Painful Diabetic Neuropathy

Advantage of novel drugs over old drugs?

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Neuropathic pain exerts a substantial impact on quality of life, particularly by causing considerable interference in sleep, daily activities, and enjoyment of life. Chronic neuropathic pain is present in 13–26% of diabetic patients (1–4). In a recent survey from Augsburg, Germany, the prevalence of painful polyneuropathy was found to be 13.3% in diabetic subjects, 8.7% in individuals with impaired glucose tolerance, 4.2% in individuals with impaired fasting glucose, and 1.2% in individuals with normal glucose tolerance (3). Independent factors significantly associated with diabetic painful neuropathy (DPN) were age, weight, and peripheral arterial disease. Pain is a subjective symptom of major clinical importance, since it is often this complaint that motivates patients to seek health care. However, in a survey from the U.K., only 65% of diabetic patients received treatment for their neuropathic pain, although 96% had reported the pain to their physician. Pain treatment consisted of antidepressants in 43.5% of cases, anticonvulsants in 17.4%, opiates in 39%, and alternative treatments in 30% (combinations possible). Whereas 77% of the patients reported persistent pain over 5 years, 23% were pain free over at least 1 year (1). Thus, neuropathic pain persists in the majority of diabetic patients over periods of several years.

MANIFESTATIONS OF PAINFUL NEUROPATHY — Chronic DPN with persistent or episodic pain that typically may worsen at night, and improve during walking, is localized predominantly in the feet. The pain is often described as a deep-seated ache, but there may be superimposed lancination, or it may be of burning thermal quality. In a clinical survey including 105 patients with DPN, the following locations of pain were most frequent: 96% feet, 69% balls of feet, 67% toes, 54% dorsum of foot, 39% hands, 37% plantum of foot, 37% calves, and 32% heels. The pain was most often described by the patients as "burning/hot," "electric," "sharp," "achy," and "tingling," which was worse at night and when tired or stressed (5). The average pain intensity was moderate, ~5.75/10 on a 0–10 scale, with the "least" and "most" pain being 3.6 and 6.9/10, respectively. Evoked pain, such as allodynia (pain due to a stimulus that does not normally cause pain, e.g., stroking) and hyperalgesia (severe pain due to a stimulus that normally causes slight pain, e.g., a pin-prick) may be present. The symptoms may be accompanied by sensory loss, but patients with severe pain may have few clinical signs. Pain may persist over several years (6) causing considerable disability and impaired quality of life in some patients (5), whereas it remits partially or completely in others (7,8), despite further deterioration in small fiber function (8). Pain remission tends to be associated with sudden metabolic change, short duration of pain or diabetes, preceding weight loss, and less severe sensory loss (7,8).

Acute DPN has been described as a separate clinical entity (9). It is encountered infrequently in both type 1 and type 2 diabetic patients presenting with continuous burning pain, particularly in the soles ("like walking on burning sand") with nocturnal exacerbation. A characteristic feature is a cutaneous contact discomfort to clothes and sheets that can be objectified as hypersensitivity to tactile (allodynia) and painful stimuli (hyperalgesia). Motor function is preserved and sensory loss may be only slight, being greater for thermal than for vibratory sensation. The onset is associated with, and preceded by precipitous and severe weight loss. Depression and erectile dysfunction are constant features. Weight loss has been shown to respond to adequate glycemic control, and the severe manifestations subsided within 10 months in all cases. No recurrences were observed after follow-up periods of up to 6 years (9). The syndrome of acute DPN seems to be equivalent to "diabetic cachexia" as described by Ellenberg (10). It has also been described in girls with anorexia nervosa and diabetes in association with weight loss (11).

The term "insulin neuritis" was used by Caravati (12) to describe a case with precipitation of acute DPN several weeks after the institution of insulin treatment. Sural nerve biopsy showed signs of chronic neuropathy with prominent regenerative activity (13), as well as epineurial arteriovenous shunting, and a fine network of vessels, resembling the new vessels of the retina, which may lead to a steal effect rendering the endoneurium ischemic (14). This may occur in analogy to the transient deterioration of a preexisting retinopathy after rapid improvement in glycemic control.

