

Epidemiology of Neuropathic Pain and Its Impact on Quality of Life

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Abstract Epidemiology is an important clinical tool in designing and evaluating management and prevention strategies, and is particularly relevant to neuropathic pain. However, there is a relative lack of accurate information available. In one sense, neuropathic pain describes a symptom or a mechanism, rather than a specific disease; on the other hand, there are sufficient similarities in the effects and response to treatment between different causes to make it worthwhile to consider neuropathic pain as a distinct condition. However, there are important specific disease-based factors that need to be considered separately. Estimates of prevalence that are based on specific causes of neuropathic pain tend to be lower (1–2%) than those that are based on reports of the classic symptoms (6–8%), and further methodological research is needed. All neuropathic pain is associated with poor general health, comparable with other severe chronic diseases. The importance of newly proposed risk factors, including genetic factors, still needs to be assessed at a population level.

Keywords Neuropathic pain · Epidemiology · Prevalence · Incidence · Chronic pain · Screening tools · Neuropathy · Diabetic neuropathy · Postherpetic neuralgia

Introduction

There have been recent important advances in our understanding of the assessment of neuropathic pain and of its underlying biological mechanisms. However, our

knowledge of its epidemiology remains relatively sketchy. There are many published studies of the proportion of individuals with specific diseases (such as diabetes, HIV, or spinal cord injury) that experience neuropathic pain. There are many fewer studies addressing the prevalence of neuropathic pain in the general population, or its impact at a societal level. There are several good reasons for this relative lack of accurate observation or measurement, which will be discussed here. Some recent studies have addressed these barriers, and the picture is emerging of a condition that is more common than previously thought, with a significant health and economic impact, with some indications for preventability, but with more research required.

Epidemiology

Epidemiology is defined as, “The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control health problems” [1]. The first part of this definition implies a descriptive science, with observation and measurement that requires statistical and clinical precision as far as possible. This is important for assessing health service and educational resource requirements. It is the second part of the definition, however, that makes epidemiology a fundamentally important discipline, crucial to medical science and relevant to physicians and to society. Epidemiology can identify specific risk factors and effective prevention or management strategies before the underlying causal mechanisms are either known or clear, leading to immediate practical interventions and further fruitful scientific approaches to the pathophysiology of the diseases in question, in parallel with population-based research. This same potential exists for neuropathic pain (Table 1).

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Table 1 Potential outcomes of the epidemiological study of neuropathic pain

To inform understanding, at a population level, of:

- Distribution and determinants
- Definition and classification
- Etiology (factors that favor development and chronicity)
- Prognosis
- Prevention
- Impact on quality of life
- Design, targeting, and evaluation of treatment strategies
- Allocation of health service resources
- Allocation of educational resources

Some Considerations and Potential Barriers

As with any epidemiological study, the crucial first step is to identify a *case definition*. For many conditions this is relatively straightforward, but represents an important barrier to an epidemiological understanding of neuropathic pain. The International Association for the Study of Pain (IASP) recently adopted the definition of neuropathic pain proposed by international consensus: “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [2, 3••]. This definition supersedes the definition previously held by the IASP: “pain initiated or caused by a primary lesion or dysfunction in the nervous system” [4]. The differences between these, though small, are important. For population-based epidemiology, it is unclear how to define a “(primary) lesion” or “disease” or whether we can diagnose neuropathic pain without requiring incontrovertible proof of these.

This brings us to a second major barrier: *case ascertainment*. Even if a practical case definition can be agreed, how do we apply this in population-based research to identify those who do and those who do not have neuropathic pain? There is now international consensus on how neuropathic pain should be assessed in primary care [5] and also in specialist settings [6••]. However, while these detailed, standardized approaches are important in clinical settings, they cannot be applied in the large-scale population-based settings that epidemiology requires.

Neuropathic pain is not necessarily a yes/no phenomenon, a fact that further complicates case definition and ascertainment. Rather than a binary model of pain (nociceptive/neuropathic, or even neuropathic/non-neuropathic), recent research suggests instead that pain is a spectrum, with a greater or lesser contribution made by neuropathic mechanisms [7]. There is not yet a clear understanding of the level of this contribution that is clinically relevant to allow an individual to be included as a “case” in any epidemiological study.

Neuropathic Pain as a Global Entity?

There is a fundamental question about the value in considering neuropathic pain as a single, global entity, rather than as a symptom of a number of different pathological conditions. It is certainly true that there are many obvious differences in the etiology of conditions such as peripheral diabetic neuropathy (PDN), postherpetic neuralgia (PHN), and HIV-related neuropathy, with clear implications for prevention, and for some aspects of management. For the reasons stated or implied above, therefore, there is certainly merit in studying the epidemiology of these distinct conditions separately.

