REVIEW ARTICLE

Epidemiology of Refractory Neuropathic Pain

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■ **Abstract** Although neuropathic pain can be acute in nature, in most patients the pain is persistent (or "refractory"). Patients with chronic neuropathic pain are seen most often in clinical practice. It consists of a number of different disease-specific indications, each of which can have differing diagnostic definitions and cutoffs. Consequently. it is difficult to estimate precisely the prevalence and incidence of neuropathic pain. The limited currently available epidemiological literature is reviewed in this article. The burden of neuropathic pain on patients and healthcare systems appears to be potentially large, with an estimated prevalence of 1.5%. Patients with neuropathic pain experience a poor health-related quality of life and consume a high level of healthcare resources. and costs. The future prioritization by healthcare policy makers for neuropathic pain treatment funding requires further data to clarify its epidemiology, the burden on the health of patients, and the demand on healthcare budgets. ■

Key Words: neuropathic pain, incidence, prevalence, epidemiology

INTRODUCTION

Neuropathic pain has been defined as pain initiated, or caused, by a primary lesion or dysfunction of the nervous system.[1] Neuropathic pain can take a variety of forms such as diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), neuropathic back and leg pain (NBLP), and complex regional pain syndrome (CRPS). Although neuroparhic pain can be acure in nature, in most patients the pain is persistent (or "refractory"}, with chronic pain being most often seen in clinical practice.[2]

A structured search of MEDLINE (PubMed} up to February 2005 was undertaken to identify studies investigating the occurrence (incidence and prevalence) of neuropathic pain, its natural history, and its health and economic burden. Given the lack of literature on refractory neuropathic pain, a broader search was undertaken. The following search terms were used.

Epidemiology OR incidence OR *prevalence*

Neuropathic pain OR indications {named)

Quality of life OR utility

Costs OR cost benefit OR cost effectiveness

The remainder of this article summarizes the evidence under each of these headings and identifies areas for future study.

OCCURRENCE

In studying the natural history of specific diseases, the proportion of patients who develop associated neuropathic pain is sometimes reported. For example, a number of studies have assessed the prevalence of PHN. Oaklander and Rissmiller estimated that chronic neuropathic pain syndrome affects roughly 10% of all herpes zoster, or shingles, patients.[3] In their study of 916 shingles patients, they found that 18% of individuals in their 50s experienced symptoms of neuralgia for 1 year or longer. This percentage increased to 48% of patients age 70 or above. Bowsher reported a 15% prevalence of

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PHN in a population of elderly herpes zoster patients.[4] Although the prevalence estimates of these two studies are broadly comparable, their methodological quality varied considerably. For example, the Bowsher study was based on the retrospective self-report of some 250 patients experiencing herpes zoster. No clinical validation of patients' reports of the duration and severity of their pain was reported.

A wide range in prevalence estimates of neuropathic pain in diabetic and back pain populations has been reported. Between 8% and 50% of all diabetics (either type I or type II, or both) have been estimated to have symptoms of diabetic neuropathy.j· Similarly, for back pain, 10% and 19% of sufferers have been estimated to have neuropatb.ic pain.[7,8] This reflects both differences in the definition, or cutoff, for neuropathic pain used by studies and their variable methodological robustness.

There are sparse published data on the occurrence of neuropathic pain in the general population. The often-cited figure of 1.5% of the population being affected by neuropathic pain comes from a report by Bennett., That study was based upon a fairly crude approximation.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."*[9]

A small number of studies have examined the occurrence of neuropathic pain in various subgroups of the general population (Table 1). Ncuropathic back pain, leg pain, and diabetic neuropathy have the highest prevalence. Those three neuropathic pains are up to 100 times more common than either PHN or CRPS. As seen in the disease-specific studies, there was a wide range in the prevalence estimates for neuropathic back pain and diabetic neuropathy. This range reflects the difficulties of epidemiological studies in this area. Variations in estimates between studies almost certainly reflect both differences in diagnostic definitions, cutoffs used, as well as other methodological aspects, including sample size and completeness of the cohort upon which figures were based. There was consistently little, or no, dara on the incidence of neuropathic pain reported by these studies.

The Neuropathic Pain Insight Study was undertaken in 2004 by Datamonitor. JO Although essentially a market research study, the Datamonitor report provided some interesting country-specific data. The report was based on an interview survey with 594 primary care physicians, surgeons, pain specialists, and neurologists in the U.S.A., Japan, France, Germany, Italy, Spain, and the U.K. The survey was designed to determine trends and differences in the epidemiology, referral patterns and treatment among five key neuropathic pain subtypes: diabetic neuropathic pain, trigeminal neuralgia, PHN, NBLP, and neuropathic pain associated with HIV infection. The authors of the report validated the survey's findings by interviews with 24 leading international neuropathic pain opinion leaders. As shown in Figure 1, the ranking of any commonality of the subtypes of neuropathic pain treated *by* interviewees was similar to that from published prevalence estimates.

