Neuropathic pain in the community

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Neuropathic pain in the community: prevalence, impact and risk factors

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Abstract

Neuropathic pain is common (7-10%), and has a high impact on individuals and society. Health-related quality of life was rated as "worse than death" by 17% of people reporting neuropathic pain. In this review we describe challenges associated with assessing neuropathic pain, particularly in primary care and population-based research. We provide an updated review of clinical, socio-demographic, psychological and genetic factors associated with its presence, severity and response to treatment, based on recent epidemiological and related research. This information adds to our understanding of the biological mechanisms of neuropathic pain clinical practice, as well as approaches to treatment and prevention. We consider some of the ways in which this will also inform clinical practice and future research directions.

1. Introduction

Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system.[87] It can be peripheral in origin, as a result of nerve injury or disease (e.g. lumbar radiculopathy, postherpetic neuralgia, diabetic or HIV-related neuropathy, or postsurgical pain), or central (e.g. post-stroke or spinal cord injury). It is characterized by unpleasant symptoms, such as shooting or burning pain, numbness, allodynia, and other sensations that are very difficult to describe. Clinically, particularly in primary care (where time for assessment is limited), it is important to identify (possible) neuropathic pain, distinguishing it from other pain types (including nociceptive pain), as it generally fails to respond to standard analgesics (e.g. non-steroidal anti-inflammatories) but requires a different analgesic approach.[25] As all analgesics potentially cause harm as well as benefit, the distinction will promote safe and effective prescribing.

However, "definite" neuropathic pain can relatively rarely be confirmed, particularly in non-specialist settings. According to the widely accepted grading system proposed by the International Association for the Study of Pain (IASP)'s Special Interest Group on Neuropathic Pain (NeuPSIG), this diagnosis requires: (1) a history of a relevant neurological lesion or disease, and pain in a neuroanatomically plausible distribution; (2) sensory signs in the same distribution; and (3) a diagnostic test confirming the lesion or disease in the somatosensory system.[26] Diagnostic tests might include imaging (e.g. MRI to demonstrate nerve lesion), intra-epidermal nerve fibre density measurement on skin biopsy, neurophysiological testing (e.g. nerve conduction studies), or genetic testing to demonstrate a relevant hereditary disorder (e.g. erythromelalgia). Note that the term "definite" in this grading system is itself relative, and the above tests do not always confirm causality.

Much therefore depends on the sharing of a clear history and the elicitation of positive or negative sensory signs. Again, though, in primary care settings, time and experience limit the possibility of detailed clinical examination and it is therefore the history that assumes dominance in the assessment of pain.[31,32] This can determine the presence of "possible" neuropathic pain,[26] and allow treatment to begin according to an evidence-based neuropathic pain prescribing pathway.[74] Moreover, there is recent and increasing recognition that some classically "non-neuropathic" painful conditions can give rise to symptoms more commonly associated with neuropathic pain, and some evidence that these symptoms respond to "anti-neuropathic" medicines, such as tricyclic

antidepressants and gabapentinoids.[84] For example, a systematic review found that pain was neuropathic in character in 23% of people with knee or hip osteoarthritis,[27] and this was found to be >6 times more likely in those who had experienced knee surgery.[89] Similarly, a Finnish study found that 34% of people with fibromyalgia had clinically verified neuropathic pain.[29] Systematic reviews have found that 18.7%-27.6% of people with cancer pain have pain with a neuropathic mechanism. [7,69]

Not everyone who experiences a lesion or disease of the somatosensory system goes on to develop neuropathic pain. For example only around 26% of those with type 2 diabetes and 21% of those who experience herpes zoster infection develop neuropathic pain.[34] While the mechanisms and associated risk factors for some of this variation are becoming understood,[14] much remains unexplained, and yet would inform prevention and mitigation. There is therefore an important role for epidemiology in our understanding of neuropathic pain.

Epidemiology is, "The study of the occurrence and distribution of health-related states or events in specified populations, including the study of the determinants influencing such states, and the application of this knowledge to control the health problems."[66] Good information on the prevalence helps to determine the resources required to address the problem, while knowledge of risk helps with diagnosis and prevention, as well as the identification of possible treatment strategies. At the population level, to inform primary care (where most neuropathic pain presents and is managed), this requires community-based studies, with large sample sizes. Just as non-specialist assessment of possible neuropathic pain relies primarily on a clinical history, so too must population studies rely on efficient reports of symptoms, as clinical examination is generally not feasible in large studies. This review updates our understanding of the prevalence of neuropathic pain in the community, and genetic and non-genetic factors associated with its presence, severity, and response to treatment, mainly from population studies.

2. Discussion

2.1 Prevalence

Estimating population prevalence with sufficient precision requires a large sample size. For example, for 95% confidence to identify a prevalence of 10% requires a sample size of ~3,500 to achieve a precision of ±1%.[22] Initial estimates of the prevalence of neuropathic pain, based on the known prevalence of underlying conditions, were approximately 1-2%.[12] Subsequently, simple questionnaires were developed and validated to determine the presence of neuropathic characteristics in any pain. These included the S-LANSS, the DN4, and PainDETECT, each with many similarities, though a few differences.[6] Based on the first two of these, general population studies with responding sample sizes of 3,002 and 23,712 found prevalences of 8% and 6.9% in the UK and France respectively.[10,86] Importantly, the cases identified were described as having "pain of predominantly neuropathic origin" or "pain with neuropathic characteristics", rather than "neuropathic pain". Based on the above IASP grading system, they could not even be described as "possible neuropathic pain" as there was no successful attempt systematically to determine an underlying lesion or disease, nor of neuroanatomically plausible distribution of pain. No subsequent published population-based study, with sufficient sample size, has been able to achieve either of

