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REVIEW

Advances in the management of diabetic neuropathy

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ABSTRACT

The authors review current advances in the therapy of diabetic neuropathy. The role of glycemic control and management of cardiovascular risk factors in the prevention and treatment of neuropathic complications are discussed. As further options of pathogenetically oriented treatment, recent knowledge on benfotiamine and alpha-lipoic acid is comprehensively reviewed. Alpha-lipoic acid is a powerful antioxidant and clinical trials have proven its efficacy in ameliorating neuropathic signs and symptoms. Benfotiamine acts via the activation of transketolase and thereby inhibits alternative pathways triggered by uncontrolled glucose influx in the cells comprising polyol, hexosamine, protein-kinase-C pathways and formation of advanced glycation end products. Beyond additional forms of causal treatment, choices of symptomatic treatment will be summarized. The latter is mostly represented by the anticonvulsive agents pregabalin and gabapentin as well as duloxetine widely acknowledged as antidepressant. Finally, non-pharmacological therapeutic alternatives are summarized. The authors conclude that combination therapy should be more often suggested to our patients; especially the combination of pathogenetic and symptomatic agents.

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Insulin, oral and injectable antidiabetic agents, lipid-lowering, anti-platelet agents as well as antihypertensive drugs are cornerstones of diabetes management and are all considered as pathogenetically oriented agents. Similarly, pathogenetically oriented, disease-modifying drugs should be considered in the therapy of diabetic neuropathy when objective signs hinting to neuropathic damage such as sensory loss, areflexia and abnormal results of qualitative sensory testing (QST) are present. In a typical diabetic patient, pain, paresthesias, sensory loss and autonomic dysfunction might usually be present as well as key symptoms of neuropathy. However, in patients with small-fiber neuropathy suffering from neuropathic pain, typical clinical measures of nerve damage are often absent. Neuropathic pain should be alleviated with symptomatic agents and as pain is to consider clear evidence of neural injury, causal therapy is also justified for the treatment of painful diabetic neuropathy.[1] Therefore, the therapy of diabetic neuropathy should often consist of a combination of

TABLE I.—*Recommended therapeutic interventions and medications for the treatment of diabetic neuropathy.*

Pathogenetic-oriented interventions and medications:
– treatment of hyperglycemia
– management of risk factors, lifestyle modification
– benfotiamine
– alpha-lipoic acid
Symptomatic medications:
– gabapentin
– pregabalin
– duloxetine

pathogenetic oriented, casual treatment and symptomatic agents (Table I).

Pathogenetic oriented treatment of diabetic neuropathy

The rationale for pathogenetic oriented casual therapy is to delay, stop or even reverse the development of neural injury and indirectly to ameliorate the symptoms of neuropathy. Causal therapy covers optimal glycemic control, managing cardiovascular risk factors and the administration of alpha-lipoic acid, benfotiamine as well as aldose-reductase inhibitors.[1] It should be noted that administration of symptomatic agents is associated with pain relief, but in contrast to disease-modifying causal therapy, the progression of diabetic neuropathy is not affected.

Treatment of hyperglycemia

It has been widely accepted that the development and progression of specific late microvascular complications in diabetes such as retinopathy, nephropathy and neuropathy are closely associated with long-term glycemic control. The better the glycemic control, the lower the incidence of these complications and, on the contrary, inadequate glycemic control may contribute to the development of microvascular complications. As for diabetic neuropathy, this association is clear in type 1 but more complex in type 2 diabetes.[2] Some experts suggested that diabetic neuropathy should be considered as two diseases rather than one.[3] Notably, several clinical trials demonstrated the benefit from enhanced glucose control in type 1 diabetes, whereas this benefit was much more modest in type 2 diabetes. Eventually, evidences are available that other factors such as obesity, hypertension, dyslipidemia, insulin resistance, inflammation may also play a role in the pathomechanism of neuropathy leading to novel therapeutic approaches for preventing or treating diabetic neuropathy in type 2 diabetes.[2, 3]

Although the association between glycemic control and microvascular complications was documented by different prospective clinical studies,[4-6] strong evidences emerged from two landmark trials that were specifically designed to test the causal relationship of glycemic control to late diabetic complications. The Diabetes Control and Complications Trial (DCCT) was performed in patients with type 1 diabetes and focused mainly on microvascular complications, whereas the United Kingdom Prospective Diabetes Study (UKPDS) was conducted in patients with type 2 diabetes and dedicated primarily to macrovascular complications.[7, 8] Both cohorts were followed after having completed the randomized phase of the trial and the results of the post-trial observational follow-up period were also published.

Diabetes Control and Complications Trial

The DCCT was a multicenter, randomized, controlled clinical trial which compared intensive insulin therapy with conventional insulin regimens in patients with type 1 diabetes.[7] Originally, 1441 patients with type 1 diabetes were randomly assigned to either intensive or conventional insulin therapy and were followed for a mean of 6.5 years between 1983 and 1993. A significant difference in HbA_{1c} values of the groups was found (mean values in patients with intensive treatment 7.4% and that in patients with conventional treatment 9.0%, $P<0.001$). As for neuropathic complications, intensive insulin treatment reduced the prevalence of clinical neuropathy by 64%. The prevalence of nerve conduction abnormalities decreased by 44%. Similarly, the prevalence of test results suggestive of autonomic dysfunction decreased by 53%. As regards cardiovascular autonomic neuropathy (R-R variability, Valsalva ratio, and

blood pressure reduction upon standing up) in general, the number of the abnormalities increased during the study in both groups. Nevertheless, within the secondary intervention group, abnormal R-R variability was less prevalent in the intensively treated group (7% at 4 and 6 years), as well as in the combined cohort (5% *vs*. 9%, P<0.0017) than among conventionally treated patients (14%, P<0.004).[9, 10] The Epidemiology of Diabetes Interventions and Complications (EDIC) trial was a longitudinal observational study involving the cohort from the DCCT.[11] Although the absolute difference in HbA1c values between the groups was only 0.1% (P=0.38) at year 11 in the EDIC study, a consistent salutary effect of intensive insulin therapy was observed. As for neuropathy, signs of both somatic and autonomic neuropathy were less frequently observed in patients with early intensive glycemic control in the DCCT/EDIC follow-up at 8 years.[12] Moreover, the benefits of former intensive insulin treatment persisted for 13-14 years after the DCCT close-out and provide evidence of a durable effect of prior intensive treatment on both peripheral [13] and autonomic neuropathy.[14]

