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Review

Painful diabetic neuropathy: Diagnosis and management

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Abstract

The prevalence of painful diabetic peripheral neuropathy (PDN) is about 20% in patients with type 2 diabetes and 5% in those with type 1. Patients should be systematically questioned concerning suggestive symptoms, as they are not usually volunteers. As PDN is due to small-fibre injury, the 10 g monofilament pressure test as well as the standard electrophysiological procedures may be normal. Diagnosis is based on clinical findings: type of pain (burning discomfort, electric shock-like sensation, aching coldness in the lower limbs); time of occurrence (mostly at rest and at night); and abnormal sensations (such as tingling or numbness). The DN4 questionnaire is an easy-to-use validated diagnostic tool. Three classes of drugs are of equal value in treating PDN: tricyclic antidepressants; anticonvulsants; and selective serotonin-reuptake inhibitors. These compounds may be prescribed as first-line therapy following pain assessment using a visual analogue scale. If the initial drug at its maximum tolerated dose does not lead to a decrease in pain of at least 30%, another drug class should be prescribed; if the pain is decreased by 30% but remains greater than 3/10, a drug from a different class may be given in association.

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Keywords: Diabetic peripheral neuropathy; Painful neuropathy; Treatment; Review; Guidelines

Résumé

Neuropathie diabétique douloureuse. Diagnostic et traitement.

La neuropathie douloureuse concerne environ 20 % des diabétiques de type 2 et 5 % des diabétiques de type 1. Elle doit être systématiquement cherchée par l'interrogatoire car les patients n'en parlent pas spontanément. C'est une complication qui concerne les petites fibres. Elle peut donc s'accompagner d'un test au monofilament et d'un électromyogramme normaux. Le diagnostic est clinique : type de douleur (brûlure, décharge électrique, froid douloureux...), horaire de survenue (plutôt au repos, plutôt la nuit), sensations anormales (fourmillement, engourdissement...). Le questionnaire DN4 est un outil diagnostique simple et validé. Trois classes médicamenteuses ont fait la preuve d'une efficacité équivalente : les antiépileptiques, les anti-dépresseurs tricycliques et les inhibiteurs mixtes de la recapture de la sérotonine et de la noradrénaline. Elles peuvent donc être prescrites en première intention, après évaluation de la douleur sur une échelle numérique. À dose maximale tolérée, si le traitement initial n'a pas permis de diminuer la douleur de 30 %, une autre classe doit être choisie. Si la douleur a diminué de 30 % mais reste supérieure à 3/10, deux classes peuvent être associées.

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Mots clés : Neuropathie périphérique diabétique ; Neuropathie diabétique ; Traitement ; Revue générale ; Recommandations

Abbreviations: PDN, diabetic peripheral neuropathy; CSDPN, chronic sensorimotor diabetic peripheral neuropathy; QoL, quality of life; IGT, impaired glucose tolerance; MNSI, Michigan neuropathy screening instrument; NNT, Number of patients to treat to obtain a beneficial effect; NNMH, Number of patients to treat to obtain a major side effect; NSAID, Non-steroidal anti-inflammatory drug; SSNRI, Selective serotonin-norepinephrine reuptake inhibitor; SRI, Serotonin reuptake inhibitor; GABA, gamma-aminobutyric acid.

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1. Epidemiology

The acute presentation of PDN is rare, and the chronic variant is by far the most common form, presenting as part of the CSDPN [1].

1.1. Prevalence and incidence

The prevalence and incidence of PDN are difficult to assess precisely: indeed, few studies have focused only on the painful form of CSDPN; and differences in the selected studied populations and diagnostic criteria account for the wide range of published estimates. However, 50% of diabetic patients with peripheral neuropathy are estimated to report painful symptoms [2–4]. Earlier studies reported a prevalence of lower-limb pain ranging from 6% [5] to 27% [6], and it was more common in type 2 (32%) than in type 1 (12%) diabetes [7]. According to a hospital-based study, the prevalence of PDN was estimated to be 11% in diabetic patients aged > 60 years [8]; a similar rate was reported in a study from Germany [9].

Three studies give more precise data, two of which were conducted in the UK in primary-care practices. The study by Daousi et al. [10] included 356 (mainly type 2) diabetic patients: from a structured questionnaire and clinical examination, CSDPN was diagnosed in nearly half the patients, but only a third of them complained of chronic pain (present for at least 1 year), giving a prevalence rate of 16% for PDN compared with 5% for chronic neuropathic pain in an age- and gender-matched non-diabetic population. Also, 12.5% of the patients with PDN reported that they had never talked about their symptoms to a physician, and 39% said they had never been treated for the condition. The study by Davies et al. [11] showed a 26% prevalence of PDN in a type 2 diabetic population; this prevalence rate rose to 44% for diabetic patients suffering from CSDPN.