these diagnostic factors. Some, such as an early study using PainDETECT (which found that 37% of people presenting to primary care with low back pain were also categorised with lumbar radiculopathy)[28] have been able to approach this in individual conditions. A systematic review of population-based prevalence studies considered the true prevalence of pain with neuropathic characteristics to be 7-10%.[34] The proportion of positive responses to the S-LANSS, DN4 and Pain DETECT screening instruments may be higher than the true population prevalence, for reasons including response bias and imperfect sensitivity and specificity.[70] Although these estimates may therefore be inflated, this means that up to 10% of people presenting in primary care should potentially embark upon an anti-neuropathic treatment pathway. It also means that around 90% should not, and that is important for avoiding harms associated with, for example, gabapentinoids (see below).

2.2 Impact

Neuropathic pain has a high impact as well as prevalence. Compared with non-neuropathic pain, neuropathic pain is likely to be rated as more severe.[78] All measured dimensions of health and quality of life (QoL) are rated worse in neuropathic pain than in non-neuropathic pain,[21] [49] [79] and this remains true even when pain is adjusted for its severity.[78] Using the EQ5D questionnaire to measure QoL, a population study found that 17% of people with pain of neuropathic characteristics produced a score less than zero, meaning that they rated QoL as "worse than death",[85] though comparison of scores between different QoL measures makes it difficult to interpret such a rating precisely[73]. The reasons for this high impact are multi-dimensional, and include the complexity, severity and unpleasantness of symptoms, and the burden and side effects of treatment (and their frequently poor outcomes).[15] This highlights the severity of the condition, and the need to understand its prevention and management.

2.3 Risk factors: non-genetic

We previously reviewed non-genetic risk factors for neuropathic pain, and these included older age, female gender, manual occupation and social deprivation, as well as various clinical and psychological factors.[77] When assessing more recent literature with respect to non-genetic factors and neuropathic pain (using relevant key terms in a non-systematic approach from 2008 onwards; **Table 1**), there are a number of observations that can be made. First, with respect to study design, the great majority of studies are cross-sectional and only a few are longitudinal [9,53,82]. This means that we are unable to determine any causal relationship in many of the associations that have been reported, and a bidirectional relationship is often plausible. Secondly, most studies do not conform to the above criteria for defining neuropathic pain,[26] so there is heterogeneity in reported associations and effect sizes. Thirdly, differences in the statistical methods make the results difficult to compare directly. Fourthly, there is not always a clear description of the size or definition of any "control" group. Nevertheless some potential risk factors are apparent.

2.3.1 Demographic risk factors

Demographic factors are generally non-modifiable but can inform awareness of risk in particular sections of the population. For example, as with chronic pain generally, older age has been consistently shown to confer risk. This is true even when controlling for potential confounding. In

particular, older age has been identified in studies of painful diabetic neuropathy,[2] [43] post herpetic neuralgia[9] [64] and neuropathic pain in myocardial infarction.[100] Likewise gender is consistently associated with neuropathic pain, potentially alluding to differing underlying biological and/or psychological mechanisms. The majority of studies report a higher prevalence of neuropathic pain and higher pain intensity amongst female participants,[64] mainly in painful diabetic neuropathy.[1] [3] [4] [43] However, a French study conducted in patients with herpes zoster found that male gender was an independent predictor of persistent post-herpetic neuralgia.[9]

There is limited evidence that ethnicity is an independent risk factor for neuropathic pain. A recent study conducted in the USA found that prevalence rates of neuropathic pain (as assessed by the PainDETECT across a range of aetiologies) in people with pain was higher in Hispanic and non-Hispanic black males and females, compared to white males and females, across all age groups analysed.[19] Furthermore, military personnel of African descent were found to be more susceptible to neuropathic pain resulting from non-freezing cold injury than their non-African counterparts.[90] One study conducted in the Middle-East region found that living in Egypt was a risk factor for neuropathic pain (compared to living in Kuwait/UAE and Lebanon), but did not specifically analyse ethnic origin.[43] However most published studies recruited from a geographically limited population and/or did not report ethnic diversity. They are also generally limited by inadequate consideration of potential confounders that include socio-economic status, cultural factors, and access to care.

2.3.2 Psychological risk factors

The relationship between neuropathic pain and psychological factors is complicated, with the presence of comorbidities such as depression, anxiety and sleep disorders suggesting shared biological and genetic pathways.[14] This area has yet to be fully explored, particularly with respect to the underlying genetics, and since there could feasibly be a reciprocal interaction in terms of the temporal relationship, longitudinal studies are particularly important for these factors. For example, in a longitudinal study of patients with post-total joint replacement neuropathic pain, a bidirectional relationship with sleep disturbance was demonstrated.[82] Another longitudinal study in the USA found an association between increasing depressive symptoms and neuropathic pain in people with HIV-sensory neuropathy (HIV-SN).[1]

Recent cross-sectional studies generally support previous findings of associations between adverse psychological health and neuropathic pain. For example poor overall mental health status was associated with neuropathic pain in patients with rheumatoid arthritis,[49] and anxiety, pain catastrophizing and fatigue were associated with the phenotypically similar neuropathic-like knee pain.[23]

