Diabetic Neuropathy

Authors
Dan Ziegler[1,2], Jutta Keller[3], Christoph Maier[4], Jürgen Pannek[5]

Affiliations
1 Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany
2 Department of Endocrinology and Diabetology, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
3 Department of Internal Medicine, Israelite Hospital, Hamburg, Germany
4 Department of Pain Medicine, Ruhr University, Bochum, Germany
5 Neuro-Urology, Swiss Paraplegic Center Nottwil, Switzerland

Bibliography
Exp Clin Endocrinol Diabetes 2021; 129: S70–S81
DOI 10.1055/a-1284-6245
ISSN 0947-7349

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

German Diabetes Association: Clinical Practice Guidelines
This is a translation of the DDG clinical practice guideline published in Diabetologie 2020; 15 (Suppl 1): S181–S195, DOI 10.1055/a-1194-1692.

Correspondence
Prof. Dr. med. Dr. h.c. Dan Ziegler, FRCPE
Institute for Clinical Diabetology, German Diabetes Center at Heinrich Heine University
Auf'm Hennekamp 65
40225 Düsseldorf
Germany
dan.ziegler@ddz.de

Note

The practice recommendation "Diabetic Neuropathy" of the DDG was developed in close alignment with the National Healthcare Guideline (Nationale Versorgungsleitlinie - NVL) "Neuropathy in Diabetes in Adulthood" (Neuropathie bei Diabetes im Erwachsenenalter), long version, version 1.2, 28 November 2011, based on the version of August 2011 [1, 2]:

German Medical Association (Bundesärztekammer - BÄK), National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung - KBV), Association of the Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften - AWMF). National Healthcare Guideline Adult Neuropathy in Diabetes in Adulthood - Long Version. Version 1.2, 2011 [cited: August 01, 2012]. Available at: http:// www.diabetes.versorgungsleitlinien.de.(▶ **Fig. 1,2**)

Internet: http://www.versorgungsleitlinien.de, http://www.awmf-leitlinien.de

In June 2016 the National Healthcare Guideline was reviewed by the members of the guideline group. Until completion of the updated version (expected January 2020), several sections have been designated as "under revision" (National Healthcare Guideline Neuropathy in Diabetes in Adulthood - Long Version. 1st edition, 2011. version 5. AWMF register no.: nvl-001e. Available at: http://www.leitlinien.de/nvl/diabetes/neuropathie). Subject to revision of the National Healthcare Guideline, the sections revised in this Practice Tool reflect the position of DDG.

Diabetic Sensorimotor Polyneuropathy

Definition, risk factors and comorbidities

Diabetic neuropathy is a clinically manifested or subclinical disease of the peripheral nerves that occurs as a consequence of diabetes mellitus without other underlying causes. It can affect the somatic and/or autonomic nervous system. The risk of distal symmetric polyneuropathy (DSPN) and autonomic neuropathy increases with the following risk factors, indicators and co-morbidities:

- Diabetes duration
- Diabetes control (hyperglycemia)
- Arterial hypertension
- Peripheral artery disease (PAD)
- Mönckeberg's sclerosis
- Diabetic retinopathy and nephropathy
- Depression
- Visceral obesity
- Hyperlipidemia

- Alcohol and/or nicotine abuse
- Insufficient physical activity
- Demographic factors (age, height, body weight)

DSPN contributes to the etiology of diabetic foot syndrome in 85-90% of cases and is thus of paramount significance in the risk constellation for foot ulcers and amputation.

In addition, it is deemed an important predictor of cardiovascular morbidity and mortality.

The prevalence of DSPN in patients with manifest type 1 and type 2 diabetes is approximately 30 %. Approximately 13–26 % of patients with diabetes have painful neuropathy.

Classification

Based primarily on clinical criteria, different manifestations can be distinguished:

- Subclinical neuropathy (no symptoms or clinical findings, but abnormal quantitative neurophysiological tests)
- Chronic painful neuropathy (frequent)
- Acute painful neuropathy (insulin neuritis) (rare)
- Painless neuropathy (frequent)
- Focal neuropathies, e. g. diabetic amyotrophy (rare)
- As a complication the diabetic-neuropathic foot syndrome including foot ulcers, neuro-osteoarthropathy and amputation.

Screening

Screening for DSPN should encompass the following data and examinations (always bilateral):

- History with personal and diabetes-specific data (see H 3 "Basic Diagnostics") as well as risk factors/indicators and clinical correlations for DSPN.
- Assessment of neuropathic positive and negative symptoms (e.g. sensory abnormalities, pain, cramps, numbness), especially patient-reported pain intensity, pain localization and pain triggering situations (using validated questionnaires).
- Inspection and clinical examination (skin color, trophic disorders, foot deformities, foot ulcers, injuries, skin temperature).
- Screening for foot complications and PAOD (see National Healthcare Guideline "Type 2 Diabetes Foot Complications").
- Simple neurological examination techniques: testing the Achilles tendon reflexes, vibration sensation with the C64 Hz tuning fork according to Rydel-Seiffer as well as the touch/pressure sensation with the 10 g monofilament. If any one of the above three examinations yields pathological findings, a basic diagnostic clarification (see "Basic Diagnostics") should be performed.

In people with type 2 diabetes, screening for diabetic sensorimotor and/or autonomic neuropathy should take place at the time of initial diagnosis of diabetes, and in people with type 1 diabetes not later than five years after diabetes diagnosis.

Basic Diagnostics

The basic diagnostic procedures include examinations conducted by a general practitioner, internist or diabetologist that are absolutely required in order to diagnose diabetic sensorimotor polyneuropathy and to identify patients at risk early on. In addition, complications of diabetic neuropathy (e.g. foot complications) should be diagnosed and treated at an early stage. Both legs and feet should be inspected, clinically examined and comparatively evaluated. A diagnostic clarification should be conducted in all symptomatic patients, especially in those with pain of unknown origin or other neuropathic symptoms, as well as in all asymptomatic patients who show abnormalities at screening (see "Screening").

The inspection of the legs and feet should include:

- Skin: color, turgor, fissures, blistering, subcutaneous bleeding,
- Hyperkeratosis and callus formation,
- Healed foot lesions, hypohidrosis or anhidrosis,
- Signs of bacterial infection and/or mycosis,
- Foot deformities (e. g. neuro-osteoarthropathy (DNOAP or Charcot arthropathy), hammer toes, claw toes),
- Foot ulcer with exact description of localization, extent and concomitant infection.