Taken together DCTT documented in patients with type 1 diabetes that intensive (versus conventional) insulin therapy with better glycemic control resulted in a significantly reduced risk of diabetic polyneuropathy and cardiovascular autonomic neuropathy and the prevalence and incidence of both neurological complications remained lower in the formerly intensive (*versus* conventional) therapy group during the EDIC trial at years 16/17.[15] Clearly, better glycemic control provided long-term, sustained beneficial effect on the subsequent risk of late complications. This phenomenon was designated as "metabolic memory" [16] that may occur even in diabetic neuropathy, specifically in cardiovascular autonomic neuropathy and, less evidently, in diabetic polyneuropathy.[17]

The United Kingdom Prospective Diabetes Study

Originally, the UKPDS was intended to explore the relationship of metabolic control to the late complications of type 2 diabetes.[7] The study population consisted of 5102 patients with newly diagnosed type 2 diabetes, finally 4209 patients were randomized either to conventional treatment (target blood glucose level <15.0 mmol/L) or to intensive treatment (target blood glucose level <6.0 mmol/L). Lifestyle modification was primarily used in the former while sulfonylurea or insulin in the latter group. As for antidiabetic treatment, the trial protocol allowed switching patients over to combination therapy. Obese patients (with body weight beyond 120% of the ideal value) were assigned to metformin treatment; this sub-group of patients was analyzed separately. The UKPDS was an open study; the average duration of the prospective study was 10.1 years. As for overall metabolic control, the difference between the median HbA_{1c} levels of patients with conventional *versus* intensive therapy was statistically significant over the entire study (7.9% *vs*. 7.0%; P<0.0001). Intensive treatment reduced the incidence of microvascular endpoints by 25% (P=0.0099), compared to conventional therapy.[18] As for neuropathic complications (as reflected by biothesiometer findings), the relative risk decreased by 16 per cent at the 9th year (P=0.033) and by 40 per cent at the 15th year (P=0.0052). After completing the trial, the investigators decided to monitor the subsequent progress of the study subjects. The overall (mean) duration of observation (intervention + post trial follow-up) was 16.8 years (range: 16 to 30 years). During the decade after the end of the UKPDS, changes in the incidence of microvascular complications were more favorable in the intensive (sulfonylurea/insulin) treatment arm than in the conventional treatment (lifestyle modification) arm.[19] This occurred even though the initial difference observed in the metabolic status of the two groups disappeared rapidly and definitively after the end of the randomized phase of the study. This phenomenon was defined as metabolic legacy.

Cochrane Library data

The enhanced glucose control for preventing and treating diabetic neuropathy was as-

sessed in 2012. According to the high-quality evidences available, improved glycemic control prevents the development of clinical neuropathy and reduces nerve conduction and vibration threshold abnormalities in type 1 diabetic patients. Nevertheless, enhanced glucose control reduces the incidence of clinical neuropathy, although this was not formally statistically significant in type 2 diabetes.[20] The clinical significance of intensive *versus* conventional glucose control in type 1 diabetes was evaluated in 2014. Using intensive glucose control, the risk of developing microvascular complications was reduced compared to conventional treatment; as for diabetic neuropathy the relative risk reduction was as high as 0.35 (95% CI: 0.23 to 0.53, P<0.00001). The benefit was mainly from studies in younger patients at early stages of the disease.[21]

The clinical significance of intensive *versus* conventional glycemic control for treating diabetic foot ulcers (as a consequence of diabetic polyneuropathy) was investigated in both type 1 and type 2 diabetic patients in 2016. Unfortunately, the authors could not find any completed randomized clinical trials with results in this field, therefore, the question remained unanswered.[22] Notably, benefits of intensive glycemic control for preventing or treating diabetic neuropathy need to be weighed against the elevated risk of hypoglycemia including severe episodes as well.[20, 21] To sum up, there is a documented relationship of long-term glucose control to diabetic neuropathy which proved to be robust in type 1 and less definitive in type 2 diabetes. Undoubtedly, near-normoglycemia should be considered as a prerequisite of preventing or treating neuropathic complications in diabetes. Nevertheless, it should be remembered that intensive glucose control may increase the risk a hypoglycemia but it could be diminished by appropriate care with individualized, patients-centered treatment approaches.

Management of risk factors

The pathophysiological mechanisms of diabetic neuropathy are still not completely understood, despite the thorough studies in the recent years. These trials suggest that neither the degree, nor the duration of hyperglycemia explain the development of neuropathy. According to these findings, different risk factors of neuropathy should be studied in the background of pathophysiology of diabetic neuropathy.[23] Type 1 diabetic patients were involved in the Pittsburgh Epidemiology of Diabetes Complication Study III, where the prevalence of cardiovascular autonomic neuropathy and its association with potential risk factors were assessed.[24] The results of this study proved that cardiovascular risk factors such as hypertension, LDL-cholesterol, triglyceride and HDL-cholesterol were independent risk factors of cardiovascular autonomic neuropathy in type 1 diabetic patients. In the EURODIAB IDDM Complications Study, age, duration of diabetes, metabolic control, background or proliferative retinopathy, smoking, low HDL-cholesterol, elevated diastolic blood pressure, elevated fasting triglyceride, previous severe ketoacidosis, and microalbuminuria were associated with development of peripheral neuropathy.[25] During the follow-up of the prospective study [26] adjusting for HbA_{1c} level and diabetes duration, increased total and LDL-cholesterol, triglyceride, von Willebrand factor concentrations, increased body weight and BMI, micro- and macroalbuminuria, hypertension and smoking were all related to the overall prevalence of peripheral neuropathy. Using multivariate regression model, after adjusting results for diabetic complications and all other risk factors, diabetes duration (odds ratio [OR] 1.25), current HbA_{1c} level (OR=1.64) and its change during follow-up (OR=1.44), BMI (OR=1.2), smoking (OR=1.68), the presence of cardiovascular disease (OR=2.12), and retinopathy (OR=1.45) proved to be independent predictors of peripheral neuropathy. The presence of cardiovascular disease doubled the risk of peripheral neuropathy regardless of any other cardiovascular risk factors Multivariate regression analysis showed, that age (OR=1.3/life decade), HbA_{1c} level (OR=1.2%), systolic blood pressure (OR=1.1/10 mmHg), postural dizziness (OR=1.97), distal, symmetrical

