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Review

Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: International expert consensus recommendations

Dan Ziegler[a,b,*], *Solomon Tesfaye*[c], *Vincenza Spallone*[d], *Irina Gurieva*[e,f], *Juma Al Kaabi*[g,h], *Boris Mankovsky*[i], *Emil Martinka*[j,k], *Gabriela Radulian*[l], *Khue Thy Nguyen*[m], *Alin O Stirban*[n], *Tsvetalina Tankova*[o], *Tamás Varkonyi*[p], *Roy Freeman*[q], *Péter Kempler*[r], *Andrew JM Boulton*[s]

[a] *Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany*
[b] *Department of Endocrinology and Diabetology, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany*
[c] *Diabetes Research Department, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom*
[d] *Department of Systems Medicine, Endocrinology Section, University of Rome Tor Vergata, Rome, Italy*
[e] *Department of Endocrinology, Federal Bureau of Medical and Social Expertise, Moscow, Russia*
[f] *Department of Endocrinology, Russian Medical Academy of Continuous Professional Education, Moscow, Russia*
[g] *Zayed Centre for Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates*
[h] *Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, Abu Dhabi, United Arab Emirates*
[i] *Department of Diabetology, National Medical Academy for Postgraduate Education, Kiev, Ukraine*
[j] *National Institute of Endocrinology and Diabetology, Lubochna, Slovak Republic*
[k] *Faculty of Health Sciences University of Ss. Cyril and Methodius in Trnava, Slovak Republic*
[l] *"N. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania*
[m] *Ho Chi Minh City University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam*
[n] *Asklepios Klinik Birkenwerder, Birkenwerder, Germany*
[o] *Department of Endocrinology, Medical University - Sofia, Sofia, Bulgaria*
[p] *Department of Internal Medicine, Faculty of Medicine, University of Szeged, Szeged, Hungary*
[q] *Department of Neurology, Harvard Medical School, Boston, MA, United States*
[r] *Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary*
[s] *Faculty of Biology, Medicine and Health, University of Manchester and Manchester University Foundation Trust, Manchester, UK*

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ABSTRACT

Diabetic sensorimotor polyneuropathy (DSPN) affects around one third of people with diabetes and accounts for considerable morbidity, increased risk of mortality, reduced quality

* Corresponding author.at: Institute for Clinical Diabetology, German Diabetes Center at Heinrich Heine University, Auf'm Hennekamp 65, 40225 Düsseldorf, Germany.
E-mail address: dan.ziegler@ddz.de (D. Ziegler).
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of life, and increased health care costs resulting particularly from neuropathic pain and foot ulcers. Painful DSPN is encountered in 13–26% of diabetes patients, while up to 50% of patients with DSPN may be asymptomatic. Unfortunately, DSPN still remains inadequately diagnosed and treated. Herein we provide international expert consensus recommendations and algorithms for screening, diagnosis, and treatment of DSPN in clinical practice derived from a Delphi process. Typical neuropathic symptoms include pain, paresthesias, and numbness particularly in the feet and calves. Clinical diagnosis of DSPN is based on neuropathic symptoms and signs (deficits). Management of DSPN includes three cornerstones: (1) lifestyle modification, optimal diabetes treatment aimed at near-normoglycemia, and multifactorial cardiovascular risk intervention, (2) pathogenetically oriented pharmacotherapy (e.g. α-lipoic acid and benfotiamine), and (3) symptomatic treatment of neuropathic pain including analgesic pharmacotherapy (antidepressants, anticonvulsants, opioids, capsaicin 8% patch and combinations, if required) and non-pharmacological options. Considering the individual risk profile, pain management should not only aim at pain relief, but also allow for improvement in quality of sleep, functionality, and general quality of life.

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1. Introduction

Diabetic neuropathy represents a condition that develops in the context of diabetes and cannot be attributed to other causes of peripheral neuropathy [1–3]. It manifests in the somatic and/or autonomic components of the peripheral nervous system. Diabetic sensorimotor polyneuropathy (DSPN) is the commonest form affecting approximately one third of people with diabetes, while its yearly incidence amounts to approximately 2% [4]. DSPN has been defined as a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates [5]. A simpler DSPN definition for clinical

practice is the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes [2,3]. Chronic peripheral neuropathic pain has been defined as persistent or recurrent pain lasting ≥3 months caused by a lesion or disease of the peripheral somatosensory nervous system [6]. Neuropathic pain due to diabetes has been defined as pain arising as a direct consequence of abnormalities in the somatosensory system in people with diabetes after exclusion of other causes [7]. Chronic painful DSPN is encountered in up to one fourth of people with diabetes [4]. Measures of DSPN have been identified as predictors of all-cause mortality and future neuropathic foot ulcerations as well as cardiovascular morbidity and mortality [8–10]. In the DIAD study, both sensory deficits and neuropathic pain were independent predictors of cardiac death or nonfatal myocardial infarction [11]. A community-based study from the UK, showed that reduced pressure sensation to a 10 g monofilament predicted cardiovascular morbidity [12]. In the ACCORD trial, a history of DSPN was the most important predictor for increased mortality in type 2 diabetes individuals receiving highly intensive diabetes therapy aimed at HbA1c < 6.0% [13]. A retrospective cohort study showed an increased risk of vascular events and mortality in type 2 diabetes patients with painful compared to those with non-painful DSPN [14] and in an epidemiological survey peripheral neuropathy was found to be common and independently associated with mortality in the U.S. population both with and without diabetes [15].

Despite its major impact on morbidity and mortality, DSPN remains an underestimated condition by physicians and patients alike. In a German population-based survey, 77% of the cases with DSPN were unaware of having the disorder, defined as answering “no” to the question “Has a physician ever told you that you are suffering from nerve damage, neuropathy, polyneuropathy, or diabetic foot?”. Approximately one quarter of the subjects with known diabetes had never undergone a foot examination [16]. In a German educational initiative, painful and painless DSPN were previously undiagnosed in 57 and 82% of the participants with type 2 diabetes, respectively [17]. Likewise, in cross-sectional studies in Qatar, 80% of type 2 diabetes patients with DSPN reported that they had previously not been diagnosed with or treated for this condition [18,19]. Underdiagnosis and hence underestimation of DSPN was also frequent in South-East Asia, possibly due to a lack of consensus on screening and diagnostic procedures [20]. Indeed, it has recently been reasoned that the challenge in most countries in this region is that even simple diagnostic tools such as the tuning fork are only available in a specialist setting [20]. Among U.S. physicians using a 10 g monofilament, only 31 and 66% were able to correctly identify mild/-moderate and severe DSPN, respectively [21].