The third study—a multicentre study recently conducted in Belgium of 1111 diabetic patients—estimated the prevalence rates of CSDPN and PDN using validated tools [12]. In every patient, hypoaesthesia was tested using the Neuropen®, a device that assesses both pain and pressure (monofilament) perception, and allows CSDPN to be identified with confidence [13]. Patients complaining of pain completed the DN4 neuropathic pain diagnostic questionnaire to confirm that the pain was of neuropathic origin. Mean diabetes duration was significantly longer in type 1 (16 years) compared with type 2 (11 years) diabetic patients. The prevalence of CSDPN was 43%, and was higher in type 2 (51%) than in type 1 (26%) diabetics; also, around one-third of these patients had lower-limb neuropathic pain with a prevalence of PDN of 14%, which was higher in type 2 (18%) than in type 1 (6%) diabetic patients. These estimates from specialized centres are similar to those reported in primary-care practice [10,11].

In France, a prevalence rate of 8% was reported for PDN; however, this study was of questionable reliability [15].

Taking all these studies into consideration, the prevalence of PDN may be estimated at 15–20% in type 2 and about 5% in

type 1 diabetic patients. The incidence rate would be around 2% per year [16].

1.2. Quality of life

PDN greatly alters the QoL, as shown by many studies [4,11,12,17]. Benbow et al. [18] reported that scores were significantly lower in patients with PDN for five of the six health-related QoL domains (energy, sleep, pain, physical mobility and emotional reactions). In the study by Van Acker et al. [12], whereas painless CSDPN appeared to not have a significant impact on QoL, PDN was associated with severe alterations in both the physical and mental components of QoL. The deleterious impact was particularly marked on sleep and joy in life [3,17–19]. Many studies have shown a significant relationship between pain intensity and worsening of self-assessed health status [3,20].

1.3. Cost of illness

The average annual cost of pain medication as monotherapy in patients with PDN is estimated to be about \$300. However, the cost varies widely according to the type of medication, and increases substantially when several drugs are used. Furthermore, extra medical costs due to physician visits and neurological tests, as well as indirect costs associated with loss of productivity, should be added to the pharmaceutical cost of treating PDN [21,22].

1.4. Risk factors

The results of studies of risk factors for PDN are sometimes conflicting [23,24], but age and diabetes duration have been the most frequently reported risk factors [5,6,9,12,25,26]. Harris et al. [6] showed that arterial hypertension was significantly associated with PDN. Tall stature has been implicated as a risk factor for neuropathy because of the length-dependent deterioration of nerve fibres [27,28]; however, unlike sensitivity loss, the patient's height was not a significant, independent factor for the occurrence of pain [25]. The role of hyperglycaemia is not clear as regards the painful component of CSDPN [5,6,10,25]. Painful neuropathy has been associated with IGT [29]. Around 10% of patients with IGT and 4% with moderate fasting hyperglycaemia suffer from painful neuropathy [9,30]. On the other hand, IGT can also be seen in 30–55% of patients with idiopathic sensitive neuropathy and especially in those complaining of pain [31,32]. In the study by Sumner et al. [29], 26 out of 73 patients with peripheral neuropathy of unknown origin had IGT (36%) and 15 were diabetic (21%); neuropathy was painful in 77% of those with IGT and in 93% of the diabetic patients. The severity of neuropathy, as assessed by the results of electrophysiological studies and the density of intradermal neural fibres, was less marked in cases of IGT than of diabetes, and mostly involved nerve fibres of small diameter. Autonomic dysfunction, also due to preferential damage to small nerve fibres, may be present in cases of IGT [33].

In the study of Van Acker et al. [12], neuropathy was associated with obesity, and with low high-density lipoprotein (HDL) cholesterol and high plasma triglyceride levels. This relationship was particularly marked in the presence of PDN, suggesting that some components of the metabolic syndrome could play a role not only in the development of neuropathy [34,35], but also of neuropathic pain. However, as IGT and the metabolic syndrome are frequently associated, it is difficult to distinguish between confounding factors, and the relationship of cause and effect.

The role of a genetic predisposition and/or environmental factors has been suggested by Galer et al. [3], who reported that a large percentage (56%) of patients with PND also had first- or second-degree relatives who suffered from PND.

PND can have an acute onset shortly after a sudden improvement of glycaemic control, usually related to the initiation of insulin treatment (so-called ‘insulin neuritis’) [23,24,36–42]. On the other hand, a similar clinical condition has been described, but in association with poor glycaemic control and rapid weight loss [43,44] and, sometimes, in girls with eating disorders. As yet, no epidemiological study is available of these acute painful forms of diabetic neuropathy that are known to be rare [1,24,45,46].

2. Pathophysiology

Diabetic polyneuropathy always involves damage to the small neural fibres [47,48]. However, a distinction must be made with the small myelinated (A-delta) fibres that are associated with sensitivity to cold and prick, and the small unmyelinated (C) fibres that are responsible for sensitivity to heat and pain (Table S1; see supplementary material associated with this article online). These small fibres are not assessed by electrophysiological procedures. Autonomic fibres (sympathetic and parasympathetic nerves) are also part of this small-fibre group. In contrast, the large myelinated fibres responsible for sensitivity to touch (tested by monofilament) and proprioception (tested by tuning fork) are affected later (Table S1; see supplementary material associated with this article online), and electrophysiological procedures explore only these large neural fibres.