However, there are also good reasons for considering the distinct clinical entity of neuropathic pain, particularly from the population or nonspecialist perspective, where most neuropathic pain presents and is managed. Irrespective of the underlying disease or lesion, there is a common pattern of symptoms and signs, and the effect of the pain on an individual’s life is generally independent of its cause. While there are differences in the pathophysiological mechanisms of different causes of neuropathic pain, there are also many similarities in these, no matter what the underlying cause. Most importantly from a clinical perspective, there are many similarities in the response to treatment, and these differ importantly from responses in non-neuropathic pain, pharmacologically [8, 9] and nonpharmacologically [10]. Thus, while it is important to isolate and address treatable underlying causes, assessment and management, at least in the nonspecialist setting, can generally proceed on the basis of neuropathic pain as a single entity.

Note, though, that current and emerging research may not always render this comparatively simplistic approach appropriate. For example, Baron et al. [11•] identified five distinct subtypes of neuropathic pain based on symptoms and sensory profiles, occurring with different frequencies in different neuropathic conditions. It is not clear yet whether these have implications for management and response to treatment. Earlier evidence does suggest at least two different subtypes of PHN, with some different responses to topical treatments [12] and newer evidence of different responses to treatment of burning mouth syndrome were found, depending on whether the mechanism appeared to be central or peripheral [13]. Ultimately, it is possible that treatment of neuropathic pain may need to be targeted specifically according to mechanism and likely response, with individual genetic factors proving important [14]. There is still much research required before these can be identified and applied in a human clinical setting. Most intervention studies that currently inform treatment have been based on distinct diagnostic classifications, and there is still confirmation required that some specific treatments are effective in some or all other neuropathic pain conditions. Further, in

HIV-related neuropathic pain, standard neuropathic pain treatment with amitriptyline and gabapentin has been found to be relatively ineffective [15–17] while there is some evidence for the effectiveness of nonstandard treatment with cannabis [18, 19]. The more such evidence emerges, the more we may need to subdivide the epidemiology of neuropathic pain.

Furthermore, while it is likely that the great majority of individuals who experience pain with neuropathic features are assessed and managed in nonspecialist settings (primary care or hospital clinics without a specialist interest in neuropathic pain), neurologists and pain specialists utilize more complex treatment modalities. Many of these are specific to distinct diagnostic conditions, and would not be informed by population-based epidemiology of neuropathic pain as a single global entity.

Epidemiology of Neuropathic Pain: Current Knowledge

Irrespective of these considerations, however, there is some good information that is highly relevant to our understanding of neuropathic pain.

First, there are well-established estimates of the overall population prevalence of neuropathic pain based on estimates of the prevalence of the main etiological conditions: about 1% in the United Kingdom [20] and about 2% in the United States [21]. There is a caveat that these are probably underestimates [22], partly because they fail to consider idiopathic causes and partly because they do not include the neuropathic contribution to pain more traditionally considered as nociceptive. On the other hand, these estimates may “double count” individuals who have neuropathic pain arising as a result of two or more separate causes.

Second, there is good information on the incidence and prevalence of some of the important specific causes of neuropathic pain. For example, we have reasonable estimates of the prevalence of diabetes (eg, 2.8% worldwide in 2000) [23], the lifetime incidence of herpes zoster (HZ [approximately 24%]) [24], and the global prevalence of HIV (with 34 million people affected in 2010 [<http://www.who.int/hiv/data/en/index.html>]).

Third, there are some good studies that show us the proportion of individuals with these conditions that experience neuropathic pain. For example, 26.4% of those with type 2 diabetes had painful PDN [25], 8.0% of those diagnosed with HZ infection had PHN after 30 days [26], and 37.0% of those with chronic low back pain had a predominantly neuropathic component to their pain [27].

Fourth, a number of brief screening instruments have been developed, aimed at identifying neuropathic pain in population-based research [28]. These are based on the typical features of neuropathic pain (symptoms and self-

examined signs), and were validated in clinic-based populations. Although there are some differences in the details of these instruments, they are generally based on the presence or absence of the same main characteristics (eg, paraesthesia, shooting pains, numbness). The value of these instruments in population-based research is limited by an absence of validation studies in general population settings; hence, their positive and negative predictive value in this setting is unknown. Nonetheless, some studies have used them to identify pain with neuropathic features in large general populations. For example, Torrance et al. [29] found a prevalence of “pain of predominantly neuropathic origin” of 8.2% in the United Kingdom, and Bouhassira et al. [30] found a prevalence of “chronic pain with neuropathic features” of 6.9% in France.

