RECOMMENDATIONS FOR DIABETIC POLYNEUROPATHY TREATMENT

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SUMMARY – Diabetes is a chronic disease that requires continual medical care and patient self-management education in order to prevent acute complications and to reduce the risk of long-term complications. Diabetes is the leading known cause of neuropathy in developed countries, and neuropathy is the most common complication and the leading source of morbidity and mortality in diabetes patients. Diabetic polyneuropathy is primarily symmetric sensory neuropathy, initially affecting distal lower extremities. Patients have evidence of nerve damage at the time their diabetes is diagnosed in 10%-18% of cases, suggesting that even early impairment of glucose handling, classified as prediabetes, is associated with neuropathy. It is important to appreciate that there are other causes of neuropathy; these should be considered if there is any aspect of the history or clinical presentation suggesting features atypical of diabetic neuropathy. Diagnosis of diabetic neuropathy should be established according to clinical manifestations of the disease, laboratory findings (altered glucose metabolism) and results of electrophysiological examinations. Treatment of painful diabetic polyneuropathy rests on a two-pronged approach: modification of the underlying disease and control of pain symptoms. The goals of painful diabetic polyneuropathy pharmacotherapy should be reduction of pain for maximum relief commensurate with acceptable side effects and restoration/improvement in functional measures and quality of life.

Key words: *Diabetic neuropathy – therapy; Pain – therapy; Pain – analysis; Guideline*

Introduction

Diabetes is a chronic disease that requires continual medical care and patient self management education in order to prevent acute complications and to reduce the risk of long-term complications. According to the last diagnostic and classification criteria, the classification of diabetes includes:
1) prediabetes:
   • impaired fasting glycemia
   • impaired glucose tolerance
2) diabetes mellitus type 1
3) diabetes mellitus type 2
4) diabetes due to other causes: genetic β-cell defects, diseases of exocrine pancreas (cystic fibrosis), drug or chemical-induced
5) gestational diabetes

Diagnosis of diabetes should be established according to clinical signs of diabetes and blood tests (fasting plasma glucose, glycosylated hemoglobin and oral glucose tolerance test)[1]. Diabetes is the leading known cause of neuropathy in developed countries, and neuropathy is the most common complication and the leading source of morbidity and mortality in diabetes patients. The prevalence of neuropathy in diabetes patients has been estimated to approximately 20%. Diabetic neuropathy is implicated in 50%-75% of nontraumatic amputations. These conditions are

the consequence of diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervorum). There are many forms of diabetic neuropathy including symmetric polyneuropathy, autonomic neuropathy, radiculopathies, mononeuropathies, and mononeuropathy multiplex[1-3].

Pathophysiology

Generally, vascular complications of diabetes can be divided into microvascular (diabetic nephropathy, neuropathy and retinopathy) and macrovascular (coronary disease, cerebrovascular disease and peripheral artery disease) complications. Risk factors for diabetic neuropathy have not yet been ascertained, but may include advanced age, duration of diabetes, lipotoxicity and glucotoxicity, genetic susceptibility, inflammation, and oxidative stress[1].

The central pathomorphological mechanism of these complications is atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and arterial wall injury in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from low density lipoprotein (LDL) particles accumulate in the endothelial part of the vessel wall. Angiotensin II may promote the oxidation of such particles. Then monocytes infiltrate arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction; these ruptures and bleeding into the plaque are more frequent in diabetic patients. In addition to atheroma formation, there is strong evidence for increased platelet adhesion, hypercoagulability, impaired nitric oxide generation and increased free radical formation as well as altered calcium regulation in diabetic patients[1-3].

Clinical Manifestations

Diabetic polyneuropathy is primarily symmetric sensory neuropathy, initially affecting distal lower ex-

tremities. In 10%-18% of cases, patients have evidence of nerve damage at the time their diabetes is diagnosed, suggesting that even early impairment of glucose handling, classified as prediabetes, is associated with neuropathy. Sensory loss ascends with progression of the disease and, when reaching approximately mid-calf, appears in the hands. This gradual evolution and typical "stocking-glove" sensory loss reflects preferential damage according to axon length; the longest axons are affected first. Motor involvement with frank weakness occurs in the same pattern, but only later and in more severe cases[4].

Diabetic neuropathy affects all peripheral nerves: pain fibers, motor neurons, autonomic nerves. It therefore necessarily can affect all organs and systems since all are innervated. Painful diabetic polyneuropathy (PDN) may result from several varieties of diabetic neuropathy, the most common of which is distal sensory neuropathy. PDN can be further divided into acute and chronic PDN, or into stimulus independent and stimulus evoked PDN. Symptoms usually develop gradually over years and vary depending on the nerve(s) affected[5,6]:

- numbness and tingling of extremities
- dysesthesia (decreased or lost sensation to a body part)
- diarrhea
- erectile dysfunction
- urinary incontinence (loss of bladder control)
- impotence
- facial, mouth and eyelid drooping
- vision changes
- dizziness
- muscle weakness
- difficult swallowing
- speech impairment
- fasciculation (muscle contractions)
- anorgasmia
- burning or electric pain

Different nerves are affected in different ways.