A population-based survey from Germany revealed that only 38% of patients with painful DSPN (i.e. with average pain level during the past 4 weeks ≥4 on the numeric pain rating scale with 0 indicating no pain and 10 indicating worst pain imaginable) received medical treatment which comprised predominantly nonsteroidal anti-inflammatory drugs for which efficacy has not been demonstrated in neuropathic pain conditions [22]. Underdiagnosis and under-/mistreatment of DSPN in clinical practice may be related to a poor acceptance of guidelines. A survey among German family practitioners indicated that only 51% were clearly positive about guidelines and considered them to provide benefits for patient care. Implementation of clinical guidelines is often perceived as complicated and/or restricting the freedom of action for physicians [23].

The aim of the present report originating from an ***International Consensus Conference on diagnosis and treatment of diabetic sensorimotor polyneuropathy in clinical practice*** which took place virtually on 11th and 12th of November 2020 on the occasion of the World Diabetes Day is to provide clear, condensed, comprehensive and practical recommendations and algorithms for the screening, diagnosis and treatment of DSPN in clinical practice.

2. Consensus finding process

A panel of 15 experts comprising 14 diabetologists and 1 neurologist was selected for their contributions and specific expertise in the field of diabetic neuropathy including the chair (DZ) and three co-chairs (AJMB, PK, ST). More specifically, the participants were selected (1) to represent different geographical regions in the EU, UK, Eastern Europe, Russia, Middle East, Asia, and United States, (2) based on their position as key opinion leaders and chair functions in national and international medical associations, and (3) given their previous contributions to international consensus panels. Around half of the participants had contributed to the Toronto Consensus Panel on Diabetic Neuropathy (AJMB, RF, PK, ST, VS, TV, DZ), while three participants coauthored the Position Statement of the American Diabetes Association (AJMB, RF, DZ). The final list of invited experts was aligned among the chairmen before the participants were officially invited.

During the consensus finding process, experts shared their personal clinical experience and routine in diagnosing and treating DSPN and examined the recent literature and current guidelines to provide consensus recommendations and define algorithms for screening, diagnosis and treatment of DSPN that are relevant specifically for clinical practice. The aim was to derive consensus recommendations from published data, where available, using a hierarchical approach considering evidence from systematic reviews, meta-analyses, and single RCTs and to utilize the participating experts’ own clinical experience where evidence from clinical trials is lacking. To reach a consensus, the Delphi method was applied which is a structured communication technique where a panel of experts answers questionnaires in ≥2 rounds [24]. The number of voting rounds was not prespecified as the intention was to reach a consensus on each topic.

The first Delphi round was conducted via SurveyMonkey® before the conference comprising qualitative open-ended as well as “tick-box style” questions (see supplement 1) which were developed and aligned among the chairmen before the link was provided to all participants. The aim of the survey was to gather information about invited experts’ clinical practice and derive drafts for consensus recommendations and algorithms. The drafts were then discussed among and adjusted by the experts during the conference which was organized by Wörwag Pharma according to the instructions

Table 1 – Recent guidelines for pharmacotherapy of painful diabetic sensorimotor polyneuropathy (DSPN) and neuropathic pain in general.

	Painful DSPN					Neuropathic pain				
	ADA (US) 2017 [2]	IDF 2017 [27]	AAN (US) 2011 [28]	Canada 2018 [29]	DDG (Germany) 2021 [30]	NeuPSIG 2015 [31]	France 2020 [32]	NICE (UK) 2013/2020[&] [33]	JSPC (Japan) 2018 [34]	EFNS 2010 [35]
Tricyclic antidepressants	1	1	2	2	1	1	1	NC	1	1
Duloxetine	1	1	2	2	1	1	1	1	1	1
Venlafaxine	1	NC	2	2	NC	1	1	NR	NR	1
Gabapentin	1	1	2	2	1	1	1	1	1	1
Pregabalin	1	1	1	1	1	1	2[$]	1	1	1
Sodium channel blockers	NC	NC	NC	2[+]	NC	NR	NR	NR	NC	NR
Tramadol	3	2	2	3	1	2	2[§]	NR	2	2/3
Opioids	3[#]	2	2	3	2	3**	3	NR	3	2/3
Capsaicin 8% patch	NC	NC	2	NC	1	2	2[§]	NR	NC	NC
Lidocaine 5% patch	NC	NC	NC	NC	NC	2	1***	NC	NR	NC
α-Lipoic acid	NR	1*/2*	NC	NC	1	NC	NC	NC	NC	NC

Footnotes/Abbreviations: 1 = 1st line; 2 = 2nd line; 3 = 3rd line; NR = not recommended; NC = not considered; *intravenously, +valproate, #oxycodone not recommended, **tapentadol inconclusive, §weak recommendation, &non-specialist settings, ***focal pain; ADA: American Diabetes Association, IDF: International Diabetes Federation, AAN: American Academy of Neurology, DDG: German Diabetes Association, NeuPSIG: Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP), NICE: National Institute for Health and Care Excellence, JSPC: Japanese Society of Pain Clinicians, EFNS: European Association of Neurological Societies

by the chairmen. The second Delphi round was also conducted via SurveyMonkey® directly after the conference and included a voting on the finetuned statements and algorithms. A 9-point scale with the following numeric and descriptive anchors was used to measure agreement: strongly disagree (1), disagree (3), neutral (5), agree (7), and strongly agree (9). Ratings of ≤ 6 were considered as "disagreement" and ratings of ≥ 7 were considered as "agreement". A consensus was defined *a priori* based on $\geq 75\%$ of participants agreeing with the statement/algorithm. This approach is based on the results of a systematic review by Diamond et al. which reported a median threshold for finding a consensus at 75% (range: 50–97%) in Delphi studies [24]. For each statement and algorithm, the level of agreement is presented as the percentage vote of 15 experts.

3. Implementation of guidelines into clinical practice

In general, the main reasons for introducing clinical practice guidelines are to improve the quality of medical care and reduce health care disparities [25]. Guidelines for the screening, diagnosis and management of DSPN are of particular interest for both general practitioners and specialists, due to the high prevalence of the condition, its socioeconomic and health impact, the interdisciplinary nature, the need to weigh the potential risks against the proven benefits of a treatment for individual patients, and to make the best use of available resources [26]. Existing guidelines focusing on painful DSPN or neuropathic pain in general show inconsistencies as to their recommendations of pharmacotherapies as 1st, 2nd and 3rd line treatments [2,27–35] (Table 1), which may lower their credibility and create confusion [26]. The same applies to systematic reviews which are frequently inconclusive [36]. Conclusiveness of evidence was higher in systematic reviews which included more participants and randomized controlled trials (RCTs), searched more databases, conducted meta-analysis, and examined the quality of evidence [37].