Despite the large number of studies, it has still not been possible to allocate the occurrence of nerve-related pain to a particular type of lesion [49]. Recent studies of the intraepidermal nerve endings, as a means to analyze small fibres, showed that a major loss of these endings was associated with neuropathic pain only in patients who had little or no objective signs of neuropathy, thereby suggesting that the loss of nerve endings is not sufficient to induce pain [50].

Using microneurographic recordings that can study unmyelinated C-fibre function, the sensitization of C nociceptors was shown in diabetic patients with neuropathy, as well as a decrease in the number of mechanoresponsive to mechano-insensitive nociceptors and the presence of abnormal fibres (probably degenerated). As a consequence, the distribution of C nociceptors is modified and their excitability altered [51].

Mechanisms that might explain nociceptor hyperexcitability include dysregulation of the synthesis and function of ionic

channels (mainly sodium channel) [52], and a genetic susceptibility, as suggested by a mutation of the gene coding for a unit of the sodium channel (NaV1.7); this channel is largely present in the dorsal root ganglion of the peripheral nerves of most nociceptors. The mutation has been identified especially in patients with erythromelalgia, whose symptoms are characterized by paroxysmal pain (burning) in the limbs associated with vasomotor dysfunction [53].

3. Diagnosing diabetic polyneuropathy

3.1. Diabetic polyneuropathy, ‘at-risk’ foot and neuropathic pain: how to tell the difference

3.1.1. Chronic sensorimotor diabetic peripheral neuropathy and foot at risk for ulceration

CSDPN is distal, symmetrical and often asymptomatic. The subjective symptoms are usually discrete or absent, although the diagnosis can be made on examination using the Neuropen [13]. Resembling a small pen, this device has a 10 g monofilament that tests the touch/pressure sensation (large nerve fibres) at one end, and a blunt needle at the other end for assessing sharpness/pain sensation (small fibres) (Table S1; see supplementary material associated with this article online). The Neuropen enables screening for CSDPN with good sensitivity and specificity. A screening diagnostic scale such as the MNSI can also be used to calculate a probability score for CSDPN based on a questionnaire and physical examination [24,54].

In CSDPN, the large nerve fibres are damaged later than the small ones. This means that the monofilament and tuning fork (128 Hz) test become abnormal only at a late stage of CSDPN. The risk of foot ulceration in diabetic patients is due to damaged large nerve fibres. The tuning fork and monofilament tests are therefore not tools for diagnosing CSDPN or PDN, but for screening patients whose feet may be at risk of skin ulceration. Thus, a normal monofilament test does not argue against a diagnosis of CSDPN.

Electrophysiological tests have no place in the diagnosis of CSDPN, as they can be normal when only small-diameter fibres are damaged. Such procedures should be performed only when the clinical presentation is atypical and the diabetic origin uncertain (asymmetrical symptoms or involvement of the upper limbs).

3.1.2. Diabetic peripheral neuropathy

PDN is due to the involvement of the small nerve fibres [55,56], and its diagnosis is based on the patient’s history and physical examination. The symptoms of neuropathic pain are highly varied in contrast to nociceptive pain [14]. The pain occurs usually at rest, and is typically worse at night and sometimes relieved by walking barefoot. The pain may be moderate or severe and spontaneous or provoked by some external stimuli. Some patients complain of allodynia induced by contact with bedclothes or diapers, or provoked by a non-painful thermal stimulus; other patients are prone to hyperalgesia (Appendix S1: Glossary; see supplementary material associated with this article online). Finally, the pain may be described as sudden

burning discomfort, a stabbing or an electric shock-like sensation; paraesthesia and dysaesthesia are also frequently reported, including squeezing, tingling or numbness. These symptoms may be isolated or variably associated.

Physical examination should look for signs typical of small-fibre involvement, such as a decrease in prick or temperature perception, or allodynia induced by touching or rubbing. Signs of autonomic neuropathy may be associated when A-delta fibres are damaged.

Involvement of large-diameter fibres, as assessed by the 10 g monofilament and tuning fork tests, usually arises later. However, these two tests as well as electrophysiological procedures, which detect only lesions of the large fibres, may be completely normal in painful neuropathy.

A number of questionnaires have been developed to help practitioners diagnose neuropathic pain [57]. The DN4 questionnaire is of particular interest, as it can be rapidly completed, is easy to use and has a good diagnostic performance: for a score $\geq 4/10$, it has a sensitivity of 83% and a specificity of 90% for diagnosing neuropathic pain (Appendix S2; see supplementary material associated with this article online).

Once neuropathic pain has been diagnosed, the intensity of the pain needs to be assessed, using a visual analogue or numerical (10-point) scale, before introducing any treatment in order to evaluate treatment efficacy.

3.2. Diagnostic problems

Any pain occurring in a diabetic patient is not necessarily due to neuropathy and, conversely, diabetic neuropathy is not always painful. Studies in a large number of patients [14,56,58–61] suggest that, in most cases, a clinical approach may be sufficient for diagnosis.