Clinical examination should encompass the following:

- Peripheral pulse status (palpation of the foot pulses in the posterior tibial artery and the dorsalis pedis artery on both sides);
- Checking skin temperature, skin turgor and sweating;
- Assessment of foot deformities as a sign of diabetic neuro-osteoarthropathy (DNOAP or Charcot arthropathy) as well as assessment of muscle and joint function;
- Evaluation of the patient's gait, close inspection and touch control of shoes and inlays (changes to the upper and lining material, excessive wear-out of the soles, footprint on the inlays, wound secretion on the inlays, wear-and-tear of the padding material).

Acute changes of the skin, soft tissue or joints with or without trauma strongly suggest a serious complication. Hence, infection or diabetic neuro-osteoarthropathy must be ruled out in such cases. An infection is indicated by the presence of a skin lesion (entry site). For this reason, the skin should be carefully examined for lesions.

Subjective symptoms are clinically evaluated using the Neuropathy Symptom Score (NSS) and the severity of sensory deficits with the Neuropathy Disability Score (NDS) [3] or the Michigan Neuropathy Screening Instrument (MNSI) [4] (https://eprovide.mapi-trust.org/instruments/michiganneuropathy-screening-instrument#contact_and_conditions_of_use) (▶ **Fig. 1**). NDS ≥ 3 or MNSI ≥ 2.5 points indicates clinical DSPN. In presence of neuropathic symptoms (NSS ≥ 3) or deficits (NDS ≥ 3 or MNSI ≥ 2.5) alone, DSPN is considered as possible, while in presence of both neuropathic symptoms and deficits, DSPN is considered to be probable [5].

Motor function is tested by checking the ability to spread the toes, stretch the toes (toe walking), and flex the toes (make claws) and feet against resistance as well as by assessing heel walking.

If present, the intensity of neuropathic pain is recorded using the Numerical Rating Scale (NRS): 11 points on a scale of 0 = no pain to 10 = worst pain imaginable.

Follow-up

The intervals of follow-up examinations and, as needed, any further diagnostic procedures (see below) are based on the individual risk. If no neuropathy is present, neuropathy screening should be carried out once a year. If the screening indicates the presence of neuropathy, the diagnosis should be ascertained by basic diagnostics, possibly by adding further diagnostic procedures. If diabetic neuropathy is suspected or present, at least semi-annual follow-up should take place depending on the individual disease situation. If PAD and/or foot deformities are present additionally, examination intervals of three months are recommended.

Advanced Diagnostics

If the suspected symptom-based diagnosis of diabetic neuropathy cannot be ascertained by the basic diagnostic procedures, specific investigations (electroneurography and quantitative sensory testing, particularly if a so-called small fiber neuropathy is suspected) should be performed. To this end, the patient should be referred to a physician familiar with the aforementioned methods.

In the case of etiologically unclear or treatment-resistant pain, a physician with experience in diagnosing and treating pain should be involved. The pain documentation should preferably contain an indication of the level (intensity) and subjective severity or endurability (tolerability) of pain as well as documentation of the constellations triggering the pain (pain at rest, pain evokable by touch and/or load-dependent pain [standing, walking]). The latter are atypical for painful neuropathy.

Important Differential Diagnoses

Differential diagnosis includes medications (e. g. chemotherapy), metals, toxins (e. g. alcohol), renal insufficiency, PAD, vitamin B deficiency (B1, B6, B12), tumor diseases, paraproteinemia, infections (e. g. HIV, Lyme disease), vasculitides, inherited neuropathies, endocrine disorders (hypothyroidism, acromegaly), immune neuropathies, impingement syndromes.

The process of diagnostic exclusion should be based on the following minimally required standard set of laboratory tests: complete blood count, creatinine, CRP, TSH, vitamin B12, folic acid, alanine aminotransferase (ALAT), gamma-GT, immunoelectrophoresis.

Referral to a neurologist is indicated if one or more of the following findings apply:

- Motor deficits predominate over the sensory deficits
- Rapid development and progression of symptoms
- Marked asymmetry of the neurological deficits, mononeuropathy and cranial nerve dysfunction
- Progression of symptoms despite optimization of glycemic control
- Symptoms present initially in the upper extremities
- Other neurological symptoms beyond the diabetic polyneuropathic syndrome
- Family history of neuropathy

Referral to a pain management specialist is indicated if the etiology of pain remains unclear and/or if the basic symptomatic pain therapy described below is not sufficiently effective or is not tolerated.

General Treatment Strategies and Prevention

Important therapeutic goals for patients with type 1 or type 2 diabetes include the improvement in quality of life, empowerment of those affected by dealing with their disease, prevention of microvascular (retinopathy, nephropathy) and macrovascular complications, neuropathy and diabetic foot syndrome as well as prevention and treatment of symptoms of the disease. The goals of therapy should be individualized both in patients with type 1 and type 2 diabetes. These goals depend on, among others, (co-)morbidity, age, life expectancy and quality of life of the persons affected.

Patients with all forms and stages of neuropathy should be advised concerning their lifestyle habits, diabetes therapy and foot care. Depending on the patient's requirement, appropriate therapists and, if possible, relatives should be involved. In patients with type 1 and type 2 diabetes, glycemic control should be adapted to the individual patient and his comorbidity and risk profile.

Early optimization of metabolic control and existing risk factors (e. g. smoking, excessive alcohol consumption, arterial hypertension) in people with diabetes may prevent or at least retard or slow the progression of diabetic neuropathy. Patients with diabetic neuropathy should be recommended to consume alcohol in moderate amounts at most and give up smoking.

Patients with DSPN and loss of sensitivity with or without foot disproportions or foot deformities should receive guideline-based shoe supply.

Pain Therapy

If patients with DSPN do not feel impaired in their daily activities, there is no need to treat their symptoms (▶ **Fig. 2**). Successful individualized pain therapy starts with a pain analysis. Pharmacotherapy of painful DSPN is primarily symptomatic. It should be supplemented by non-pharmacological therapeutic modalities.

Before initiating pharmacotherapy, a detailed medication history should be taken. The choice of pharmacotherapy for DSPN should take into account frequent comorbidities and contraindications. Non-invasive, non-pharmacological therapy options such as psychotherapy/behavioral therapy, transcutaneous electrical nerve stimulation (TENS), muscle stimulation (high-tone external muscle stimulation) or acupuncture can be included as part of a multimodal pain therapy. If adequate pain relief is not achieved after 12 weeks of therapy and the pain has a major negative impact on the patient's quality of life, a pain management specialist should be consulted for further therapy. Electrical spinal cord stimulation may be indicated in patients resistant to pharmacotherapies, but should be performed only in specialized units.