2.3.3 Social/lifestyle risk factors

Neuropathic pain is associated with a number of behavioural and social factors, some of which are sufficiently modifiable to make them important targets for preventative measures. These factors are important as they are those most amenable to modification by the patients themselves. This is illustrated by alcohol and smoking, which are both associated with neuropathic pain.[11] [64] While smoking was identified as a risk factor in a longitudinal study,[11] we still need longitudinal studies

to establish the temporal relationship with alcohol (whose consumption might increase after the onset of neuropathic pain). Increased physical activity has been found to confer a protective effect against neuropathic pain in patients with comorbid diabetes and myocardial infarction.[100]

Body mass index (BMI)/weight and waist circumference have been found to be associated with neuropathic pain in diabetic populations.[2] [43] [80] [99] Obesity can also place joints under strain, and limit physical activity, which are potential explanations for its association with neuropathic pain found in rheumatoid arthritis.[42]

Finally, poor health-related QoL also appears to be predictive of neuropathic pain,[3] as well as an outcome (as noted above).

2.3.4 Clinical risk and biomarkers for neuropathic pain

In diabetes, a longer disease duration has been associated with painful diabetic neuropathy[2] [43] and there have been associations found with diabetes type,[43] [79] though these are contradictory between type 1 and type 2 diabetes. The association of nephropathy with neuropathic pain is likely to be a result of both arising as complications of diabetes.[2] [11] The same is probably true of peripheral arterial disease, which has been found to be associated with neuropathic pain in two studies and arises as a complication of diabetes.[99,100] Similarly, biomarkers such as low HDL and high triglycerides are all associated with diabetes as well as with neuropathic pain[2] and further longitudinal analysis is required to establish their apparent role in neuropathic pain.

Away from diabetes, detectable plasma viral load at study entry, current or past combination antiretroviral therapy (CART), and history of opioid abuse predict neuropathic pain in patients with HIV-SN.[53] The association of CART is thought to reflect the more advanced nature of HIV disease, compared to those who were CART-naïve. Pain itself appears to predict neuropathic pain, with multiple regional pains found to be associated with neuropathic-like knee pain (NKP),[23] and high pain intensity and interference associated with the development of post herpetic neuralgia.[11] Given that neuropathic and nociceptive pain can both be present at the same time, it is interesting to note that the association with multiple pain regions comes from a multinomial regression analysis that includes a heterogeneous group of participants with “possible” NKP, as well as those with “definite” and “no” NKP (as defined by the PainDETECT). Additionally, the extent of hyperalgesia around a surgical incision 48 hours after bone surgery was associated with subsequent chronic post-surgical neuropathic pain.[55]

2.4 Risk factors: genetic

There is evidence from a recent twins study that neuropathic pain encompasses a substantial heritable component (37%), indicating that genetic factors are likely to contribute to the inter-individual variability.[58] Attention has therefore turned to identifying genetic factors associated with neuropathic pain. These can help elucidate the underlying biological mechanisms, and therefore potential treatment targets, as well as improving assessment of risk. Challenges such as sample size requirements and the need for consistent approaches to phenotyping have limited most conclusions and prevented replicability so far, but there have been some recent advances towards addressing these.[35]

Specific genes have been associated with rare monogenic disorders, including congenital sensitivity to pain with anhidrosis, paroxysmal extreme pain disorders and erythromelalgia which are caused by gain-of-function or loss-of-function mutations in a voltage-gated sodium channel gene (*SCN9A*).[18,24,97] Individuals affected with hereditary neuropathy and debilitating neuropathic pain have been reported to carry Trp101 stop mutations in Myelin protein zero (*MPZ*).[67]

However, any genetic predisposition to the presence, severity or progression of common neuropathic pain conditions, or their response to treatment, probably results from multiple genes. A recent systematic review highlighted the success and limitations of the 29 published genetic association studies examining the risk of developing neuropathic pain up to 2017.[91] Most of the studies had applied a candidate gene approach, and they identified susceptibility genes that are mainly involved in the following functions: **neurotransmission or ion channels** (catechol-O-methyltransferase (*COMT*), opioid receptor Mu 1 (*OPRM1*), GTP cyclohydrase (*GCH1*), *SCN9A*, voltage-dependent calcium channel gamma subunit 2 (*CACNG2*), solute carrier family 6 member 4 protein (*SLC6A4*)); **immune responses** (human leukocyte genes (HLA-A, -B, -DRB1and -DQB1), tumour necrosis factor alpha (*TNFA*), interleukin-6 (*IL6*), *IL10*, and *IL1R2*)); and **iron metabolism** (aconitase 1 (*ACO1*), beta-2-microglobulin (*B2M*), bone morphogenetic protein 6 (*BMP6*), transferrin (TF), ceruloplasmin (CP), transferrin receptor (*TFRC*), frataxin (*FXN*) and solute carrier family 11 member 2 (*SLC11A2*)) (Figure 1).