The following findings should alert the physician to consider causes for neuropathy other than diabetes and referral for a detailed neurological workup:

- Pronounced asymmetry of the neurological deficits
- Predominant motor deficits, mononeuropathy, and cranial nerve involvement
- Rapid development or progression of the neuropathic impairments
- Progression of the neuropathy despite optimal glycemic control
- Development of symptoms and deficits only in the upper limbs
- Family history of nondiabetic neuropathy
- Diagnosis of neuropathy cannot be ascertained by clinical examination

The most important differential diagnoses from the general medicine perspec-

Table 1—*Pharmacological treatment options for painful neuropathy*

Approach	Compound/measure	Dose per day	Remarks	NNT
Optimal diabetes control	Diet, oral antidiabetic drugs, insulin	Individual adaptation	Aim: A1C ≤6.5–7%	
Pathogenetically oriented treatment	α-Lipoic acid (thioctic acid)*	600 mg i.v. infusion	Duration: 3 weeks	6.3†
		600–1,800 mg orally	Favorable safety profile	2.8–4.2†
First-line symptomatic treatment				
TCAs	Amitriptyline	(10-)25–150 mg	NNMH: 15	2.1
	Desipramine	(10-)25–150 mg	NNMH: 24	2.2/3.2
	Imipramine	(10-)25–150 mg	CRR	1.3/2.4/3.0
	Clomipramine	(10-)25–150 mg	NNMH: 8.7	2.1
	Nortriptyline	(10-)25–150 mg	Plus fluphenazine	1.2
Selective serotonin norepinephrine reuptake inhibitors	Duloxetine‡	(30-)60–120 mg	NNMH (60 mg): 18	5.3 (60 mg)
			NNMH (120 mg): 9	4.9 (120 mg)
	Venlafaxine	75–225 mg	NNMH (75–225 mg): 21	6.9 (75–225 mg)
			NNMH (150–225 mg): 17	4.6 (150–225 mg)
α$_2$-δ ligands	Pregabalin‡	(50-)300–600 mg	NNMH (300 mg): 23	6.0 (300 mg)
			NNMH (600 mg): 11	4.0 (600 mg)
	Gabapentin	(300-)1,800–3,600 mg	Evidence weaker than for pregabalin	3.8/4.0
Second-line symptomatic treatments				
Local treatment	Capsaicin (0.025%) cream	q.i.d. topically	Maximum duration: 6–8 weeks	
Weak opioids	Tramadol	50–400 mg	NNMH: 7.8	3.1/4.3
Strong opioids	Oxycodone	10–100 mg	Add-on treatment pioid-specific problems	2.6

*Available only in some countries; †≥50% symptom relief after 3 and 5 weeks; ‡licensed in U.S. and European Union; CRR, concentration-response relationship; NNMH, number needed for major harm.

tive include neuropathies caused by alcohol abuse, uremia, hypothyroidism, vitamin B12 deficiency, peripheral arterial disease, cancer, inflammatory and infectious diseases, and neurotoxic drugs.

PHARMACOLOGICAL TREATMENT BASED ON PATHOGENETIC CONCEPTS

Recent experimental studies suggest a multifactorial pathogenesis of diabetic neuropathy. From the clinical point of view, it is noteworthy that based on the various pathogenetic mechanisms, therapeutic approaches could be derived, some of which have been evaluated in randomized clinical trials. These drugs have been designed to favorably influence the underlying neuropathic process, rather than for symptomatic pain treatment. Because in the foreseeable future normoglycemia 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 hyperglycemia. For clinical use, α-lipoic acid is licensed and used for treatment of symptomatic polyneuropathy in several coun-

tries worldwide, whereas epalrestat is marketed in Japan and India.