Fifth, we see a common set of factors associated with neuropathic pain (though longitudinal studies are required to determine whether these are risk factors, outcomes, or the result of confounding by other variables). They include female sex, older age, manual working, indicators of deprivation, and poor general health [29–31, 32•]. Health-related quality of life (HRQoL) scores have been found to be worse than in non-neuropathic pain when compared to a number of chronic disease conditions [31]. In addition, a number of potentially modifiable risk factors have been found for specific conditions such as PDN [33, 34], PHN [35], and postsurgical pain [36].

Meanwhile, research is underway aimed at achieving international consensus on a practical definition of neuropathic pain for epidemiological research, and on how the results of questionnaire-based screening instruments relate to clinically assessed neuropathic pain. Furthermore, the availability and quality of data from large computerized routine primary care databases is increasing, with the intriguing possibility of assessing the prevalence and health-related impact of neuropathic pain in populations numbering in the millions [37, 38]. The continued development and refinement of disease-specific assessment instruments will allow further detailed epidemiology of these conditions and of the proportions affected by neuropathic pain.

A recent comprehensive literature review of general population-based studies of the epidemiology of neuropathic pain provides an overview of current knowledge [39]. Several studies have examined the epidemiology of neuropathic pain as a single entity (Table 2). In postal surveys using validated screening instruments, Torrance et al. [29], using the Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) [40], found a prevalence of 8.2% in the United Kingdom [29] while Bouhassira et al. [30], using the Neuropathic Pain Diagnostic Questionnaire (DN4) [41], found a prevalence of 6.9% in France. While these instruments were well validated in pain clinic settings, their positive predictive value in a general

Table 2 Prevalence of pain with neuropathic characteristics in the general population

Study	Sample size/location	Study method	NeuP case ascertainment method/instrument	Definition	Prevalence
Bouhassira et al. [30]	23,712/France	Postal survey, general population sample	DN4	“Chronic pain with neuropathic characteristics”	6.9%
Dieleman et al. [37]	9,311/Netherlands	General practice research database	Search using free text and ICPC codes, then manual review of the electronic patient records	“Neuropathic pain”	0.8% ^a
Gustorff et al. [42]	7,707/Austria	Interview survey “performed via internet inquiry”; pre-registered pool, representative of general population	Selected items from S-LANSS and DN4	“Neuropathic pain”	3.3%
Torrance et al. [29]	3,002/United Kingdom	Postal survey, general population sample	S-LANSS	“Pain of predominantly neuropathic origin”	8.2%
Toth et al. [44]	1,207/Canada	Computerized telephone interview of a random sample of general population	DN4	“Chronic pain with neuropathic pain symptoms”	17.9%
Yawn et al. [43]	3,575/United States	Postal survey, medical records, telephone interview, and clinical examination	Clinical examination; S-LANSS; Berger criteria; self-report	NeuP	Clinical examination: 9.8% S-LANSS: 8.8% Berger criteria: 3.0% Self-reported: 12.4%

NeuP neuropathic pain; DN4 Neuropathic Pain Diagnostic Questionnaire; ICPC International Classification of Primary Care; S-LANSS Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs

^aDieleman et al. [37] give incidence, not the prevalence

population setting remain unknown, and these may represent overestimates. Those who responded positively to the questionnaires are likely to represent “possible neuropathic pain” [2], but further validation studies are needed. In addition, Gustorff et al. [42], using an unvalidated selection of the S-LANSS and DN4 instruments, found a prevalence of 3.3% in Austria, though it was not clear how the questions were administered in this study. Dieleman et al. [37] reviewed routine primary care records in The Netherlands, seeking recorded diagnoses of neuropathic pain conditions, and found an annual incidence of 0.8%; this review excluded cases of mixed pain or neuropathic pain without a specific diagnosis. Other recent published studies include one in the United States by Yawn et al. [43] using the S-LANSS and finding a population prevalence of 8.8%, consistent with the previous estimates [29]. However, a smaller Canadian telephone survey by Toth et al. [44], using the DN4, found a prevalence of 17.9%.