3.2.1. Peripheral artery disease of the lower limb

The most common diagnostic error is to superficially question the patient about the ‘pain in the legs’ and to consider the pain to be mainly related to arterial disease [62,63]. If Doppler ultrasonography is required, it should be correctly interpreted: pain related to arterial disease occurs only if stenosis is $> 70\%$. Simple parietal lesions do not induce pain and may be associated with a genuine diabetic painful neuropathy. Also, the diagnosis of neuropathic pain should be a positive diagnosis, not a diagnosis made by exclusion of other causes [64].

3.2.2. Other causes of neuropathic pain

Mononeuritis, entrapment syndromes (particularly Morton’s neuroma) and congenital or acquired spinal stenosis can also induce neuropathic pain. Each of these conditions has specific characteristics: painful mononeuritis (focal neuropathy) is generally unilateral or asymmetrical and localized to a defined neuroanatomical area (dermatome), and a typical example is cruralgia, which is commonly seen in diabetic patients and may be associated with symptomatic polyneuropathy; spinal stenosis induces radicular lumbosacral pain, which occurs only when walking and with symptoms of typical intermittent claudication

[65]; it is sometimes associated with discopathy, and electrophysiological studies may confirm the radicular involvement.

3.2.3. Other differential diagnoses

Restless legs syndrome may be associated with paraesthesia and dysaesthesia of the lower limbs. Symptoms occur at rest particularly before sleep and are associated with an urge to move the legs, sometimes associated with periodic movements of the lower limbs. Symptoms are alleviated by voluntary movements and walking [66]. Co-morbidities—whether local, regional or systemic—should be carefully monitored [64], and venous insufficiency, hip or knee chondropathy and muscle disorders must also be assessed.

4. Treatment

4.1. Drug treatments

There is now a consensus among experts that the analgesic efficacy of drug treatments for neuropathic pain is independent of the aetiology of neuropathy. However, most trials of neuropathic pain have been conducted in DPN and postherpetic neuralgia. A number of drug classes are available for treatment, but there are still only a few large-scale comparative studies (see the evidence-grading system for drugs in Appendix S3 in the supplementary material associated with this article online).

The benefit/risk ratio of the drugs available for neuropathic pain is generally evaluated using the NNT—the number of patients that have to be treated to obtain one additional beneficial outcome, such as pain improved by at least 50%, with the active drug *vs* the placebo—and the number needed for major harm (NNMH)—the number of patients that have to be treated to obtain one major side effect compared with a placebo (Table 1).

4.1.1. Level 1 analgesics [paracetamol, salicylates and non-steroidal anti-inflammatory drugs (NSAIDs)]

These drugs are considered ineffective or poorly effective against neuropathic pain [67,68].

4.1.2. Tricyclic antidepressants

These drugs have been widely used for the treatment of neuropathic pain. Their analgesic effects are independent of their antidepressant effects, and mainly involve their action on descending norepinephrine-related inhibitory systems. Efficacy (amitriptyline, imipramine, clomipramine) has been demonstrated in several placebo-controlled studies (level A) [69–78], although these were generally of short duration and included only a small number of patients. The efficacy was similar across all of these drugs [79] (Appendix 1; see supplementary material associated with this article online).

To minimize side effects, the treatment should be initiated at low dosages in the evening (10 mg/day of amitriptyline, for example) and titrated progressively (for example, 10 mg every 7 days up to 150 mg/day for clomipramine).

Side effects are dose-dependent and may limit the use of these drugs, and include sedation, anticholinergic effects (dry

Table 1

Efficacy and side effects of the most commonly used pharmacological agents for painful diabetic neuropathy.

| Drug class | INN | NNMH | NNT |
|--------------------------|---------------|-------------------|--------------------|
| TCAs | Amitriptyline | 15 | 2.1 |
| | Desipramine | 24 | 2.2/3.2 |
| | Imipramine | | 1.3/2.4/3.0 |
| | Clomipramine | 8.7 | 2.1 |
| SSNRIs | Duloxetine | 18 (60 mg/J) | 5.3 (60 mg/J) |
| | | 9 (120 mg/J) | 4.9 (120 mg/J) |
| | Venlafaxine | 21 (75–225 mg/J) | 6.9 (75–225 mg/J) |
| | | 17 (150–225 mg/J) | 4.6 (150–225 mg/J) |
| $\alpha_2\delta$ Ligands | Pregabalin | 23 (300 mg/J) | 6.0 (300 mg/J) |
| | Gabapentin | 11 (600 mg/J) | 4.0 (600 mg/J) |
| Opioids | Oxycodone | | 2.6 |
| | Tramadol | 7.8 | 3.1/4.3 |

(Adapted from [38])

INN: International non-proprietary name; NNMH: number needed for major harm (number of patients who have to be treated with a drug to show one major adverse effect); NNT: number needed to treat (number of patients who have to be treated with a therapy to observe a clinically relevant effect in one patient); TCAs: tricyclic antidepressants; SSNRIs: selective serotonin-norepinephrine reuptake inhibitors; $\alpha_2\delta$ Ligands: ligands to the alpha-2-delta subunit of voltage-activated calcium channels.

mouth, constipation, blurred vision, sweating, tachycardia, urinary retention), adrenergic effects (orthostatic hypotension, impotence) and weight gain. Anticholinergic effects and weight gain are especially prominent with amitriptyline [80]. The main contraindications include prostatic adenoma, recent myocardial infarction, glaucoma and heart conduction abnormalities. Imipramine and clomipramine are approved for treating ‘neuropathic pain’ in France, and amitriptyline for ‘peripheral neuropathic pain’ and ‘refractory pain’.