α-Lipoic acid (thioctic acid)

Accumulating evidence suggests 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. Antioxidant treatment with α-lipoic acid has been shown to prevent these abnormalities in experimental diabetes, thus providing a rationale for potential therapeutic value in diabetic patients. In Germany, α-lipoic acid is licensed and has been used for treatment of symptomatic diabetic neuropathy for over 40 years. According to a meta-analysis comprising 1,258 patients, infusions of α-lipoic acid (600 mg i.v./day) ameliorated neuropathic symptoms and deficits after 3 weeks (15). Moreover, the Symptomatic Diabetic Neuropathy (SYDNEY) 2 trial suggests that treatment for 5 weeks using 600 mg q.d. α-lipoic acid orally reduces the chief symptoms of diabetic polyneuropathy including pain, paresthesias, and numbness to a clinically meaningful degree (16). In a multicenter

randomized double-masked parallel group clinical trial (NATHAN 1), 460 diabetic patients with stage 1 or stage 2a polyneuropathy were randomly assigned to oral treatment with α-lipoic acid 600 mg q.d. ($n = 233$) or placebo ($n = 227$) for 4 years. After 4 years, neuropathic deficits progressed significantly on placebo and improved on α-lipoic acid, and the drug was well tolerated throughout the trial (17). Clinical and postmarketing surveillance studies have revealed a highly favorable safety profile of this drug.

SYMPTOMATIC PHARMACOLOGICAL TREATMENT OF PAINFUL NEUROPATHY

Diabetic painful neuropathy 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 have been validated. Nonetheless, there is agreement that patients should be offered the available therapies in a stepwise fashion. Effective pain treatment consists of a fa-

Table 2—*Treatment of painful neuropathy under consideration of comorbidities, side effects, and drug metabolism*

	Duloxetine	Pregabalin	Tricyclics	Opioids	α-Lipoic acid
Depression	+	n	+	n	n
Obesity	N	−	−	n	n
Generalized anxiety disorder	+	+	NA	NA	NA
Sleep disturbances	+	+	+	+	NA
Coronary heart disease	n	N	−	n	n
Autonomic neuropathy	NA	NA	−	−	+
Fasting glucose	(−)*	n	(−)*	N	n**
Hepatic failure	−	n	§	§	n
Renal failure	−	Adapt dose	§	§	n
Drug interactions	−	n	−	n	n

Effect: +, favorable; −, unfavorable; n, neutral; NA, not available; *slight increase possible; **slight decrease possible; §dependent on individual agent.

vorable balance between pain relief and adverse events without implying a maximum effect (18–21).

The various pharmacological treatment options are summarized in Table 1. The advantages and disadvantages of the various drugs and drug classes used for treatment of DPN under consideration of the various comorbidities and complications associated with diabetes are summarized in Table 2. Before any decision regarding the appropriate treatment, the diagnosis of the underlying neuropathic manifestation should be established (18). 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 favorably influencing the underlying neuropathy (19). A number of trials have been conducted to evaluate the efficacy and safety of these drugs, but only a few included large patient samples.

The relative benefit of active treatment over a control in clinical trials is usually expressed as the relative risk, the relative risk reduction, or the odds ratio. 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 helps 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 (22). The NNTs and numbers needed to harm for the individual agents used in the treatment of DPN are given in Table 1.

Tricyclic antidepressants
Psychotropic agents, among which tricyclic antidepressants (TCAs) have been evaluated most extensively, constitute an important component in the treatment of chronic pain syndromes for >30 years. Putative mechanisms of pain relief by antidepressants include the inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems, and the antagonism of N-methyl-D-aspartate receptor that mediates hyperalgesia and allodynia. Imipramine, amitriptyline, and clomipramine induce a balanced reuptake inhibition of both norepinephrine and serotonin, whereas desipramine is a relatively selective norepinephrine inhibitor. The NNT (95% CI) for a ≥50% pain relief by TCA is 2.4 (2.0–3.0) (20). The number needed to harm is 2.8 for minor AEs and 19 for major AEs (Table 1). Thus, among 100 diabetic patients with neuropathic pain who are treated with antidepressants, 30 will experience pain relief by ≥50%, 30 will have mild AEs, and 5 will discontinue treatment due to severe AEs. The mean NNT for drugs with balanced reuptake inhibition is 2.2, whereas it is 3.6 for the noradrenergic agents (20).