polyneuropathy (OR=1.9), and retinopathy (OR=1.7) are independent risk factors of autonomic neuropathy.[27] The presence of abnormal vibration perception threshold was associated with the increases of foot ulceration (4.5-fold), gangrene (3.6-fold), lower extremity bypass surgery or angioplasty (4-fold), and amputation (6-fold). The independent risk factors of abnormal vibration sensation threshold were HbA1c level, hypertension (OR=1.82), smoking (OR=1.85), BMI (OR=1.26), and nephropathy (OR=1.2).[16] The EURODIAB Complications Study further strengthened the relationship between traditional cardiovascular risk factors and peripheral neuropathy. Similar results have been demonstrated in another study where the traditional cardiovascular risk factors showed correlation with the development of neuropathy even in newly diagnosed type 1 diabetic patients.[28] Among type 2 diabetic patients, the Steno 2 study (8-year-long, intensified, multifactorial interventional study) established that the conventional treatment of cardiovascular risk factors had significant impact on the development of cardiovascular autonomic neuropathy, but no effect was found on peripheral neuropathy.[29] These results suggest that complex treatment that was applied in the Steno 2 study should be ensured for patients with type 2 diabetes with increased risk for vascular complications. The Taiwanian Diabetes Study, a retrospective cohort investigation confirmed the relationship between cardiovascular risk factors and diabetic peripheral neuropathy among type 2 diabetic patients. HbA_{1c} and cardiovascular risk factors such as elevated blood pressure, elevated triglyceride, low HDL-cholesterol and high LDL-cholesterol were significantly associated with neuropathy.[30] In a prospective, 10-year-long multicenter, primary care study, Ybarra-Munoz *et al*.[31] showed that diabetic peripheral neuropathy was significantly associated with baseline cardiovascular disease. Using logistic regression analysis, increased risk of peripheral neuropathy was correlated with cardiovascular disease (OR=2.32, 95% CI: 1.03-5.22), diabetes duration and LDL-cholesterol levels. Autonomic and sensory neuropathy were tested in different stages of glucose intolerance in a recently published trial.[32] According to the results, the predictive markers of cardiovascular autonomic neuropathy were age, postprandial glycemia, central obesity, diastolic blood pressure, and QTc interval. In addition, hyperglycemia, age and glycation were the predictors of sensory neuropathy. Roustit *et al.*[33] found that endothelial dysfunction may be the link between neuropathy and cardiovascular risk factors. Flow-mediated dilatation (FMD) was assessed in diabetic patients and FMD strongly associated with neuropathy disability score. In conclusion, earlier and recent studies support the connection between cardiovascular risk factors and the development as well as progression of diabetic neuropathy among diabetic patients. Thus, reduction of the risk factors is an important part of the pathogenetic-oriented treatment of neuropathy.

Vitamin D deficiency and neuropathy

The classical function of vitamin D is related to calcium and phosphate homeostasis and bone mineralization. Several studies have reported an association between vitamin D deficiency and cardiovascular diseases, tumors, autoimmune conditions and overall mortality. Low vitamin D levels may be associated with increased incidence of diabetes and neurodegenerative diseases, as well. The role of vitamin D in the development of neuropathy is still unclear. There are a few data available concerning the relationship between vitamin D and neuropathy.[34] Lee *et al*. examined 51 patients with type 2 diabetes who had deficient 25-hydroxy-vitamin D (25OHD) serum levels and diabetic neuropathy. Following 3 months of vitamin D administration, the score values of neuropathy-induced pain were reduced by 50%.[35] Vitamin D deficiency has been shown to be more common in diabetic patients who have symptoms of distal symmetrical polyneuropathy. In a case study, a 38-year-old male patient is reported with a history of diabetes for 27 years as well as neuropathic symptoms for 10 years that made him unable to work required analgesics for pain management. After the cor-

rection of his vitamin D deficiency (serum 25OHD: 16.5 ng/mL), symptoms of diabetic neuropathy improved dramatically and the dosage of pain killers could be reduced considerably.[36] In another trial, the authors aimed to assess the correlation between neuropathy and vitamin D deficiency.[37] The study tested 87 patients of type 2 diabetes with and 123 without neuropathy. The average serum 25OHD concentration was significantly lower among diabetic patients with neuropathy compared to those without. More than 81% of the patients with neuropathy suffered from vitamin D deficiency, while in the other group, this ratio was 60.4%. Vitamin D deficiency appears to be an independent risk factor for diabetic peripheral neuropathy in some studies, however, further work is required to confirm whether vitamin D supplementation could prevent or delay its onset. Skulli *et al*. assessed serum vitamin D levels in type 2 diabetic patients with and without neuropathy.[38] Patients with peripheral diabetic neuropathy were older and had longer diabetes duration. Vitamin D levels were significantly lower among patients with neuropathy compared to subjects without neuropathy. Moreover, the proportion of patients with vitamin D deficiency, *i.e*. 25OHD <20 ng/mL, was significantly higher in the group with neuropathy. Ahmadieh *et al*.[39] investigated the relationship between 25OHD levels and microvascular complications in patients with type 2 diabetes. Diabetic neuropathy was evaluated using the UK screening score. Mean 25OHD levels were lower in subjects with diabetic neuropathy compared to those without the diseases. Furthermore, using a cut off value of 20 ng/mL for 25OHD, diabetic neuropathy was more prevalent in subjects with vitamin D deficiency than those with levels above ≥20 ng/mL (63% *vs*. 42%, P=0.03). After adjustment for HbA_{1c}, age, smoking, BMI and duration of diabetes in a logistic regression model, diabetes duration and 25OHD levels were significant predictors of diabetic neuropathy. The potential role of vitamin D deficiency was investigated in the development of diabetic foot ulcers as well.[40] The study was conducted in 162 diabetic patients without and 162 with foot ulcers. Lower 25OHD levels were found in patients with diabetes having foot ulcers than in those without. This observation may raise questions about the role of vitamin D deficiency in the development of diabetic plantar ulcers. However, further clinical trials must be conducted to confirm these data. These studies suggest a potential association between vitamin D deficiency and diabetic peripheral neuropathy in patients with type 2 diabetes, but no definite conclusion has been reached. Based on a recently published meta-analysis, the above data have been corroborated, and vitamin D seems most likely to play a significant role in the development of peripheral neuropathy in type 2 diabetic patients.[41] In summary, these data raise the possibility that vitamin D supplementation may be an effective adjuvant therapy for alleviating neuropathic pain and for slowing or inhibiting/stopping the progression of neuronal damage. It may be important to consider vitamin D deficiency in the management of neuropathy, whether or not with symptoms, and to supplement vitamin D when necessary.