Neuropathy Symptom Score (NSS)*

Symptoms in the legs	Yes	No	
Burning	☐ 2	☐ 0	
Numbness	☐ 2	☐ 0	
Tingling	☐ 2	☐ 0	☐ Points
Fatigue	☐ 1	☐ 0	
Cramping	☐ 1	☐ 0	
Aching	☐ 1	☐ 0	☐ Points
Localization			
Feet	☐ 2		
Calves	☐ 1		
Elsewhere	☐ 0		☐ Points
Time of appearance			
Nocturnal exacerbation	☐ 2		
Day and night	☐ 1		
Daytime alone	☐ 0		
Woken from sleep	add ☐ 1		☐ Points
Improved by			
Walking	☐ 2		
Standing	☐ 1		
Sitting or lying down	☐ 0		☐ Points

Total score: ☐ points

Score:

3 – 4 = mild symptoms
5 – 6 = moderate symptoms
7 – 10 = severe symptoms

*In each section, the maximum number of points can only be assigned once (five times in total)

Neuropathy Disability Score (NDS)

Ankle reflexes	Side	right	left
Reflexes	Present	☐ 0	☐ 0
	Present with reinforcement	☐ 1	☐ 1
	Absent	☐ 2	☐ 2
Vibration perception threshold (tuning fork)			
Measurement at great toe base joint**			
	Present	☐ 0	☐ 0
	Reduced or absent	☐ 1	☐ 1
Pain sensitivity (pin-prick)			
Measurement at great toe			
	Present	☐ 0	☐ 0
	Reduced or absent	☐ 1	☐ 1
Temperature sensitivity			
Measurement at dorsum of the foot			
	Present	☐ 0	☐ 0
	Reduced or absent	☐ 1	☐ 1

Total score: ☐ points

Score:

3 – 5 = mild deficits
6 – 8 = moderate deficits
9 – 10 = severe deficits

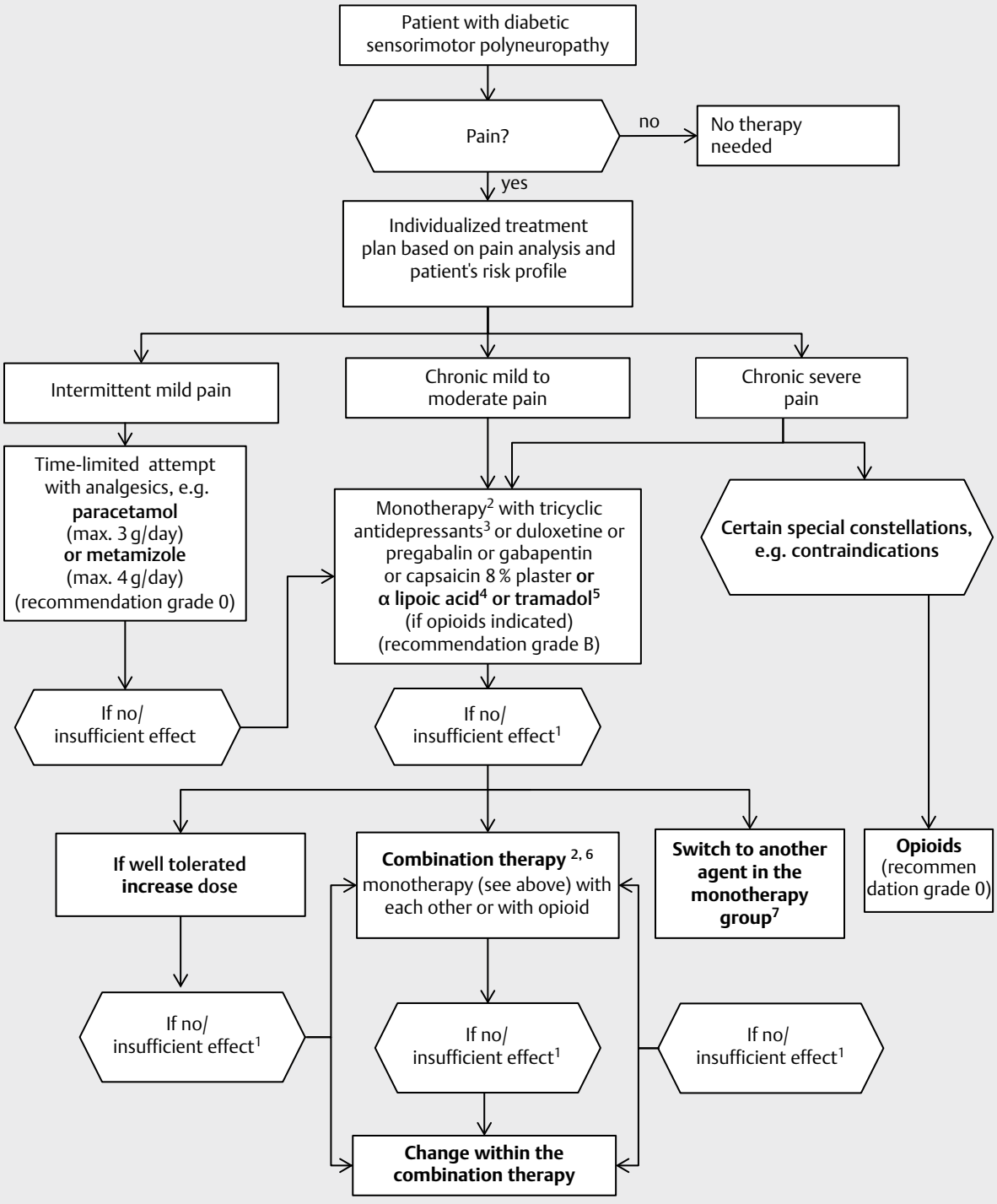
**Age-dependent normal ranges see Table 1

***Note: A high NSS score does not necessarily indicate severe symptoms but may rather reflect typical neuropathic symptoms. Furthermore, other neuropathic symptoms may be present that are not included in the NSS (e.g. unsteady gait, foreign body or cold sensation).