The most frequent AEs of TCAs include tiredness and dry mouth. The starting dose should be 25 mg (10 mg in frail patients) and taken as a single nighttime dose 1 h before sleep. It should be increased by 25 mg at weekly intervals until pain relief is achieved or AEs occur. The maximum dose is usually 150 mg/day. Amitriptyline is frequently the drug of first choice, but alternatively, desipramine may be chosen for its less pronounced sedative and anticholinergic effects. The effect is comparable in pa-

tients with and without depression and is independent of a concomitant improvement in mood. The onset of efficacy is more rapid (within 2 weeks) than in the treatment of depression. The median dose for amitriptyline is 75 mg/day, and there is a clear dose-response relationship. In two studies of imipramine, the dose was adjusted to obtain the optimal plasma concentration of 400–500 nmol/l to ensure maximum effect. The target concentration could be attained in 57% of the patients (20).

The notion that the character of the neuropathic pain is predictive of response, so that burning pain should be treated with antidepressants and shooting pain with anticonvulsants, is obviously unfounded, since both pain qualities respond to TCAs. Most evidence of efficacy of antidepressants comes from studies that have been conducted over only several weeks. However, many patients continue to achieve pain relief for months to years, although this is not true for everyone. Tricyclic antidepressants should be used with caution in patients with orthostatic hypotension and are contraindicated in patients with unstable angina, recent (<6 months) myocardial infarction, heart failure, history of ventricular arrhythmias, significant conduction system disease, and long QT syndrome. Thus, their use is limited by relatively high rates of AEs and several contraindications.

Selective serotonin reuptake inhibitors
Because of the relative high rates of AEs and several contraindications of TCA, it has been questioned whether patients who are unable to tolerate these could alternatively be treated with selective serotonin reuptake inhibitors. These agents specifically inhibit presynaptic reuptake of serotonin, but not norepinephrine, and unlike the tricyclics, they lack the postsynaptic receptor blocking effects and quinidine-like membrane stabilization. Three studies showed that treatment with paroxetine and citalopram, but not fluoxetine, resulted in significant pain reduction. Paroxetine appeared to influence both steady and lancinating pain qualities (20). The therapeutic effect was observed within 1 week and was dependent on the plasma levels, being maximal at concentrations of 300–400 nmol/l. In addition to the relatively low rates of AEs, the advantage of selective serotonin reuptake inhibitors compared with the tricyclic compounds is the markedly lower risk of

mortality due to overdose. However, a recent case-control study suggested that selective serotonin reuptake inhibitors moderately increased the risk of upper gastrointestinal bleeding to a degree approximately equivalent to low-dose ibuprofen. The concurrent use of nonsteroidal anti-inflammatory drugs, or aspirin, greatly increases this risk. Because of these limited efficacy data, selective serotonin reuptake inhibitors have not been licensed for the treatment of neuropathic pain.

Serotonin norepinephrine reuptake inhibitors

Because selective serotonin reuptake inhibitors have been found to be less effective than TCAs, recent interest has focused on antidepressants with dual selective inhibition of serotonin and norepinephrine (serotonin norepinephrine reuptake inhibitors), such as duloxetine and venlafaxine. The efficacy and safety of duloxetine was evaluated in three controlled studies using a dose of 60 and 120 mg/day over 12 weeks (23). In all three studies, the average 24-h pain intensity was significantly reduced with both doses, compared with placebo treatment, the difference between active and placebo achieving statistical significance after 1 week. The response rates defined as ≥50% pain reduction were 48.2% (120 mg/day), 47.2% (60 mg/day), and 27.9% (placebo), giving an NNT of 4.9 (95% CI 3.6–7.6) for 120 mg/day and 5.2 (3.8–8.3) for 60 mg/day (23). The numbers needed to harm based on discontinuation due to AEs were 8.8 (6.3–14.7) for 120 mg/day duloxetine and 17.5 (10.2–58.8) for 60 mg/day (23). Pain severity, rather than variables related to diabetes or neuropathy, predicts the effects of duloxetine in diabetic peripheral neuropathic pain. Patients with higher pain intensity tend to respond better than those with lower pain levels (24). The most frequent AEs of duloxetine (60/120 mg/day) include nausea (16.7/27.4%), somnolence (20.2/28.3%), dizziness (9.6/23%), constipation (14.9/10.6%), dry mouth (7.1/15%), and reduced appetite (2.6/12.4%). These AEs are usually mild to moderate and transient. To minimize these effects, the starting dose should be 30 mg/day for 4–5 days. In contrast to TCAs and some anticonvulsants, duloxetine does not cause weight gain, but a small increase in fasting blood glucose may occur (25).