Benfotiamine

Thiamine (TH), vitamin B_1, plays a major role in cellular metabolism. In its active form of TH diphosphate, it serves as cofactor for several enzymes involved in the synthesis of neurotransmitters, antioxidant substances, nucleic acids and glucose metabolism. One of these enzymes is the transketolase (TK), plays a major role in glucose metabolism.[42] The TH prodrug benfotiamine, is an S-acyl TH derivative [43] with a superior bioavailability to TH hydrochloride and is therefore preferred for clinical use to treat TH deficiencies. Benfotiamine, as an activator of TK, directs glucose substrates to the pentose phosphate pathway which represents a non-toxic degradation path. As a consequence, a reduced concentration of glycolysis' intermediate products and subsequently a decreased flux through the four hyperglycemia-induced pathways occurs.[44, 45] For benfotiamine, direct antioxidant effects have also been described.[46] By means of above mentioned mechanisms, TH and ben-

fotiamine could reduce the development of diabetic complications including neuropathy. In a randomized, placebo-controlled, double-blind study, Haupt *et al.* investigated the efficacy of benfotiamine given over 3 weeks at doses of 400 mg/day to 40 patients with type 1 or type 2 diabetes mellitus and neuropathy.[47] The authors used a neuropathy score according to evaluate symptoms along with the vibration perception threshold. In the group receiving the active drug compared to placebo, a significant improvement in the neuropathy score was observed, while no changes of the tuning fork test occurred. The main effect on symptoms was the decrease in pain. The largest study with benfotiamine was that performed by Stracke *et al.*[48] This was a phase III double-blind, placebo-controlled study in 165 patients with symmetrical, distal diabetic polyneuropathy with type 1 or type 2 diabetes mellitus randomized to one of 3 treatments: benfotiamine 3×200 mg per day, benfotiamine 3×100 mg per day or placebo three times a day for 6 weeks. Results were analyzed in the intension to treat (ITT) and per-protocol (PP) group (N.=133 and N.=124 patients, respectively). The primary outcome parameter Neuropathy Symptom Score (NSS) improved significantly at a benfotiamine dose of 600 mg/day compared to placebo in the PP group, while in the ITT group, the NSS improvement remained slightly above the level of significance (P=0.055). Even though the TSS (Total Symptom Score) improvement was more pronounced at the higher benfotiamine dose and increased with treatment duration, this difference was not significant after 6 weeks of treatment. In the TSS, best results were obtained for the symptom "pain," whereas "paresthesia" showed nearly no effect. Authors also reported a good safety profile of benfotiamine treatment. Besides monotherapy, benfotiamine is applied in combinations. In a double-blind, placebo-controlled study performed by Lederman *et al.*, the effect of a 3-week treatment with either a benfotiamine combination (two capsules four times daily, each capsule containing 40 mg benfotiamine, 90 mg pyridoxine, 0.25 mg cyancobalamin and 2 mg adenosine phosphate) or placebo was investigated in 20 subjects with manifest diabetic neuropathy.[49] A significant improvement in symptoms and vibratory perception threshold in the benfotiamine/vitamin B group compared to placebo was proven. Stracke *et al.* made an intervention over 12 weeks in a double-blind, randomized, placebo-controlled manner in 24 diabetic (type 1 or type 2) patients with diabetic neuropathy.[50] An oral combination of benfotiamine (40 mg), pyridoxine hydrochloride (90 mg) and cyanocobalamin (0.25 mg) was administered; 320 mg benfotiamine/day for the first 2 weeks and 120 mg benfotiamine/day for the last 10 weeks were applied. A significant improvement in nerve conduction velocity in the peroneal nerve and a statistical trend towards improvement of the metatarsal vibration perception threshold were found in the verum *versus* the placebo group. In support of their results, authors showed that a long-term observation of 9 patients with benfotiamine over a period of 9 months reproduced these findings. Winkler *et al.* conducted an open clinical trial on 36 patients with diabetic neuropathy randomized into 3 groups and administered a benfotiamine-vitamin B combination at high doses (corresponding to 320 mg benfotiamine/day), or medium doses (corresponding to 120 mg benfotiamine/day), or benfotiamine alone (150 mg benfotiamine/day) for 6 weeks.[51] For the assessment of neuropathy following parameters were assessed: pain sensation (modified analogue visual scale), vibration sensation and the current perception threshold on the peroneal nerve at 3 frequencies: 5, 250 and 2000 Hz. An overall beneficial therapeutic effect on the neuropathy status was seen in all three groups as soon as after 3 weeks of therapy (P<0.01). The most pronounced changes occurred in the group of patients receiving the high dose of benfotiamine-vitamin B. The authors' conclusion was that benfotiamine is most effective in large doses, but effectiveness was demonstrated also in the lower dosage, monotherapy group. Concluding the trials with benfotiamine, this TH prodrug is preferred for clinical use due to its superior bioavailability and even benfotiamine seems to be most effective in the treatment

of diabetic neuropathy at higher daily doses. For short-term treatments (6 weeks), doses of 600 mg/day are required to alleviate diabetic neuropathy symptoms; while for longer therapy duration (6 months or longer) the dose can be lowered to 300 mg/day.