▶ **Fig. 1** Diagnostic criteria for diabetic sensorimotor neuropathy. Adapted from ref. 3 Source: German Medical Association (Bundesärztekammer - BÄK), National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung - KBV), Association of Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften - AWMF). National Healthcare Guideline Neuropathy in Diabetes in Adulthood - Long Version, 1st Edition. Version 5. 2011. Available from: www.dm-neuropathie.versorgungsleitlinien.de; DOI: 10.6101/AZQ/000 302. [rerif]

Principles of Pharmacotherapy for Painful Diabetic Polyneuropathy

1 Therapy of painful diabetic polyneuropathy offers symptomatic relief, but does not treat the underlying cause.
2 Pharmacotherapy of chronic neuropathic pain associated with diabetes mellitus should begin as soon as possible if the pain negatively impacts the patient's quality of life.
3 Pain therapy should not merely mitigate pain, but should also improve the quality of sleep, mobility and overall quality of life.
4 Pharmacotherapy is selected on the basis of the efficacy and general risk profile of the specific agents under consideration of known or potential comorbidities.
5 If medications show comparable analgesic efficacy, the compound with the lowest organ toxicity and particularly with the lowest risk for cardiovascular and renal side effects should be selected.
6 Consequently, agents with increased renal and cardiovascular long-term risks (e.g. NSAIDs, COX-2 inhibitors) are not indicated for therapy of diabetic neuropathic pain.
7 Analgesic efficacy should be tested individually.
8 The required dose should be titrated individually to the lowest effective dose, whereby the maximum allowed dose should not be exceeded.



[1] If patients respond to therapy, maintenance therapy may be attempted.
[2] Select agent according to the patient's risk profile
[3] Preferably amitriptyline
[4] Alternatively benfotiamine, if necessary
[5] Alternatively try tilidine, if necessary
[6] Agents from one class (antidepressants: TZA, duloxetine; anticonvulsants: pregabalin, gabapentin; opioids: tramadol, strong opioids) should not be combined with each other
[7] Try sodium channel blocker or cannabinoids

▶ **Fig. 2** Algorithm for pharmacotherapy of painful diabetic sensorimotor neuropathy. Data modified according to source: German Medical Association (Bundesärztekammer - BÄK), National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung - KBV), Association of Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften - AWMF). National Healthcare Guideline Neuropathy in Diabetes in Adulthood - Long Version, 1st Edition. Version 5. 2011. Available from: www.dmneuropathie.versorgungsleitlinien.de; DOI: 10.6101/AZQ/000 302. [rerif]

9 The efficacy of pharmacotherapy should not be assessed earlier than two weeks after an adequate dose has been achieved. Agents without analgesic efficacy should not be further prescribed.
10 Analgesic combination therapy is recommended only if the combination improves the effectiveness of each individual component and/or lowers the risk by reducing the doses of the individual components.
11 Psychotropic drugs without analgesic potency are not indicated for pain therapy. Combination preparations with caffeine, benzodiazepines or muscle relaxants are not indicated and carry a risk of abuse and dependence.

The following realistic goals of pharmacotherapy for neuropathic pain are worthwhile:
1 Pain reduction of 30-50% on the Visual Analog Scale (VAS) or the 11-point Numerical Rating scale (NRS);
2 Improvement in sleep quality;
3 Improvement in quality of life;
4 Maintenance of social activities and participation;
5 Maintenance of the ability to work.

The aforementioned treatment targets must be discussed with the patient both before and during the course of therapy in order to keep the patient's expectations at a realistic level. In this way disappointments are avoided which may result in pain amplification.

Diabetic Autonomic Neuropathy

Classification and prognosis

Apart from diabetic sensorimotor polyneuropathy, diabetic autonomic neuropathy (DAN) is the most frequent form of peripheral neuropathy. Only function tests can be used to distinguish between symptomatic and asymptomatic manifestations. In principle, DAN can affect any organ innervated by the autonomic nerves. DAN is classified according to affected organs and functional systems, based on clinical and phenomenological criteria.

The pathomechanisms and risk factors discussed for the pathogenesis of DAN are principally the same as for diabetic sensorimotor polyneuropathy.

In light of the current knowledge, DAN undoubtedly has significant negative consequences in terms of reduced life expectancy, increased risk for end-organ damage and impaired quality of life. The risk of mortality within 16 years is 3.5-fold increased in patients with diabetes diagnosed with diabetic cardiovascular autonomic neuropathy (DCAN) by at least 2 tests compared to those without DCAN [6] (▶ **Table 1**).

Screening

There are no suitable test procedures to screen for diabetic autonomic neuropathy. However, the following symptoms can serve as an indication, albeit with low specificity and sensitivity. These symptoms should be recorded at the screening intervals within the frame of early detection [7]:
- Resting tachycardia
- Gastrointestinal disorders (dyspepsia, constipation, diarrhea, fecal incontinence)
- Disorders of bladder function, sexual dysfunction
- Hypoglycaemia unawareness
- Impaired sweat secretion
- Blood glucose fluctuations that cannot be explained otherwise

The Survey of Autonomic Symptoms (SAS) is a validated a simple questionnaire including 12 questions for autonomic symptoms [8] (▶ **Table 2**).

▶ **Table 1** Simple neurological examination methods for diagnosis of diabetic sensorimotor neuropathy (always performed bilaterally) [1, 2].

Quality	Examination	Findings in diabetic sensorimotor polyneuropathy
Pain sensation	▪ With toothpick, disposable needle or Neurotip ▪ It should be asked: "Is it painful? "(not: "Can you feel the needle?")	Bilateral limb section-wise demarcation (e. g."stocking-" or "sock"-wise distribution)
Touch sensation	E.g. with cotton-ball swab	Bilateral limb section-wise demarcation (e. g. "stocking-" or "sock"-wise distribution)
Pressure and touch sensation	10 g monofilament on the plantar aspect of the 1st and 2nd metatarsal bone; plantar distal aspect of great toe; in addition, on the basis of the 3rd and 5th metatarsal bone as applicable. Caveat: examination should not be carried out on areas with callus.	Positive screening test: absent sensation in at least one skin area
Temperature sensation	▪ With cold metal (e. g. tuning fork), ice watercooled test tube or TipTherm	Bilateral limb section-wise demarcation (e. g. "stocking-" or "sock"-wise distribution)
Vibration sensation as measured with C64 Hz Rydel-Seiffer tuning fork	▪ First at great toe base joint; if sensation is both sides = 0/8, examination should be carried out at a proximal location (medial malleolus)	Lower limit of normal proximal to great toe base joint: ▪ For ages up to 39 years 5/8[1] ▪ For age 40–59 years 4.5/8[1] ▪ For age 60–74 years 4/8[1] ▪ For age ≥ 75 years 3.5/8[1] Bilaterally reduced or non-evokable
Proprioceptive reflexes	Ankle reflex and knee reflex	

[1] Lower limits of normal for vibration sensation [10].

