EPIDEMIOLOGY OF REFRACTORY NEUROPATHIC PAIN

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General Considerations: Neuropathic pain (NP) is an important component of many chronic pain conditions, estimated to be present in ∼25% of chronic pain patients but remains frequently undiagnosed. It has long been recognized as a unifying hypothesis of many variously expressed pathophysiological mechanisms rather than as a single neural pain mechanism. These different mechanisms can result in common clinical features, such as spontaneous and evoked pains, and is identified in clinical practice when accompanied by other evidence of nervous system dysfunction.

Although NP pain can be acute in nature, in most patients the pain is persistent (or "refractory"), with chronic pain being most often seen in clinical practice [1]. The term refractory has been advocated as well for types of NP pain not responding to treatment.

The spectrum of clinically suspected NP pain ranges from obvious NP conditions such as post-amputation pain, painful neuropathies, trigeminal and postherpetic neuralgia, post-stroke central pain, and cancer NP pain to pain conditions with none or vague signs of nerve damage such as low back pain. Based on clinical experience NP is claimed to have specific characteristics: spontaneous and evoked pain such as allodynia, hyperalgesia, pinprick evoked pain and a specific set of pain descriptors.

Epidemiology remains the least documented aspect of NP pain syndromes. The paucity of information regarding the incidence and prevalence of NP in the general population has been a limiting factor in the development of clinical research and management programs. This situation reflects the discord regarding the definition of NP pain, the lack of standardised diagnostic criteria and consequently, the absence of a validated, reliable and simple clinical instrument that could be used in large population-based surveys [2].

The definition of neuropathic pain as "pain initiated, or caused, by a primary lesion or dysfunction of the nervous system [3], is not simple to use in clinical practice, because the presence or absence of nerve dysfunction, regardless of symptoms, is difficult to establish, and there is no clear relationship between underlying pain mechanisms, physical signs and subjective pain experience [4]. This makes the identification of neuropathic pain by clinicians a continuing challenge. Despite this, it remains common practice to classify chronic pain into two mutually exclusive, mechanism-based categories; either nociceptive in origin or neuropathic. Attal and Bouhassira (2004) [5] question whether it is time to adopt an alternative approach to defining chronic pain. They ask whether pain can have degrees of neuropathic components and, therefore, whether pain should be viewed as 'more or less neuropathic.' Bennet et al have previously supported this argument and advocate that a more flexible model of chronic pain is appropriate. They have also suggested that it
might be more appropriate to identify pain of predominantly neuropathic origin (POPNO) rather than an all or nothing phenomenon [6].

**Epidemiology in General Population:** On the light of the above considerations it is not surprising that the published data on the occurrence of neuropathic pain, especially in the general population suffering of NP pain, are rare. The true incidence of NP pain is unknown, but it is believed to be under-diagnosed and treated inadequately [7]. Incidence rates of NP pain are mainly estimates; they are scanty and mostly address single types, whereas the spectrum of the disease is wide. The often cited figure of 1.5% of the population being affected by NP pain comes from an earlier report by Bennett [8]. The author's stated basis for this prevalence estimate was as follows: "In view of all the possible causes of neuropathic pain, the prevalence of neuropathic pain can be conservatively estimated at 0.6% of the US population (more than 1.6 million patients). However, the total is dramatically influenced by low-back pain. Even if this includes only 1 back-pain patient in 10, the number of US patients increases by almost 3 million. By this calculation, neuropathic pain affects 1.5% of the population. Crude estimates in the range 1-3% have been proposed by Dworkin et al and Irving et al [9, 10].

Two recent postal surveys, carried out in large community samples from UK [11] and France [12], using different NP pain questionnaires (S-LANSS in UK and DN4 in France), reported similar estimates of the prevalence of chronic pain with NP characteristics in the general population, around 7-8%. Interestingly, these population-based studies showed that the subset of respondents with NP features have several associated clinical characteristics which differ from others with chronic pain, even after controlling for pain severity. These include significantly worse quality of life, greater interference from pain, and pain of longer duration.

One limitation, inherent to this approach, is the lack of direct information regarding the aetiology of pain and the use of screening tools to identify NP pain. In other words, how sure can we be that a positive responder to a postal screening tool would be diagnosed with neuropathic pain if seen by a pain specialist in a clinic [13]? This question has been addressed by Weingarten and colleagues on a community validation study of the S-LANSS scale [14]. They mailed nearly 6000 questionnaires to community adults and received over 3500 replies. A sub-sample of these respondents was invited for clinical assessment and comparison was made between clinical assessment and responses to S-LANSS. The authors report that the S-LANSS performed less well than expected from its performance in earlier validation studies. Based on this they cast doubt on the use of the S-LANSS (and perhaps by inference all screening tools for neuropathic pain) to determine the prevalence of NP pain in populations, even though the prevalence of NP pain derived from their own survey (8.8%) is very close to that reported by others, using the same questionnaire [11].