However, the Datamonitor report suggests rhat rhe lower prevalence of some neuroparhic pain types might reflect under-diagnosis. For example, the quoted preva-

Table 1. Summary of published neuropathic pain incidence and prevalence estimates

	Incidence per 100,000 Population per Year				Prevalence per 100,000 Population			
	Estimate	Country	Methods	Comments	Estimate	Country	Methods	Comments
Postherpetic neuropathy	No data				6.8-38.3[16]	Iceland	*DIP*	1- to 12-month duration
					185[11]	U.S.A.	Not stated	
Diabetic neuropathy	No data				5422	U.K.	D/P	Lifetime
					1140[23]	U.S.A.	Not stated	
					222[1]•	U.S.A.	**Not stated**	
Neuropathic back and leg pain	No data				778[1„19]	**U.S.A.**	Not stated	Care sought for 3 months or more
					7600[19]	U.S.A.	**S**	Pain intense, disabling, and chronic
					5800'°	U.K.	S	Disability pension
					6500[21]	Spain	S	
CRPS I	5.5[17]	Sweden	*DIP*	Used IASP	20.6[17]	Sweden	*DIP*	
CRPS II	**0.8**[17]	Sweden	DIP	criteria for	4.2"	Sweden	*DIP*	
				CRPS	**48**[11]	U.S.A.	Not stated	

D. databaie; P, prospective; R. retrospective; S, survey; CRPS, complex regional pain syndrome; IASP, International Association for the Study of Pain.

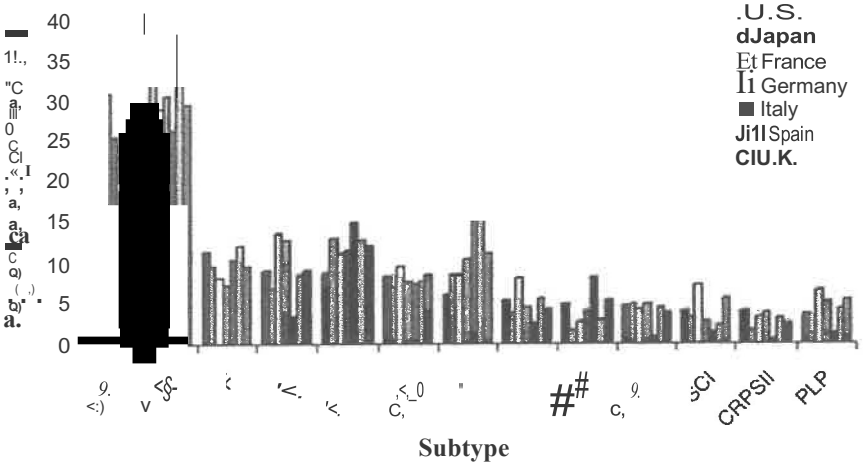

figure 1. Percentage of diagnosed neuropathic pain patients {reproduced with permission from the Neuropathic Pain Insight Study, 2004[10]}. DNP: diabetic neuropathy; NLBP, neuropathic leg and back pain; F, fibromyalgia; **PN,** pofyneuropathies; PHN, postherpetic neuralgia; CTS, carpal tunnel syndrome; TN, trigeminal neuralgia; MN, mononeuropathies; HIVNP, HIV-related neuropathic pain; CRPSI, complex regional pain syndrome type I; SCI, spinal cord injury; CRPSII, complex regional pain syndrome type II; PLP, phantom limb pain.

[ence of CRPS may simply reflect a syndrome that is little understood and poorly diagnosed at the primary care level-although this is not surprising, as CRPS has an unclear pathophysiology and comprises a range of symptoms that bridge neuropathic and vasculopathic pain syndromes. Interviewed physicians indicated that CRPS makes up about 10% of the overall diagnoses of chronic neuropathic pain but represents only about 2% of the primary care diagnoses. The condition was much more likely to be diagnosed by pain specialists or surgeons (but surprisingly, less often diagnosed by neurologists}. Only in Germany did primary care physicians tend to diagnose CRPS almost as frequently as specialists. In Italy there was a universally low rate of diagnosis (about 2%) by primary care physicians and specialists. Because CRPS appears to be consistently under-diagnosed by most primary care physicians, it would seem likely that many patients are referred later in the course of their disease, making treatment more difficult.

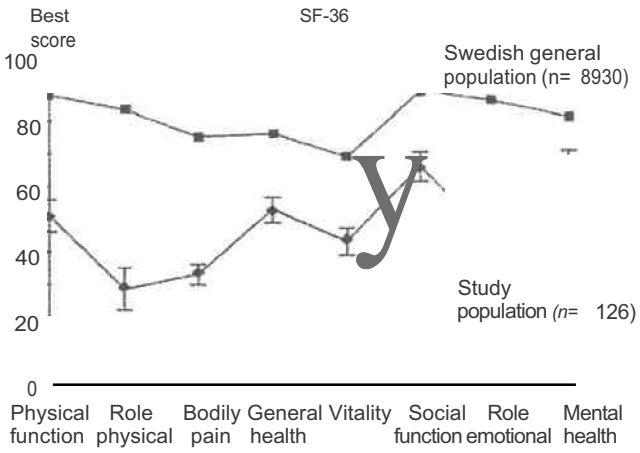

Figure 2. Health-related quality of life in neuropathic pain patients compared to general population (reproduced with permission from Mayer-Rosberg et al. 2001[11]). SF-36 mean score and 95% confidence intervals of patients with PNP and the Swedish general population. All differences are statistically significant. PLP, phantom limb **pain.**

BURDEN AND COSTS

Traditionally, assessment of the burden of a condition, or disease, is based on an understanding of both its impact on patient health, particularly health-related quality of life, and healthcare resources or costs. Few studies were identified that have assessed the impact of neuropathic pain on quality of life and healthcare costs.