Sensorimotor polyneuropathy

Longer nerve fibers are affected to a greater degree than shorter ones because nerve conduction velocity is slowed in proportion to the nerve length. In this case, decreased sensation and loss of reflexes occurs first in the toes of each foot, and then extends upward. Usu-

ally, this condition is described as glove-stocking distribution of numbness, sensory loss, dysesthesia and nighttime pain. The pain can feel like burning, pricking sensation, achy or dull. Pins and needles sensation is common. Loss of proprioception, the sense of the limb in space, is affected early. These patients cannot feel when they are stepping on a foreign body, like a splinter, or when they are developing a callous from an ill-fitting shoe. Consequently, they are at risk of developing ulcers and infections on the feet and legs, which can lead to amputation. Similarly, these patients can get multiple fractures of the knee, ankle or foot, and develop a Charcot joint. The loss of motor function results in dorsiflexion, contractures of the toes, loss of the interosseous muscle function, and leads to contraction of the digits, so called hammer toes. These contractures occur not only in the foot but also in the hand, where the loss of the musculature makes the hand appear gaunt and skeletal. The loss of muscular function is progressive[4-6].

Autonomic neuropathy

The autonomic nervous system is composed of nerves serving the heart, gastrointestinal system and genitourinary system. Autonomic neuropathy can affect any of these organ systems. The most commonly recognized autonomic dysfunction in diabetics is orthostatic hypotension, or fainting when standing up. In case of diabetic autonomic neuropathy, it is due to the failure of the heart and arteries to appropriately adjust heart rate and vascular tone to keep blood continually and fully flowing to the brain. This symptom is usually accompanied by the loss of the usual change in heart rate seen with normal breathing. These two findings suggest autonomic neuropathy.

Gastrointestinal tract manifestations include delayed gastric emptying, gastroparesis, nausea, bloating, and diarrhea. Because many diabetics take oral medication for their diabetes, absorption of these medicines is greatly affected by the delayed gastric emptying. This can lead to hypoglycemia when an oral diabetic agent is taken before meal and does not get absorbed until hours or sometimes days later, when there is normal or low blood sugar already. Sluggish movement of the small intestine can cause bacterial overgrowth, made worse by the presence of hyperglycemia. This leads to bloating, gas and diarrhea.

Urinary symptoms include urinary frequency, urgency, incontinence, and retention. Again, because of urine retention, urinary tract infections are frequent. Urinary retention can lead to bladder diverticula, stones, and reflux nephropathy[4-6].

Cranial neuropathy

When cranial nerves are affected, oculomotor (3rd) neuropathies are most common. The oculomotor nerve controls all of the muscles that move the eye, with the exception of the lateral rectus and superior oblique muscles. It also serves to constrict the pupil and open the eyelid. The onset of diabetic third nerve palsy is usually abrupt, beginning with frontal or periorbital pain and then diplopia. All of the oculomotor muscles innervated by the third nerve may be affected, except for those that control pupil size. This is because pupillary function within CNIII is found on the periphery of the nerve (in terms of a cross sectional view), which makes it less susceptible to ischemic damage (as it is closer to the vascular supply). The sixth nerve, the abducens nerve, which innervates the lateral rectus muscle of the eye (moves the eye laterally), is also commonly affected but the fourth nerve, the trochlear nerve (that innervates the superior oblique muscle, which moves the eye downward) involvement is unusual. Mononeuropathies of the thoracic or lumbar spinal nerves can occur and lead to painful syndromes that mimic myocardial infarction, cholecystitis or appendicitis. Diabetics have a higher incidence of entrapment neuropathies, such as carpal tunnel syndrome[4-6].

Complications

Diabetic neuropathy is frequently insidious in onset and can lead to the formation of foot ulcers and muscle and joint disease. Progressive sensory loss predisposes to ulcer formation. Foot ulcers are usually classified into two groups: acute ulcers secondary to dermal abrasion from poorly fitting shoes; and chronic plantar ulcers occurring over weight-bearing areas. Chronic ulceration is probably multifactorial, due to a combination of diabetic neuropathy (with decreased pain sensation), autonomic dysfunction and vascular insufficiency.

Distal motor axonal loss results in atrophy of intrinsic foot muscles and an imbalance between the strength in toe extensors and flexors. This ultimately

Table 1. The most frequent causes of polyneuropathy

1) Metabolic: Diabetes mellitus Uremia Hypothyroidism Porphyria Amyloidosis Vitamin B deficiency Folic acid deficiency	Cervical or lumbar radiculopathy Complex regional pain syndrome Spinal cord injury Stump pain **4) Infections:** Herpes zoster HIV Borelliosis Epstein Barr virus

2) Toxic:
Alcohol
Medications:
  amiodarone
  cisplatin
  dapsone
  d4T (stavudine)
  ddC (zalcitabine)
  ddL (didanosine)
  disulfiram
  FK506
  hydralazine
  isoniazid
  metronidazole
  nitrofurantoin
  paclitaxel
  phenytoin
  vincristine
Heavy metals:
  arsenic
  lead
  mercury
  thalium
	5) Immune:
	Guillain-Barré syndrome
	Multiple sclerosis
	Monoclonal gammopathies
	Eosinophilia-myalgia syndrome
	
