New drugs to prevent or treat diabetic polyneuropathy

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Clinical impact of diabetic polyneuropathy

Diabetic neuropathy has been defined as a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes mellitus without other causes of peripheral neuropathy. It includes manifestations in the somatic and/or autonomic parts of the peripheral nervous system [1], which are being classified along clinical criteria. However, due to the variety of the clinical syndromes with possible overlaps, there is no universally accepted classification. The most widely used classification of diabetic neuropathy has been proposed by Thomas [2], who differentiates between diffuse symmetric polyneuropathies on the one hand and focal and multifocal neuropathies on the other.

In this review I will focus on distal symmetrical sensory or sensorimotor polyneuropathy (DSP), which represents the most important clinical manifestation affecting approximately 30% of the hospital-based diabetic population and 20% of community-based samples of diabetic patients. The incidence of DSP is approximately 2% per year. The most important aetiological factors that have been associated with DSP are poor glycaemic control, diabetes duration, and height, with possible roles for hypertension, age, smoking, hypoinsulinaemia and dyslipidaemia [3]. Moreover, DSP is related to both lower extremity impairments, such as diminished position sense, and functional limitations, such as walking ability [4]. There is accumulating evidence suggesting that not only surrogate markers of microangiopathy such as albuminuria but also those used for polyneuropathy such as nerve conduction velocity and vibration perception threshold may predict mortality in diabetic patients [5, 6]. Elevated vibration perception threshold also predicts the development of neuropathic foot ulceration, one of the most common causes of hospital admission and lower limb amputation among diabetic patients [7].

Neuropathic symptoms are present in 15–20% of diabetic patients, 7.5% of whom experience chronic neuropathic pain [8]. Pain associated with diabetic neuropathy exerts a substantial impact on quality of life, particularly by interfering with sleep and enjoyment of life [9]. Despite this significant impact, one-quarter of diabetic patients and one-fifth of non-diabetic subjects had received no treatment for their pain according to a 1990 survey [8]. Pain is a subjective symptom of major clinical importance as it is often this complaint that motivates patients to seek health care. People with diabetes experience more chronic pain than the non-diabetic population. It has been found that 25% of diabetic patients had chronic pain compared with 15% of non-diabetic subjects [8]. This difference is largely attributable to the pain associated with polyneuropathy.

Pain associated with diabetic neuropathy exerts a substantial impact on quality of life

Pathogenetic mechanisms

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. Most data have been generated in the diabetic rat model, on the basis of which two approaches have been chosen to contribute to the clarification of the pathogenesis of diabetic neuropathy. Firstly, it has been attempted to characterize the pathophysiological, pathobiochemical and structural abnormalities that result in experimental diabetic neuropathy. Secondly, specific therapeutic interventions have been employed to prevent the development of these alterations, to halt their progression or to induce their regression despite concomitant hyperglycaemia.

At present, the following seven pathogenetic mechanisms are being discussed. However, they are no longer regarded as separate hypotheses but as a complex interplay of multiple interactions between metabolic and vascular factors [10]:

- increased flux through the polyol pathway that leads to accumulation of sorbitol and fructose, *myo*-inositol depletion and a reduction in Na^+,K^+-ATPase activity;
- disturbances in n-6 essential fatty acid and prostaglandin metabolism that result in alterations of nerve membrane structure and microvascular and haemorrheological abnormalities;
- endoneural microvascular deficits with subsequent ischaemia and hypoxia as well as generation of reactive oxygen species (oxidative stress) and so-called hyperglycaemic pseudohypoxia;
- increased activity of protein kinase C;
- deficits in neurotrophism leading to reduced expression and depletion of neurotrophic factors such as nerve growth factor (NGF), neurotrophin-3 and insulin-like growth factor, and alterations in axonal transport;
- accumulation of non-enzymatic advanced glycation endproducts on nerve and/or vessel proteins;
- immunological processes with autoantibodies to vagal nerve, sympathetic ganglia and adrenal medulla as well as inflammatory changes.

From a clinical point of view it is important to note that, based on these pathogenetic mechanisms, therapeutic approaches could be derived, some of which have been evaluated in randomized clinical trials (*Table I*). These treatments include the inhibition of the increased flux through the polyol pathway by aldose reductase inhibitors (ARI); correction of the deficits in essential fatty acid and prostanoid metabolism by substitution of γ-linolenic acid contained in evening primrose oil; administration of antioxidants (α-lipoic acid) to reduce the enhanced formation of reactive oxygen species that induce increased oxidative stress; improvement in endoneurial blood flow and resulting hypoxia by vasodilating agents such as ACE inhibitors, prostaglandin analogues, a protein kinase C β inhibitor and C-peptide; neurotrophic support by administration of recombinant human NGF; inhibition of non-enzymatic glycation and formation of advanced glycation endproducts by aminoguanidine; and immunosuppressive treatment.