▶ **Table 2** Survey of Autonomic Symptoms (SAS) to screen for autonomic symptoms. Source: [8]

	Q1a. Have you had any of the following health symptoms during the past 6 months? (1 = Yes; 0 = No)	**Q1b. If you answered yes in Q1a, how much would you say the symptom bothers you? (1 = Not at all; 2 = A little; 3 = Some; 4 = A moderate amount; 5 = A lot)**
Symptom/health problem		
1. Do you have lightheadedness?	1 0	1 2 3 4 5
2. Do you have a dry mouth or dry eyes?	1 0	1 2 3 4 5
3. Are your feet pale or blue?	1 0	1 2 3 4 5
4. Are your feet colder than the rest of your body?	1 0	1 2 3 4 5
5. Is sweating in your feet decreased compared to the rest of your body?	1 0	1 2 3 4 5
6. Is sweating in your feet decreased or absent (for example, after exercise or during hot weather)?	1 0	1 2 3 4 5
7. Is sweating in your hands increased compared to the rest of your body?	1 0	1 2 3 4 5
8. Do you have nausea, vomiting, or bloating after eating a small meal?	1 0	1 2 3 4 5
9. Do you have persistent diarrhea (more than 3 loose bowel movements per day)?	1 0	1 2 3 4 5
10. Do you have persistent constipation (less than 1 bowel movement every other day)?	1 0	1 2 3 4 5
11. Do you have leaking of urine?	1 0	1 2 3 4 5
12. Do you have difficulty obtaining an erection (men)?	1 0	1 2 3 4 5

[a]Number of symptoms reported: _____ (sum of column A, 0–12 for men and 0–11 for women); total symptom impact score: _____ (sum of column B, 0–60 for men and 0–55 for women).

Diagnosis

The patient should be asked about the symptoms of autonomic dysfunction when the medical history is taken, especially in view of the need to establish a differential diagnosis and the option of choosing a symptomatic, organ-specific therapy. The full clinical picture of symptomatic DAN affecting multiple organs is encountered only rarely. Usually, the clinical picture shows a heterogeneous pattern of symptoms originating from various organ systems. This can lead to erroneous interpretations.

When diagnosing diabetic sensorimotor neuropathy, possible manifestations of DAN should also be considered, as DCAN coexists in approximately 50 % of the cases. Likewise, there are also correlations between DAN and other chronic complications of diabetes (retinopathy, nephropathy).

The diagnostic clarification is basically the same as for sensorimotor neuropathy (see above). In addition, cardiovascular autonomic function tests and organ-specific examinations are performed in collaboration with other specialists (▶ **Table 3**). The basic diagnostic approach encompasses all examinations carried out by office-based general practitioners, internists, and diabetologists as a minimum standard. Further diagnostic procedures are performed by specialists: neurologists/ cardiologists for evaluation of syncope, gastroenterologists for gastrointestinal symptoms, and urologists for urogenital disorders.

Diabetic Cardiovascular Autonomic Neuropathy (DCAN)

CAN is encountered in about 20 % of patients with diabetes [6] and is characterized by reduced heart rate variability (HRV) as an early sign of vagal damage, which is often detectable before clinical symptoms manifest themselves in the cardiovascular system and

1. HEART RATE VARIABILITY DURING DEEP BREATHING → EXAMINATION PROCEDURE

To measure HRV during deep breathing, the supine subject breathes at a rate of 6 breath cycles per minute for 1-2 minutes. Each inspiration and each expiration lasts 5 seconds. The “E/I ratio” (R-Rmax / R-Rmin) is computed from the cycle with the longest R-R interval during expiration (R-Rmax) divided by the shortest R-R interval during inspiration (R-Rmin).

Normal values:

- age: 20–30 yr ≥ 1.12;
- age: 31–49 yr ≥ 1.11;
- age: 50–69 yr ≥ 1.10;
- age: ≥ 70 yr ≥ 1.09.

2. HEART RATE VARIABILITY IN RESPONSE TO STANDING UP → EXAMINATION PROCEDURE

The supine subject stands up next to the examination couch. The ECG recording is started the moment the subject begins to rise. As a HRV measure the “30:15 ratio” (R-Rmax / RRmin) is defined as the longest R-R interval between beats 20 and 40 divided by the shortest R-R interval between beats 5 and 25 after standing up.

Normal values:

- age: 20–49 yr ≥ 1.10;
- age: 50–79 yr ≥ 1.09;
- age ≥ 80 yr ≥ 1.08.

3. ORTHOSTATIC TEST → EXAMINATION PROCEDURE

For the orthostatic test, the blood pressure is taken two times within one minute in the supine position and subsequently directly after standing up and thereafter every 30 seconds for 3minutes. The normal range for the decrease in systolic blood pressure is ≤ 27 mmHg. Other professional societies have recommended that orthostatic hypotension be diagnosed in the presence of orthostatic symptoms when the decrease in systolic blood pressure is ≥ 20 mmHg.

other organ systems. Advanced CAN stages show an increase in resting heart rate (predominantly vagal lesion) and orthostatic hypotension (predominantly sympathetic lesion).

According to the recommendations of the Toronto Consensus Conference [6], initial diagnosis and follow-up should include at least two autonomic reflex tests for the detection of DCAN: HRV and the orthostatic test. Hence, the basic diagnostic tests include measurement of HRV during deep breathing and upon standing up, as well as blood pressure changes during the orthostatic test, with the following diagnostic constellations:

1 One abnormal HRV test: possible or early DCAN, which needs to be confirmed in further course;
2 At least two abnormal HRV tests: definitive or confirmed DCAN;
3 Orthostatic hypotension in addition to abnormal HRV tests: severe or advanced DCAN.

All symptomatic patients in whom the basic diagnostic tests have not revealed a definite abnormal finding undergo further, computer-aided tests performed by a specialist. In addition to confirming the diagnosis, these tests serve to establish the severity and risk assessment or prognosis of DCAN.