	6) Genetic:
	Fabry disease
	HSMN (hereditary sensorimotor neuropathy)
	
	7) Vascular:
	Cerebrovascular disease (ischemic and hemorrhagic stroke)
	Vasculitis
	
	8) Carcinomatous:
	Paraneoplastic syndrome
	
	9) Diverse:
	Syrinx
	Epilepsy
	ALS
	
	10) Head and face neuralgia:
	Trigeminal
	Glosopharyngeal

3) Traumatic: Carpal tunnel syndrome	Hypoglossal

leads to chronic metatarsal-phalangeal flexion (claw-toe deformity), which shifts weight to the metatarsal heads. This weight shift results in the formation of calluses that can fissure, become infected and ulcerate. There may also be other arthropathic changes including collapse of the arch of the midfoot and bony prominences, leading to Charcot arthropathy, fragmentation and sclerosis of bone[4-6].

Differential Diagnosis

It is important to appreciate that there are other causes of neuropathy, these should be considered if there is any aspect of the history or clinical presentation suggesting features atypical of diabetic neuropathy (e.g., signs of a systemic disease: vascular, metabolic, toxic, carcinomatous, infectious, immune, genetic, etc.) (Table 1)[7-9].

Diagnostic Criteria

The earliest signs of diabetic neuropathy probably reflect the gradual loss of integrity of both large myelinated and small myelinated and unmyelinated nerve fibers. The loss of vibratory sensation and altered proprioception reflect large-fiber loss. Impairment of

pain, light touch and temperature is secondary to the loss of small fibers. Decreased or absent ankle reflexes occur early in the disease, while a more widespread loss of reflexes and motor weakness are late findings. Diagnosis of diabetic neuropathy should be established according to clinical manifestations of the disease, laboratory findings (altered glucose metabolism) and results of electrophysiological examinations (electromyoneurography)[8].

Michigan Neuropathy Screening Score is a simple screening test to diagnose diabetic neuropathy in outpatient clinics. On this simple examination, the following questions are addressed:

- Do the feet show dry skin, callus, fissure, infection or deformities? The presence of any of these indicators of neuropathy is scored as one point and an additional point is added if an ulcer is present.
- What is the vibration sense on the dorsum of the great toes? reduced (0.5 points) or absent (1 point).
- What is the Achilles tendon reflex? absent (1 point) or present with reinforcement (0.5 points).

A score greater than 2 indicates neuropathy with both high specificity (95 percent) and sensitivity (80 percent). The Michigan Neuropathy Screening Test can be administered by any health care professional involved in the treatment of diabetic patients[4,8].

Tuning fork test as a simple test using a 128 Hz tuning fork to examine vibration perception can be used to screen for diabetic polyneuropathy. A 128 Hz tuning fork is placed on the interphalangeal joint of the right hallux.

- The score is 2 points, if the patient feels no vibration.

When the patient feels vibration at the hallux, the still vibrating tuning fork is immediately placed at the dorsal wrist, and the patient is asked to compare the strength of vibration at the two sites.

- The score is 1 point if the vibration feels stronger at the wrist.
- The score is 0 points if the vibration feels no difference at the wrist.

Normal score is 0 points, mild to moderate deficit is 1, and severe deficit is 2.

This tuning fork test has widespread utility in clinical practice because it is simple, brief, valid and reliable[4,8].

United Kingdom screening test. In the United Kingdom, investigators have developed a two-part diagnostic test consisting of a simple symptom score and physical examination:

- What is the sensation felt? burning, numbness, or tingling in the feet (2 points); fatigue, cramping, or aching (1 point). Maximum is 2 points.
- What is the location of symptoms? feet (2 points); calves (1 point); elsewhere (no points). Maximum is 2 points.
- Have the symptoms ever awakened you at night? yes (1 point).
- What is the timing of symptoms? worse at night (2 points); present day and night (1 point); present only during the day (no points). Maximum is 2 points.
- How are symptoms relieved? walking around (2 points); standing (1 point); sitting or lying, or no relief (no points). Maximum is 2 points.

Total symptom score can then be determined:

- 0 to 2 – normal
- 3 to 4 – mild neuropathy
- 5 to 6 – moderate neuropathy
- 7 to 9 – severe neuropathy

A similar quantitative score can be made for physical findings:

- What is the Achilles tendon reflex? absent (2 points for each foot); present with reinforcement (1 point for each foot).
- What is vibration sense? absent or reduced (1 point for each foot).
- What is pin prick sensation? absent or reduced (1 point for each foot).
- What is temperature sensation? reduced (1 point for each foot).

The neurologic signs score can then be determined:

- 0 to 2 – normal
- 3 to 5 – mild neuropathy
- 6 to 8 – moderate neuropathy
- 9 to 10 – severe neuropathy

Peripheral neuropathy is considered to be present if there are moderate or severe signs (≥6 points), even in the absence of symptoms, or if there are at least mild signs (≥3 points) in the presence of moderate symptoms (≥5 points). A neurologic sign score of 8 or more indicates that the patient's feet are at a high risk of ulceration[4,8].