Therefore, there are methodological aspects of sampling and clinical assessment which might preclude robust conclusions regarding screening tools and final epidemiological findings in this context.
Incidence in Special Populations: Painful diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) are the most commonly studied peripheral neuropathic pain syndromes. However, less frequent neuropathic pain conditions also contribute to the overall disease burden, but there is a paucity of epidemiologic data for many of these conditions, and many reviews of neuropathic pain do not distinguish among the various syndromes.

A descriptive analysis of the epidemiology and drug treatment of neuropathic pain as managed by UK primary care physicians looked on the incidence of incident post-herpetic neuralgia (n = 12,386); trigeminal neuralgia (8268); phantom limb pain (451) and painful diabetic neuropathy (4719) from computerised UK general practice records (1992-2002). The Incidences per 100,000 person years observation of 40 (95% CI 39-41) for post-herpetic neuralgia, 27 (26-27) for trigeminal neuralgia, 1 (1-2) for phantom limb pain and 15 (15-16) for painful diabetic neuropathy are reported, with rates decreasing over time for phantom limb pain and post-herpetic neuralgia and increasing for painful diabetic neuropathy. Due to methodology, prevalence was not estimated in this study [7].

In a study aiming to calculate the incidence rates of neuropathic pain conditions in the Dutch general population and to assess treatment strategies in primary care database between 1996 and 2003, among 362,693 persons contributing 1,116,215 person years (PY), were identified 9135 new cases of neuropathic pain (IR: 8.2/1000 PY, 95%CI: 8.0-8.4) [15]. Mononeuropathy and carpal tunnel syndrome were the most frequent types with 4.3 and 2.3 cases/1000 PY followed by diabetic peripheral neuropathy and post-herpetic neuralgia at 0.72 and 0.42/1000 PY. Neuropathic pain was 63% more common in women than in men and peaked between the ages 70 and 79.

Diabetic Peripheral Neuropathy - DPN

Historically, epidemiologic studies of DPN have not differentiated between patients with and without pain, but have included pain as one of several inclusion criteria. Also, most studies do not indicate, whether patients with NP pain resulting from aetiology other than diabetes, have been excluded. In the literature, the prevalence of PDN ranges from 10% to 20% of patients with diabetes and from 40% to 50% of those with diabetic neuropathies [16, 17].

While an adjusted annual incidence of 54 per 100,000 has been reported for diabetic polyneuropathy in an urban general population in the U.K. [18], prevalence estimates within the diabetes population ranged from 16.3% to 50%. This variability in prevalence is likely due to differences in definition, method of assessment, and patient selection. Based on data from the National Health and Nutrition Examination Survey (NHANES) in the U.S.A., 28.5% of individuals with diabetes were estimated to have peripheral neuropathy defined as at least one area upon monofilament testing of both feet [19].

A detailed evaluation of PDN was undertaken in a European multicenter study of 1,171 patients with diabetes type 1 and 2 and served to illustrate the complex nature of PDN. Significantly lower pain in both the lower (11.6% [75/ 647] v/s 32.1% [168/524]) and upper (7.1% v/s 16.6%)
extremities in patients with type 1 (mean duration, 10 years) compared with type 2 diabetes, respectively [20].

**Postherpetic Neuralgia:** Data from an older, community-based study, from Minnesota reported an annual incidence of approximately 11.6 per 100,000 person-years [21]. A subsequent British general-population study provided good agreement, reporting an adjusted annual incidence of PHN of 11 per 100,000 and a lifetime prevalence of 70 per 100,000 [22]. An unadjusted incidence of 40.2/100,000 patient-years was reported in a more recent study that used the U.K. GPRD over a study period January 1992- April 2002 [7]. The study showed a trend toward a significant decrease in incidence over the study period (P < 0.001). The estimated prevalence of PHN in the population of patients with HZ ranges from 7% to 27%, with the lower estimate coming from an Icelandic study [23] and the higher estimate from a community-based study in the U.K. [24] with PHN in both studies considered at 3 months after HZ.