Gastrointestinal Autonomic Neuropathy

Gastrointestinal symptoms occur frequently in patients with diabetes mellitus. They lead to significantly impaired quality of life and require a diagnostic work-up and differential diagnosis. The history recorded within the basic diagnostic clarification should include detailed information about the following signs and symptoms: gastrointestinal symptoms including dysphagia/odynophagia, abdominal pain, nausea, vomiting, bloating, flatulence, diarrhea, constipation, fecal incontinence or blood in stool; duration and possible worsening of gastrointestinal symptoms; presence of B-symptoms (fever, weakness, weight loss) and their impact on quality of life.

Structural and infectious diseases should be excluded for all new onset complaints which have not yet been adequately diagnosed and which show a progressive course or are accompanied by warning symptoms (e. g. bleeding, anemia, early satiety, unexplained weight loss in excess of 10 %, dysphagia/ odynophagia, persistent vomiting, family or personal history of gastrointestinal tumors, previous peptic ulcers, enlarged lymph nodes, palpable masses, malnutrition, blood in stool, paradoxical diarrhea, age > 50 years). When symptoms last longer than 4 weeks and are subjectively troublesome, it should be decided, on the basis of these symptoms, whether to refer the patient to a specialist (e. g. to a physician experienced in gastroenterology) for further diagnostic clarification immediately or to try therapy first.

It is especially important to exclude relevant differential diagnoses, because numerous serious gastrointestinal disorders can manifest only through mild and/or non-specific symptoms, especially at their early stages. This applies, for example, to all gastrointestinal malignancies as well as disorders such as celiac disease and peptic ulcer.

Autonomic Neuropathy of the Urogenital Tract

Diabetic cystopathy is considered to be primarily a neurogenic sensorimotor dysfunction. Within the basic diagnostic clarification, every patient with diabetes should be regularly asked about micturition symptoms (micturitions per day, residual urine, urinary tract infections, weak urine stream, whether straining/use of abdominal muscles is required when urinating, incontinence) as well as about satisfaction with sexual life. In addition, a medication history should be taken so that undesirable side effects on the urinary tract can be recognized. The basic diagnostic steps should also include a micturition diary that is kept for 48 hours (frequency of micturition, voided volume and fluid intake volume). Another 48-hour micturition diary should be kept whenever the history information changes. In asymptomatic patients, the history should be taken annually.

In cases of functional sexual disorders, the basic diagnostic approach consists of targeted history questions directed at the couple. A more thorough work-up is indicated in cases of troublesome sexual life. The IIEF5 questionnaire (International Index of Erectile Function-5) is available for men [9] (▶ **Tables 4,5**).

Patients with micturition complaints should be referred to a urologist for further examination if they have increased residual urine (> 20 % of bladder capacity or > 100 mL) or recurrent urinary tract infections (i.e. more than three urinary tract infections over a period of one year).

Perioperative Care

Patients with DCAN have higher perioperative morbidity and mortality than those without DCAN. When elective surgery is to be performed, the following simple preoperative measures should be taken in order to detect any relevant autonomic neuropathies: medical history with basic personal and diabetes-specific data, risk factors/indicators and clinical correlates for diabetic sensorimotor and autonomic neuropathies; physical examination; and assessment of previous findings including previous anesthesia charts. Extended hemodynamic monitoring in patients with diabetic neuropathy is not mandatory, not even during major surgery. Like patients without neuropathy, those with diabetic autonomic neuropathy are allowed to eat solid meals up to six hours and drink clear liquids up to two hours before anesthesia induction.

Therapy

The foregoing principles of general treatment strategies for and prevention of diabetic sensorimotor neuropathy apply to autonomic neuropathies in the same way. However, with respect to pharmaco-

▶ **Table 3** Clinically important manifestations, associated diagnostics and special therapy of autonomic diabetic neuropathy in diabetes mellitus. Source: [2, 7].

Organ manifestations and clinical picture	Examination method	Therapy
Cardiovascular system		
▪ Resting tachycardia ▪ Reduced heart rate variability ▪ Orthostatic hypotension ▪ Exercise intolerance (inadequate increase of heart rate and blood pressure during physical activity) ▪ Perioperative instability with frequent drops in blood pressure and heart rate ▪ Reduced or absent perception of myocardial ischemia during physical activity ▪ Silent myocardial infarction or myocardial infarction with few symptoms ▪ Prolongation of the QT interval ▪ Sudden cardiac death	Basic diagnostics ▪ HRV while breathing deeply and after change of posture ▪ Orthostatic test Further diagnostics Autonomic function tests (test battery): ▪ Resting HRV (frequency and time domain) ▪ E/I ratio while breathing deeply ▪ Max/min 30:15-ratio ▪ Valsalva ratio (Valsalva maneuver) ▪ Orthostatic test ▪ 24-h HRV, syncope work-up	Cardiovascular autonomic neuropathy ▪ In general no special treatment necessary (important: diagnosis and therapy of coronary heart disease and heart failure) ▪ For sinus tachycardia cardioselective beta-blockers Orthostatic hypotension ▪ General measures: liberal salt intake, physical training, compression stockings, avoidance of hypotensive medications ▪ Medications with short half-lives that increase blood pressure (Midodrine) ▪ Fludrocortisone (start with a low dose)
Gastrointestinal tract		
All gastrointestinal manifestations	Basic GI diagnostics: ▪ Medical history ▪ Exclusion of structural and infectious diseases	
Dysphagia and reflux disease	*Further diagnostics:* Stage 1: ▪ Esophagogastroduodenoscopy ▪ Other imaging, as applicable Stage 2: ▪ Esophagus manometry ▪ 24-h pH monitoring with/without impedance measurement	Dysphagia: ▪ General measures ▪ Prokinetic agents in individual cases Reflux: ▪ Proton-pump inhibitors
Diabetic gastropathy (dyspepsia, postprandial hypoglycemia)	Stage 1: ▪ Esophagogastroduodenoscopy ▪ Abdominal sonography ▪ If necessary, other imaging examinations ▪ Laboratory tests Stage 2: ▪ Gastric emptying scintigraphy ▪ 13C-octanoic acid breath test	Gastroparesis (gastropathy): ▪ Dietary change: frequent, small, low fibre meals with less fat ▪ Adjust injection to meal interval ▪ Prokinetic agents (all off-label): metoclopramide, domperidone, possibly prucalopride, erythromycin for severe refractory symptoms ▪ Antiemetics can be added to the symptomatic therapy of nausea and vomiting (antihistamines, 5-HT3-antagonists), as applicable ▪ Gastric electrical stimulation (“gastric pacemaker”) ▪ Jejunal feeding tube ▪ Parenteral nutrition
Diabetic cholecystopathy	Laboratory tests, abdominal sonography	Cholecystectomy for symptomatic cholecystolithiasis as needed
Diabetic diarrhea (enteropathy) and exocrine pancreatic insufficiency	Stage 2: ▪ Endoscopy ▪ Abdominal sonography ▪ Laboratory tests, including examination of stool for pathogenic organisms ▪ Other imaging, as applicable Stage 2: ▪ Lactose/fructose/sorbitol hydrogen breath test ▪ Glucose hydrogen breath test ▪ Fecal elastase-1, as applicable ▪ Lactulose hydrogen breath test, as applicable ▪ D-xylose absorption test, as applicable	Diarrhea: ▪ Bulking agents ▪ Loperamide ▪ Cholestyramine ▪ Clonidine ▪ Octreotide ▪ In case of bacterial overgrowth of the small intestine: broad-spectrum antibiotics (e. g. ciprofloxacin, metronidazole, doxycycline, one after the other, for 10 days each); alternatively: (better tolerated, but off-label) Rifaximin over 10 days with medicinal yeast (e. g. Perenterol) Severe exocrine pancreatic insufficiency: ▪ Pancreatic enzymes