4.1.3. Selective serotonin-norepinephrine reuptake inhibitors (SSNRIs)

These drugs have been more recently developed, based on the significant role of norepinephrine in endogenous pain modulation through the descending norepinephrine inhibitory pathway. Well-conducted studies have shown some efficacy with duloxetine in PDN (level A) [81,83]. A significant improvement in sleep disturbance and QoL has also been reported. The maximum effect is obtained with a dose of 60 mg/day (Table 1) [84,85]; the use of higher dosages does not improve efficacy, but is instead associated with more frequent side effects [81,82].

Duloxetine (30 or 60 mg tablets) is approved only for the pain associated with diabetic neuropathy. A slow titration, starting at 30 mg, may reduce the occurrence of side effects, including somnolence, nausea, dizziness, constipation, dry mouth and loss of appetite. Severe hepatitis has been rarely reported. In clinical trials, duloxetine treatment was discontinued by around 20% of patients because of side effects. Liver disease, renal failure (creatinine clearance < 30 mL/min) and glaucoma are contraindications for duloxetine. Also, the drug can raise blood pressure, and must not be combined with inhibitors of CYP1A2 (fluvoxamine, ciproflaxine, enoxacine).

Venlafaxine has also shown efficacy in PDN [86,87], but is not approved for treating painful neuropathy. The treatment, starting at 37.5 mg/day may be progressively increased by steps of 75 mg/week to up to 150–225 mg/day. The slow-release form can be administered once a day. Side effects are similar to those described above for duloxetine, although cardiovascular adverse events are more frequent (electrocardiographic abnormalities and increases in blood pressure with higher dosages).

4.1.4. Selective serotonin reuptake inhibitors (SSRIs)

Two randomized controlled studies, but with methodological flaws (level B), have suggested some efficacy with paroxetine [88] and citalopram [89]. Nevertheless, in one comparative study, their efficacy was less than that of tricyclic antidepressants [88], and another reported no efficacy with fluoxetine [73]. A systematic review concluded that SSRIs have only limited and clinically non-significant effects on neuropathic pain. The most frequent side effects of SSRIs include dizziness, somnolence, headache and nausea.

4.1.5. Anticonvulsants

Despite its name and its structural similarity to GABA, gabapentin does not act directly on the GABAergic system. Its analgesic effects are probably mostly related to its binding to the alpha-2-delta subunit of the voltage-gated calcium channels of the central nervous system, thereby inducing a decrease in the release of glutamate.

Gabapentin has been proved effective against neuropathic pain in a number of randomized controlled studies (level A) [90–94] (Table 1). The analgesic effects were associated with a significant positive impact on sleep disturbance and QoL.

Plasma concentrations of gabapentin are not directly proportional to the dose administered, as its digestive absorption depends on the saturable transport system. This explains why high dosages given three or four times a day are necessary [95]. However, a recent double-blind randomized controlled trial showed that a slow-release formulation given once a day was equally effective for PDN [96]. Gabapentin is not significantly metabolized in humans and has only a few interactions with concomitant pharmacological treatments. However, as gabapentin is only eliminated by the kidneys as unchanged drug, dosages need to be adjusted in patients with renal impairment [95].

The starting dose should be 300 mg TID, with a progressive increase every 7 days up to 1200–3600 mg/day. Discontinuation of gabapentin should also be progressive (tapered).

The main side effects include somnolence, asthenia, dizziness, gastrointestinal disorders, dry mouth and headache. Weight gain and peripheral oedema have also been reported. Gabapentin is currently approved for peripheral neuropathic pain.

Pregabalin has been marketed more recently, and its mechanisms of action are similar to those of gabapentin. The efficacy of pregabalin for neuropathic pain has been shown in several good-quality studies (level A) [97–101]. The NNT to obtain a reduction in pain intensity of at least 50% is six patients at a dose of 300 mg/day, and four patients at a dose of 600 mg/day [102]

(Table 1). Sleep disturbance and anxiety are also significantly reduced by the treatment.

Pregabalin is not metabolized in the liver, and only eliminated by the kidneys. There are no significant pharmacological interactions with other drugs. Thus, it is not necessary to adjust dosages according to liver function, although the daily dose needs to be adapted in patients with renal failure. The starting dose is 150 mg/day BID, to be progressively increased every 3–7 days up to 600 mg/day BID. Discontinuation of treatment should also be progressive.