2.4.1 Candidate gene studies

The most frequently investigated gene was *COMT* (five studies) but this was not significantly associated in meta-analysis.[91] However, a recent study (n=590) reported that a *COMT* variant confers an increased risk of distal neuropathic pain in HIV-SN patients of European and African ancestry.[96] Moreover, *COMT* variants were also associated with pain intensity in patients who underwent lumbar discectomy.[71] Similarly, studies have reported the association of *OPRM1* variants with neuropathic pain susceptibility inconsistently in different populations. This may be due to heterogeneous case-control criteria and small sample sizes.[91] One study found an association between *OPRM1* variants and pain intensity in post-operative patients.[63] HLA genes were consistently replicated in association with persistent neuropathic pain after shingles[72,83] or surgery.[20] *GCH1* variants were found to be associated with neuropathic pain susceptibility in post-surgery patients [36] and pain sensitivity in patients with HIV-SN.[38] Cytokine gene (*IL6*) harbouring variants were reported to be associated with sciatica [62] but not with post-surgical pain in patients who had undergone breast cancer surgery[81]. The latter study also found associations between polymorphisms in the cytokine genes (*IL10* and *IL1R2*) and post-surgical pain[81]. Separately, *TNF* polymorphisms or haplotypes have shown significant association with neuropathic pain susceptibility in post-operative patients [46] and pain intensity in Black Southern Africans With HIV-SN.[39] Several genetic polymorphisms in iron-metabolism genes (*ACO1*, *B2M*, *CP*, *FXN, TF, TFRC, BMP6* and *SLC11A2*)[45] and a variant in an ion channel gene (*CACNG2*)[61] have been investigated by single studies, but not yet been replicated. Notably, the best known sodium ion channel gene associated with rare neuropathic pain conditions (*SCN9A*) has also been shown to be associated with the presence and severity of neuropathic pain in diabetes.[51]. However, a recent study reported no association between either a specific variant in *SCN9A*, or a variant in nerve growth factor gene, tropomyosin-related kinase A (*TrkA*), and trigeminal neuralgia presence or severity.[16] Missense

mutations in *SCN11A* have also been found in patients with painful peripheral neuropathy[40], and a recent study identified a pathological mutation in *SCN10A* in diabetic patients with painful neuropathy.[33] A genetic variant in potassium channel alpha subunit (*KCNS1*) gene was associated with the presence of neuropathic pain caused by multiple aetiologies [17], and in a separate study *KCNS1* haplotypes were associated with pain intensity in patients with HIV-SN.[38] Purinergic receptor 7 (*P2RX7*) harbouring variants were associated with pain sensitivity in diabetic patients with neuropathic pain.[88] Almost all of these studies had relatively small sample sizes and varying phenotyping. Thus, specific causative variants for NeuP have yet to be definitively identified.

2.4.2 Genome-wide association studies

Genome-wide association studies (GWAS), with hypothesis-free scanning of the whole genome, can provide novel biological insights into common and complex traits. There have been five GWAS focusing on neuropathic pain susceptibility published to date, examining populations with diabetic neuropathic pain, post-surgical pain or sciatica and cancer-related neuropathic pain, all in patients of European ancestry. These each used different phenotyping methods including electronic dispensed medication records, the PainDETECT questionnaire, self-administered questionnaires and physician diagnosis based on symptoms. Two, using medication records alone (one with additional recorded neuropathy assessment), were performed in a diabetic population and found novel suggestive variants near glial cell line-derived neurotrophic factor family receptor alpha 2 (*GFRA2*), high mobility group box 1 (*HMGB1P46*) and zinc finger and SCAN domain containing 20 (*ZSCAN20*), but these have not yet been replicated in an independent study.[56,57] A meta-analysis of GWAS of neuropathic pain in post-surgical pain patients found a new suggestive variant near the protein kinase c alpha (*PRKCA*) gene which is involved in receptor signalling and apoptosis signalling.[93] A large-scale meta-analysis of GWAS in sciatica found two novel genome-wide significant loci near nuclear factor I B-type (*NFIB*) and myosin superfamily 5 A (*MYO5A)* in the discovery study and replicated the locus near *NFIB* in an independent Finnish population.[50] A recent GWAS of neuropathic pain in head and neck cancer patients with neuropathy found four novel genome-wide significant loci near the sortin nexin (*SNX8*), purkinje cell protein 2 (*PCP2*), Kininogen-l (*KNG1*) and RAR-related orphan receptor alpha (*RORA*) genes.[68] These findings still require replication, and their potential biological roles in neuropathic pain are unclear. Separately, a recent GWAS identified 16 susceptibility loci for carpal tunnel syndrome (which often includes neuropathic pain); these were mostly associated with growth and structural processes.[95]

2.5 Factors associated with response to treatment

In comparison to the presence and onset of neuropathic pain, there are relatively few epidemiological studies analysing response to treatment.

2.5.1 Non-genetic factors

The few studies that have been conducted in treatment response have tended to be exploratory *post-hoc* analyses of pre-existing clinical trials focussing on a specific set of drugs (either antidepressants or anticonvulsants) in patients with diabetes,[54] [75] [98] [101] although one study has additionally assessed people with post-herpetic neuralgia.[92]

Of the recommended first-line medications for neuropathic pain, duloxetine and pregabalin have been the most studied in this context. Higher baseline pain intensity was associated with better responses to duloxetine in patients with diabetic peripheral neuropathic pain,[55] whilst severe sleep disturbance was associated with better responses to pregabalin.[92] A further study found that pain reduction in response to duloxetine was greater in the subset of patients with no mood symptoms, which is an interesting finding considering duloxetine is an antidepressant.[54] Conversely, better responses were found in patients with depression who were treated with duloxetine rather than gabapentinoids.[101] Finally, a study of three antidepressants (imipramine, venlafaxine and escitalopram) and two anticonvulsants (pregabalin and oxcarbazepine) in painful polyneuropathy found that people with diabetes had better response to the anticonvulsants (mainly driven by oxcarbazepine) than people without diabetes, and people with a shorter duration of neuropathic pain had a better response to the antidepressants.[75]