In a 6-week trial comprising 244 patients, the analgesic response rates were 56, 39, and 34% in patients given 150– 225 mg venlafaxine, 75 mg venlafaxine, 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 AEs were tiredness and nausea (26). Duloxetine, but not venlafaxine, has been licensed for the treatment of DPN.

Calcium-channel modulators (α_2-δ ligands)

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. Among others, they involve an interaction with the system L-amino acid transporters and high affinity binding to the $\alpha2$-δ subunit of voltage-activated calcium channels. In an 8-week multicenter dose escalation trial including 165 patients with DPN, 60% of the patients on gabapentin (3,600 mg/day achieved in 67%) had at least moderate pain relief compared with 33% on placebo. Dizziness and somnolence were the most frequent AEs observed in ~23% of the patients (27).

Pregabalin is a more specific α_2-δ ligand with a sixfold higher binding affinity than gabapentin. The efficacy and safety of pregabalin was reported in a pooled analysis of seven studies over 5–13 weeks in 1,510 patients with DPN. The response rates defined as ≥50% pain reduction were 47% (600 mg/day), 39% (300 mg/day), 27% (150 mg/day), and 22% (placebo), giving an NNT of 4.0, 5.9, and 20.0 (28). The most frequent AEs for 150–600 mg/day were as follows: dizziness (22.0%), somnolence (12.1%), peripheral edema (10.0%), headache (7.2%), and weight gain (5.4%) (29). The evidence supporting a favorable effect in DPN is far more solid, and dose titration is considerably easier for pregabalin than gabapentin, which is frequently underdosed in clinical practice.

Sodium channel blockers

Although carbamazepine has been widely used for treating neuropathic pain, it cannot be recommended in DPN due to the limited available data. Its successor drug, oxcarbazepine (30), as well as other sodium channel blockers, such as topiramate (31) and lamotrigine (32), showed only marginal or no efficacy and, hence, have not been licensed for the treatment of DPN.

Potential systemic AEs associated with intravenous lidocaine have led to the development of a newer and potentially safer agent, the topical lidocaine patch 5% (Lidoderm), a targeted peripheral analgesic. In patients with postherpetic neuralgia, the lidocaine patch 5% has demonstrated relief of pain and tactile allodynia with a minimal risk of systemic AEs or drug interactions (33). Studies in patients with DPN are under way.

Topical capsaicin

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is an alkaloid and the most pungent ingredient in the red pepper. It depletes tissues of substance P and reduces neurogenic plasma extravasation, the flare response, and chemically induced pain. Substance P is present in afferent neurons innervating skin, mainly in polymodal nociceptors, and is considered the primary neurotransmitter of painful stimuli from the periphery to the central nervous system. Several studies have demonstrated significant pain reduction and improvement in quality of life in patients with DPN after 8 weeks of treatment with capsaicin cream (0.075%). Six double-blind placebo-controlled trials (656 patients) were pooled for analysis of neuropathic conditions. The relative benefit of topical capsaicin (0.075%) compared with placebo was 1.4 (95% CI 1.2–1.7) and the NNT was 5.7 (4.0–10.0) (28). Treatment should be restricted to a maximum of 8 weeks, since during this period, no adverse effects on sensory function (due to the mechanism of action) were noted in diabetic patients. However, a skin blister study in healthy subjects showed that there is a 74% decrease in the number of nerve fibers as early as 3 days after topical capsaicin application, suggesting that degeneration of epidermal nerve fibers may contribute to the analgesia induced by the drug (34). This finding questioning the safety of capsaicin in the context of an insensitive diabetic foot limits its use.