A number of studies have examined the epidemiology of specific neuropathic pain diagnoses in the general population [39], including studies of PHN, neuropathic pain originating in the back, PDN, and multiple specified neuropathic pain conditions. The prevalence of PHN (persistent pain 3 months after a diagnosis of HZ) was reported by 2.6–14.5% [30, 45–48] of HZ patients, and was as high as 20% in those aged 80 years or older. PDN prevalence was found to be between 8% and 20% of those with type 2 diabetes [25, 49], and the prevalence of neuropathic pain originating in the back ranged from 2.2% [50] to 13% [27]. The differences and wide ranges in these figures reflect the challenges described above, including differences in study populations, data collection methods, and whether or not a clinical examination was carried out, as well as the quality of data entered into routine medical records.

The case identification and ascertainment methods in these studies included interview surveys with or without standardized identification instruments and/or brief clinical examination; mail surveys with a range of diagnostic instruments; and computerized medical records reviews. Thus, there was considerable heterogeneity in the methods, and therefore, in the results of these studies. There also was a wide range of sample sizes, and therefore, the precision of the estimates also varies considerably. The results are nonetheless informative for future epidemiological research, as well as providing an interim understanding of the epidemiology [39].

Health and Quality of Life Associated with Neuropathic Pain

Irrespective of the study method or prevalence estimate, studies are consistent in finding that neuropathic pain is

associated with poor general health in every dimension in which health is assessed (physical, psychological, and social) [31, 32•, 51, 52]. A recent large postal questionnaire survey ($n=4,554$) in the French general population [32•] found respondents who reported pain with neuropathic characteristics had a higher degree of impairment in all dimensions relating to quality of life and sleep and had higher anxiety/depression scores compared to those reporting pain without neuropathic pain characteristics and those without pain. Those with neuropathic pain also made greater use of health care facilities and use of specialist services, such as a neurologist or pain specialist. This detrimental impact on quality of life was found to be related to the neuropathic character of the pain, independently of its severity and duration. In the United Kingdom, another population study, using the Short Form (SF)-36 General Health Questionnaire, found HRQoL to be as severely affected in the presence of neuropathic pain as in clinical depression, coronary artery disease, recent myocardial infarction, or poorly controlled diabetes [31]. Similarly, this study also found that health and function were worse in the presence of neuropathic pain than with non-neuropathic pain of the same severity. A recent systematic review of health utilities in neuropathic pain confirmed these findings, and found that it was the intensity of neuropathic pain, rather than its cause, that was most important in determining the extent of its health impact [53•]. Attal et al. [32•] suggest that it is the particular features, the strange and unpleasant signs and symptoms of this type of pain, and the distressing and unpleasant nature of the symptoms themselves that impact on quality of life. In addition, patients with neuropathic pain are often poorly responsive or undertreated with appropriate pharmacotherapy [54].

Risk Factors for Neuropathic Pain and its Prevention

One of the benefits of epidemiological study is the identification of risk factors that allow prevention of the condition under study. Factors found in population studies to be associated with neuropathic pain include older age, female sex, manual occupation, being unable to work, living in a rural area or council-rented accommodation, and lower educational attainment [29, 30, 37]. This current knowledge comes from cross-sectional studies, and therefore, the relationship between cause and effect of factors found to be associated with neuropathic pain cannot properly be distinguished. Therefore, longitudinal studies are required. These sociodemographic factors are not generally amenable to medical intervention (though they further highlight the negative health effects of deprivation, where political intervention would be valuable). The associations with poor general health, described above, suggest that attention to physical,

psychological, and social health is likely to reduce the risk of developing neuropathic pain. This intuitive hypothesis requires specific testing, but psychosocial interventions will certainly improve the overall health of patients with neuropathic pain, improving their sense of control [51], reducing its impact, and minimizing further disability.

There are risk factors that have been identified for specific causes of neuropathic pain. For example, good diabetic control reduces the risk of PDN as well as its overall impact [55]. In patients with diabetes, additional risk factors for neuropathy (not necessarily painful) include smoking, hypertension, obesity, hypercholesterolemia, and duration of diabetes [33, 34]. Therefore, it is clear that prevention of neuropathic pain is one of the important reasons for good management of diabetes. It is, of course, even clearer that the greatest risk factor for PDN is diabetes itself, and therefore, factors such as diet and lifestyle are crucial. As described above, PHN is more likely to arise in older sufferers of HZ infection. Other risk factors for PHN include immunocompromise and indicators of more severe HZ disease (painful prodrome, intense acute pain, severe rash) [56], in addition to neuropathic quality of pain and interference with activities of daily living and physical health [57]. Awareness of these factors and early aggressive treatment of shingles symptoms is therefore likely to reduce subsequent PHN. Although treatment with antiviral drugs reduces the incidence of PHN at 1 month, it remains unclear whether this translates to a reduced long-term prevalence [56, 58, 59]. As with diabetes, prevention of HZ infection would also prevent PHN. Administration of the zoster vaccine reduced the incidence of HZ infection by 51% and of PHN by 66% in a randomized controlled trial [56].