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy

Since in the foreseeable future normoglycaemia will not be achievable in the majority of diabetic patients, the advantage of the aforementioned treatment approaches is that they may exert their effects despite prevailing hypergly-

Table I: *Treatment of diabetic neuropathy based on the putative pathogenetic mechanisms.*

Abnormality	Compound	Effect of treatment	Status of RCTs
Polyol pathway ↑	Aldose reductase inhibitors	Nerve sorbitol ↓	
	Sorbinil		Withdrawn (AE)
	Tolrestat		Withdrawn (AE)
	Ponalrestat		Ineffective
	Zopolrestat		Withdrawn (marginal effects)
	Zenarestat		Withdrawn (AE)
	Epalrestat		Marketed in Japan
	Fidarestat		Studies ongoing
myo-Inositol ↑	*myo*-Inositol	Nerve *myo*-inositol ↑	Equivocal
γ-Linolenic acid synthesis ↓	γ-Linolenic acid	EFA metabolism ↑	Withdrawn (effective: deficits)
Oxidative stress ↑	α-Lipoic acid	Oxygen free radicals ↓	Effective in RCTs (studies ongoing)
	Vitamin E	Oxygen free radicals ↓	Effective in one RCT
Nerve hypoxia ↑	Vasodilators	NBF ↑	
	ACE inhibitors		Effective in one RCT
	Prostaglandin analogues		Effective in one RCT
Protein kinase C ↑	Protein kinase C β inhibitor	NBF ↑	RCTs ongoing
C-peptide ↓	C-peptide	NBF ↑	Studies ongoing
Neurotrophism ↓	Nerve growth factor	Nerve regeneration, growth ↑	Ineffective
LCFA metabolism ↓	Acetyl-L-carnitine	LCFA accumulation ↓	Ineffective
Non-enzymatic glycation ↑	Aminoguanidine	AGE accumulation ↓	Withdrawn

RCT, randomized clinical trial; AE, adverse events; EFA, essential fatty acid; NBF, nerve blood flow; LCFA, long-chain fatty acid; AGE, advanced glycation endproduct.

caemia. Experimental studies of low-dose combined drug treatment suggest enhanced drug efficacy mediated by facilitatory interactions between drugs. Thus, administration of low doses of an α-lipoic acid/γ-linolenic acid conjugate corrected the nerve conduction and nerve blood flow deficits [11] as well as sciatic nerve contents of NGF, substance P and neuropeptide Y [12] in diabetic rats, suggesting a synergistic action of these compounds.

In future, combinations of certain drugs that produce synergistic effects could be used as therapeutic options

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Treatment based on pathogenetic concepts

Aldose reductase inhibitors (ARI)

An increased flux through the polyol pathway resulting in multiple biochemical abnormalities in the diabetic nerve is thought to play a major role in the pathogenesis of diabetic neuropathy. ARI block the increased activity of aldose reductase, the rate-limiting enzyme that converts glucose to sorbitol. The first trials of ARI in diabetic neuropathy were published 20 years ago. The various compounds that have been evaluated are alrestatin, sorbinil, ponalrestat, tolrestat, epalrestat, zopolrestat and zenarestat. Except for epalrestat, which is marketed in Japan, none of these agents could be licensed due to serious adverse effects (sorbinil, tolrestat, zenarestat) or lack of efficacy (ponalrestat, zopolrestat).

A meta-analysis of 13 clinical trials with ARI revealed a marginal effect on peroneal motor nerve conduction velocity (NCV) of 1.24 m/s and an even weaker effect on median motor NCV of 0.69 m/s after 1 year [13]. Data of 738 subjects from three trials of tolrestat showed a benefit equal to 1 m/s in a pooled analysis of NCV in all the nerves studied [14]. The following degrees of changes in motor and sensory NCV that are associated with a change in the Neuropathy Impairment Score of two points have been considered to be clinically meaningful in controlled clinical trials: median motor NCV 2.5 m/s, ulnar motor NCV 4.6 m/s, peroneal motor NCV 2.2 m/s, median sensory NCV 1.9 m/s, and sural sensory NCV 5.6 m/s [15]. According to this suggestion the changes in NCV obtained from the ARI trials so far do not appear to reflect a meaningful magnitude of a treatment effect. In a recent 1-year phase II trial of zenarestat including 208 patients with diabetic polyneuropathy, a dose-dependent improvement in small myelinated fibre loss and peroneal NCV was observed [16], but subsequent large phase III trials of zenarestat had to be prematurely terminated due to a significant deterioration in renal function in some patients.

Only a few large-scale trials reported the effects of ARI on neuropathic pain. In a multicentre trial of tolrestat in 219 patients with symptomatic polyneuropathy, paraesthetic symptoms but not pain were significantly improved after 1 year [17]. In the Sorbinil Retinopathy Trial including 497 patients, no favourable effect on the neuropathic symptoms could be detected after a median follow-up of 39 months [18]. In a 12-week controlled study including 196 patients, complete pain relief was noted in 48.6% of the patients receiving epalrestat compared with 22.6% of those on placebo [19]. Thus, only this one trial reported that ARI treatment is associated with pain relief.