Pain quality and intensity can be estimated with the ***Neuropathic Pain Scale***, the ***Neuropathic Pain Questionnaire***, and other scales. There are several different aspects of pain we are interested to measure: pain intensity (0-10), pain sharpness (0-10), heat (0-10) or cold (0-10), dullness (0-10), overall unpleasantness (0-10), how sensitive the skin is to light touch (0-10), how itchy pain is (0-10), time quality of pain (background *vs.* flare-up, all the time *vs.* sometimes), and surface pain (0-10) *vs.* deep pain (0-10). Many people are able to tell the difference between many aspects of their pain: for example, how much it hurts and how unpleasant or annoying it is. Although often the intensity of pain has a strong influence on how unpleasant the experience of pain is, some people are able to experience more pain than others before they feel very bad about it. There are scales for measuring different aspects of pain. For one patient, a pain might feel extremely hot, but not at all dull, while another patient may not experience any heat, but feels his/her pain is very dull. We expect from the patient to rate very high on some of the scales and very low on others.

An assessment of global function, sleep, psychological comorbidity, and other issues should be undertaken to determine the effect of diabetic neuropathy on the patient's quality of life, using a neuropathy-specific tool such as the ***Norfolk Quality of Life for Diabetic Neuropathy (QOL-DN) instrument***. It is composed of 46 items. Items 1-7 are nerve fiber-related symptoms (numbness, tingling/pins and needles, electric shocks, superficial peripheral pain, deep pain, weakness, and other symptoms). Items 8-11 inquire about duration of symptoms, symptoms at night, and current medications. Items 12-15 cover neuropathy diagnosis and related complications. Questions 8-15 are not included in the statistical analysis of the scales. With items 16-37, subjects respond to questions about the degree of physical problems that interfere with their activities of daily living. These items are scored on a five-point

Likert scale (0, no problem to 4, severe problem). Items 38-46 are generic questions about health and not specific to neuropathy. They are also measured on a five-point Likert scale[4,8].

Treatment

Treatment of DPN rests on a two-pronged approach: modification of the underlying disease and control of pain symptoms. Disease modification includes tight glycemic control, which in one study reduced the risk of development of clinical diabetic neuropathy in patients with insulin-dependent diabetes by as much as 62%. The maintenance of ideal body weight and normal lipid levels is also fundamental to the prevention of diabetic neuropathy. Recognition of the clinical symptomatology produced by the various pathogenic mechanisms described above will ultimately provide a logical basis for pain treatment selection. Intensive glucose control (HbA_{1c} ≤7 mmol/L) with diabetic diet, peroral antidiabetic agents or insulin, particularly when instituted early in DM, delay or prevent clinically manifest DPN. There is still no cure for DPN, as pharmacotherapy can only treat the symptoms of DPN[10,12].

The goals of DPN pharmacotherapy should be:

- Reduction of pain for maximum relief commensurate with acceptable side effects.
- Restoration/improvement in functional measures and quality of life.

Patients with painful DPN may share some comorbidities (anxiety, depression, sleep disorders) with those having chronic pain, requiring treatment in referral pain center. The main pharmacological agents, their mechanisms of action, recommended doses, side effects and level of evidence are shown in Tables 2, 3 and 4.

Pharmacotherapy

Antidepressants

Tricyclic antidepressants (TCAs) are accepted choices in neuropathic conditions and a meta-analysis of randomized clinical trials indicated their efficacy in treating painful diabetic (DPN) and nondiabetic polyneuropathy.

Table 2. Diabetic neuropathy – mechanisms of action, recommended doses and side effects of specific drugs

Drug	Recommended dosage	Main characteristics
Tricyclic antidepressants (TCAs)		
Amitriptyline	Initially 10-25 mg at bed time; titrate in increments 10-25 mg based on effectiveness/tolerability to 100-150 mg/day	• Balanced monoamine reuptake inhibition • Oldest, best known, commonly used as a golden standard for TCA • Contraindicated MAOIs, in cardiovascular disease • Avoid SNRIs and tramadol
Nortriptyline	Initially 10 mg at bed time; titrate in increments 10-25 mg based on effectiveness/tolerability to 50-100 mg/day	• Active metabolite of amitriptyline • Avoid SNRIs and tramadol
Imipramine	Initially 10 mg at bed time; titrate in increments 10-25 mg based on effectiveness/tolerability to 50-100 mg/day	• Balanced monoamine reuptake inhibition • Contraindicated MAOIs, in cardiovascular disease • Avoid SNRIs and tramadol
Desipramine	Initially 10 mg at bed time; titrate in increments 10-25 mg based on effectiveness/tolerability to 50-100 mg/day	• Predominantly norepinephrine reuptake inhibition • active metabolite of imipramine • Contraindicated MAOIs, in cardiovascular disease • Avoid SNRIs and tramadol
Voltage channel blockers		
Carbamazepine	Initially 200 mg/day; titrate in increments of 100 mg q 12 h to max 1200 mg/day	• Voltage-gated sodium-channel block • Contraindicated in pts with bone marrow depression and acute porphyria • Caution in hepatic dysfunction • Monitor patients for leukopenia • Avoid MAOIs, TCAs, $\alpha_2\delta$ CCMs
Oxcarbazepine	Initially 300 mg/day; titrate in increments of 100 mg q 12 h to max 2400 mg/day	• Voltage-gated sodium- and calcium-channel block • Monitor patients total blood count • Lower dosage in pts with renal impairment (CrCl <30 mL/min) • Avoid MAOIs, TCAs, $\alpha_2\delta$ CCMs
Valproic acid	Starting dose is 125-250 mg q 12 hours, max 1200 mg/day	• Contraindicated in pregnancy due to congenital abnormalities • Hyperandrogenism due to elevated testosterone levels and ovarian cysts • Caution in hepatic dysfunction • Monitor patient total blood count
Lamotrigine	Initially 25 mg first week, then titrate in increments 25 mg/day every week to max 400 mg/day	• Presynaptic voltage-gated sodium-channel inhibition and thus reduced release of presynaptic transmitters • Antidepressant effect appropriate if comorbid depression and intolerant/unresponsive to duloxetine, TCAs or venlafaxine • Discontinue if rash develops, unless rash clearly not drug related • Abrupt discontinuation may precipitate seizures
Topiramate	Initially 25-50 mg, then titrate in increments 25 mg/day every week to max 800 mg/day	• Voltage-gated sodium-channel blockade inhibition of glutamate release by an action on AMPA/kainite receptors • Abrupt discontinuation may precipitate seizures
Alpha-delta 2 calcium channel modulators/anticonvulsants ($\alpha_2\delta$ CCMs)		
Gabapentin	Initially 300 mg at bed time – 1&2 days, bid days 3&4, tid days 5&6; continue titration based on effectiveness/tolerability up to max 1800 mg/day; reduce dosage if renal insufficiency	• Binding to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels with reduced release of presynaptic transmitters • Avoid other $\alpha_2\delta$ CCMs • Abrupt discontinuation may precipitate seizures