Alpha-lipoic acid

Oxidative stress, impaired antioxidant defense and subclinical tissue inflammation are decisive factors in the pathogenesis of diabetic neuropathy.[52] Endoneurial blood flow diminishes as an early consequence of these abnormalities. Alpha-lipoic acid (ALA) is the only fat and water-soluble antioxidant. After uptake into cells and tissues, it is reduced to dihydrolipoic acid (DHLA). ALA and DHLA prevent or mitigate diabetic neuropathy through its multiple antioxidant and anti-inflammatory effects. They act as biological antioxidants, as metal chelators, reducing the oxidized forms of other antioxidant agents such as vitamin C and E, increasing the antioxidant superoxide dismutase and glutathione peroxidase content, and modulating the signal transduction of several pathways, like insulin and nuclear factor kappa B.[53, 54] ALA has an insulin-mimetic activity, so as an additional benefit, it may improve glycemic control and lipid profile.[54] ALA has also shown to improve endothelial dysfunction.[55] These effects also restore the nutritive blood supply of neurons.[56] A human study showed a normalization of the increased advanced glycation end products (AGE) formation and a reduction of the hexosamine pathway for combined benfotiamine and ALA therapy.[57] Clinically relevant effects on neuropathic pain are seen after only 3-5 weeks of ALA treatment, which is unexpectedly rapid for an antioxidant. Moreover, compared to the medications currently in use, ALA has shown to be safe, even in patients with renal and liver failure.[53, 58] ALA was parenterally administered in the randomized, placebo-controlled, multicenter ALADIN (Alpha-Lipoic Acid in Diabetic Neuropathy) study. The efficacy and safety of intravenous ALA was evaluated during three weeks in three different doses, namely 1200, 600, and 100 mg in comparison to placebo, in 328 type 2 diabetic patients with symptomatic diabetic polyneuropathy.[59] Significant improvements were documented from baseline TSS (5 points, $P<0.001$ in the 600-mg group; 4.5 points, $P=0.003$ in the 1200-mg group), and there were significant reductions in the individual components of TSS — burning, paresthesia, and numbness — in the 600- and 1200-mg groups. The Hamburg Pain Adjective List proved significant reductions in pain with 600- and 1200-mg treatment groups compared with placebo. The efficacy of the 1200 mg daily dose did not surpass that of the 600-mg dose; however, it was associated with a significantly higher incidence of gastrointestinal adverse reactions. The Symptomatic Diabetic Neuropathy (SYDNEY) Trial was a single-center, randomized, double-blind placebo-controlled trial including 120 type 1 and 2 diabetic patients with symptomatic, distal, sensory-motor neuropathy received either 600 mg ALA during five days a week for three weeks by intravenous infusion, or placebo.[60] The primary endpoint was the change in the TSS. Similar to the results of the ALADIN trial, a significant treatment effect was first noted in the ALA group relative to the placebo group by day 4; there was subsequent steady improvement thereafter. Analyzing the components of TSS separately revealed significant alleviation of all components in the ALA group. Importantly, the Neuropathy Impairment Score (NIS) — a measure of neuropathic damage — also improved significantly compared to placebo. Ziegler *et al*.[61] conducted a meta-analysis of four clinical studies (ALADIN, ALADIN III, SYDNEY, and NATHAN II [Thioctic Acid in Diabetic Neuropathy]) evaluating the efficacy of parenteral ALA therapy in diabetic polyneuropathy. Analyzing the pooled study population revealed that the daily TSS scores and the NIS of patients receiving ALA improved significantly compared to the placebo group. Analyzing the individual components of NIS demonstrated a significant improvement of the most important items, namely of the pin prick test, protective pressure sensation, and the Achilles tendon reflex ($P<0.05$ for all three).

The Oral Pilot (ORPIL) study was a single-center, randomized, double-blind placebo-controlled trial including 24 patients with type 2 diabetes mellitus.[62] In the treatment group ALA 600 mg was administered orally three times daily. After 3 weeks of oral ALA there was a significant reduction in the mean TSS for the feet. Those in the treatment group also reported a significant improvement in the burning component of the TSS. There were no differences in the adverse events between groups, and no specific side effects were reported. The findings of ORPIL study were supported by the SYDNEY 2 trial.[63] It was a randomized, double-blind, placebo-controlled study evaluated the efficacy of oral treatment with ALA in three different doses (600, 1200, and 1800 mg) for 5 weeks. Compared to baseline, the TSS score decreased by 4.9 points (52%) in patients receiving 600 mg, by 4.5 points (48%) in those taking 1200 mg, and by 4.7 points (51%) in subjects treated with 1800 mg ALA daily. The changes seen in the treatment groups were all significant ($P<0.05$) *versus* placebo, but no major between-group differences were detected. However, it was unclear, if the significant improvements seen after 3-5 weeks of oral administration of ALA are clinically relevant. Therefore, Garcia-Ancala *et al*. conducted a multicenter, randomized, withdrawal open-label study over 20 weeks.[64] In this study patients with symptomatic polyneuropathy were initially treated with high dose ALA (3×600 mg orally) for 4 weeks (phase 1). Subsequently, responders were randomized to receive ALA (600 mg/day) or to ALA withdrawal for 16 weeks (phase 2). During the initial 4-week phase, the TSS decreased from 8.9 to 3.5 points in the responders ($P<0.05$). During phase 2, continuation of ALA treatment resulted in a further TSS decline by 32% ($P<0.05$) and it was safe, but the TSS remained unchanged in the ALA withdrawal group. The ALADIN II study evaluated the effect of long-term (2-year) oral dosing with ALA on neuropathic symptoms and electrophysiological parameters.[65] At the beginning, 1200 or 600 mg of intravenous ALA or placebo was administered once daily for 5 consecutive days before the patients were enrolled in the oral treatment groups (receiving 600 or 1200 mg ALA daily) or to the placebo group. Except for a single parameter (distal motor latency measured on the tibial nerve) all electrophysiological indices (conduction velocity in the sensory fibers of the sural nerve, sensory action potential of the sural nerve, conduction velocity of motor fibers in the tibial nerve) improved significantly in both actively treated groups, compared to the placebo group. In the multicenter, randomized, double-blind NATHAN I trial, 460 diabetic patients with polyneuropathy were randomly assigned to oral treatment with 600 mg ALA once daily or placebo for 4 years.[66] Four-year treatment with ALA was associated with improvement of neuropathic impairments, but not nerve conduction attributes. The DEKAN (Deutsche Kardiale Autonome Neuropathie) study evaluated the effects of ALA in 73 patients with cardiovascular autonomic neuropathy.[67] In this 4-month-long study, the subjects with type 2 diabetes were randomized for treatment either with 800 mg/day oral ALA, or with placebo. Autonomic function was evaluated by the spectral analysis of heart rate variability (HRV). Treatment with ALA significantly increased the low-frequency (LF) component. The improvement of HRV by ALA was supported also by an almost significant increase of the high-frequency (HF) component, as well as by the significant increases of time domain parameters. ALA reduced the incidence of postural dizziness, weakness, and syncope significantly, whereas they had become more common in the placebo group. In summary, in patients with advanced polyneuropathy, it is recommended to start treatment with ALA by administering 600-mg daily doses by intravenous infusion, over 5 to 15 days. Subsequently, intravenous administration should be replaced by oral dosing, with 600 mg ALA in most cases. Uninterrupted oral dosing greatly contributes to the preservation of the efficacy of the initial course of infusions. It was proven that alpha-lipoic acid improves symptoms of diabetic polyneuropathy more effectively when clinicians pair this with better glucose control of the patient with diabetes.[68]

Symptomatic treatment

Pain and dysesthesias such as burning sensation and numbness are the leading symptoms that prompt patients with neuropathy to require medical aid. The effective reduction of these chronic symptoms results an improvement of quality of life including comorbidities such as sleeping disorders, anxiety, depression, daily functions, social relations.[69] No doubt that symptomatic treatment is very important and at first is chosen for patients with symptoms and without an objective sign of neuronal damage or deficits. These treatment modalities have no effect on the progressive pathogenesis of neuropathy but exert specific modulating actions on the processes directing to pain. Accordingly, in case of purely symptomatic therapy the progression of neuropathy might be expected; thus, the question raises about the relevance of a combined symptomatic-pathogenesis-based treatment even in patients with symptoms only.[70] Interestingly, the current first-tier symptomatic therapeutic approaches were all originally introduced for use in entirely different disorders than alleviating symptoms, including some antiepileptic and antidepressant substances (Table I). Individual patient factors, such as renal and liver functions, age, disease duration, current medications, comorbidities all should be considered when choosing a symptomatic treatment.[71]