γ-Linolenic acid

Two multicentre trials have demonstrated improvement in neuropathic deficits and NCV after 1 year of treatment with γ-linolenic acid in diabetic peripheral neuropathy [20, 21]. However, after γ-linolenic acid could not be licensed on the basis of these data in the UK, no further trials were initiated.

α-Lipoic acid (thioctic acid)

There is accumulating evidence suggesting that free-radical-mediated oxidative stress is implicated in the pathogenesis of diabetic neuropathy by inducing neurovascular defects that result in endoneurial hypoxia and subsequent nerve dysfunction [10]. Antioxidant treatment with α-lipoic acid has been shown to prevent these abnormalities in experimental diabetes [11, 12], thus providing a rationale for a potential therapeutic value in diabetic patients. In Germany, α-lipoic acid has been licensed and used for the treatment of symptomatic diabetic neuropathy for more than 20 years. Thus far, five randomized placebo-controlled clinical trials have been published suggesting the following:

- Short-term treatment for 3 weeks using 600 mg thioctic acid i.v. per day appears to reduce the chief neuropathic symptoms including pain, paraesthesiae and numbness. A 3-week

pilot study of 1800 mg per day indicates that the therapeutic effect may be independent of the route of administration, but this needs to be confirmed in a larger sample size.
- Three-week treatment also improves neuropathic deficits; subsequent oral treatment for 4–7 months tends to reduce neuropathic deficits and improves cardiac autonomic neuropathy.
- Preliminary data over 2 years indicate possible long-term improvement in motor and sensory NCV in the lower limbs.
- Clinical and postmarketing surveillance studies have revealed a highly favourable safety profile of the drug [22].

Two large multicentre trials are being conducted in North America and Europe to verify the results of the ALADIN [Alpha-Lipoic Acid in Diabetic Neuropathy] studies (NATHAN 2 Study) and to evaluate the efficacy and safety of long-term treatment with α-lipoic acid over 4 years on neuropathic deficits (NATHAN 1 Study).

No clinical trials in painful diabetic neuropathy are available for other antioxidants. In a preliminary study including 21 patients with symptomatic polyneuropathy, vitamin E improved motor but not sensory NCV after 6 months, but it was not reported whether the neuropathic symptoms were influenced [23].

Vasodilators

Microvascular changes of the vasa nervorum and reduced endoneurial blood flow resulting in hypoxia are thought to be important factors in the pathogenesis of diabetic neuropathy [10]. Thus, there is a solid theoretical background to support treatment with vasodilating drugs. In a 1-year trial including 41 normotensive patients with mild neuropathy, several attributes of NCV, but not neuropathic symptoms and deficits, were improved after 1 year of treatment with the ACE inhibitor trandolapril [24]. Further studies are clearly needed to define the therapeutic role of ACE inhibitors in diabetic neuropathy.

Several open-label trials from Japan reported relief of pain or dysaesthetic symptoms after treatment with vasodilating agents such as the prostacyclin (PGI_2) analogues iloprost or beraprost and the prostaglandin derivative PGE_1-αCD after 2, 12 and 4 weeks, respectively. However, due to the uncontrolled study designs, these effects are uninterpretable. A large controlled multicentre trial including 170 patients with symptomatic polyneuropathy or foot ulcers showed a >50% improvement in pain or other neuropathic symptoms in 56% of the patients treated with an intravenous infusion of PGE_1 incorporated in lipid microspheres (lipo-PGE_1) for 4 weeks, compared with 28% on placebo. In a second trial comparing lipo-PGE_1 with PGE_1-CD in 194 patients, the corresponding rates were 51 and 35%. Side effects were observed in 7% of the patients treated with lipo-PGE_1 [25]. Further studies are needed to confirm these findings.

Nerve growth factor (NGF)

NGF selectively promotes the survival, differentiation and maintenance of small fibre sensory and sympathetic neurons in the peripheral nervous system. It is expressed in the skin and other target tissues of its responsive neuronal populations, binds to its high-affinity receptor (trk A) on nerve terminals, and exerts its trophic effects after being retrogradely transported back to the neuronal perikaryon [26]. A 6-month phase II trial including 250 patients with symptomatic diabetic neuropathy showed an improvement in the sensory component of the neurological examination and both cooling detection and heat as pain threshold, but no effect on neuropathic symptoms could be observed following treatment with recombinant human NGF [27]. In contrast, a subsequent large 12-month phase III trial failed to demonstrate a favourable effect of recombinant human NGF on subjective and objective variables of diabetic neuropathy [28]. The reasons for the latter disappointing result could be the following:
- the DSP did not progress during the trial in the placebo group;
- the dose chosen may have been below the threshold to produce an effect;
- the most distal testing site (big toe) was selected for assessment, where the most advanced neuropathic changes are expected which are less susceptible to intervention than more proximal sites;
- the primary outcome measure (Neuropathy Impairment Score at the Lower Limbs) is not sensitive to small fibre sensory dysfunction;
- the drug did not get to the target tissue;
- the manufacturing process for NGF was altered after the phase II trial prior to the phase III trial, leaving the possibility that the drug was not identical [28].