2.5.2 Genetic factors

A candidate gene association study examined the association of variants in the serotonin receptor 2C (*HTR2C*), serotonin receptor 2A (*HTR2A*), ATP Binding Cassette Subfamily B Member 1 (*ABCB1*), cytochrome (*CYP2C19*) and serotonin transporter (*SLC6A4*) genes with treatment response to escitalopram in neuropathic pain. Of these, a significant association was only found with one variant in *HTR2C*, with which carriers of the C allele experienced better pain relief than carriers of the G allele.[13] Another study tested the association of an *OPRM1* variant with response to treatment among 96 patients oxaliplatin-induced painful neuropathy. This found that the patients who carried the homozygous genotype (AA) of *OPRM1* A118G had a better response to tramadol and acetaminophen combination treatment than other carriers.[52] A recent study investigated the association of *COMT*, *OPRM1*, *ABCB1*, *CYP2C19* and *CYP2D6* variants with the response to treatment of neuropathic pain with nortriptyline and morphine in 25 Caucasian patients. Among 34 variants in these genes, they discovered a significant association ($p=4.89\times10^{-5}$) between the carriers of C allele of rs1045642 in *ABCB1* and pain relief from combination therapy (nortriptyline and morphine) after Bonferroni correction for multiple testing, but no significant association with treatment response to either nortriptyline or morphine alone. They replicated this association in thirty-seven patients who were taking amitriptyline or nortriptyline along with morphine or fentanyl from the UK Biobank cohort (p=0.02).[5] Pharmacogenomics research in neuropathic pain are still at an early stage and this finding, like others, warrants replication in a large-scale cohort of patients with neuropathic pain. GWAS using large cohorts are also needed to uncover genetic variants associated with treatment response.

2.5.3 Gabapentinoids

Available medical, interventional and psychological therapies for neuropathic pain have been recently reviewed by Colloca *et al*,[15] among others. Among the first line medical treatments recommended for neuropathic pain are the gabapentinoids – gabapentin and pregabalin.[25,74] [60] Acting as α2δ ligands at voltage-dependent calcium channels, these inhibit neuropathic pain signals and were found to have numbers-needed-to-treat (NNTs) of 7.9 and 7.2 respectively, in order to achieve significant pain relief.[25] This was sufficient for IASP to make a recommendation to the World Health Organization (WHO) for inclusion of gabapentin in their Model List of Essential

Medicines, to encourage their availability in every country.[47][94] Many of the countries which did not include a gabapentinoid in their National Essential Medicines List were likely to have a high prevalence of conditions associated with neuropathic pain (e.g. diabetes, HIV),[48] and it was estimated that >59 million people would achieve >50% reduction in neuropathic pain severity if gabapentin were available worldwide.[47] The recommendation was rejected by the WHO, though discussions are continuing.

One of the reasons for rejection was the growing recognition of harms associated with gabapentinoids.[76] [41] These include misuse, addiction and overdose, side effects including dizziness, drowsiness and fatigue, and added dangers when co-prescribed with opioids.[30] Indeed, population studies in the US, UK and elsewhere have found the prescribing rates of gabapentinoids to be rising rapidly and steadily, mirroring those previously found with opioids.[59] [44]

Gabapentinoids were recommended as first-line treatment of neuropathic pain by NeuPSIG in their detailed systematic review.[25] Alternative recommended first-line treatments, in the absence of gabapentinoids, are tri-cyclic antidepressants (TCAs, e.g. amitriptyline) and serotonin-noradrenaline reuptake inhibitors (SNRIs, e.g. duloxetine). TCAs were found to be on the Essential Medicines list of all but three countries globally, but SNRIs were listed infrequently.[48]

Summary

In summary, neuropathic pain continues to present a high prevalence and impact around the world, and we need approaches to its prevention and management that are applicable in the community, to reduce the global burden.[8] Epidemiological studies have highlighted the population distribution of neuropathic pain, and socio-demographic, psychological, and clinical factors which can inform targeted approaches. Many of these factors are similar to those associated with other chronic conditions, and require population-based public health and political management for their successful translation. Potentially, epidemiological studies can also inform the prognosis of neuropathic pain, including its natural course and factors associated with different outcomes.[37] This is of concern to patients and may inform treatment decisions, but requires longitudinal cohort studies, of which there have been few in neuropathic pain to date.[34]

Although genetic studies have shed some light on the aetiology of neuropathic pain, they generally lack (successful) replication attempts and explain only a small amount of the genetic risk.[91] Large-scale GWAS and replication in studies with consistent phenotyping are required, in combination with detailed analysis of their interaction with non-genetic factors and this will require collaborative population-based approaches to generate adequate sample sizes. One such study is underway and will report soon: DOLORisk (http://dolorisk.eu/),[65] a European consortium funded by EU Horizon 2020. DOLORisk includes an 18-month population follow-up study whose analysis will identify factors associated with exacerbation and resolution, thus informing prognosis. Meanwhile, the UK Biobank (n=500,000) has recently undertaken a re-phenotyping exercise which includes assessment of neuropathic pain using the DN4. The survey is still being completed, but an expected response of ~175,000 participants could generate 12,000 with neuropathic pain, [34] providing the largest population sample to date.

Although effective medical treatments are available for neuropathic pain, we need to be wary of the harms these can also cause, and to apply them with caution, and along with non-pharmacological treatments.