Pregabalin	Start with 50 mg bid-tid if CrCl ≥60mL/min (if lower, adjust starting dose downward); titrate in increments based on effectiveness/tolerability up to max 300 mg/day	• Binding to the $\alpha_2\delta$ subunit of voltage- dependent calcium channels with reduced release of presynaptic transmitters • Avoid other $\alpha_2\delta$ CCMs • If therapy ended, withdraw gradually over min 1 week
Serotonin-norepinephrine reuptake inhibitors (SNRIs)		
Duloxetine	Initially 60 mg/day (if renal impairment, lower starting dose and gradually increase); to blunt potential nausea, initiate therapy at 30 mg/day taken with food for first week	• Serotonin-norepinephrine reuptake inhibition • Contraindicated if concomitant MAOIs, uncontrolled narrow-angle glaucoma • Not recommended in end-stage renal disease, severe renal impairment (CrCl <30 mL/min), hepatic insufficiency, active alcoholism • Avoid other SNRIs, TCAs, tramadol
Venlafaxine	37.5 initially once daily with food; titrate in increments based on effectiveness/tolerability to max 225 mg daily (lower dosage if hepatic or renal impairment)	• Serotonin-norepinephrine reuptake inhibition • Use if non-responsive to or intolerant of first line agents • Contraindicated if concomitant MAOIs, uncontrolled narrow-angle glaucoma • Avoid SNRIs, TCAs, tramadol • If discontinuing therapy, taper off gradually
μ-Opioid-receptor agonists		
Oxycodone	10-60 mg q 12 h, based on effectiveness/tolerability; adjust starting dose downward if hepatic or renal impairment (CrCl <60 mL/min)	• μ-Opioid-receptor agonist • Tablets should be swallowed whole, not crushed or chewed
μ-Opioid-receptor agonist and monoamine reuptake inhibitor		
Tramadol	25 mg/day initially; titrate in increments of 25 mg/day (as separate doses) q 3 day to 100 mg/day (25 mg qid); thereafter in increments of 50 mg/day (as tolerated) q 3 day to 200 mg/day (50 mg qid); after titration, 50-100 mg q 4-6 h to max 400 mg/day; in cirrhosis, 50 mg q 12 h; if CrCl <30 mL/min, dosing interval q 12 h to max 200 mg/day	• μ-Opioid-receptor agonist and monoamine reuptake inhibitor • Most common side effects are constipation, sedation, nausea, dizziness and vomiting • Avoid other SNRIs, MAOIs, TCAs
Topical agents (adjunctive therapy)		
Capsaicin	Topical cream – apply 4 times daily on painful areas	• Depolarizes nervous membrane via vanilloid receptor type 1, initially stimulates, then blocks skin nerve fibers
Lidocaine	5% lidocaine patches – apply on painful areas	• Block of peripheral sodium channels and thus of ectopic discharges
Nitrates	Glyceryl trinitrate patches – apply on painful areas Isosorbide dinitrate spray – apply on painful areas	• Impaired neuronal NO generation induces hyperalgesia, topical nitrates regulate NO metabolism

Antihyperalgesic effects of tricyclic antidepressants may be related to enhancement of noradrenergic descending inhibitory pathways and partial sodium channel blockade, mechanisms that are independent of their antidepressant effects.

Starting doses of TCAs should be low and dosage should be titrated slowly until pain is adequately con-trolled or side effects limit continued titration.

Some of the third-generation antidepressants, especially venlafaxine and duloxetine, have been shown to have comparable efficacy to the TCAs, but with a better side effect profile.