Protein kinase C , inhibitor

Increased activity of protein kinase C, a family of serine-threonine kinases that regulate various

vascular functions, including contractility, haemodynamics and cellular proliferation, has been implicated in the pathogenesis of diabetic complications including neuropathy [29]. Treatment with a protein kinase C β selective inhibitor ameliorated several neuropathic deficits in experimental diabetic neuropathy [30]. Clinical trials using this agent are currently underway.

C-peptide

Recent studies suggest that C-peptide shows specific binding to cell membrane binding sites and augments skin microcirculation in type 1 diabetic patients [31], possibly via an increase in both nitric oxide production and Na^+,K^+-ATPase activity [32]. In experimental diabetic neuropathy, C-peptide administration prevented the NCV deficit, axonal atrophy, and paranodal swelling and demyelination, and produced an increase in Na^+,K^+-ATPase activity and phosphorylation of the insulin receptor [33]. A pilot study showed an improvement in small fibre sensory and autonomic function in type 1 diabetic patients [34]. Phase II and phase III trials in diabetic neuropathy are needed to confirm these preliminary data.

Symptomatic treatment of painful neuropathy

Painful symptoms in diabetic polyneuropathy may constitute a considerable management problem. The efficacy of a single therapeutic agent is not the rule, and simple analgesics are usually inadequate to control the pain. Therefore, various therapeutic schemes have been previously proposed, but none has been validated. Nonetheless, there is agreement that patients should be offered the available therapies in a stepwise fashion. Effective pain treatment considers a favourable balance between pain relief and side effects without implying a maximum effect.

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The possible treatments are summarized in *Table II*. Prior to any decision regarding the appropriate treatment option, the diagnosis of the underlying neuropathic manifestation allowing estimation of its natural history should be established. In contrast to the agents that have been derived from the pathogenetic mechanisms of diabetic neuropathy, those used for symptomatic therapy were designed to modulate the pain without favourably influencing the underlying neuropathy. A number of trials have been conducted to evaluate the efficacy and safety of these drugs, but only a few have included large patient samples.

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The relative benefit of an active treatment over a control in clinical trials is usually expressed as the relative risk, the relative risk reduction or the odds ratio [50]. However, to estimate the extent of a therapeutic effect (i.e. pain relief) that can be translated into clinical practice, it is useful to apply a simple measure that serves the physician to select the appropriate treatment for the individual patient. Such a practical measure is the 'number needed to treat' (NNT), i.e. the number of patients who need to be treated with a particular therapy to observe a clinically relevant effect or adverse event in one patient [50, 51]. This measure is expressed as the reciprocal of the absolute risk reduction, i.e. the difference between the proportion of events in the control group (Pc) and the proportion of events in the intervention group (Pi): NNT = 1/(Pc–Pi). The 95% confidence interval (CI) of NNT can be obtained from the reciprocal value of the 95% CI for the absolute risk reduction. The NNT and NNH (number needed to harm) for the individual agents used in the treatment of painful diabetic neuropathy are given in *Table II*.

New drugs for treatment of painful neuropathy

Selective serotonin reuptake inhibitors (SSRI)

Psychotropic agents, among which antidepressants have been evaluated most extensively, have constituted an important component in the treatment of chronic pain syndromes for more than 30 years. Several authors consider the tricyclic antidepressants (TCA) to be the drug

Table II: *Treatment options for painful diabetic neuropathy.*

Approach	Compound/measure	Dose per day	Remarks	NNT	Author
Optimal diabetes control	Diet, OAD, insulin	Individual adaptation	Aim: HbA_{1c} <7.0%	—	
Pathogenetically oriented treatment	α-Lipoic acid (thioctic acid)[a]	600 mg i.v. infusion 1200–1800 mg orally	Duration: 3 weeks AE rare	4.0[b]	Ziegler et al. [22]
Symptomatic treatment	*TCA*				
	Amitriptyline	(10–)25–150 mg	NNMH: 15	3.0/2.0	Max et al. [35]
	Desipramine	(10–)25–150 mg	NNMH: 24	2.2/5.0	Max et al. [35]
	Imipramine	(10–)25–150 mg	CRR	1.4/1.7/3.0	Sindrup [36]
	Clomipramine	(10–)25–150 mg	NNMH: 8.7	2.1	Sindrup [36]
	Nortriptyline	(10–)25–150 mg	+ Fluphenazine	1.6[c]	Gomez-Perez et al. [37]
	SSRI				
	Citalopram	40 mg	Small sample	7.7	Sindrup et al. [38]
	Paroxetine	40 mg	CRR	2.9	Sindrup et al. [39]
	Other antidepressants				
	Venlafaxine	150–220 mg	Abstract	4.5	Kunz et al. [40]
	NMDA antagonists				
	Memantine	40 mg	Abstract	6.7	Pellegrino [41]
	Ion channel blockers				
	Carbamazepine	200–800 mg	NNMH: 15	3.3	Rull et al. [42]
	Gabapentin	900–3600 mg	Fewer AE	3.7	Backonja et al. [43]
	Mexiletine	675 mg	Modest effect	10.3	Oskarsson et al. [44]
	Weak opioids				
	Tramadol	50–400 mg	NNMH: 7.8	3.1	Harati et al. [45]
	Local treatment				
	Capsaicin (0.075%) cream	q.i.d.Topically	Max. duration: 8 weeks	4.2[d]	Zhang & Li Wan Po [46]
Ultima ratio in pain resistant to standard pharmacotherapy	*Strong opioids*	Individual adaptation	Potential of dependence		
	ESCS		Invasive, complications	—	Tesfaye et al. [47]
Physical therapy	TENS, medical gymnastics		No AE	—	Kumar & Marshall [48]
	Balneotherapy, relaxation therapy		No AE	—	
	Acupuncture		Uncontrolled study	—	Abuaisha et al. [49]