The main side effects are somnolence, asthenia, dizziness, gastrointestinal disorders, dry mouth, headache, weight gain and peripheral oedema. Pregabalin is currently approved for both peripheral and central neuropathic pain.

Carbamazepine is the first-line treatment for trigeminal neuralgia. Early studies (level C) suggested that it might be effective in PDN [103,104] and, in France, carbamazepine is approved for neuropathic pain in adults. The usual treatment dosages are between 600 and 1600 mg/day, starting at 200 mg/day and progressively increased every 3 days by 200 mg/day, depending on the side effects and clinical efficacy.

Carbamazepine induces a number of dose-related side effects, including hepatitis, skin rash and other severe dermatological reactions (Stevens–Johnson syndrome), haematological complications (agranulocytosis), hyponatraemia and cognitive dysfunction. The drug is almost fully metabolized in the liver (CYP450, 3A4) and produces an active metabolite. In addition, carbamazepine is a powerful enzyme inducer with a large number of drug interactions. Its prescription should be carefully monitored with blood tests every 2–3 months.

In good-quality studies (level A), other anticonvulsants/antiepileptics such as lamotrigine [105,106] and oxcarbazepine [107] have not shown any clinically significant efficacy. Also, the efficacy of sodium valproate [108] remains open to discussion (level B), as two studies gave conflicting results. In addition, these agents can induce potentially serious adverse events, thus limiting their use. Furthermore, topiramate showed no significant efficacy in PDN [67]. None of these antiepileptics has official approval for their use in PDN.

However, clonazepam is one of the most prescribed antiepileptics for neuropathic pain in France. Its efficacy for paroxysmal pain was long suggested by one study of poor quality (level C) [109], but no controlled study was conducted in PDN. Its possible efficacy, reported only in practice, could be related to its hypnotic and anxiolytic properties. Nevertheless, the drug has no official authorization for the treatment of neuropathic pain.

Clonazepam is commonly administered as drops in the evening: the starting dose is usually five drops, to be increased gradually; the effective dosage varies greatly from one patient to another.

Its most common unwanted side effect is daytime somnolence. As clonazepam is a benzodiazepine, its prolonged use at high dosages can also induce tolerance, leading to a risk of physical and psychological dependence during treatment, and withdrawal syndrome on discontinuation.

4.1.6. Opioids

Extended-release oxycodone has proved its efficacy in PDN (level A) [110–112] as well as in postherpetic pain. Nevertheless, opioids should only be used for patients failing to respond to non-opioid treatment. The most frequent side effects include nausea, constipation, drowsiness, dizziness and dry mouth; the frequency of such adverse events explains why fewer than one patient in five continues the treatment beyond 1 year [67]. The rules of prescription are the same as those for any long-term morphine-like agent. Effective dosages range from 10–120 mg/day for oxycodone (40–60 mg/day on average), and from 15–300 mg/day for morphine.

Tramadol possesses agonist properties at the opioid receptors and inhibits the recapture of monoamines. Its efficacy was proven in PDN by studies of good methodology (level A), with a possible effect on allodynia [113,114]. The effective dose range is 200–400 mg/day. Tramadol is available as an immediate- or delayed-release capsule. It is advisable to start treatment using regular capsules at low dosages (50 mg/day in the evening), especially in the elderly, and then to increase dosages by steps of 50 mg every 4–7 days.

The most frequent unwanted side effects include nausea, constipation, headache, somnolence, dizziness, dry mouth and urinary disorders, although the extended-release form is better tolerated. Risk of seizure is increased when combined with drugs that lower the epileptogenic threshold, such as tricyclic antidepressants, or in patients with epilepsy. Precautionary measures for its use are imperative when associated with SSRIs because of the potential risk of serotoninergic syndrome.

4.1.7. Comparison of treatments

Comparative drug studies are relatively rare. Amitriptyline was compared with gabapentin in studies of good quality (level A) [78,115] that concluded that these two agents have similar efficacy. Amitriptyline was also compared with pregabalin in a level A study [116]: no difference in effectiveness was reported, but drowsiness was more frequent with amitriptyline (43%) than with pregabalin (20%). In another good-quality study (level A), amitriptyline and duloxetine were shown to have similar effectiveness [117]. Yet another study of good methodology, but a limited number of patients [74], found no difference between amitriptyline and lamotrigine as regards pain. However, drowsiness was more frequently reported with amitriptyline, although side effects were more serious—albeit less frequent—with lamotrigine (renal failure in 9% of patients). Finally, a meta-analysis comparing pregabalin, duloxetine and gabapentin [118] concluded that duloxetine was as effective as the other two drugs.

4.1.8. Combination therapy

Few studies have tested the efficacy of combination drug therapies. Gabapentin associated with the SSNRI venlafaxine appeared to be more effective than gabapentin alone (level C) [93]. An additive effect was found when combining gabapentin with morphine compared with monotherapy with either gabapentin or morphine alone (level A) [119]: the efficacy of the combination against pain was greater at lower doses than those used in monotherapy. Similar results were also reported

for the combination of gabapentin and a tricyclic antidepressant (nortriptyline, a metabolite of amitriptyline) in a level A study [78].