Duloxetine is a selective serotonin and norepi-nephrine reuptake inhibitor (SSNRI) that inhibits

Table 3. Classification of evidence for main categories of diabetic neuropathy drug treatment

	Level A rating	Level B rating	Level C rating or weak/discrepant results with level A/B evidence
Diabetic neuropathy	SNRI Pregabalin Gabapentin TCA Oxycodone Tramadol	Lamotrigine	Capsaicin (topical) Carbamazepine Levodopa Mexiletine NMDA antagonists Oxcarbamazepine Topiramate

the reuptake of both serotonin and norepinephrine. It has demonstrated significantly greater pain relief compared with placebo in several randomized clinical trials (RCTs) in patients with DPN. The optimal dosage of duloxetine is 60 mg/day.

Venlafaxine is an SSNRI that inhibits serotonin reuptake at lower dosages and both serotonin and norepinephrine reuptake at higher dosages. The efficacy dosage of venaflaxine is 150-225 mg/day. A 2- to 4-week period is often required to titrate to an effective dosage[18-20].

Side effects of TCAs

The most common side effects of TCAs are dry mouth, constipation, sweating, dizziness, disturbed vision, drowsiness, palpitation, orthostatic hypotension, sedation and urinary hesitation. More selective TCAs such as nortriptyline are better tolerated than the non-selective ones, with less anticholinergic effects and sedation. A suspected association between TCA treatment and sudden cardiac death has raised concern; a recent epidemiological study found a slight increase in sudden cardiac death with TCA doses greater than 100 mg/day. Therefore, caution is advised

for older patients, particularly those with cardiovascular risk factors[18-20].

The SSNRIs (duloxetine, venlafaxine) are safer to use than TCAs and are a better option in patients with cardiac disease. The relative risk of withdrawal due to side effects is low and there is no need for drug level monitoring. The most frequently observed adverse events with duloxetine are nausea, vomiting, constipation, somnolence, dry mouth, increased sweating, loss of appetite and weakness. Although immediate release venlafaxine is associated with adverse central nervous system and somatic symptoms such as agitation, diarrhea, increased liver enzymes, hypertension and hyponatremia, the extended release formulation seems to be far more tolerable, the main side effects being gastrointestinal disturbances[18-20].

Anticonvulsants

The anticonvulsant compounds are some of the best-studied drugs for neuropathic pain and there is substantial evidence for their efficacy based on meta-analyses and randomized clinical trials.

Multiple RCTs have shown the efficacy of many of these drugs in a large variety of types of neuropathic

Table 4. Recommendations for diabetic neuropathy drug treatment

Recommendations for first line	Recommendations for second line	Recommendations for third line
TCA SNRI (duloxetine) Pregabalin Oxycodone	Gabapentin Carbamazepine Lamotrigine Topiramate Venlafaxine Tramadol	Topical therapies Lidocaine Capsaicin Nitrates

pain. Unfortunately, complete relief of any form of neuropathic pain is only rarely achieved with the use of antiepileptic drugs. Usually, pain reduction by 50% is achieved in only one-half of treated patients[21].

Perhaps the most extensively studied agent is *pregabalin*, which has shown, in a large number of multicenter RCTs, clear efficacy in reducing pain and improving sleep in patients with postherpetic neuralgia and diabetic polyneuropathy. The effective dosage is 300-600 mg/day, administered in two to three divided doses. Improvement can be seen within days. Pregabalin is believed to exert its analgesic effect by binding to the α2 delta subunit of voltage-gated calcium channels on primary afferent nerves, and reducing the release of neurotransmitters from their central terminals. Multicenter RCTs have shown the efficacy of *gabapentin* at dosage of 900-3600 mg/day in the treatment of postherpetic neuralgia and diabetic polyneuropthy. Gabapentin is a GABA receptor agonist. The ability of the drug to block L-type voltage-dependent Ca^{2+} channels is the probable reason for its antiepileptic and analgesic properties[22-27].

There is also evidence for the efficacy of topiramate, lamotrigine, carbamazepine and oxcarbamazepine in the treatment of different DPN conditions. Carbamazepine and perhaps oxcarbamazepine are used as first-line therapy for trigeminal neuralgia[28,29].

Side effects of anticonvulsants

Carbamazepine (CBZ) entails frequent adverse events, which include sedation, dizziness, and gait abnormalities. Liver enzymes, blood cells, platelets and sodium levels must be monitored for at least 1 year due to the possible risk of hepatitis-anaplastic effects or hyponatremia. Induction of microsomal enzyme systems may influence the metabolism of several drugs. In contrast to CBZ, oxcarbazepine (OXC) does not entail enzymatic induction and there is little risk of crossed cutaneous allergy[37,38,40]. In the first months of treatment, sodium levels must be monitored because OXC, like CBZ, induces hyponatremia, particularly in the elderly (6% in a cohort of 54 patients). As regards other side effects, although better tolerance has been claimed with OXC compared with CBZ, this notion lacks consistent evidence from class I trials. In a recent trial in painful DPN, 27.5% of the OXC group discontinued treatment due to central or gas-

trointestinal side effects *versus* 8% on placebo[28,29].