[a]Available only in some countries; [b] 30% symptom relief; [c]combined with fluphenazine; [d]analgesic effectiveness as ascertained by the physician.
NNT, number needed to treat; OAD, oral antidiabetic drugs; AE, adverse events; NNMH, number needed for major harm; CRR, concentration-response relationship; ESCS, electrical spinal cord stimulation; TENS, transcutaneous electrical nerve stimulation.

treatment of choice for neuropathic pain [52, 53]. However, their limiting factors are the relatively high rates of adverse effects and several contraindications. Consequently, it has been considered whether patients who do not tolerate TCA due to adverse events could alternatively be treated with selective serotonin reuptake inhibitors (SSRI). SSRI specifically inhibit presynaptic reuptake of serotonin but not norepinephrine, and, unlike TCA, they lack the postsynaptic receptor blocking effects and quinidine-like membrane stabilization.

Three studies showed that treatment with paroxetine [39] and citalopram [38], but not fluoxetine [35], resulted in significant pain reduction. Paroxetine appeared to influence both steady and lancinating pain qualities [39]. The therapeutic effect was observed within 1 week and was dependent on the plasma levels, being maximal at concentrations of 300–400 nmol/l. Besides the relatively low rates of adverse events, the advantage of SSRI compared with TCA is the markedly lower risk of mortality due to overdose [54]. However, a recent case-control study suggested that SSRI moderately increased the risk of upper gastrointestinal bleeding to a degree roughly equivalent to that with low-dose ibuprofen. The concurrent use of non-steroidal anti-inflammatory drugs or aspirin greatly increases this risk [55].

Venlafaxine

Venlafaxine is an antidepressant that inhibits the reuptake of serotonin, norepinephrine and, weakly, dopamine, but unlike TCA, it does not

block the muscarinic, histaminergic and adrenergic receptors. It has been suggested that drugs with a balanced inhibition of serotonin and norepinephrine, but without the postsynaptic and quinidine-like effects of TCA, could exert similar effects but be better tolerated [56]. In a 6-week trial including 244 patients, the analgesic response rates were 56%, 39% and 34% in patients given venlafaxine 150–225 mg, venlafaxine 75 mg and placebo, respectively. Because patients with depression were excluded, the effect of venlafaxine 150–225 mg was attributed to an analgesic, rather than to an antidepressant, effect. The most common adverse effect was nausea [40].

Gabapentin

Gabapentin is an anticonvulsant structurally related to γ-aminobutyric acid, a neurotransmitter that plays a role in pain transmission and modulation. The exact mechanisms of action of this drug in neuropathic pain are not fully elucidated but among others involve the interaction with the system L-amino acid transporter and high-affinity binding to the α-2-Δ-subunit of voltage-activated calcium channels. The antihyperalgesic properties of gabapentin are at least partially modulated through spinal cord mechanisms [43].

In an 8-week multicentre dose-escalation trial including 165 diabetic patients with painful neuropathy, 60% of the patients on gabapentin (3600 mg/day achieved in 67%) had at least moderate pain relief compared with 33% on placebo. Furthermore, gabapentin treatment was associated with improvement in quality of life. Dizziness and somnolence were the most frequent adverse events in about 24% and 23%, respectively, of the patients treated with gabapentin [43].

A 6-week study comparing the efficacy of gabapentin (1800 mg/day achieved in 65%) with amitriptyline showed at least moderate pain relief in 52% and 67% of the patients, respectively [57]. Thus, no significant difference was noted between the two treatments, but given the small patient sample (n = 28), the probability of a type II (β) error was high.

Gabapentin has been suggested to be the preferred drug for patients in whom TCA are contraindicated or who do not tolerate their adverse effects [58].

Tramadol

Tramadol acts directly via opioid receptors and indirectly via monoaminergic receptor systems. Because the development of tolerance and dependence during long-term tramadol treatment is uncommon and its abuse liability appears to be low, it is an alternative to strong opioids in neuropathic pain [53].