For various pain conditions including painful DSPN, treatment adherence to published pain management guidelines was associated with lower proportions of hospitalizations, emergency department visits, and lower health care costs [38]. In the population-based Australian Diabetes, Obesity, and Lifestyle Study (AusDiab), 77% of participants with diabetes reported an eye examination within the previous 2 years, whereas only 50% reported that their feet were examined by a health care professional in the previous year [39]. Visiting a diabetes nurse in the past 12 months was an independent predictor of a foot examination. A single education session about foot examination for nurses resulted in an increase in the number of foot examinations by nurses in people with diabetes [40]. A practical approach to increase the frequency of routine foot examinations in patients with diabetes may be the incorporation into eye screening appointments. Such "one-stop" annual diabetes microvascular screening program has been shown to be feasible and well received by patients and staff alike [41–43]. A systematic review and meta-analysis of 14 studies revealed that different health education programs may help to increase foot self-care scores and reduce foot problems in people with diabetes [44]. On the other hand, the reported use of practice guidelines may not necessarily exert a measurable effect towards the intended reduction of health care disparities in patients with DSPN, but rather precipitate more clinical actions potentially contributing to increased cost of medical care as an unintended consequence [25]. Thus, further research is needed to better understand the unintended consequences of implementing clinical practice guidelines.

Table 2 – Consensus recommendations for the implementation of guidelines for DSPN into clinical practice.

	Consensus voting scale	Level of agreement
1.1 Guidelines should be clearer on diagnostic procedures, adequate treatment choices, dosing, and follow-up to encourage adoption into clinical practice.	9/strongly agree	67%
	8	13%
1.2 To ensure implementation of screening procedures even in the absence of neuropathic symptoms, risk assessment for cardiovascular and other risk factors as well as diagnosis and adequate treatment of DSPN into clinical practice, it is necessary to increase awareness and improve education about the disease among patients emphasizing their active role, health care practitioners, physicians, and relevant stake holders.	7/agree	20%
	6	0%
	5/neutral	0%
1.3 For time efficient routines in clinical practice, DSPN screening may be performed by trained staff such as nurses, diabetes educators or podiatrists and may be incorporated into e.g. eye screening or other routine procedures.	4	0%
	3/disagree	0%
1.4 A risk-based approach including screening for micro- and macrovascular complications should be applied.	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**100%***

Footnotes/abbreviations: *Ratings of ≤6 were considered as "disagreement" and ratings of ≥7 were considered as "agreement"; #A consensus was defined *a priori* based on ≥75% of participants agreeing with the statement; DSPN: diabetic sensorimotor polyneuropathy.

The consensus recommendations for the implementation of guidelines into clinical practice are given in Table 2.

4. Clinical characteristics of DSPN

DSPN usually manifests as a length-dependent distal-symmetrical, sensorimotor polyneuropathy. The most important underlying factors include age, height, obesity, hypertension, smoking, poor glycemic control, diabetes duration, hypoinsulinemia, and an adverse lipid profile [5]. DSPN is commonly but not invariably associated with autonomic involvement [2], may commence insidiously, and if intervention is not successful, it becomes progressive and chronic [2]. Lower-limb long axons appear more amenable to injury [2] and therefore DSPN clinically usually develops first in the feet. Subsequently, it progresses proximally and may also include the upper limbs. This corresponds to a "dying-back" type of axonal degeneration and patients typically present with a so-called "stocking-glove" like distribution of neuronal dysfunction [45].

Sensory nerve fiber involvement causes "positive" symptoms [46] such as pain, paresthesias, or dysesthesias as well as "negative" symptoms (signs, deficits) detectable as hypoesthesia including different sensory modalities relating to small (temperature, pain) and large fiber function (touch, pressure, vibration, position) and ataxic gait. However, this differentiation may be difficult for a symptom like "numbness" which can be classified as negative if the patient means a deficit of feeling without spontaneous symptoms or as positive if an asleep-numbness "like a hand that has gone asleep" is meant [46]. Remarkably, up to 50% of affected subjects do not report symptoms [2,3]. Conversely, up to one fourth of people with diabetes develop painful DSPN [4].

5. Screening and diagnosis of DSPN

The basic neurological assessment comprises the general medical and neurological history, inspection of the feet, and neurological examination using simple semi-quantitative bedside instruments [2].

5.1. *Patient history and assessment of neuropathic symptoms and signs*

Neuropathic symptoms include pain, characteristically described as burning, painful cold, lancinating, tingling, stabbing or shooting (electric shock–like), as well as non-painful neuropathic symptoms like paresthesias (tingling, prickling or ant-like sensations), dysesthesias (unpleasant abnormal sensation whether spontaneous or evoked), sensory ataxia (ataxic gait) or numbness (often described as "wrapped in wool" or like "walking on thick socks") [2]. Neuropathic pain may be accompanied by hyperalgesia (exaggerated response to painful stimuli) and allodynia (pain triggered by normally non-painful stimuli such as the contact of socks, shoes, or bedclothes). Neuropathic pain typically worsens at night and may interfere with daily activities and reduce the quality of life and sleep [2]. In addition to simple orientating questions, the "Douleur Neuropathique en 4 Questions" (DN4-Interview) may serve as a useful tool to screen for neuropathic pain in diabetes and may constitute a component in the assessment of painful DSPN in clinical practice [26,47,48].

Neuropathic symptoms may reflect different pathophysiology rather than signs, e.g. pain or paraesthesias may be related to the degree of compensatory regeneration rather than to the degree of nerve fiber damage. Moreover, symptoms may have a heterogeneous long-term course with

progression and regression to a similar extent [49]. Screening tools for neuropathic pain may offer guidance for further diagnostic evaluation and pain management but do not replace clinical judgment [50]. The intensity (severity) of neuropathic pain and its course can be assessed using an 11-point numeric rating scale (Likert scale) or a visual analogue scale.

Accumulating evidence indicates that the risk of polyneuropathy is increased in prediabetes [51]. In the general population of Augsburg, Southern Germany, the prevalence of polyneuropathy was 28% among subjects with known diabetes, 13% among those with impaired glucose tolerance (IGT) and 11% among those with impaired fasting glucose (IFG), while it was 7% among those with normal glucose tolerance (NGT) [52]. The corresponding prevalence rates of painful polyneuropathy were 13, 9, 4, and 1% [53]. Thus, screening of patients with prediabetes reporting symptoms of DSPN should be considered in clinical practice [2].