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Figure 1. Summary of genetic and non-genetic factors shown to be associated with the presence and/or severity of neuropathic pain

Separate file submitted

Table 1. List of studies identifying factors associated with neuropathic pain onset/presence and their characteristics

Study	Design	Population	Aetiology	NeuP Assessment	Cases/Controls	Analysis	Significant Factors	Odds Ratio (95% CI)
Ziegler et al., 2009 [99]	Cross-Sectional	Germany (Augsburg)	1. NeuP in NGT, IFG, IGT or diabetes 2. NeuP in diabetes	MNSI > 2 **and** positive response to Q2 **and** Q6	1. 34/359 2. 26/169	Stepwise multivariate binary regression	1. Age (years) Weight (kg) Diabetes PAD (ABI < 0.9) 2. Age (years) Weight (kg)* PAD (ABI < 0.9) Albuminuria (mg/L)*	1. 1.08 (1.02-1.14) 1.03 (1.00-1.05) 2.61 (1.09-6.24) 5.72 (2.44-13.39) 2. 1.08 (1.00-1.16) 1.03 (1.00-1.06) 9.27 (3.44-25.0) 1.19 (0.95-1.51)
Van Acker et al., 2009 [2]	Cross-Sectional	Belgium	DPN with NeuP	A positive Neuropen® test **and** DN4 ≥ 4	157/**?***	Multivariate binary regression	Age (per 10 years) Diabetes Duration (per 5 years) Obesity HDL (≤1mmol/L for men, ≤1.3mmol/L for women) Triglycerides (≥1.7mmol/L) Nephropathy	1.47 (1.20-1.81) 1.14 (1.02-1.28) 1.62 (1.05-2.49) 2.17 (1.38-3.41) 1.76 (1.13-2.75) 1.69 (1.10-2.59)
Ziegler et al., 2009 [100]	Cross-Sectional	Germany (Augsburg)	1. NeuP in survivors of MI with NGT, IFG, IGT or Diabetes 2. NeuP in survivors of MI with Diabetes	MNSI > 2 and positive response to Q2 **and/or** Q6	1. 61/365 2. 45/169	Stepwise multivariate binary regression	1. Age (years) Waist circumference (cm) PAD (ABI <0.9) Diabetes 2. Waist circumference (cm) Physical activity PAD (ABI < 0.9)	1. 1.06 (1.01-1.11) 1.04 (1.01-1.07) 3.65 (1.85-7.22) 2.98 (1.44-6.14) 2. 1.05 (1.01-1.09) 0.31 (0.10-0.99) 5.61 (2.43-12.96)
Parruti et al., 2010 [64]	Longitudinal	Italy	PHN	Pain in the presence of HZ (clinically diagnosed)	One-month: 226/210 3-month: 130/304 6-month: 43/?* 12-month: 33/**?***	Multivariate binary generalised estimating equations	Age (per 10 years) Smoking (current/former)	1.01 (1.00-1.02) 1.50 (1.02-2.21)

							Intense/very intense pain at presentation Trauma Missed antiviral prescription	1.85 (1.29-2.65) 2.27 (1.48-3.46) 1.46 (1.00-2.25)
Spallone et al., 2011 [80]	Cross-Sectional	Italy (Rome)	pDPN	Clinical history and examination (i.e. "*characteristics of pain and a plausible distribution concordant with* the s*ensory symptoms and signs"*	78/?*	Multivariate binary regression	BMI (kg/m^2) MDNS	1.22 (1.08-1.37) 1.27 (1.11-1.44)
Jambart et al., 2011 [43]	Cross-Sectional	Egypt Lebanon Jordan Kuwait UAE	Diabetes with NeuP (reported as pDPN)	DN4 ≥ 4	?*	Stepwise multivariate binary regress ion	Diabetes duration (≥10 years) Age[a] 50-64 years ≥65 years Type of diabetes (T1D) BMI (≥30kg/m^2) Gender (Female) Country[b] Kuwait/UAE Lebanon	2.43 (2.10-2.81) 1.75 (1.48-2.08) 2.13 (1.72-2.62) 1.59 (1.24-2.05) 1.35 (1.17-1.56) 1.27 (1.11-1.46) 0.44 (0.35-0.56) 0.66 (0.54-0.81)
Abbott et al., 2011 [1]	Cross-Sectional	UK (North-west England)	pDPN	NSS ≥ 5 and NDS ≥ 3	3242/12372	Multivariate binary regression	Type of diabetes (T2D) Gender (Female)	2.1 (1.7-2.4) 1.5 (1.4-1.6)
Bouhassira et al., 2012 [9]	Longitudinal	France	PHN	GP confirmed zoster-related pain (pain in the same area as the zoster rash) at least 3 months after rash onset.	**?***	Stepwise backwards multivariate binary regression	Gender (males) Age (≥70 years) DN4 score (≥4) ZBPI interference score SF-12 Physical Component Summary	1.81 (1.11-2.94) 1.28 (1.05-1.55) 1.78 (1.03-3.06) 1.18 (1.05-1.31) 0.72 (0.55-0.92)
Martinez et al., 2012 [55]	Cross-Sectional	France	CPSNP (following ICBH)	DN4 ≥ 4	19/63	Multivariate binary regression	Area of secondary hyperalgesia around incision at 48h post-surgery (cm^2)	1.02 (1.00-1.04)