Tramadol (up to 400 mg per day orally, mean dose 210 mg per day) has been studied in a 6-week multicentre trial including 131 patients suffering from painful diabetic neuropathy [45]. Pain relief was obtained in 44% of patients on tramadol vs. 12% on placebo. The most frequent adverse events were nausea and constipation. The NNH of 7.8 for dropouts due to adverse events was relatively low, indicating significant toxicity.

In a 4-week study of patients with painful neuropathy of different origins, one-third of which was due to diabetes, tramadol significantly relieved pain (NNT 4.3 [2.4–20]) and mechanical allodynia [59].

One conceivable mechanism for the favourable effect of tramadol could be a hyperpolarization of postsynaptic neurons via postsynaptic opioid receptors. Alternatively, the reduction in central hyperexcitability by tramadol could be due to a monoaminergic or a combined opioid and monoaminergic effect [53].

Trials to assess equivalence (e.g. vs. antidepressants) should clarify the relative potency and toxicity of tramadol in painful neuropathy.

N-methyl-D-aspartate (NMDA) receptor antagonists

Dextromethorphan

Inhibition of *N*-methyl-D-aspartate (NMDA) receptor-mediated central nervous system excitation alleviates neuropathic pain in animal models, but adverse effects of dissociative anaesthetic channel blockers such as ketamine limit clinical application. It has been hypothesized that relatively high doses of low-affinity, non-competitive channel blocking NMDA receptor antagonists such as dextromethorphan may have a more favourable therapeutic ratio than dissociative anaesthetic-like blockers [60].

In a 6-week study, 7 out of 13 patients reported moderate or greater relief of pain during dextromethorphan treatment (mean dose 381 mg/day), compared with none taking placebo, giving an NNT of 1.9 (95% CI 1.1–3.7). However, 5 of 31 patients who took dextromethorphan dropped out due to sedation or ataxia during dose escalation [60].

Memantine

In an 8-week multicentre study including 375 patients, the analgesic response rates defined as ≥50% pain relief were 44% in patients given 40 mg of the NMDA receptor blocker memantine, compared with 29% in those given placebo (NNT 6.7). There was no difference between patients treated with memantine 20 mg and placebo. The most frequent adverse effects were diarrhoea in 11% and dizziness in 26% of the patients treated with 40 mg memantine [41]. The NNT for this agent is comparable with that obtained for SSRI.

Conclusions

Although considerable improvement in the quality of randomized clinical trials has recently been achieved, no major breakthrough in terms of long-term slowing of the progression of diabetic neuropathy by drugs derived from the pathogenetic concepts has been demonstrated. Thus, several of the lessons learnt in the past have yet to be incorporated into the designs of future trials. Some of the newer drugs have been evaluated in phase II trials, the results of which require confirmation from large phase III trials. Adequate designs for randomized clinical trials in diabetic neuropathy have to consider particularly the following aspects: type and stage of neuropathy, homogeneity of the study population, outcome measures (neurophysiological markers, intermediate clinical endpoints, ultimate clinical outcomes, quality of life), natural history, sample size and study duration. It has been suggested that these trials should be long enough (3–5 years), adequately large ($n \geq 500$), include patients with mild rather than advanced neuropathy, and aim at clinically meaningful and reliable outcome measures assessed by high-quality standards which are rigorously controlled [61]. It is also conceivable that drugs interfering with the pathogenesis of diabetic neuropathy may be more effective in terms of prevention rather than intervention.

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Despite the recently accelerating publication rate for randomized clinical trials demonstrating significant pain relief with several agents, the symptomatic pharmacological treatment of chronic painful diabetic neuropathy remains a challenge for the physician. A survey of physicians experienced in treating neuropathic pain demonstrated that only a minority would judge their analgesia results as excellent or good with antidepressants (40%), anticonvulsants (35%), opioids (30%) or simple analgesics (18%) [62]. Major limiting factors are still the paucity of adequately large conclusive trials and the relatively high rates of adverse effects for several drug classes. Recent trials evaluating agents such as gabapentin or tramadol have included adequately large patient samples, but the effect on pain was not superior to that obtained with the tricyclic compounds which have been used for many years. Thus, individual tolerability will be a major aspect in the physician's treatment decision.

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There is almost no information available from controlled trials on long-term analgesic efficacy and the use of drug combinations. Combination drug use or the addition of a new drug to a therapeutic regimen may adversely lead to increased drug toxicity or decreased efficacy. Drug interactions should be more predictable based on the knowledge of which compounds induce inhibition or are metabolized by specific cytochrome P450 enzymes [63]. Drug combinations might also include those aimed at symptomatic pain relief and quality of life on the one hand and improvement or slowing the progression of the underlying neuropathic process on the other. Future trials should consider these aspects in order to optimize the current treatment strategies in painful diabetic neuropathy.