**Trigeminal Neuralgia:** The incidence of trigeminal neuralgia is reported to be between 4.3 per 100,000 persons per year, with a slightly higher incidence for women (5.9 per 100,000) compared with men (3.4 per 100,000). There is a lack of certainty regarding the aetiology and pathophysiology of TN. The epidemiology of TN has been described in three large population studies, one in the U.S.A. performed in Rochester, Minnesota [25], and two in the U.K. [6, 26]. The U.S. study reported an annual age- and gender-adjusted incidence of 4.7/100,000, which was lower than the rate of 8/100,000 reported in a U.K. general practice study of neurological disorders. As TN is an episodic disease with pain-free intervals, an overall incidence rate of 5 to 8/100,000 may provide the best population estimate based on age- and gender adjusted data.

**HIV - Related Neuropathies:** The presence of human immunodeficiency virus (HIV) is often associated with several different types of neuropathies including distal symmetrical polyneuropathy (DSP), inflammatory demyelinating polyneuropathy multiplex (MM), autonomic neuropathy, and diffuse infiltrative lymphocytosis syndrome (DILS). These neuropathies may also occur secondary to treatment, as many of the drugs used in the management of HIV patients are known to be neurotoxic, especially the antiretrovirals, although the antibacterials, anticancer drugs, and other agents may also be contributory factors. Using a sample size, weighted average from data in the identified studies, the frequency of HIV-related neuropathy was calculated to be 48%, with an average frequency of painful HIV-related neuropathy of 35%. This is probably the best estimate given the available data [19].

**Back Pain and Cervical Radiculopathy:** Available epidemiological data from 3 studies (pain DETECT 1, pain DETECT 2, and the German back pain research network study) were used in a study a total of 21,047 subjects, aiming to model the prevalence of NP back pain in the general adult population. Approximately 4% of the general adult population experienced back pain with a neuropathic component [27]. The best epidemiologic data on cervical cervical radiculopathy come from a population-based study in Rochester, Minnesota, which reported a gender and age-adjusted annual incidence of 83.2/100,000 population, and a peak age-specific incidence rate of 202/100,000 in the 50 to 54 year age group. A confirmed disc protrusion was responsible for CR in only 21.9% of
patients. During the median duration of follow-up of 4.9 years, recurrence of the condition occurred in 31.7%. Neck and arm pain was reported in nearly all subjects (97.5%) and 89.7% reported paresthesias, which were nearly all unilateral [28].

**Central NP Pain:** A more recent definition states that central NP pain is pain arising as a direct consequence of lesion or decease affecting the central nervous somatosensory system [29] Figures of central pain are very high, namely in patients who have Multiple sclerosis 28%, Syringomyelia 75%, Spinal cord injury 60-70%, Stroke patients 8% [30] As for amputation pain most studies have reported prevalence in excess of 80%.

**Cancer Related NP Pain:** NP pain in cancer arises following injury to peripheral or central neurons, in a similar manner to such pain arising from a non-cancer injury. Much of our knowledge of NP cancer pain is based on peripheral originating events (nerve compression, tumor invasion, chemotherapy) with little known about central NP pain. Although the exact prevalence of NP pain in cancer patients remains unknown, it is predicted that at least 15-20% of patients are likely to suffer from NP pain during the course of the disease, and an even higher proportion, almost 1/3 at advanced stages of the disease [31]. In our own institution out of 1183 cancer patients using with cancer 33 28% had definite NP pain characteristics (DN4>5) [32].

**The Burden of NP Pain to Society:** Patients with NP pain have greater medical co-morbidity than age- and sex-adjusted controls, which makes determining the humanistic and economic burden attributable to NP challenging. Health-related quality of life (HR-QOL) is substantially impaired among patients with NP. Patients describe pain-related interference in multiple HR-QOL and functional domains, as well as reduced ability to work and reduced mobility due to their pain. In addition, the spouses of NP patients have been shown to experience adverse social consequences related to NP [33]. The substantial costs to society of NP derive from direct medical costs, loss of the ability to work, loss of caregivers’ ability to work and possibly greater need for institutionalization or other living assistance. The full costs of NP to society, has not been determined.

**Conclusion:** The observed variability in incidence and prevalence rates of NP pain is often a product of the geographic setting (eg, specific country, rural vs. urban setting), time period evaluated, source of data (eg, patient self-report vs. medical records, general practitioners vs. specialists), and diagnostic or disease definitions. Furthermore, some of the less prevalent syndromes may potentially be associated with greater pain severity and disability than more prevalent neuropathies, and thus may be associated with a greater individual burden.

**Bibliography**