Small and large nerve fiber damage most frequently coexist in DSPN. Conclusive evidence from prospective studies for the postulated progression from early involvement of small fibers (inducing pain and/or dysesthesias as first symptoms) to later large-fiber dysfunction is missing [45,49,54]. In contrast, there is evidence in patients recently diagnosed with type 2 diabetes suggesting that parallel damage to small and large nerve fibers occurs early in the course of diabetes [55]. Hence, testing both small and large nerve fiber function with appropriate bedside tests is equally important.

The clinical examination of DSPN includes the use of semi-quantitative bedside instruments [45]. In clinical practice, assessment of large sensory nerve fiber function mainly comprises the measurement of vibration sensation (Rydel-Seiffer tuning fork or an alternative vibrating instrument), position sense (proprioception), and touch/pressure perception (e.g. with 10 g monofilament or alternatively the Ipswich touch test) [2,45,56–58]. Since vibration sensation declines physiologically with age, it is important to consider age-dependent normative values (lower limits for normal sensation using the Rydel-Seiffer tuning fork on the dorsal aspect of the hallux are 5/8 for age $\leq$ 39, 4.5/8 for age 40–59, 4/8 for age 60–74, 3.5/8 for age $\geq$ 75 years) [56]. When an automated device such as the Biothesiometer, Neurothesiometer, Maxivibrometer, Vibrameter, Vibratron or CASE IV System is used to quantitatively measure vibration perception threshold [59], age-related reference values provided by the manufacturer can be applied. If the monofilament test is applied to the dorsum of the big toe, it identifies DSPN. If applied to the sole of the foot, it may also be used to identify patients with high ulceration risk [2,60]. Small nerve fiber function can be assessed in clinical practice primarily by testing pain/sharp sensation (pinprick) and temperature discrimination [2,45,61,62]. Tools for assessment of autonomic small nerve fiber function such as the Neuropad® indicator test to determine cutaneous sweat production [63] or Sudoscan® to measure electrochemical skin conductance [64] may be used, but these devices were applied by the panel too infrequently in clinical practice to allow for a representative statement (see supplement 2).

5.2. *Differential diagnosis*

The following findings should alert the physician to consider causes for DSPN other than diabetes and trigger referral for a detailed neurological work-up: (1) predominant motor rather than sensory deficits, (2) pronounced asymmetry of the neurological deficits, (3) rapid development or progression of symptoms or deficits (4) mononeuropathy and cranial nerve involvement, (5) progression of the neuropathy despite optimizing glycemic control, (6) onset of symptoms and deficits in the upper limbs, (7) family history of non-diabetic neuropathy, (8) neurological findings exceeding those typical for DSPN, and (9) diagnosis of DSPN cannot be ascertained by clinical examination with the aforementioned semi-quantitative bedside tests [63].

The most important differential diagnoses from the general medicine perspective include neuropathies caused by alcohol abuse, uremia, hypothyroidism, monoclonal gammopathy, vitamin B12 deficiency, paraproteinemias, peripheral arterial disease, cancer, inflammatory and infectious diseases, and neurotoxic drugs. Differential diagnosis of DSPN should also consider that the causes may vary between different countries as well as urban and rural areas [20]. A meta-analysis found that diabetes patients treated with metformin had an increased risk of vitamin B12 deficiency showing dose- and duration-dependent reductions of serum vitamin B12 concentrations [65]. Annual assessment of the vitamin B12 status in people with diabetes treated with metformin was suggested [65].

The consensus recommendations for screening, clinical diagnosis, and differential diagnosis of DSPN are listed in Table 3.

The consensus recommendations for the individual modalities of sensory examination are shown in Table 4. Notably, clear evidence and detailed guidance on how to perform the semi-quantitative bedside tests and assess their results is often lacking in the literature.

For standardized assessment of the severity of both neuropathic symptoms and signs, various scores may be used, which vary with respect to their individual components [66–73] (Table 5).

To facilitate the physician's decisions, algorithms for screening, diagnosis, and management of DSPN in clinical practice were developed (Figs. 1-3). The corresponding levels of agreement are summarized in Table 6.

The consensus recommendation for an algorithm to screen for and diagnose DSPN in clinical practice is shown in Fig. 1.

6. Treatment of DSPN and neuropathic pain

There are three major principles in the management of DSPN: (1) optimal diabetes treatment including lifestyle modification, intensive glucose control and multifactorial cardiovas-

Table 3 – Consensus recommendations for screening, clinical diagnosis, and differential diagnosis of DSPN.

	Consensus voting scale	Level of agreement
Screening	9/strongly agree	53%
2.1 Patient history should encompass neuropathic pain characteristics, assessment of pain severity and interference with daily activities and sleep.	8	13%
	7/agree	34%
2.2 For screening or identification of neuropathic pain characteristics, appropriate questionnaires such as DN4 may be used.	6	0%
	5/neutral	0%
2.3 Patient history should encompass non-painful symptoms (e.g. paresthesias, numbness, sensory distortion).	4	0%
	3/disagree	0%
2.4 For clinical diagnosis of DSPN in practice, validated scores for neuropathic symptoms (e.g. NSS) and signs (e.g. NDS, MNSI-E) may be used.	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed[#]	**100%***
Diagnosis	9/strongly agree	40%
3.1 Bilateral impairment of vibration sensation with tuning fork (large fiber) and/or pinprick test (small fiber) may be appropriate as minimal criteria for diagnosis of DSPN in clinical practice.	8	13%
	7/agree	47%
3.2 The presence of neuropathic pain and signs of DSPN in the same distribution is suggestive of painful DSPN.	6	0%
	5/neutral	0%
3.3 Neuropathic pain in a plausible neuroanatomical distribution, i.e. distal symmetrical, may occur in the absence of a clinically evident DSPN.	4	0%
	3/disagree	0%
3.4 A single abnormal screening test bilaterally suggests the presence of DSPN and may require a more extended diagnostic workup.	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed[#]	**100%***
Differential diagnosis	9/strongly agree	46%
4.1 Consider other causes of polyneuropathy, e.g. drug-induced, by history.	8	27%
	7/agree	20%
4.2 Assessment of vitamin B12, serum protein electrophoresis, eGFR, TSH, blood count, magnesium and liver enzymes may be advisable.	6	0%
	5/neutral	0%
4.3 In addition, assessment of vitamin D status may be advisable.	4	0%
	3/disagree	7%
4.4 Consider referral to neurologist where appropriate.	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed[#]	**93%***

Footnotes/abbreviations: *Ratings of ≤6 were considered as "disagreement" and ratings of ≥7 were considered as "agreement"; [#]A consensus was defined *a priori* based on ≥75% of participants agreeing with the statement; DSPN: diabetic sensorimotor polyneuropathy; DN4: "Douleur Neuropathique en 4 Questions"; NSS: Neuropathy Symptom Score; NDS: Neuropathy Disability Score; MNSI-E: Michigan Neuropathy Screening Instrument Examination part; eGFR: estimated glomerular filtration rate; TSH: Thyroid-stimulating hormone.