							DN4 score at 48h post-surgery	1.75 (1.10-2.60)
Bouhassira et al., 2013 [11]	Cross-Sectional	France	Diabetes with NeuP	DN4 ≥ 3 (in patients with pain duration ≥ 3 months)	156/595	Stepwise multivariate binary regression	Diabetic nephropathy Triglycerides (>1.6 mmol/L) History of alcoholism	2.59 (1.55-4.32) 2.87 (1.60-5.01) 3.07 (1.41-6.68)
Malvar et al., 2015 [53]	Longitudinal	USA	HIV-SN with NeuP	Clinician-administered assessment and self-report	131/362	Mixed-effects multivariate binary regression with backwards elimination based on AIC	Plasma VL at study entry (detectable) CART use at study entry Lifetime history of opioid abuse/dependence Time-updated severity of depressive symptoms BDI-II 14-19 BDI-II 20-28 BDI-II 29-63	1.54 (1.01-2.35) 2.44 (1.03-5.80) 2.31 (1.08-4.95) 1.66 (0.92-3.00) 1.89 (1.03-3.49) 2.99 (1.41-6.31)
Koop et al., 2015 [49]	Cross-Sectional	Netherlands	RA with NeuP	PainDETECT ≥ 13	61/98 ?*	Multivariate binary regression	SF-36 physical component summary SF-36 mental component summary	0.91 (0.86-0.97) 0.96 (0.92-1.00)
Ito et al., 2018 [42]	Cross-Sectional	Japan	RA with NeuP	PainDETECT ≥ 13	42/258	Multivariate binary regression with backwards elimination	DAS28-ESR non-CR BMI ≥ 22	3.87 (1.76-8.51) 2.48 (1.13-5.17)
Stocks et al., 2018 [82]	Longitudinal	UK (Nottingham)	Post-TJR (knee or hip) with NeuP	PainDETECT ≥ 13	**?***	Cox regression model	Sleep disturbance (MOS-SS ≤ 60)	2.75 (1.21-6.26)[c]
Fernandes et al., 2018 [23]	Cross-Sectional	UK (East Midlands)	KP with NeuP (reported as NKP)	Modified PainDETECT 13-18 = Possible NKP ≥ 19 = Definite NKP	Definite = 366 Possible = 462 No = 1685	Multivariate Multinomial Regression	Injury (around knee) Nodal OA Hyperlipidaemia Diabetes Multiple regional pain Anxiety (HADS>8) Depression (HADS>8)	1.50 (1.12-2.00)[d] 1.80 (1.28-2.53)[d] 1.36 (1.01-1.84)[d] 1.52 (1.04-2.23)[d] 1.93 (1.46-2.53)[d] 3.17 (2.38-4.23)[d] 2.99 (2.14-4.19)[d]

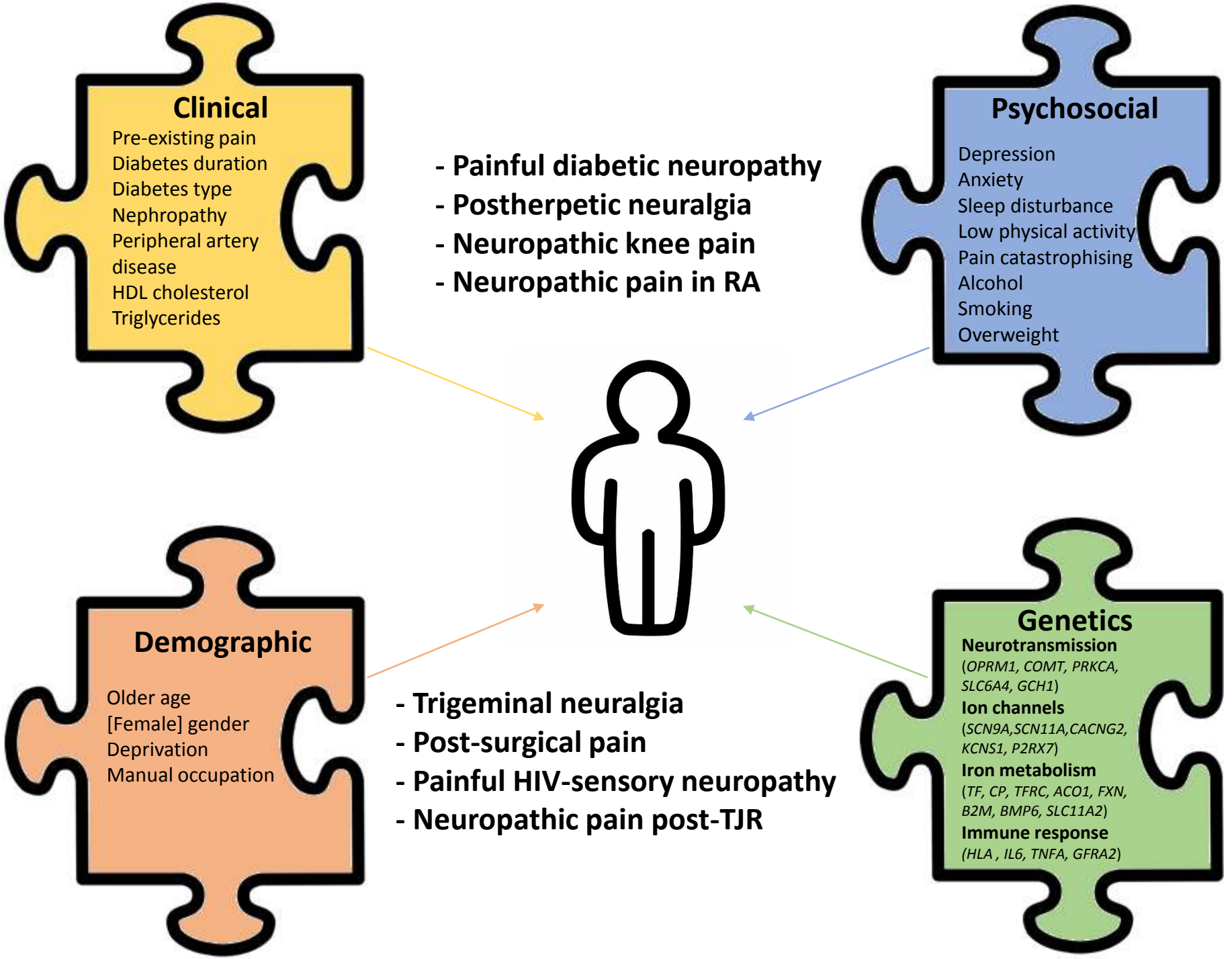
							Pain Catastrophising (PCS≥24) Fatigue seldom/sometimes often/always Fibromyalgia	5.37 (2.93-9.84)[d] 2.45 (1.38-4.38)[d] 5.37 (3.08-9.35)[d] 4.07 (2.49-6.66)[d]
Solaro et al., 2018 [79]	Cross-Sectional	Italy	MS with NeuP (distinguished as TN, LP, ON or ongoing NeuP)	Exclusion of other likely causes of pain, pain with a plausible neuroanatomical distribution, DN4 ≥ 4 and a compatible demyelinating lesion	184/286	Multivariate binomial regression	Disability (EDSS)	1.33 (1.18-1.49)
Alkhatatbeh et al., 2019 [3]	Cross-Sectional	Jordan	T2D with NeuP	PainDETECT 0-12 = NociP 13-18 = Unclear ≥ 19 = NeuP	NeuP = 64 Unclear = 58 NociP = 117	Multivariate ordinal regression	Gender (Female)	2.45 (1.29-4.67)
Barbosa et al., 2019 [4]	Cross-Sectional	Portugal	T1D with DSPN and NeuP (reported as painful DSPN)	DN4 ≥ 4 and LANSS ≥ 12 (in participants with MNSI ≥ 6)	Painful DSPN = 67 painless DSPN = 85 no pain, no DSPN = 208	Multivariate multinomial regression	Diabetes duration (years) Gender (Females) Hypertension HbA1c (%)	1.06 (1.03-1.09)[e] 2.14 (1.17-3.92)[e] 2.72 (1.30-5.68)[e] 1.19 (1.02-1.40)[e]

