simplex
7804 Dizziness and giddiness
3883 Tinnitus
3510 Bells palsy
37853 Fourth or trochlear nerve palsy
3885 Disorders of acoustic nerve
78194 Facial weakness
854 Intracranial injury of other and unspecified nature
370 Keratitis
9961 Mechanical complication of other vascular device, implant, and graft
37181 Corneal anesthesia and hypoesthesia
V410 Problems with sight
E870 Accidental cut, puncture, perforation, or hemorrhage during medical care
E871 Foreign object left in body during procedure
E878 Surgical operation and other surgical procedures as the cause of abnormal reaction of patients, or of later complication, without mention of misadventrue at the time of operation
E879 Other procedures, without mention of misadventure at the time of procedure, as the Cause of abnormal reaction of patient, or of later complication
9954 Shock due to anesthesia
9950 Other anaphylactic shock
C2939 Unspecified transient mental disorder in conditions classified elsewhere
C3209 Meningitis due to unspecified bacterium
C3229 Meningitis, unspecified
C3429 Hemiplegia, unspecified
C3682 Diplopia
C3899 Unspecified hearing loss
C4340 Cerebral thrombosis
C5070 Due to inhalation of food or vomitus
C5990 Urinary tract infection, site not specified
C9973 Respiratory complications
C9981 Hemorrhage or hematoma or seroma complicating a procedure
C9985 Postoperative infection

Acknowledgements

Too many people helped me to finish my current work for me to name them all. Furthermore, the risk of naming people includes the risk of forgetting people who might very well have been crucial for completion of this work. I would sincerely like to thank each and every one of you who helped me to accomplish this task.

Bibliography

Koopman JS, Kunthonluxamee A, Dieleman JP, Huygen FJ, Sturkenboom MC.
Cluster headache and head trauma: A Dutch population-based study.
Submitted

Koopman JS, Huygen FJ, Dieleman JP, de Mos M, Sturkenboom MC.
Pharmacological treatment of neuropathic facial pain in the Dutch General population.
2010 Mar;11(3):264-72

Koopman JS, Dieleman JP, Huygen FJ, de Mos M, Martin CG, Sturkenboom MC.
Incidence of facial pain in the general population.
Pain. 2009 Dec 15; 147(1-3):122-7

Koopman JS, Vrinten DH, van Wijck AJ.
Efficacy of microcurrent therapy in the treatment of chronic nonspecific back pain: a pilot study.
Clin J Pain. 2009 Jul-Aug ;25(6):495-9.

de Mos M, Huygen FJ, Dieleman JP, Koopman JS, Stricker BH, Sturkenboom MC.
Medical history and the onset of complex regional pain syndrome (CRPS).
Pain. 2008 Oct 15;139(2):458-66.

Koopman JS, Baoutou Y.
De betrouwbaarheid van troponine en CK-MB bij patiënten met een subarachnoidale bloeding (SAB)
NTvA. 2009 Feb; 21(1).

Koopman JS, Vrinten DH, van Wijck AJ:
Elektroanalgesie bij de behandeling van acute en chronische pijn: Mogelijkheden, technieken, literatuur.
NTPP. 2008

Koopman JS.
Genetisch verbeteren en de doelen van de gezondheidszorg
Verslag. 2005