Table 4 – Consensus recommendations for sensory examination in DSPN.

	Consensus voting scale	Level of agreement
Vibration sensation 5.1 Vibration sensation may be tested using a tuning fork. 5.2 The dorsal big toe (interphalangeal joint) constitutes the primary examination site. 5.3 When using a Rydel-Seiffer tuning fork, age-dependent thresholds according to Martina et al. 1998 are available [56]. 5.4 For automated devices, thresholds provided by the manufacturer are applicable. 5.5 If a calibrated tuning fork is not available, a simpler vibrating tool or tuning fork using an "on-off" or double-dummy technique with mock-applications may be used [60].	9/strongly agree	73%
	8	20%
	7/agree	7%
	6	0%
	5/neutral	0%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**100%***
Pressure/touch sensation 6.1 Pressure/touch sensation may be tested using a 10g monofilament or cotton wool/Q-tip or tissue. 6.2 This test can identify DSPN and feet at high risk of ulceration depending on the application site. 6.3 For identification of DSPN: - The dorsum of the big toe constitutes the primary examination site [60]. - Pressure/touch sensation is considered impaired if in total ≥5 out of 8 contacts (4 per foot) are not sensed by the patient [60]. 6.4 In resource-limited situations the Ipswich touch test may be an alternative [57,58]. 6.5 Allodynia can be assessed with a cotton wool/Q-tip, soft brush or tissue and by asking the patient if the stimulus provokes a painful sensation.	9/strongly agree	40%
	8	27%
	7/agree	33%
	6	0%
	5/neutral	0%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**100%***
Pain/sharp sensation 7.1 Pain or sharp sensation may be tested using a Neurotip™/Neuropen®, pinprick or similar. 7.2 The dorsal side of the big toe and foot constitutes the primary examination site. 7.3 Pain sensation is considered impaired if ≥2 out of 3 contacts per foot are not perceived as "painful" by the patient. 7.4 Painful areas may be tested for hyperalgesia.	9/strongly agree	60%
	8	20%
	7/agree	13%
	6	0%
	5/neutral	0%
	4	7%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**93%***
Temperature sensation 8.1 Temperature sensation may be tested using a Tiptherm®, cold tuning fork or similar. 8.2 The dorsal side of the foot and big toe constitute the primary examination sites. 8.3 Temperature sensation is considered impaired if ≥2 out of 3 contacts per foot are not correctly discriminated.	9/strongly agree	52%
	8	7%
	7/agree	27%
	6	0%
	5/neutral	0%
	4	0%
	3/disagree	7%
	2	7%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**86%***

Footnotes/abbreviations: *Ratings of ≤6 were considered as "disagreement" and ratings of ≥7 were considered as "agreement"; #A consensus was defined *a priori* based on ≥75% of participants agreeing with the statement; DSPN: diabetic sensorimotor polyneuropathy.

Table 5 – Scores for assessment of neuropathic symptoms and signs.

Score	NSS [66]	TSS [67]	NTSS-6 [68]	mTCNS [69]	NDS [66]	MNSI-E [70]	UENS [71]
Neuropathic symptoms	**X**	**X**	**X**	**X**	**–**	**–**	**–**
Burning	X	X	X	X			
Tingling/prickling	X	X	X	X			
Numbness/insensitivity	X	X	X	X			
Weakness	X	–	–	X			
Cramps	X	–	–	–			
Ataxia	–	–	–	X			
Pain/aching/tightness	X	X	X	X			
Sharp, shooting, lancinating pain	–	–	X	–			
Allodynia/hyperalgesia	–	–	X	–			
Upper limb symptoms	–	–	–	X			
Neuropathic signs	**–**	**–**	**–**	**X**	**X**	**X**	**X**
Foot inspection/ulcers				–	–	X	–
Ankle reflex				–	X	X	X
Muscle strength				–	–	–	X
Proprioception				X	–	–	X
Vibration sensation (tuning fork)				X	X	X	X
Pressure sensation (10 g monofilament)				–	–	X[a]	–
Light touch sensation				X	–	–	–
Pain sensation				X	X	–	X
Allodynia/hyperesthesia				–	–	–	X
Temperature sensation				X	X	–	–
Validation of score	**No**	**No**	**Yes** [68]	**Yes** [69,72]	**No**	**Yes**[a] [70,72,73]	**Yes** [71,72]
Threshold for DSPN (points)	**≥3***	**No**	**≥6**	**≥3**	**≥3***	**≥2.5**	**≥3**

Footnotes/abbreviations: X included in score; - not included in score; NSS: Neuropathy Symptom Score; TSS: Total Symptom Score; NTSS-6: Neuropathy Total Symptom Score-6; NDS: Neuropathy Disability Score; MNSI-E: Michigan Neuropathy Screening Instrument Examination part; mTCNS: Modified Toronto Clinical Neuropathy Score; UENS: Utah Early Neuropathy Scale; [a] validated before monofilament test was included in the score; DSPN: diabetic sensorimotor polyneuropathy; * minimum acceptable criteria for diagnosis of DSPN were defined as NDS ≥ 6 with or without NSS ≥ 3 or NDS ≥ 3 with NSS ≥ 6.

cular risk intervention, (2) pathogenetically oriented pharmacotherapy, and (3) symptomatic pain relief.

6.1. *Causal treatment*

In the large Look AHEAD study including overweight or obese participants with type 2 diabetes, a less prominent increase in neuropathic symptoms, but not neuropathic signs was observed in the group receiving an intensive lifestyle intervention program focusing on weight loss through reduced caloric intake and increased physical activity compared with the control group that was assigned to a diabetes support and education program [74]. The DCCT/EDIC study demonstrated that intensive insulin therapy aimed at achieving near-normal glycemia is essential to prevent, albeit not completely, or delay progression of DSPN in patients with type 1 diabetes. However, there is no convincing evidence in type 2 diabetes patients to suggest that intensive diabetes therapy has a favorable effect on the development or progression of DSPN. The Steno 2 Study assessed the effect of multifactorial cardiovascular risk intervention on diabetic complications, but could not demonstrate a favorable effect on DSPN [75–77]. Nonetheless, there is general agreement that glucose control should be optimized to prevent or slow the progression of DSPN in people both with type 1 and type 2 diabetes [2].