▶ **Table 3** Continued.

Organ manifestations and clinical picture	Examination method	Therapy
Diabetic constipation (hypomotility of the colon)	Stage 1: ▪ Digital rectal examination ▪ Ileocolonoscopy ▪ Laboratory tests ▪ Abdominal sonography, as applicable ▪ Other imaging, as applicable Stage 2: ▪ (MRT) defecography ▪ Anorectal manometry ▪ Hinton test ▪ Neurological examinations	Constipation: ▪ Sufficient liquid, fiber and physical activity ▪ Gelling agents (pectins, psyllium preparations) ▪ Fiber-rich foods (e. g. wheat bran, linseed) ▪ Laxatives (e. g. sodium picosulfate, bisacodyl, macrogol, lactulose/lactitol) depending on tolerance and efficacy ▪ Biofeedback for rectal emptying disorder, as applicable ▪ Prucalopride for delayed transit (a prokinetic agent, approved for laxative-refractory constipation)
Diabetic fecal incontinence	Stage 1: ▪ Digital rectal examination ▪ Rectal endosonography ▪ (MRI) defecography Stage 2: ▪ Anorectal manometry ▪ Neurological examinations, as applicable	Fecal incontinence: ▪ Antidiarrheal medications ▪ Pelvic floor gymnastics ▪ Biofeedback ▪ Sacral nerve stimulation in refractory cases, if applicable
Urogenital tract		
Diabetic cystopathy bladder emptying dysfunction	Basic diagnostics ▪ Micturition diary over 48 h	Cystopathy: ▪ Behavioural changes ▪ Electrical stimulation ▪ Biofeedback ▪ Anticholinergics ▪ Beta-3 adrenergic receptor agonists ▪ Alpha receptor blockers ▪ Antibiotic therapy, as applicable ▪ Bladder neck incision ▪ Self-catheterization ▪ Suprapubic cystostomy
	Further diagnostics ▪ Specific questionnaire (e. g. International Prostate Symptom Score (IPSS) questionnaire ▪ Uroflowmetry ▪ Residual urine measurement ▪ Digital rectal examination for men ▪ Urodynamic testing, as applicable	
Erectile dysfunction	Basic diagnostics Stage 1: ▪ Sexual history, IIEF-5 ▪ Laboratory tests ▪ Total (free) testosterone, prolactin, FSH, LH Stage 2 (optional): ▪ Test with a PDE-5 inhibitor (sildenafil, vardenafil, tadalafil)	Erectile dysfunction: ▪ Avoidance of medication side effects (caused by antihypertensives, tranquilizers, antidepressants) Stage 1: ▪ Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil) Stage 2: ▪ Erection aid system (vacuum pump) ▪ Corpus cavernosum auto-injection therapy Stage 3: ▪ Corpus cavernosum implant
	Further diagnostics Stage 3 (only if surgical therapy is planned/ indicated): ▪ Intracavernosal injection test ▪ Doppler/duplex sonography ▪ Cavernosometry/cavernosography ▪ Nocturnal tumescence measurement	Hypogonadism: ▪ Testosterone substitution
Neuroendocrine system (endocrine dysfunction)		
Hypoglycemia-associated autonomic dysfunction ▪ Blunted or absent hormonal counter-regulation ▪ Hypoglycemia unawareness ▪ Increased glucose threshold for hypoglycemia symptoms at blood glucose lowering ▪ Decreased catecholamine secretion when standing or upon physical exertion	▪ Tight blood glucose control (in particular self-monitoring), in particular during the night	▪ Avoidance of symptomatic and asymptomatic (often nocturnal) hypoglycemia ▪ Hypoglycemia awareness training (blood glucose awareness training; BGAT)

▶ **Table 3** Continued.

Organ manifestations and clinical picture	Examination method	Therapy
Sudomotor and vasomotor functions		
▪ Dyshidrosis, anhidrosis ("dry feet") ▪ Gustatory sweating	Sweat tests: QSART: Quantitative sudomotor axon reflex test TST: Thermoregulatory sweat test SSI: Silastic sweat imprint ACHSST: Acetylcholine sweatspot test Neuropad: Indicator plaster Sudoscan: Cutaneous electrochemical conductivity	▪ Topical agents containing fat or urea ▪ Avoidance of exposure to intense heat ▪ Prophylaxis in case of identified cause of sweating (dietary components) ▪ Anticholinergic drugs, clonidine (low dose) ▪ Topical glycopyrrolate cream ▪ In focal hyperhidrosis, botulinum toxin (Botox) can be tried
Pupillomotor system		
▪ Miosis ▪ Impaired pupil reflexes ▪ Reduced dark adaptation	▪ Clinical examination ▪ Infrared pupillography (constriction rate, dilatation rate, latency of pupillary light reflex)	▪ Advise patient of impaired dark adaptation and danger of night blindness ▪ Danger of glaucoma (check intraocular pressure)
Respiratory system		
▪ Central respiratory dysregulation with reduced respiratory drive in response to hypercapnia or hypoxemia ▪ Sleep apnea syndrome ▪ Respiratory arrest	Sleep laboratory, as applicable	Continuous positive airway pressure (CPAP) therapy, as applicable

▶ **Table 4** The IIEF-5 questionnaire (5-item International Index of Erectile Function). Data according to [9].