Opioids

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. In DPN, tramadol (up to

400 mg/day orally, mean dose: 210 mg/day orally) has been studied in a 6-week multicenter trial including 131 patients (35). Pain relief was 44% on tramadol versus 12% on placebo. The most frequent AEs were nausea and constipation. The number needed to harm of 7.8 for dropouts due to AEs was relatively low, indicating significant toxicity. One conceivable mechanism for the favorable 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.

Most severe pain requires administration of strong opioids, such as oxycodone. Although there is little data available on combination treatment, combinations of different substance classes should be used in patients with pain resistant to monotherapy. Two trials over 4 and 6 weeks have demonstrated significant pain relief and improvement in quality of life after treatment with controlled-release oxycodone, a pure μ agonist, in a dose range of 10–100 mg (mean 40 mg/day) in patients with DPN whose pain was not adequately controlled on standard treatment with antidepressants and anticonvulsants that were not discontinued throughout the trial (36,37). As expected, AEs were frequent and typical of opioid-related AEs. A recent study examined the maximum tolerable dose of a combination treatment of gabapentin and morphine compared with monotherapy of each drug. The maximum tolerable dose was significantly lower and efficacy was better during combination therapy than with monotherapy, suggesting an additive interaction between the two drugs (38). The results of these studies suggest that opioids should be included among the therapeutic options for DPN, provided that careful selection of patients unresponsive to standard treatments, regular monitoring, appropriate dose titration, and management of AEs are ensured. Combination therapy using antidepressants and anticonvulsants may also be useful, particularly if monotherapy is not tolerated due to AEs.

Lacosamide

Lacosamide is a novel anticonvulsant that selectively enhances the slow inactivation of voltage-dependent sodium channels, but in contrast to the aforementioned sodium channel blockers, does not influence the fast sodium channel inactivation. Its second putative mechanism is an interaction with a neuronal cytosolic protein, the collapsin response mediator protein 2 (crmp-2), which plays an important role in nerve sprouting and excitotoxicity. Lacosamide has been evaluated in several studies in DPN, three of which have been published (39–41). In a phase II trial, lacosamide ($n = 60$) (100–400 mg/day or maximal tolerated dose) was compared with placebo treatment ($n = 59$). The pain relief on the Likert scale was -1.21 points with lacosamide and -0.87 points with placebo ($P = 0.039$). Most frequent AEs versus placebo were headache (18 vs. 22%), vertigo (15 vs. 8%), and nausea (12 vs. 7%). However, the drug was not approved by the Food and Drug Administration and European Medicines Agency for DPN in 2008, but further clinical trials may follow in the future.

CONCLUSIONS — Advanced knowledge in neurobiology of neuropathic pain and an increasing perception of the commercial value of analgesic agents have led to a burst of research into novel pharmaceutical approaches. According to a recent review (42), at least 50 new molecular entities have reached the clinical stage of development, including glutamate antagonists, cytokine inhibitors, vanilloid-receptor agonists, catecholamine modulators, ion-channel blockers, anticonvulsants, opioids, cannabinoids, COX inhibitors, acetylcholine modulators, adenosine receptor agonists, and several miscellaneous drugs. Eight drugs are presently in phase III trials. Strategies that may show promise over existing treatments include topical therapies, analgesic combinations, and, in the future, gene-related therapies. Although several novel analgesic drugs have recently been introduced into clinical practice, the pharmacologic treatment of chronic DPN remains a challenge for the physician. Individual tolerability remains a major aspect in any treatment decision. Whether the efficacy and safety of the newer and older compounds differ has not been systematically addressed in comparative trials, but clinical experience indicates that the rates of AEs of the newer compounds may be lower than those of the older ones, such as tricyclic antidepressants. Almost no information is available from controlled trials on long-term analgesic efficacy. Only a few studies have used drug combinations, indicating that the latter may result in enhanced efficacy.

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