References

1. Consensus statement. Report and recommendations of the San Antonio conference on diabetic neuropathy. *Diabetes Care* 1988; 11: 592–7.
2. Thomas PK. Metabolic neuropathy. *J R Coll Physicians London* 1973; 7: 154.
3. Shaw JE, Zimmet PZ. The epidemiology of diabetic neuropathy. *Diabetes Rev* 1999; 7: 245–52.
4. Resnick HE, Vinik AI, Schwartz AV et al. Independent effects of peripheral nerve dysfunction on lower-extremity physical function in old age. The Women's Health and Aging Study. *Diabetes Care* 2000; 23: 1642–7.

5. Forsblom CM, Sane T, Groop PH et al. Risk factors for mortality in Type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia* 1998; 4: 1253–62.
6. Coppini DV, Bowtell PA, Weng C et al. Showing neuropathy is related to increased mortality in diabetic patients — a survival analysis using an accelerated failure time model. *J Clin Epidemiol* 2000; 53: 519–23.
7. Abbott CA, Vileikyte L, Williamson S et al. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diabetes Care* 1998; 21: 1071–5.
8. Chan AW, MacFarlane IA, Bowsher DR et al. Chronic pain in patients with diabetes mellitus: comparison with non-diabetic population. *Pain Clinic* 1990; 3: 147–59.
9. Galer BS, Gianas A, Jensen MP. Painful diabetic neuropathy: epidemiology, pain description, and quality of life. *Diabetes Res Clin Pract* 2000; 47: 123–8.
10. Cameron NE, Cotter MA. Metabolic and vascular factors in the pathogenesis of diabetic neuropathy. *Diabetes* 1997; 46 (suppl 2): S31–7.
11. Cameron NE, Cotter MA, Horrobin DH, Tritschler HJ. Effects of α-lipoic acid on neurovascular function in diabetic rats: interaction with essential fatty acids. *Diabetologia* 1998; 41: 390–9.
12. Hounsom L, Horrobin DF, Tritschler H et al. A lipoic acid-gamma linolenic acid conjugate is effective against multiple indices of experimental diabetic neuropathy. *Diabetologia* 1998; 41: 839–43.
13. Nicolucci A, Carinci F, Cavaliere D et al. A meta-analysis of trials on aldose reductase inhibitors in diabetic peripheral neuropathy. *Diabetic Med* 1996; 13: 1017–26.
14. Nicolucci A, Carinci F, Graepel JG et al. The efficacy of tolrestat in the treatment of diabetic peripheral neuropathy. A meta-analysis of individual patient data. *Diabetes Care* 1996; 19: 1091–6.
15. Dyck PJ, O'Brien PC. Meaningful degrees of prevention or improvement of nerve conduction in controlled clinical trials of diabetic neuropathy. *Diabetes Care* 1989; 9: 649–52.
16. Greene DA, Arezzo JC, Brown MB, Zenarestat Study Group. Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy. *Neurology* 1999; 53: 580–91.
17. Boulton AJM, Levin S, Comstock J. A multicentre trial of the aldose-reductase inhibitor, tolrestat, in patients with symptomatic diabetic neuropathy. *Diabetologia* 1990; 33: 431–7.
18. Sorbinil Retinopathy Trial Research Group. The Sorbinil Retinopathy Trial: neuropathy results. *Neurology* 1993; 43: 1141–9.
19. Goto Y, Hotta N, Shigeta Y et al. Effects of an aldose reductase inhibitor, epalrestat, on diabetic neuropathy. Clinical benefit and indication for the drug assessed from the results of a placebo-controlled double-blind study. *Biomed Pharmacother* 1995; 49: 269–77.
20. The γ-Linolenic Acid Multicenter Trial Group. Treatment of diabetic neuropathy with γ-linolenic acid. *Diabetes Care* 1993; 16: 8–15.
21. Horrobin DF. Essential fatty acids in the management of impaired nerve function in diabetes. *Diabetes* 1997; 46 (suppl 2): S90–3.
22. Ziegler D, Reljanovic M, Mehnert H, Gries FA. α-Lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials. *Exp Clin Endocrinol Diabetes* 1999; 107: 421–30.
23. Tütüncü NB, Bayraktar M, Varli K. Reversal of defective nerve conduction with vitamin E supplementation in Type 2 diabetes. *Diabetes Care* 1998; 21: 1915–8.
24. Malik RA, Williamson S, Abbott C et al. Effect of angiotensin-converting-enzyme (ACE) inhibitor trandolapril on human diabetic neuropathy: randomised double blind placebo controlled trial. *Lancet* 1998; 352: 1978–81.
25. Toyota T, Hirata Y, Ikeda Y et al. Lipo-PGE_1, a new lipid-encapsulated preparation of prostaglandin E_1: placebo- and prostaglandin E_1-controlled multicenter trials in patients with diabetic neuropathy and leg ulcers. *Prostaglandins* 1993; 46: 453–68.
26. Fernyhough P, Tomlinson D. The therapeutic potential of neurotrophins for the treatment of diabetic neuropathy. *Diabetes Rev* 1999; 7: 300–11.
27. Apfel SC, Kessler JA, Adornato BT et al. Recombinant human nerve growth factor in the treatment of diabetic polyneuropathy. *Neurology* 1998; 51: 695–702.
28. Apfel SC, Schwartz S, Adornato BT et al. Efficacy and safety of recombinant human nerve growth factor in patients with diabetic polyneuropathy. *J Am Med Assoc* 2000; 284: 2215–21.
29. Koya D, King GL. Protein kinase C activation and the development of diabetic complications. *Diabetes* 1998; 47: 859–66.
30. Nakamura J, Kato K, Hamada Y et al. A protein kinase C-β-selective inhibitor ameliorates neural dysfunction in streptozotocin-induced diabetic rats. *Diabetes* 1999; 48: 2090–5.
31. Forst T, Kunt T, Pohlmann T et al. Biological activity of C-peptide on the skin microcirculation in patients with insulin-dependent diabetes. *J Clin Invest* 1998; 101: 2036–41.
32. Forst T, Dufayet de la Tour D, Kunt T et al. Effects of proinsulin C-peptide on nitric oxide, microvascular blood flow and erythrocyte Na^+,K^+-ATPase activity in diabetes mellitus. *Clin Sci* 2000; 98: 283–90.
33. Sima AAF. C-peptide deficiency plays a prominent pathogenetic role in type 1 diabetic neuropathy. *Acta Neuropathol* 2000; 99: 459.
34. Johansson B-L, Borg K, Fernqvist-Forbes E et al. Beneficial effects of C-peptide on incipient nephropathy and neuropathy in patients with Type 1 diabetes mellitus. *Diabetic Med* 2000; 17: 181–9.
35. Max MB, Lynch SA, Muir J et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; 326: 1250–6.
36. Sindrup SH. Antidepressants in the treatment of diabetic neuropathy symptoms. Pharmacodynamic, -kinetic, and -genetic aspects. *Dan Med Bull* 1994; 41: 66–78.
37. Gomez-Perez FJ, Rull JA, Dies H et al. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. *Pain* 1985; 23: 395–400.
38. Sindrup SH, Bjerre U, Dejgaard A et al. The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy. *Clin Pharmacol Ther* 1992; 52: 547–52.
39. Sindrup SH, Gram LF, Brosen K et al. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 1990; 42: 135–44.
40. Kunz NR, Goli V, Lei D, Rudolph R. Treating painful diabetic neuropathy with venlafaxine extended release. *Diabetes* 2000; 49 (suppl 1): A165.
41. Pellegrino RG. Memantine reduces neuropathic pain in diabetics. 52nd Annual Meeting of the American Academy of Neurology, San Diego, CA, 2000.
42. Rull JA, Quibrera R, Gonzalez-Millan H, Castaneda LO. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. *Diabetologia* 1969; 5: 215–8.
43. Backonja M, Beydoun A, Edwards KR et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *J Am Med Assoc* 1998; 280: 1831–6.
44. Oskarsson P, Ljunggren J-G, Lins P-E, the Mexiletine