4.1.9. Treatment costs

These are presented in Table S2 (see supplementary material associated with this article online).

4.1.10. 'Emergent' treatments

A recent study involving a small number of subjects showed no superiority of the cannabinoid compounds over placebo in the treatment of PDN [120]. However, numerous other experimental agents are currently in development, such as ABT-594, an agonist of the nicotinic receptor in cholinergic neurons that was proved effective in a double-blind, randomized, placebo-controlled trial of 266 patients with PND; however, there was a high rate of side effects [121]. In addition, a study involving a small number of patients with PND suggested that intradermal injection of botulinum toxin type A might be able to alleviate pain and improve quality of sleep [122].

4.2. Non-pharmacological treatments

Transcutaneous electrical nerve stimulation (TENS) has been the subject of a few randomized studies [123], and can be recommended in cases of pain in a limited area (level B). More invasive treatments, such as central neurostimulation, may be discussed for patients unresponsive to pharmacological treatments. Other non-drug treatments, such as acupuncture

and psychotherapy, are available, although recommendations are not possible, given that very few trials have been carried out and with conflicting results.

4.3. Pathogenetic treatments

4.3.1. Glycaemic control

The Diabetes Control and Complications Trial (DCCT) clearly established that poor glycaemic control is associated with the occurrence or worsening of peripheral neuropathy [124], but whether improvements in glycaemic control can decrease neuropathic pain intensity is still a subject of debate.

In addition, proving that a treatment for painful neuropathy is effective in the long-term is difficult, as a decrease in pain intensity does not necessarily mean that the anatomical lesions are improving. In fact, neuromuscular biopsies have shown that the improvement of pain is associated with the disappearance of nerve fibres [125,126].

Studies involving a large number of patients, such as the BARI 2D study in patients with coronary disease [127], suggest that a decrease in HbA_{1c} is not associated with improvement of neuropathic pain [128]. Sorensen et al. [25] reported similar results. A few studies gave the opposite view, but the number of included patients was often very small (level C) [129]. In type 1 diabetic patients with PDN, the role of glycaemic excursions was evaluated using a continuous glucose measurement system [130], which showed that the number of glycaemic excursions is not related to the level of neuropathic pain. Also, continuous subcutaneous insulin infusion did not improve pain [129]. Indeed,

Table 2

Advantages and disadvantages of the most commonly used pharmacological agents for painful neuropathy.

| INN | Trade name | Advantages | Disadvantages |
|---------------------------------------|-------------------------------------|---|---|
| Gabapentin | Neurontin® or generic drugs | No major drug interactions | Adverse events Titration TID Cost |
| Duloxetine | Cymbalta® | Easy and rapid dose titration Taken daily Antidepressant/antianxiety effects | Adverse events Drug interactions |
| Pregabalin | Lyrica® | No major drug interactions Antianxiety effect | Adverse events Titration Cost |
| Amitriptyline/Imipramine/Clomipramine | Laroxyl® Tofranil® Anafranil® | Drops Low cost Antianxiety effect (clomipramine) Antidepressant effect at high doses | Titration scheme Anticholinergic/ adrenergic effects |
| Oxycodone Morphine (slow-release) | Oxycontin LP® | Beneficial effect on possibly associated inflammatory pain | Adverse events Physical dependence |
| Tramadol | | Beneficial effect on possibly associated inflammatory pain | Adverse events Physical dependence |
| Carbamazepine | Tegretol® | | Titration scheme Enzyme inducer Adverse events Cost |
| Clonazepam | Rivotril® | Drops Low cost | No available study of analgesic effects Somnolence, memory problems Dependence, withdrawal syndrome |

INN: International non-proprietary name.

as already mentioned above, the increase in pain intensity may be the result of too-rapid glycaemic normalization.

Pancreas transplantation is a good means of studying the impact of normalizing blood glucose levels. However, studies of peripheral neuropathy outcomes in the first year after pancreas transplants gave discordant conclusions [131,132]. Over the first 4 years, peripheral neuropathy did not improve [133], although improvements in electrophysiological data and pain levels were later observed [134,135]. These results need to be interpreted with caution, as the studies involved kidney plus pancreas transplantation. Therefore, it is possible that the improvement of the uraemic syndrome related to kidney transplantation, which is also involved in painful neuropathy, might explain this beneficial effect.

4.4. Other treatments

Many treatments have been proposed to prevent or improve peripheral neuropathy, such as aldose reductase inhibitors, inhibitors of glycation, protein kinase C- β inhibitors, angiotensin-converting enzyme inhibitors and nerve growth factors [24]. Two meta-analyses and two randomized studies suggest that the antioxidative properties of alpha-lipoic acid may improve peripheral neuropathy symptoms such as pain and motor dysfunction [38]. This product, however, is not available in France. The use of capsaicin [137] and lidocaine [138] have also been proposed.