The most common side effects of gabapentin (GBP) and pregabalin include dizziness, somnolence, peripheral edema, and dry mouth, with a similar frequency for both drugs. Whilst GBP is widely accepted as highly tolerable even at high dosages (>2400 mg), the reports on pregabalin change remarkably with the daily dose: with 150 to 300 mg there is almost no difference from placebo, whilst the withdrawal rate reaches 20% with 600 mg[22-27].

Lamotrigine is generally well tolerated. Side effects include dizziness, nausea, headache and fatigue. However, it may induce potentially severe allergic skin reactions. Lamotrigine should not be used in combination with valproate[30-32].

Opioids

Opioids may be useful, especially in acute stage, but their use for chronic pain management remains somewhat controversial. A meta-analysis of intermediate term studies with opioids (up to eight weeks) showed a significant reduction in pain scale measurement for patients with DPN, comparable to results with maximal dose gabapentine.

Patients are candidates for opioid therapy after all other appropriate therapies have failed.

Opioids exert their analgesic effect through at least four groups of receptors. The distribution of these receptors throughout the body, along with their tissue densities within numerous organ systems, account for the global and varied effects of these drugs.

Opioids are available in a variety of preparations. In addition to common, PO, IM and IV route of administration, they may be given transdermally (fentanyl as buprenorphine patch), transmucosally (fentanyl oral), and intraspinally[33-36].

Side effects

The most common side effects of opioids are constipation, sedation, nausea, dizziness and vomiting. The risk of cognitive impairment has been reported to be negligible, although morphine may impair attention at very high dosages. Tramadol has been reported to induce dizziness, dry mouth, nausea, constipation and somnolence with significantly more dropouts compared with placebo. There is an increased risk of seizures in patients with a history of epilepsy or re-

ceiving drugs that may reduce the seizure threshold. Serotonergic syndrome (various combinations of myoclonus, rigidity, hyperreflexia, shivering, confusion, agitation, restlessness, coma, autonomic instability, fever, nausea, diarrhea, flushing, and rarely rhabdomyolysis and death) may occur if tramadol is used as an add-on treatment to other serotonergic medications (particularly selective serotonin reuptake inhibitors, SSRIs)[33-36].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in patients with musculoskeletal or joint abnormalities secondary to long-standing neuropathy; joint deformities may actually be the primary source of pain. Both ibuprofen (600 mg four times daily) and sulindac (200 mg twice daily) can lead to substantial pain relief in patients with diabetic neuropathy.

There is a theoretical concern that NSAIDs may impair nerve circulation and worsen nerve injury due to inhibition of prostacyclin synthesis. Cautious use of this class of drugs is warranted until this possibility is fully evaluated[12].

Others

Levodopa has been evaluated as the possible treatment in some cases of painful diabetic neuropathy (double-blind placebo-controlled study, 100 mg levodopa plus 25 mg benserazide to be taken three times *per* day for 28 days). The results seemed promising and levodopa may be a choice for pain control in neuropathy for which we do not have many alternative treatments[37].

Some clinical studies have shown efficacy of dextromethorphan (400 mg/day) and memantine (55 or 35 mg/day) in the treatment of DPN. The mean reduction in pain intensity was 6% with dextromethorphan and 2% with memantine. In subjects who responded to dextromethorphan, there was a significant dose-response effect on pain intensity ($P=0.035$). Selective approaches to pain-relevant *N*-methyl-d-aspartate receptors are warranted[38,39].

Diabetic autonomic neuropathy is extremely difficult to treat, and the risks and adverse effects frequently outweigh the benefits of most pharmacological therapies. The symptoms may be ameliorated with fludrocortisone, clonidine, midodrine, dihydroergotamine or caffeine, octreotide, ACE inhibitors, and β-blockers. Gastroparesis may be improved with metoclopramide or erythromycin, but glycemic control is perhaps the best long-term treatment. Erectile dysfunction may respond to phosphodiesterase inhibitors, vacuum-constriction devices, and intracavernosal injections[40].

Nonspecific pharmacological treatment options

Alpha-lipoic acid

One of the mechanisms implicated in the pathogenesis of diabetic neuropathy is increased oxidative stress. As a result, antioxidants have been studied for their potential to diminish oxidative stress, improve the underlying pathophysiology of neuropathy, and reduce pain. Based on data of randomized clinical trials, we suggest treatment with oral α-lipoic acid 600 mg once daily for patients with symptomatic painful diabetic polyneuropathy[1-3,40,41].

Acetyl-L-carnitine

Acetyl-L-carnitine (ALC), the acetylated ester of the amino acid L-carnitine, has been evaluated in patients with diabetic peripheral neuropathy. According to data from two randomized controlled trials of identical design, an intention to treat analysis of 1257 DPN patients showed ALC 1000 mg (but not 500 mg) three times daily compared with placebo to be associated with significant improvement in pain scores in one of the studies and in the combined cohort. The benefit of ALC requires confirmation, particularly since significant improvement was not seen in both trials or at the lower dose of ALC[1,40,41].

Protein kinase C inhibition

Elevated protein kinase C activity is thought to play a substantial role in the etiology of diabetic microvascular complications. Studies have been conducted using a protein kinase C-β inhibitor (LY333531). A preliminary study suggested the possibility of this agent to improve positive symptoms of allodynia and prickling pain. Large phase III multicenter clinical trials are in progress[1,40,41].