ABI, ankle brachial index; AIC, Akaike information criterion; BDI-II, Beck Depression Inventory – second edition; BMI, body mass index; CART, combination antiretroviral therapy; CI, confidence interval; CPSNP, chronic postsurgical neuropathic pain; CR, clinical remission; DAS28-ER, disease activity score-28 based on erythrocyte sedimentation rate; DN4, Douleur Neuropathique en 4 Questions; DPN, diabetic peripheral neuropathy; DSPN, distal symmetrical polyneuropathy; EDSS, Expanded Disability Status Scale; GP, general practitioner; HADS, Hospital and Anxiety Depression Scale; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HIV-SN, human immunodeficiency virus-sensory neuropathy; HZ, Herpes zoster; ICBH, iliac crest bone harvest; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; KP, knee pain; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; LS, Lhermitte's phenomenon; MCS, mental component summary; MDNS, Michigan Diabetic Neuropathy Score; MER, Middle East Region; MI, myocardial infarction; MNSI, Michigan Neuropathy Screening Instrument; MOS-SS, Medical Outcomes Study Sleep Scale; MS, multiple sclerosis; NDS, neuropathy disability score; NeuP, neuropathic pain; NGT, normal glucose tolerance; NKP, neuropathic knee pain; NociP, nociceptive pain; NSS, neuropathy symptom score; OA, osteoarthritis; OS, optic neuritis; PAD, peripheral arterial disease; PCS, pain catastrophizing scale; pDPN, painful diabetic peripheral neuropathy; PHN, post-herpetic neuralgia; RA, rheumatoid arthritis; SF-12/36, 12/36-item Short Form Health Survey; T1D, type 1 diabetes; T2D, type 2 diabetes; TJR, total joint replacement; TN, trigeminal neuralgia; UK, UAE, United Arab Emirates; United Kingdom; USA, United States of America; VL, viral load; ZBPI, Zoster Brief Pain Inventory.

*? indicates where numbers are unclear or missing in the paper

[a]versus <50 years as reference group
[b]versus Egypt as reference group
[c]Hazard ratio
[d]Odds ratios relate to the definite NeuP group with No NeuP as the reference
[e]Odds ratios relate to the pDSPN group with no DSPN and no pain as the reference in Model 4

Figure 1


Clinical
Pre-existing pain
Diabetes duration
Diabetes type
Nephropathy
Peripheral artery disease
HDL cholesterol
Triglycerides
- Painful diabetic neuropathy
- Postherpetic neuralgia
- Neuropathic knee pain
- Neuropathic pain in RA
Psychosocial
Depression
Anxiety
Sleep disturbance
Low physical activity
Pain catastrophising
Alcohol
Smoking
Overweight
Demographic
Older age
[Female] gender
Deprivation
Manual occupation
- Trigeminal neuralgia
- Post-surgical pain
- Painful HIV-sensory neuropathy
- Neuropathic pain post-TJR
Genetics
Neurotransmission
(OPRM1, COMT, PRKCA, SLC6A4, GCH1)
Ion channels
(SCN9A,SCN11A,CACNG2, KCNS1, P2RX7)
Iron metabolism
(TF, CP, TFRC, ACO1, FXN, B2M, BMP6, SLC11A2)
Immune response
(HLA , IL6, TNFA, GFRA2)

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