Anticonvulsants

The general beneficial effect of anticonvulsants in painful neuropathy is originated from the reduction of the central hyperexcitability responsible for chronic pain in neuropathy. Carbamazepine was one of the first and previously widely applied anticonvulsant drug in patients with diabetic neuropathy but altogether two placebo-controlled studies were published on that with poor quality of evidence more than 40 years ago.[72] The low efficacy in the routine clinical practice and the high number of side effects resulted in the removal of carbamazepine from the recommended drugs for painful neuropathy. Further antiepileptic drugs like valproic acid, oxcarbamazepine, lacosamide, lamotrigine, and topiramate have been studied in patients with painful diabetic neuropathy. These trials prove marginal efficacy or no effect with relatively high number of adverse events. As the benefit/risk ratio is not in favor, these drugs are not among the recommended first line agents in the treatment in painful diabetic neuropathy. Large evidence base supports the efficacy of two anticonvulsants, gabapentin and pregabalin in the treatment of painful diabetic neuropathy as several randomized placebo-controlled trials were conducted in diabetic patients with these drugs.[73]

Gabapentin

The analgesic effect of gabapentin was proven more than 20 years ago. The symptom alleviation is explained by its binding to the α2-δ subunit of voltage-dependent Ca channels in the cell membranes of presynaptic neurons responsible for pain.[74] This binding results in a reduced Ca influx to presynaptic neurons leading to a less pronounced neurotransmitter release. The reduction of neurotransmitter substance availability moderates the pathogenetic hyperexcitability of neurons involved in the genesis of diabetic neuropathic pain. The first study on diabetic patients [75] had a randomized, double-blind, placebo-controlled design. The 8-week-long double blind phase consisted of a 4-week dose titration period and a 4-week fixed-dose period. During the first 4 weeks, patients received gradually titrated dosages of gabapentin (week 1: 900 mg/day; week 2: 1800 mg/day, week 3: 2400 mg/day and week 4: 3600 mg/day) or placebo. During the second 4 weeks of the treatment phase, patients' treatment remained at their maximum tolerated dosage. There was a significant improvement in the gabapentin group in comparison with placebo groups in mean pain scores from week 2 until week 8. Moreover, the mean sleep interference score decreased as early as at week 1 significantly in gabapentin-treated patients compared to placebo and this difference remained significant till the end of the treatment phase. An enhanced quality of life was clearly

proven by the analysis of secondary outcome measures. In this study, the uptitrated gabapentin monotherapy achieved a rapid onset effect on pain with mild and tolerable adverse effects. Only 900 mg/day of gabapentin was applied in another study in diabetic patients resulting a very poor efficacy supporting the theory that without appropriate uptitration this medication is not effective.[76] Data from 5 randomized, placebo-controlled trials including diabetic patients also revealed the efficacy of gabapentin at doses from 1800 to 3600 mg/day.[77] Several trials compared the effect of gabapentin with the antidepressant amitriptyline in painful diabetic neuropathy. In general, these trials demonstrated greater or equivalent improvement in pain with gabapentin than amitryptilin, moreover gabapentin was better tolerated than amitriptyline in most of the cases.[78] Mild to moderate dizziness, somnolence, ataxia, peripheral edema and fatigue were the most frequent adverse events in the studies with gabapentin. The tolerability was enhanced with extended release gabapentin in patients with painful diabetic neuropathy.[79] The studies reveal that gabapentin has a rapid effect on pain in diabetic patients and the efficacy strongly depends on the gradual, tolerable uptitration of the dose for achieving the desired analgesic effect.

Pregabalin

Pregabalin has a higher potency to bind to the similar α2-δ subunit in the presynaptic membrane than gabapentin. It has a linear absorption in the therapeutic dose range (150-600 mg/day) with a rapid onset of action.[80] This pharmacokinetic profile results a stable, non-variable effect and ensures an easy dosing without a long titration process. Several important prospective, double blind trials in patients with diabetic painful neuropathy provided the data between 2004 and 2008 about the efficacy of different doses of pregabalin. A significant reduction of the pain intensity and other secondary variables were observed by the end of the first week and this effect was consequently kept until the final week of the trials. In general, the 300 and 600 mg daily doses had significant response in comparison with placebo.[81] A 75 mg daily dose had no or moderate effect. The higher doses were associated with a higher incidence of adverse events including moderate severity of somnolence, weight gain and dizziness but relatively low number of pregabalin treated diabetic patients discontinued treatment due to safety reasons.[82] The rapid-onset effect of pregabalin and the considerable reduction of pain, sleeping disorders, anxiety and further quality of life parameters also explains the high completion rate of the studies. A cross-over double blind study compared the efficacy and safety of pregabalin and amitriptylin in patients with painful diabetic neuropathy.[83] The evaluation of pain scores showed no significant difference between treatments and the improvement with both agents was seen from the first week. More patients on pregabalin preferred the treatment and adverse events with amitriptyline were more frequent. A meta-analysis of 19 randomized placebo-controlled trials of pregabalin for peripheral neuropathic pain conditions, including diabetic peripheral neuropathy revealed that the effect of pregabalin is irrespective of the length of time since the onset of neuropathic pain.[84] Pooled data from 11 placebo-controlled trials elucidated that pregabalin was effective in diabetic patients with both moderate and severe baseline pain.[85] Patients with more severe pain showed greater improvements, so severity of pain predicted the therapuetic response of pregabalin. From the available studies, it is evident that pregabalin has a rapid onset, characteristic, significant effect in painful neuropathy. Its efficacy, simple dosing, safety and tolerability explain that pregabalin is recommended as the preferred α-2-δ agonist in the treatment of painful neuropathy in dose from 300-600 mg/day.[86]

