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Pharmacological Treatment of Neuropathic Facial Pain in the Dutch General Population

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Abstract: **Few drugs are registered for treatment of neuropathic facial pain (NFP), and not much is known about treatment choices for NFP in daily practice. Patients with NFP were identified in the IPCI-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. 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 to 2,478 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 3 months. The median duration until failure was 251 days. 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.**

Perspective: ***This drug-utilization study describes the pharmacological treatment of different forms of neuropathic facial pain in daily practice. Although treatment is mostly initiated rapidly by general practitioners in a correct way, it often contains off-label or off-guideline medication. Failure of the initial treatment is common and occurs rapidly as well.***

Key Words: *Drug utilization study, trigeminal neuralgia, postherpetic neuralgia, glossopharyngeal neuralgia, general population.*

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 daily functioning. Each year, 21.7 out of 100,000 persons are newly diagnosed with one of these diseases according to recent data.[15]

The most common type of neuropathic facial pain is trigeminal neuralgia, which presents with paroxysmal, unilateral facial pain in 1 or more branches of the 5th cranial nerve. Other forms include facial postherpetic neuralgia, occipital neuralgia with referred pain in the face, 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.[4,10,16,17,22]

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.[3] For trigeminal neuralgia, the guidelines recommend

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carbamazepine (level A level of evidence [LOE]) but also oxcarbazepine (level B LOE), and even baclofen and lamotrigine (level C LOE).[3] For postherpetic neuralgia, they recommend tricyclic antidepressants, gabapentine, pregabalin and opioids (level A LOE).[3] Capsaicin, tramadol, topical lidocaine, and valproate have a lower efficacy or are less well evaluated (level B LOE).[3] In the Netherlands, only carbamazepine is officially registered for trigeminal neuralgia. Gabapentine is registered for peripheral neuralgia which might include postherpetic neuralgia and local neuralgias.[18] Pregabalin is registered for peripheral and central neuropathic pain, which covers all forms of neuropathic facial pain.[18] 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, occipital neuralgia, local 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 approximately 800,000 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.[21] 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.[7] 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.[1] 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.[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 to September 2006) with at least 1 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 nonresponding practices. Follow-up started at the beginning of the study period or the date that 1 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).[2] 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 3-step approach for case ascertainment. First, 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 1 episode of typical symptoms was recorded in the records, and as "possible" if only 1 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." Second, GPs were requested to confirm the presence and type of facial pain of all "possible" cases. In addition, they were asked to send anonymous hard copies of all specialist letters regarding this diagnosis. All returned information was independently evaluated by 2 medical doctors (JK, MM) to classify cases as "probable" or "no case." Discrepancies were arbitrated by a pain specialist (FH). Third, to further ensure the validity of the diagnosis, a random sample of 250 patients of all initial "probable" and "possible" cases (742) from step 1 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)