6.2. *Pathogenetically oriented pharmacotherapy*

The pathogenesis of diabetic neuropathy is multifactorial [78]. Hyperglycemia and dyslipidemia result in a substrate excess in mitochondria leading to mitochondrial dysfunction and overproduction of reactive oxygen species (ROS) and reactive carbonyls. ROS and carbonyl stress-mediated nuclear DNA damage activates poly(ADP-ribose) polymerase-1 (PARP1). Upstream inhibition of key glycolytic enzymes by oxidative stress activates major pathways implicated in the development of diabetic neuropathy: polyol pathway, hexosamine pathway, protein kinase C (PKC) activity, and advanced glycation end products (AGEs) pathway [79]. Based on these pathogenetic mechanisms, pharmacotherapies have been introduced to favorably influence the underlying neuropathic process rather than for symptomatic pain treatment [80].

For clinical use, the antioxidant α-lipoic acid and the thiamine derivative (prodrug) and AGE inhibitor benfotiamine are licensed as drugs and approved for treatment of DSPN in several countries worldwide [81,82]. Actovegin, a deproteinized ultrafiltrate of calf blood and poly(ADP-ribose) polymerase (PARP) inhibitor, is authorized mainly in Russia and eastern European countries, while the aldose reductase inhibitor epalrestat is marketed only in Japan and India [83,84]. Several meta-analyses demonstrated that infusions of α-lipoic acid (600 mg i.v./day) ameliorated neuropathic symp-

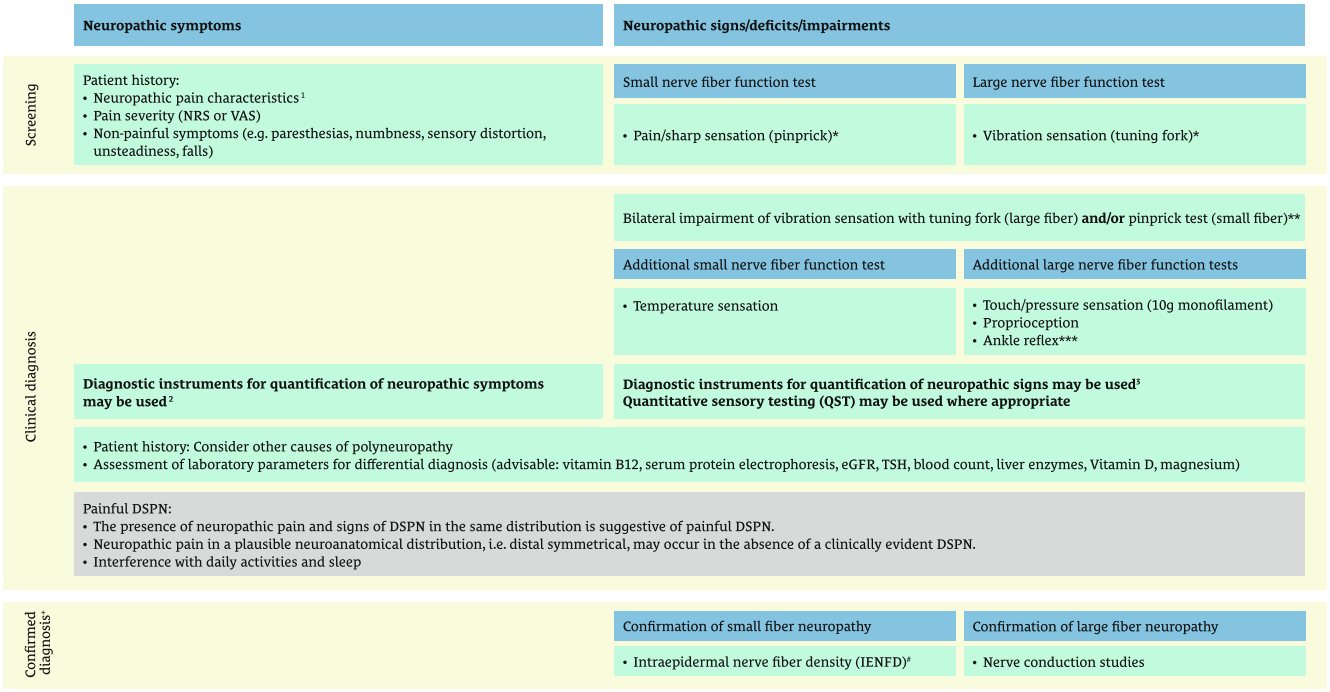

Fig. 1 – Consensus recommendation of an algorithm for screening and diagnosing DSPN in clinical practice. Footnotes/Abbreviations: * For screening purposes the application of one single test may be appropriate. A single abnormal screening test bilaterally suggests the presence of DSPN and may require a more extended diagnostic workup; ** minimal criteria for diagnosis of DSPN in clinical practice; *** CAVEAT: healthy elderly might show absent reflexes; + Confirmed diagnosis of DSPN based on Toronto Consensus criteria [5], consider referral to neurologist where appropriate; # Usually restricted to rare difficult cases in whom the diagnosis is uncertain. [1]The "Douleur Neuropathique en 4 Questions" (DN4-Interview) may be used to screen for neuropathic pain characteristics. [2]Includes e.g. the Neuropathy Symptom Score (NSS), Total Symptom Score (TSS) or Neuropathy Total Symptom Score-6 (NTSS-6). [3]Includes e.g. the Neuropathy Disability Score (NDS), Michigan Neuropathy Screening Instrument Examination part (MNSI-E), Modified Toronto Clinical Neuropathy Score (mTCNS) or Utah Early Neuropathy Scale (UENS). DSPN: diabetic sensorimotor polyneuropathy; eGFR: estimated glomerular filtration rate; NRS: numeric rating scale; VAS: visual analogue scale; TSH: thyroid-stimulating hormone.