Antidepressants

Although chronic pain frequently causes depression and depression can be manifested in chronic painful symptoms, the main effect of antidepressants on painful neuropathy is more than repairing mood.[87] The efficacy of several

antidepressants was proven in patients with painful neuropathy even without depressive symptoms. Their effect is explained by the inhibition of the hyperexcitability with activation of the endogenous pain inhibitory system in the spinal cord. The activation is achieved by the inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems responsible for pain alleviation leading to an increased availability of these neurotransmitters. A further beneficial antidepressant effect could be an action on opioid, adrenergic, serotonin, γ-Aminobutyric acid (GABA) and N-Methyl-D-Aspartate receptors. Tricylic antidepressants (TCA) with balanced reuptake inhibition of both norepinephrine and serotonin were among the first recommended options for treatment of painful neuropathy for many years including amitriptyline, clomipramine, desipramine, imipramine, maprotiline and nortryptyline. Although the efficacy of TCA-s is proven, the high rate of adverse events restricts their application. The most frequent side effects are central or anticholinergic, including dry mouth, constipation, sweating, blurred vision and orthostatic hypotension with the risk of falls particularly in elderly patients.[88] Side effects like sedation and tiredness necessitates TCA administration in the evening. Amitriptyline is the most widely used agent from tricyclic agents nowadays for painful diabetic neuropathy.[89] Selective serotonin reuptake inhibitors, such as fluoxetine, paroxetine, citalopram and escitalopram with much less adverse effects are theoretically well-established medications against painful neuropathy, but the poor efficacy in the published trials does not allow their application with this indication. In the last years, a dual selective serotonin and noradrenaline reuptake inhibitors, mainly duloxetine, are regarded as one of the most efficient and tolerable treatments for pain reduction among patients with diabetic neuropathy.

Duloxetine

The efficacy of duloxetine is due to its selective inhibition of the presynaptic reuptake of both serotonin and norepinephrine in those descending central neuronal tracts that inhibit the pain generation. Selectivity means that duloxetine has no or negligible affinity to dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, or GABA receptors and does not inhibit monoamine oxidase.[90] This selectivity is the key of the low frequency of side effects. Duloxetine does not require a titration and administered once a day due to its linear pharmacokinetics. The efficacy and safety of duloxetine were evaluated in three controlled, double blind studies in diabetic patients over 12 weeks. In all three studies,[91-93] diabetic patients with certain pain scores were included and those with significant depression were excluded. As a common finding, 60 and 120 mg daily doses achieved a significant pain reduction by the first week and this continued throughout the study compared with placebo. Further secondary measures, most of health outcomes and quality of life scores improved significantly for more patients treated with duloxetine 60 and 120 mg/day compared to placebo. The analgesic effect was independent of the antidepressant action in these studies as mood disorder was not present in patients at baseline characteristics. Duloxetine was well tolerated and the rate of discontinuation was generally low. Somnolence, nausea, dry mouth and constipation were the most frequent adverse events with tolerable severity. The conclusions of the randomized early trials suggest that the recommended dose of duloxetine in the management of painful diabetic neuropathy is 60 mg once daily, and some additional benefit may be obtained from doses up to 60 mg twice daily. Longer-term studies of 26 week, 28 week and 52 week durations,[94-96] revealed a consequent efficacy in comparison with placebo or routine treatment of painful diabetic neuropathy. The cardiovascular safety of duloxetine was concluded from a pooled meta-analysis while a small increase in A1C was reported in people with diabetes treated with duloxetine.[73] A retrospective analysis of placebo-controlled duloxetine studies found that pain severity, rather than other variables related to diabetes or neuropathy predicts the

effects of duloxetine in diabetic peripheral neuropathic pain.[97] Patients with higher baseline pain measure tend to respond better than those with lower pain severity. The literature data point to the rapid onset effect of 60 or 120 mg duloxetine in painful diabetic neuropathy with a proven long-term pain reduction.

Other symptomatic agents

Opioids

The opioids play an important role in the treatment of unbearable chronic pain but questions arise about their long-term effect and the risk of sedation, tolerance, addiction or abuse. Tramadol, a synthetic opioid is a centrally acting analgesic with weak μ-opioid receptor agonist activity and inhibition of norepinephrine and serotonin reuptake. It was better than placebo in a randomized placebo-controlled trial of 6 weeks' duration and a 6 months' follow-up in painful neuropathy suggested that symptomatic relief could be maintained for longer duration.[98] In addition, the frequency of side effects was high in the tramadol group. Tapentadol is a centrally active analgesic with a dual mode of action: μ-opioid receptor agonist and norepinephrine-reuptake inhibitor. A randomized-withdrawal, placebo-controlled trial with tapentadol ER concluded that diabetic patients who were randomized to tapentadol ER, more than half of them reported at least a 30% improvement in pain.[99] Oxycodone, a strong μ opioid agonist has a greater availability and potency than morphine, but with less side-effect profile, has also been studied in painful diabetic neuropathy. The controlled release formulation reduced pain intensity in monotherapy or in combination treatment in double-blind trials.[100] Although opioids had significant effects in a few randomized trials their use remains controversial due to the high risk of adverse effects and possible misuse.

Topical agents

The well-known local anesthetic agent, lidocaine is ideal for topical application in patients with painful diabetic neuropathy. A systemic review of 23 studies revealed that the effect of the 5% lidocaine patch was comparable with amitriptyline, gabapentin and pregabalin. Fewer and less severe adverse events were detected in lidocaine-treated patients than is the case for systemic agents.[101] Capsaicin is a potent, highly selective vanilloid receptor subtype 1 agonist that causes depolarization of the neuron and leads to a selective loss of small epidermal fibers. Topical application of capsaicin also proved to be effective in pain relief in diabetic neuropathy Capsaicin cream was more effective than placebo in painful diabetic neuropathy in a meta-analysis of 4 randomized, double-blind, placebo-controlled trials.[102] A recent study indicated that in patients with painful diabetic neuropathy the capsaicin 8% patch provided modest improvements in pain and improved sleep quality compared with a placebo patch. It was well tolerated as systemic adverse events were not present and was not associated with any sensory dysfunction due to neuron loss.[103]

Combination of symptomatic treatments

Combination therapy ensures better efficacy as more agents with different modes of action act on symptoms and improved tolerability because compounds may be employed below their individual dose. Pregabalin and gabapentin were studied in combinations with opioids (morphine, oxycodone). An improvement on pain scores in the combination therapy was found in most of the studies, only the frequencies of side effects limited the extension of applications.[104, 105] The efficacy and safety of the high-dose monotherapy and the average dose of pregabalin and duloxetin in combination was analyzed in the Combo DN study. Patients were randomized at the first period of the study to 300 mg/day pregabalin or 60 mg/day duloxetine dose for 8 weeks. The patients who did not report a ≥30% decrease in mean pain score (non-responders) were treated either with combination therapy (300 mg/day pregabalin + 60 mg/day duloxetine) or a higher dose pregabalin (600 mg/day) or dulox-

etine (120 mg/day) monotherapy for 8 more weeks. Combination therapy was not superior over high-dose monotherapy in pain scores, but further secondary efficacy measures consistently favoured the combination of pregabalin and duloxetine. Safety and tolerability were not affected when 60 mg/day duloxetine and 300 mg/day pregabalin were combined, and adverse events were comparable with high-dose monotherapy.[106] Further evaluation of data showed that in patients with severe pain, the treatment effect trended in favor of high-dose monotherapy, whereas combination therapy appeared to be more beneficial in patients with moderate and mild pain.[107]