Study Group. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. *Diabetes Care* 1997; 20: 1594–7.
45. Harati Y, Gooch C, Swenson M et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology* 1998; 50: 1842–6.
46. Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin. A meta-analysis. *Eur J Clin Pharmacol* 1994; 46: 517–22.
47. Tesfaye S, Watt J, Benbow SJ et al. Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy. *Lancet* 1996; 348: 1698–701.
48. Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. *Diabetes Care* 1997; 20: 1702–5.
49. Abuaisha BB, Costanzi JB, Boulton AJM. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. *Diabetes Res Clin Pract* 1998; 39: 115–21.
50. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; 318: 1728–33.
51. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *Br Med J* 1995; 310: 452–4.
52. McQuay HJ, Tramer M, Nye BA et al. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; 68: 217–27.
53. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999; 83: 389–400.
54. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. *Br Med J* 1995; 310: 221–4.
55. Abajo FJ, Rodriguez LAG, Montero D. Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *Br Med J* 1999; 319: 1106–9.
56. Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. *Neurology* 2000; 55: 915–20.
57. Morello CM, Leckband SG, Stoner CP et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999; 159: 1931–7.
58. Low PA, Dotson RM. Symptomatic treatment of painful neuropathy. *J Am Med Assoc* 1998; 280: 1863–4.
59. Sindrup SH, Andersen G, Madsen C et al. Tramadol relieves pain and allodynia in polyneuropathy: a randomized, double-blind, controlled trial. *Pain* 1999; 83: 85–90.
60. Nelson KA, Park KM, Robinovitz E et al. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997; 48: 1212–8.
61. Pfeifer MA, Schumer MP, Gelber DA. Aldose reductase inhibitors: the end of an era or the need for different trial designs?. *Diabetes* 1997; 46 (suppl 1): S82–9.
62. Davies HTO, Crombie IK, Lonsdale M, Macrae WA. Consensus and contention in the treatment of chronic nerve-damage pain. *Pain* 1991; 47: 191–6.
63. Virani A, Mailis A, Shapiro LE, Shear NH. Drug interactions in human neuropathic pain pharmacotherapy. *Pain* 1997; 73: 3–13.