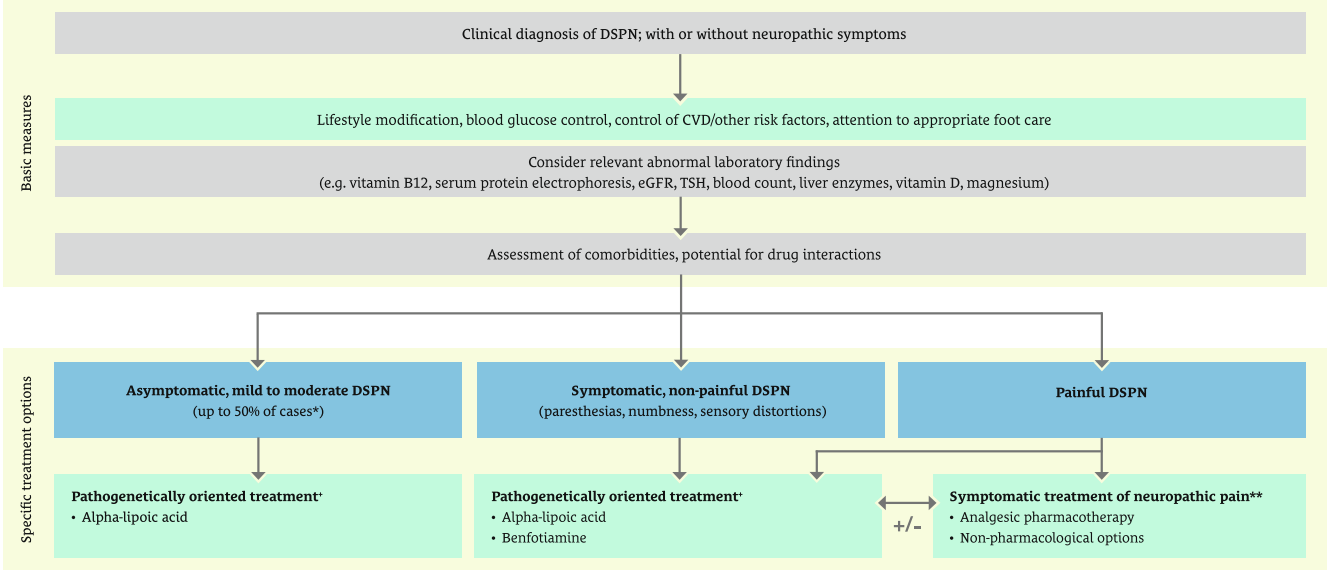

Fig. 2 – Consensus recommendation of an algorithm for the choice of treatment options for DSPN in clinical practice. Footnotes/abbreviations: + If available. Also improves deficits/impairment/signs; *according to Pop-Busui et al. [2]; ** for more details see Fig. 3 (algorithm for analgesic combinations); CVD: cardiovascular disease; DSPN: diabetic sensorimotor polyneuropathy; eGFR: estimated glomerular filtration rate; TSH: thyroid-stimulating hormone; QoL: quality of life.

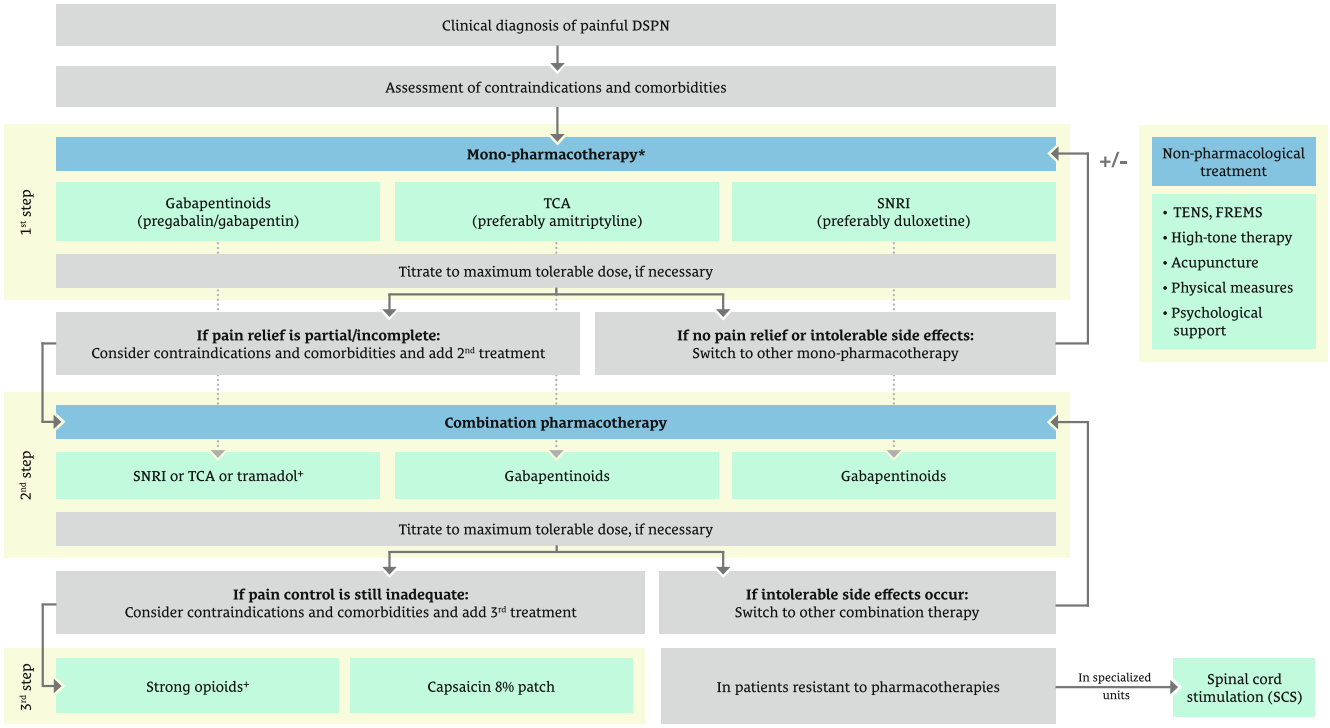

Fig. 3 – Consensus recommendation of an algorithm for analgesic pharmacotherapy and non-pharmacological treatment options in painful DSPN in clinical practice. Footnotes/abbreviations: * Pathogenetically oriented treatment approaches may also be considered; DSPN: diabetic sensorimotor polyneuropathy; TCA: tricyclic antidepressants; SNRI: serotonin-norepinephrine reuptake inhibitors; TENS: transcutaneous electrical nerve stimulation; FREMS: frequency-modulated electromagnetic neural stimulation; + for short term use only, whenever possible.

Table 6 – Levels of agreement for algorithms for screening, diagnosis and management of DSPN in clinical practice as depicted in Figs. 1-3.