Meyer-Rosberg and colleagues assessed health-related quality of life using the Short-Form 36 (SF-36} in a group of 126 adults with chronic neuropathic pain.11 Significantly worse SF-36 scores were seen in this neuropathic population compared to the general population (Figure 2). A similar reduction in health-related quality of life has been observed across the subtypes of neuropathic pain. A recent study across 17 U.S. centres found the SF-36 scores of individuals with chronic low back pain scored 1-2 standard deviations lower compared to age- and gender-adjusted general population norms.[12] In their randomized controlled trial of spinal cord stimulation, Kemler and colleagues reported patients with CRPS type I had a pretreatment mean utility score of 0.20 on the EQ-5D scale.[13] An EQ-5D score of O represents "death," while a score of 1 indicates "perfect health."

Using a large U.S. health insurance claims database in 2000, Berger and colleagues identified (using ICD-9

Table 2. Annual healthcare charges of patients with neuropathic pain vs. controls in 2000 (U.S. dollars)

	Mean Charges (95% confidence intervals)	
	Patient5 with Neuropathic Pain (n = 55,686)	Matched Controls (n = 55,686)
Inpatient care	9,329 (9047-9602)	3355 (3201-3523)
Outpatient care	6,859 (6773-6945)	1900 (1849-1954)
Outpatient medications		
Pain-related	293 (287-299)	62 (60-64)
All other	874 (864-884)	399 (393-403)
Total medications	1,167 (1154-1180)	461 (454-467)
Total charges	17,355 (17,042-17,658)	5715 (5535-5901)

Modified from Berger et al. 2004.[14]

codes) 55,586 patients with painful neuropathic pain.[14] They also identified age- and sex-matched controls, each of whom had not had a neuropathic pain encounter in that same calendar year. For each patient, they assessed healthcare charges including inpatient care, outpatient services, and prescription medications. Although matching for age and sex only may have resulted in some selection bias, the annual healthcare charges were th.ree-fold higher for neuropathic patients than matched controls ($17,355 vs. $5715). The breakdown of costs is summarized in Table 2. Interestingly, the authors of this study noted that few neuropathic patients were rece.iving specific drug treatments for their condition. Fm:-thermore, their costs did not include patient costs such as travel or indirect costs of lost productivity. Both these factors would further accentuate the overall costs of neuropathic pain.

FUTURE DATA NEEDS

There are a number of challenges in studying the epidemiology of neuropathic pain. Neuropathic pain is a symptom of a number of severe chronic diseases. As the emphasis is often the disease itself, neuropathic pain is under-diagnosed. However, its negative impact on patient's quality of life and high demand on healthcare costs make neuropathic pain an important area for funue data collection.

There are a number of areas for future research. Epidemiological studies need to apply a standard operational definition of neuropathic pain so that incidence and prevalence estimates can be consistently compared across indications. Further data are required on the level and severity of pain and health-related quality of life associated with different indications of neuropathic pain. Such studies need to use standardized pain and health-related quality of life measures. When possible, standardized pain ratings are needed to compare between different populations.[15] This is particularly the case for back pain, where there is currently a wide range of neuropathic pain.

One important population study (STOPNEP) has recently presented *its* findings.[25] This large epidemiological survey (a quota sample of more than 20,000 members of the French public surveyed) assessed the prevalence of ch.tonic pain and neuropathic pain. The findings of this population study were rather surprising-the prevalence of chronic pain in France is more than 31%; of these, 20% have the characteristics of neuropathic pain (ie, some 6% of the total population).

Finally, more cost-of-illness studies are needed to quantify the economic impact of neuropathic pain and clarify how its costs vary by indication and severity. Given the impact of neuropathic pain on patients and care.rs, future studies should consider both healthcare and non-healthcare costs.

CONCLUSIONS

Neuropathic pain is apparently common, with an estimated prevalence in the general population of 1.5%. However, because neuropathic pain consists of a number of different disease-specific indications, each of which can have differing diagnostic definitions and cutoffs, it is difficult to estimate precisely its prevalence and incidence. Studies to date indicate the burden of neuropathic pain on patients and healthcare systems to be potentially large. Neuropathic pain patients experience a poor health-related quality of life and consume a high level of healthcare resources and costs. The future prioritization by healthcare policy makers of the funding of treatments neuropathic pain requires further data on its epidemiology, the burden on the health of patients, and the demand on healthcare budgets.

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