Public health initiatives and general health measures are also likely to be important in addressing the other main causes of neuropathic pain. Diet and lifestyle, for example, will reduce the occurrence of illnesses that lead to surgical intervention, and therefore the incidence of postsurgical neuropathic pain. Education and promotion of sexual health are vital in the prevention of HIV and its related neuropathy. Population measures to reduce the incidence of stroke, such as the diagnosis and treatment of hypertension and hypercholesterolemia, will reduce the prevalence of central post-stroke pain. Public campaigns aimed at reducing the occurrence and duration of back pain will prevent lumbar radiculopathy.

Economic Impact/Costs of Neuropathic Pain

The overall economic impact of chronic neuropathic pain has not been measured in a single study. There is some evidence that patients with either PHN or PDN have significant greater costs of excess health care utilization and

diagnostic procedures, medications, and interventional treatments than patients who have a history of the same condition (HZ and diabetes) but without neuropathic pain [65]. Dworkin et al. [65] suggest that these cost estimates undoubtedly underestimate the total burden to society of PHN and PDN, because as well as significant health care utilization costs, there is personal and societal burden, possibly including psychosocial and emotional disorders as well as decreased productivity and lost work time, none of which are often included in the analysis of costs.

A recent review of the costs associated with neuropathic pain and the cost-effectiveness of available treatments also concluded that there are likely to be substantial societal costs [60]. This review identified only three studies that attempted to quantify the societal costs attributable to neuropathic pain: for HZ, the average total cost to society was £524 per patient over a 6-month period (year 2003 values); estimated lifetime health service costs associated with PHN care were £1,600 (adjusted to year 2006 values); and estimated carpal tunnel syndrome costs were C\$13,700 (year 1996 values). In another review [61], the average annual pain medication cost per patient with PDN pain was estimated at US\$1,004.

There have been several recent estimates of the costs of HZ and PHN. In Taiwan, overall hospitalization rate for HZ was 16.1 cases per 100,000 person-years and the medical care expenditure costs of HZ estimated for each home-care case and per hospitalized case were about €53.30 and €1,224.70, respectively [62]. In the United Kingdom, the mean direct cost of HZ and PHN was £397 at 3 months, with both HZ and PHN costs increasing markedly with pain severity [47]. Similarly, in Spain, the mean cost per patient for the management of PHN was €549 (US\$752) (SD €580 [US\$795]) [48]. In another study, researchers examined the health care service use and costs for patients with chronic low back pain (CLBP), with and without neuropathic components, from a claims database in the United States [63]. The total direct costs of CLBP-related resource use were ~US \$96 million over a 12-month follow-up, and CLBP with a neuropathic component accounted for 96% of total costs. However, patients with neuropathic pain may have been more likely to seek treatment and, therefore, patients with CLBP without a neuropathic pain component may be under-represented. Overall though, these cost estimates demonstrate a significant burden on health care systems. Similarly, disproportionately high costs associated with back pain with a neuropathic component have been reported elsewhere [64].

Conclusions

In summary, and despite the important barriers to full understanding of its epidemiology, it is clear that neuropathic

pain is both common and important (to individuals and society). It is associated with worse health and quality of life than non-neuropathic pain, and its incidence, prevalence, and impact are likely to increase with the aging population. Physicians and health service providers need to be increasingly aware of the problem and use the information available on its distribution and risk factors to target education, treatment, and prevention.

Effective treatment is available, but further research is still required on prevention. Current research priorities for epidemiology include the attainment of agreed “gold standard” case definition and ascertainment methods, the translation of these into practical instruments validated in population-based epidemiological studies, longitudinal studies for the identification of modifiable risk factors, and trials of treatment and prevention strategies based on these. Newer epidemiological techniques (such as genetic epidemiology), ongoing research into the basic sciences on the mechanisms of neuropathic pain, and the translation of these findings to human population samples are equally important. Crucially, these research modalities should all inform and be informed by each other.

Disclosures Dr. Blair H. Smith has received a grant from Pfizer; has received honoraria from Eli Lilly; has received payment for the development of educational presentations from Grünenthal; and has received travel expense compensation from Grünenthal and Eli Lilly. Dr. Nicola Torrance received a grant from Pfizer.

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- Of importance
- Of major importance

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