Over the past 6 months (For each question, tick only one answer that best describes the individual situation):					
1. How do you rate your **confidence** that you could get and keep an erection?	Very low	Low	Moderate	High	Very high
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Almost never/ never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always/ always
Points	1	2	3	4	5

therapy of symptomatic diabetic autonomic neuropathy, it must be noted that only a few larger controlled studies are available (exception: erectile dysfunction), so that some recommendations are based on additional evidence from studies performed in patients without diabetes who had the corresponding symptoms (▶ **Table 3**).

Therapeutic modalities for DCAN that extend beyond physical measures should be conducted only in facilities with competence in treating DCAN. Beta adrenergic blocking agents with intrinsic sympathomimetic activity (e.g. pindolol) and tricyclic antidepressants at clinically effective doses (e.g. amitriptyline, imipramine) should not be administered to patients with DCAN due to their unfavorable influence on HRV and increased risk of cardiac arrhythmias.

Manifest gastrointestinal disorders should be treated symptomatically and by the standards that also apply to patients without diabetes mellitus. However, diabetes specific risks and contraindications should be taken into account. Quantifiable gastrointestinal dysfunction which is not associated with subjective complaints, relevant morphological changes or impaired glycemic control does not require treatment.

Patients with diabetic gastropathy with accelerated gastric emptying should be advised to eat small meals that are distributed over the day and to avoid rapidly absorbed carbohydrates. Patients with diabetic gastroparesis should be advised to modify their diet, i.e. to eat small meals that are distributed throughout the day, with reduced fat and few fibres. General measures such as chewing thoroughly before swallowing and maintaining upright posture (for at least 30 min) after meals should be recommended. If symptoms persist, prokinetic agents can be tried. The approval of metoclopramide and domperidone has been restricted so that their administration as prokinetic drugs is an off-label use. The following criteria must be considered for off-label use: (1) proven efficacy, (2) favorable benefit-risk profile, (3) lack of alternatives - attempt at

▶ **Table 5** Interpretation of the IIEF-5 score for diagnosis of erectile dysfunction. Data according to [9].

Points for questions 1–5	Score (total)	Interpretation of erectile dysfunction (ED)
Question 1: _	5–7	Severe ED
Question 2: _	8–11	Moderate ED
Question 3: _	12–16	Mild to moderate ED
Question 4: _	17–21	Mild ED
Question 5: _	22–25	No ED
Points:		

healing. The treatment options for symptomatic gastrointestinal disorders are listed in ▶ **Table 3**.

Treatment of bladder dysfunction (diabetic cystopathy) should address the patient's subjective complaints (e.g. micturition complaints, urinary tract infections). Since some of the possible consequences of diabetic cystopathy (e. g. postvoid residual urine with subsequent damage to the upper urinary tract) can progress without symptoms or with only very discrete symptoms, a detailed and targeted history is the prerequisite for the recognition of these consequences, prevention of complications and the specific therapy. Behavioral training such as "timed voiding" (micturition by the clock) or "double voiding" (two urinations within a short period of time) can be conducted as initial measures, since improvement of bladder voiding is possible without medication or surgical intervention. Overall, the symptoms and consequences of diabetic cystopathy can only be influenced to a limited extent by pharmacotherapy. Urinary tract infections have to be considered as complicated in people with diabetes mellitus, if the metabolic situation is unstable and in presence of manifest diabetic complications. The duration of therapy for complicated urinary tract infections should be at least 7 days.

Symptomatic pharmacotherapy of various organ and functional systems (see Practical Tools, ▶ **Table 3**) should normally be initiated by appropriate specialists within the interdisciplinary cooperation.

Conflict of Interest

DZ received research funds from the companies Wörwag, Novartis and Mitsubishi Tanabe, honoraria for lectures from the companies Meda, Wörwag, BerlinChemie, Takeda, Lilly Grünenthal, Procter & Gamble, Novaremed, Bayer, Nevro and Impeto Medical and honoraria for consulting from the companies Meda, Wörwag, Takeda, Berlin-Chemie, Pfizer, Trigo Care, Grünenthal, Procter & Gamble, Novaremed, Bayer, Nevro Astellas, Teva, Lilly, Biogen, Novartis, Mitsubishi Tanabe, Shire, Allergan and Mundipharma.

References

[1] Haslbeck M, Redaèlli M, Parandeh-Shab F et al. Diagnostik, Therapie und Verlaufskontrolle der sensomotorischen diabetischen Neuropathien. In: Scherbaum WA, Lauterbach KW, Renner R, Hrsg. Evidenzbasierte Diabetes-Leitlinien DDG; 1. Aufl 2000 ISBN: 3-933740-12-6

[2] Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Neuropathie bei Diabetes im Erwachsenenalter – Langfassung. 2011. Version 1.2 http:// www.diabetes.versorgungsleitlinien.de; http://www.awmf-leitlinien.de

[3] Young MJ, Boulton AJ, MacLeod AF et al. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993; 36: 150–154

[4] Feldman EL, Stevens MJ, Thomas PK et al. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. Diabetes Care 1994; 17: 1281–1289

[5] Dyck PJ, Albers JW, Andersen H et al. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev 2011; 27: 620–628

[6] Spallone V, Ziegler D, Freeman R et al. Cardiovascular autonomic neuropathy in diabetes: Clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 2011; 27: 639–653

[7] Haslbeck M, Luft D, Neundörfer B et al. Deutsche Evidenz-basierte Diabetes-Leitlinie DDG. Diagnose und Therapie der autonomen diabetischen Neuropathien. Diabetes und Stoffwechsel 2001; 10: 113–132

[8] Zilliox L, Peltier AC, Wren PA et al. Assessing autonomic dysfunction in early diabetic neuropathy: The Survey of Autonomic Symptoms. Neurology 2011; 76: 1099–1105

[9] Rosen RC, Cappelleri JC, Smith MD et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Functi on (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999; 11: 319–326

[10] Martina ISJ, van Koningsveld R, Schmitz PIM et al. Measuring vibration threshold with a graduated tuning fork in normal aging and in patients with polyneuropathy. J Neurol Neurosurg Psychiatry 1998; 65: 743–747