Non-pharmacological treatment

Non-pharmacological treatments such as lifestyle modifications (physical exercise, diet, control of risk factors), physiotherapy, surgical treatment, electrical stimulation, magnetic therapy, laser therapy, psychological support, Reiki massage, medical acupuncture, or other alternative therapies, are aiming to relieve the symptoms of painful diabetic neuropathy and to improve quality of life of the patients. During the preparation of the evidence-based guideline of the American Academy of Neurology and sister societies the experts reviewed each article published until 2008, and systematically analyzed all 11 articles scientifically relevant to non-pharmacological therapies.[108] This guideline confirmed the efficacy of electrical stimulation and recommended its use in painful diabetic neuropathy; whereas it could not recommend magnetic field treatment, low-intensity laser therapy, and Reiki therapy due to lack of scientific evidence.[108] Results from recent prospective, randomized, controlled trials published after 2008 have been also included in the present review. Beneficial effects of intensive lifestyle intervention were confirmed in recently published Look AHEAD study enrolling 5145 randomized overweight or obese patients with type 2 diabetes mellitus treated for 9-11 years.[109] Weight reduction and increased physical activity could significantly reduce neuropathic pain quantified by Michigan Neuropathy Screening Instrument (MNSI) questionnaire score during the first year of active treatment and this beneficial effect could be maintained for years. During continuation Look AHEAD study MNSI physical examination score did not differ between active intervention and diabetes support and education control groups 1-2.3 years after the end of the treatment. However, monofilament light touch sensation combined for both toes was significantly ($P<0.008$) better in intensive lifestyle modification group. Long-term aerobic exercise training (4 sessions of 1 hour supervised brisk walking on a treadmill each week) could positively modify both motor and sensory neuromuscular parameters in diabetic patients.[110] The effects of physiotherapy interventions and surgical procedures have been investigated on severe painful diabetic neuropathy. Foot strengthening, stretching and functional training for 12 weeks could slightly improve plantar pressure distribution and foot rollover in patients with diabetic polyneuropathy.[111] Biofeedback method using portable in-shoe foot pressure measurement system reduced high plantar pressure leading to suitable foot off-loading.[112] Off-loading with total contact casting over removable cast walker or therapeutic shoes can also improve wound healing in diabetic foot ulceration according to recent guideline by the Society for Vascular Surgery.[113] However, surgical release and decompression of multiple peripheral nerves at the site of anatomic narrowing is considered unproven by the American Academy of Neurology due to lack of prospective randomized controlled trials.[108, 114] Neither low-intensity laser therapy (905 nm) could decrease the pain scores significantly ($P=0.07$) in a randomized, double-masked, sham therapy-controlled clinical trial,[108, 115] nor anodyne monochromatic infrared photoenergy therapy (890 nm) was effective in measures for pain scores, vibration perception threshold, or quality of life [116] in the treatment of sensory neuropathy of diabetic patients. Repetitive and cumulative exposure to low-frequency pulsed electromagnetic fields could not reduce foot pain due to diabetic peripheral neuropathy in a randomized, double-blind,

placebo-controlled study.[117] The use of static, permanent, magnetic insoles produced slight pain reduction determined by Visual Analogue Scale.[118] Electrical stimulation proved to be effective and recommended for the treatment of painful diabetic neuropathy by the guideline; however the therapeutic benefits differed in various models.[108] For example, the symptoms of patients with painful diabetic neuropathy wearing silver-plated stocking electrodes night-time for 6 weeks did not improve in a double-blind, controlled, cross-over study.[119] Percutaneous electrical stimulation using needle electrodes decreased pain scores, increased physical activity, and improved sense of well-being and quality of sleep in patients with diabetic neuropathy.[120] Transcutaneous electrical nerve stimulation in combination with amitriptyline could also alleviate symptomatic pain.[121] Ten sessions of frequency-modulated electromagnetic neural stimulation (FREMS), lasting up to 3 weeks, caused a small, but significant reduction in Visual Analogue Score pain scores, and increased sensory tactile perception and motor nerve conduction velocity in patients suffering from painful diabetic neuropathy in a randomized, double-blind cross-over clinical study.[122] However, three series of these ten FREMS sessions, applied 3 months apart, did not improve nerve conduction velocity of the peroneal, tibial, or sural nerves in a long-term, randomized, double-blind, placebo-controlled multicenter trial.[123] Although both daytime and night-time pain scores were significantly reduced after the series, this beneficial effect was no longer measurable 3 months after treatment sessions.[123] Electrical stimulation of the dorsal structures of the spinal cord could reduce severe, resistant, painful diabetic neuropathy,[124] and the beneficial effects endured for many years.[125] Recently, a prospective, randomized, two-center clinical study proved that spinal cord stimulation resulted in significant relief of severe lower limb pain not responding to conventional therapy in 59% of patients with diabetic neuropathy within 6 months [126] and this therapeutic effect was sustained for 24 months in the extension phase of the study.[127] Nonetheless, electrical spinal cord stimulation through implanted octapolar lead is suitable only for selected cases due to risk of severe adverse events including subdural hematoma and infections.[126, 127]

TABLE II.—*Possible combinations for the treatment of diabetic neuropathy.*

Possible combinations in the management of diabetic neuropathy
– Combination of pathogenetic-oriented treatments
– Combination of symptomatic treatments
– Combination of pathogenetic-oriented and symptomatic treatments

The rationale for combination treatment diabetic neuropathy

Diabetes mellitus itself is often treated with two or three hypoglycemic agents. In addition, control of hypertension usually requires more than three antihypertensive agents while the use of combinations in lipid-lowering and anti-platelet therapy is also very common. On the contrary, combination therapy of diabetic neuropathy is often neglected. The administration of a single agent in a suboptimal dose and for an insufficient period of time is a usual scenario leading to therapeutic failure. As a consequence, the first agent is replaced by another without the optimization of treatment duration or dosing. In the treatment of diabetic neuropathy as a chronic complication, long-term administration and dose titration is necessary. Moreover, combination therapy of diabetic neuropathy should be much more often applied (Table II). On the one hand, in patients with severe neuropathic damage or foot ulcers, the use of combined pathogenetic oriented agents seems to be reasonable. On the other hand, when painful symptoms are present, combination of pathogenetic oriented and symptomatic therapy is advisable.

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