5. Therapeutic recommendations

Treatments for PDN aim to decrease pain intensity (symptomatic treatment) and, wherever possible, improve QoL (Table 2 and Appendix 1). Such treatments are not intended to act on abnormal sensations (dysaesthesia), but only on pain. Patients need to be informed that the complete disappearance of pain is rarely achieved.

Pain intensity (as determined by a visual analogue scale, for example) and its consequences have to be evaluated before starting treatment and at each step of titration. A decrease in pain of at least 30% is considered clinically acceptable [136]. If the pain intensity decreases by <30% with the maximum tolerated dose, then changing the drug class is recommended (expert consensus).

For low-intensity pain (<3/10), it is possible to start with a first-level analgesic drug, as these compounds are well tolerated and inexpensive—but they usually lack efficacy. For more severe pain ($\geq 3/10$), and relying only on the evidence found in the published studies so far (most of which are sponsored by pharmaceutical companies), it would be recommended to first use gabapentin, duloxetine, pregabalin or tricyclic antidepressants such as clomipramine. These drugs have similar efficacy on pain, although each one also has advantages and disadvantages (Table 2). Tricyclic antidepressants, for example, have potentially more serious side effects, but are less expensive and formulated as drops, which facilitates titration whereas, with duloxetine, titration is easy and it is taken only once a day, but it comes with many side effects. The initial choice of treatment

may also be influenced by the co-morbidities associated with PDN, such as depression, insomnia and anxiety.

Clonazepam has never been evaluated in controlled studies. It has the advantages of being a sedative taken at night, formulated as drops and having no serious side effects, but it can induce dependence, as with other benzodiazepines. It can also be given as an add-on treatment at night. However, as its efficacy has never been proven, its use should be discouraged.

The efficacy of antidepressants in the SSRI class and of the antiepileptic drugs (lamotrigine, topiramate, oxcarbazepine, lacosamide) is low or inconsistent, and the evidence for the efficacy of carbamazepine is insufficient. Furthermore, the latter comes with many side effects, some of which are serious.

Whatever the agent(s) used, if efficacy is incomplete (efficacy >30%, but pain intensity >3/10), it is recommended to give a second drug from another class (for example, an antidepressant with an antiepileptic drug). As a last resort, opioids or even morphine can be used (Appendix 1).

Reminders and guidelines (see the decision tree in Appendix 1)

- There is no firm evidence that strict glycaemic control can alleviate pain; sudden improvements in glycaemic control may even precipitate pain or worsen painful symptoms.
- Pain intensity must be assessed before initiating any pharmacological treatment, and reassessed at each step of titration of drug dosage.
- For low-intensity pain (<3/10), level 1 analgesics (WHO ladder) may be given, but their efficacy is generally low.
- For pain with an intensity $\geq 3/10$, the following agents are recommended as first-line therapy: amitriptyline (Laroxyl®) or clomipramine (Anafranil®) at an average effective dosage of 75 mg/day; duloxetine (Cymbalta®: 60 mg/day); gabapentin (Neurontin® or generic drugs: 1200–3600 mg/day); and pregabalin (Lyrica®: 150–600 mg/day, average effective dosage: 300 mg/day). All of these drugs are of similar efficacy, and dosages must be gradually increased step-by-step according to side effects and pain relief (titration scheme). They do, however, differ in manageability (titration scheme, number of tablets per day), cost and tolerability.
- As a rule, a drug is deemed successful if it reduces pain intensity by at least 30% at the maximum tolerated dose.
- If a drug is without efficacy, it is advisable to try another drug.

- If a drug is effective for pain relief, but pain intensity remains >3/10, it is recommended to add another drug from a different class: if possible, the add-on drug should have an additive effect to relieve pain (so the combination of gabapentin and pregabalin, for example, is not advisable).
- Tramadol or strong opioids such as morphine and oxycodone are to be used only if first-line therapeutic agents (alone or in combination) have failed to adequately control pain.
- Regarding clonazepam (Rivotril®), no randomized controlled study is available for its putative effect on pain. As with all benzodiazepines, the long-term use of clonazepam can induce physical dependence.

Disclosure of interest

A. Hartemann: Lilly, Pfizer, Sanofi-Aventis. N. Attal: Pfizer, Boehringer Ingelheim/Lilly, Grunenthal, Daiichi. D. Bouhassira: Pfizer, Boehringer, Astra-Zeneca, Johnson & Johnson, Grunenthal, Pierre Fabre, Astellas, Esteve, Medtronic, Newron, Sanofi-MSD and Sanofi-Aventis. I. Dumont: none. H. Gin: Lilly, Boehringer-Ingelheim, Pfizer. S. Jeanne: Lilly. G. Saïd: Lilly. J.L. Richard: Lilly, Johnson and Johnson, Quigley Pharma.

Appendix A. Supplementary data

Supplementary material (Tables S1, S2; Appendices S1–S3) associated with this article can be found at <http://www.sciencedirect.com>, at doi:10.1016/j.diabet.2011.06.003.

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