Aldose reductase inhibitors

In addition to lowering blood glucose concentrations, another potential approach is to minimize the toxicity of hyperglycemia. To the degree that sorbitol accumulation might play a role in diabetic neuropathy, the use of an aldose reductase inhibitor to prevent sorbitol formation might be beneficial. In the studies reported thus far, there has usually been no improvement in pain, an inconsistent effect on paresthesias, and an improvement in nerve conduction in some but not all nerves[1,40,41].

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibitors play a major role in the treatment of hypertension and in the prevention of progression of nephropathy in patients with diabetes. ACE inhibitors presumably act by inhibiting the production of angiotensin II, thereby lowering systemic and intraglomerular pressures. By mechanisms that are less clear, these drugs may also be beneficial in diabetic retinopathy and neuropathy[1,40,41].

Surgical decompression

Surgical decompression of multiple peripheral nerves (called the Dellon procedure) is an alternative, controversial method for treating DPN. The purported rationale for surgical decompression is based on the notion that the metabolic stress of diabetes renders peripheral nerves susceptible to compressive injury at sites of potential nerve entrapment, and that compressive injury of multiple peripheral nerves is what leads to symptoms in most patients.

While there is some experimental evidence that favors this hypothesis, other evidence to the contrary suggests that diabetes may partially prevent axonal injury by the development of resistance to axonal degeneration after nerve compression. In addition, there are no appropriately designed trials to support the use of surgical decompression of multiple peripheral nerves as a treatment for symptomatic DPN. Therefore, this treatment is not recommended[1-3,40,41].

Nonpharmacological treatment

Acupuncture

Acupuncture is a complementary and alternative medical modality. Since 1998, a considerable number of acupuncture studies have been reported. It has been integrated into palliative care medicine. Most of controlled clinical trials (23/27) have shown results favoring acupuncture use for the conditions such as nausea, vomiting and pain. They also have shown that acupuncture is safe and clinically cost-effective for management of common symptoms in palliative care and hospice patients. There is the risk of skin irritation or allergic reaction from application of needles to the skin, but these problems are relatively rare and easily managed by shifting the needle position. There is not yet enough evidence-based treatment recommendations (level C)[20-22,66].

Transcutaneous electrical nerve stimulation

High frequency (80-110 Hz) and low frequency (2-10 Hz) transcutaneous electrical nerve stimulation (TENS) differ in their ability to relieve pain and in the central nervous system alterations they produce. High frequency TENS relieves secondary allodinya *via* muscarinic and μ opioid receptor dependent mechanisms, while low frequency TENS relieves secondary allodynia *via* serotonin, muscarinic and δ opioid receptor-dependent mechanism. In addition, recent evidence indicates that high and low frequency TENS may produce distinct cortical activation patterns when producing analgesia. There are not yet enough evidence-based treatment recommendations (level C). TENS produces none of the side effects associated with drug therapy. There is the risk of skin irritation or allergic reaction from the application of electrodes to the skin, but these problems are relatively rare and easily managed by shifting the electrode position[1-3,40,41].

Others

Laser therapy, mechanotherapy (massage), electrotherapy (galvanization, iontophoresis), ultrasound therapy, thermotherapy (cold and warm), hydro/balneotherapy and behavioral therapy (relaxation, biofeedback) have been tried. There is still no evidence-based treatment recommendations due to the lack of controlled studies in this field (level C)[1,40,41].

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Sažetak

PREPORUKE ZA LIJEČENJE DIJABETIČNE POLINEUROPATIJE

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Dijabetes spada u skupinu kroničnih bolesti koja zahtijeva stalno medicinsko praćenje te izobrazbu bolesnika o mjerama prevencije kako bi se spriječio razvoj komplikacija. U razvijenim zemljama dijabetes je vodeći uzrok neuropatija, a neuropatije su jedna od najčešćih komplikacija dijabetesa, te najveći uzrok pobola i smrtnosti u bolesnika s dijabetesom. U trenu kada se postavi dijagnoza dijabetesa 10%-18% bolesnika već ima oštećenje živaca, što govori u prilog činjenici da čak i početni poremećaji metabolizma glukoze pod zajedničkim nazivnikom preddijabetes mogu uzrokovati neuropatiju. Kod postavljanja dijagnoze dijabetične neuropatije treba isključiti i druge uzroke neuropatija ako se radi o atipičnoj kliničkoj slici ili nekim drugim istodobnim bolestima. Dijagnoza se postavlja u skladu sa smjernicama, a na osnovi kliničke slike, laboratorijskih nalaza (poremećaj metabolizma glukoze) i rezultata elektrofizioloških pretraga. Liječenje bolne dijabetične polineuropatije temelji se na dva dugoročna načela, a to su liječenje osnovne bolesti (dijabetes) i liječenje bolne sastavnice. Osnovni ciljevi liječenja bolne sastavnice su smanjenje boli uz prihvatljive rizike i nuspojave uzimanja specifičnih lijekova te poboljšanje kvalitete života.

Ključne riječi: *Dijabetična neuropatija – terapija; Bol – terapija; Bol – analiza; Smjernica*