Figure 1 Screening and diagnosing DSPN in clinical practice		**Figure 2** Choice of treatment options for DSPN in clinical practice		**Figure 3** Analgesic pharmacotherapy and non-pharmacological treatment options in painful DSPN	
Consensus voting scale	**Level of agreement**	**Consensus voting scale**	**Level of agreement**	**Consensus voting scale**	**Level of agreement**
9/strongly agree	46%	9/strongly agree	33%	9/strongly agree	39%
8	27%	8	40%	8	27%
7/agree	20%	7/agree	13%	7/agree	27%
6	0%	6	7%	6	7%
5/neutral	0%	5/neutral	0%	5/neutral	0%
4	0%	4	0%	4	0%
3/disagree	7%	3/disagree	0%	3/disagree	0%
2	0%	2	7%	2	0%
1/strongly disagree	0%	1/strongly disagree	0%	1/strongly disagree	0%
Overall agreement Consensus endorsed#	**93%***	**Overall agreement Consensus endorsed#**	**86%**	**Overall agreement Consensus endorsed#**	**93%***

Footnotes/abbreviations: *Ratings of ≤6 were considered as "disagreement" and ratings of ≥7 were considered as "agreement"; #A consensus was defined *a priori* based on ≥75% of participants agreeing with the statement; DSPN: diabetic sensorimotor polyneuropathy.

Table 7 – Dosages, adverse events and scientific evidence of pharmacotherapies used in the management of DSPN in clinical practice.

Drug	Class	Initial dose (mg/d)	Maintenance dose (mg/d)	Dosage regimen	Maximum authorized dose (mg/d)*	Very frequent adverse events**	Level of evidence
Pathogenetically oriented treatment of symptomatic DSPN							
α-lipoic acid°	Antioxidant	600 (oral or i.v.)	600 (oral)	1 shot	600 (i.v. and oral)	None	Meta-analyses [87–94]
Benfotiamine°	Vitamin B1 derivative	120–600	300	1 shot or spread over the day	450	None	RCTs [96,100]
Symptomatic treatment of painful DSPN							
Gabapentin°	α2δ Calcium channel ligand	300–600	1200–3000	3–4 divided dosages	3600 (if no renal impairment)	Somnolence, dizziness, ataxia, viral infections, fatigue, fever	Meta-analyses§ [94,97,98] Cochrane Review [99]
Pregabalin#$	α2δ Calcium channel ligand	75–150	150–450	2–3 divided dosages	600 (if no renal impairment)	Somnolence, dizziness, headache	Meta-analyses [93,94,97,98,101,102] Cochrane Review [103]
Duloxetine#$	SNRI	30	60	1 shot	120	Somnolence, headache, nausea, dry mouth	Meta-analyses [93,94,97,98,101,102,104] Cochrane Review [106]
Venlafaxin (ext. release)	SNRI	37.5	150–225	2–3 divided dosages	375	Insomnia, dizziness, sedation, headache, nausea, dry mouth, constipation, hyperhidrosis (incl. night sweats)	Meta-analyses [93,94,98,101,104]
Amitriptyline°	TCA	10–25	25–100	2 doses	150 (doses above 100 mg should be used with caution)	Somnolence, dizziness, headache, dysarthria, aggression, dry mouth, nausea, constipation, weight gain, hyperhidrosis, tachycardia, palpitation, orthostatic hypotension, tremor, accommodative dysfunction, nasal congestion, drowsiness	Meta-analyses [98,104]
Tramadol°$ (ext. release)	Weak μ-opioid, SRI	50–100	100–200	Spread over the day	400	Vertigo, nausea	Meta-analyses [93,94,101]
Oxycodone°$ (ext. release)	Strong μ-opioid	10–20	20–50	Spread over the day	400 (in single cases)	Sedation (fatigue to drowsiness), vertigo, headache, nausea, constipation (in individual cases up to intestinal obstruction), emesis, pruritus	Meta-analyses [94,98] Cochrane Review [105]
Tapentadol°$ (ext. release)	Strong μ-opioid, NSRI	50–100	up to 200	Spread over the day	500	Somnolence, vertigo, headache, nausea, emesis	Meta-analyses [93,94,101,102]
Topical analgesics							
Capsaicin 8% patch#$	TRPV1 agonist	n.a.	n.a.	Plaster applied for 30 min every 60–90 days	716 (equivalent to 4 plasters)	Pain and erythema at application site	Single RCT [107]

Footnotes/Abbreviations: ° National authorizations for treatment of DSPN; # Authorization by the European Medicine Agency (EMA) for the treatment of (neuropathic) pain or painful DSPN; $ Authorization by the U.S. Food and Drug Administration (FDA) for the treatment of (neuropathic) pain or painful DSPN; * based on Summary of Product Characteristics (SPCs) of originator products according to EMA or the Federal Institute for Drugs and Medical Devices in Germany (BfArM); ** Frequency of events ≥ 1/10 according to SPCs of originator products by EMA or BfArM; §mixed results; DSPN: diabetic sensorimotor polyneuropathy; i.v.: intravenous; n.a.: not applicable; RCTs: randomized controlled trials. TRPV1: Transient receptor potential vanilloid-1; SRI: Serontinin reuptake inhibitors; SNRI: serotonin-norepinephrine reuptake inhibitors; TCA: tricyclic antidepressants

toms and deficits (signs, impairments) after 3 weeks. Moreover, treatment for 5 weeks and 6 months using α-lipoic acid 600 mg QD and BID orally, respectively, reduced the main symptoms of DSPN including pain, paresthesias, and numbness [82,85–94]. In the NATHAN 1 trial, neuropathic deficits were improved after 4 years in patients with mild to moderate largely asymptomatic DSPN [86]. By contrast, vitamin E (mixed tocotrienols) as another antioxidant did not reduce neuropathic symptoms after 1 year of treatment [95]. The BENDIP study showed that neuropathic symptoms, with NSS as the primary endpoint, were improved after 6 weeks of treatment using a benfotiamine dose of 300 mg BID but not 300 mg QD [96]. Additional long-term RCTs could further strengthen the rationale for use in clinical practice. Both α-lipoic acid and benfotiamine, have favorable safety profiles even during long-term treatment. An overview on the usual dosages, most frequent adverse events, and scientific evidence is given in Table 7 [87–94,96–107].

The consensus recommendations for pathogenetically oriented pharmacotherapy of DSPN are summarized in Table 8.

6.3. *Symptomatic treatment of painful DSPN*

The following general considerations in the pharmacotherapy of neuropathic pain require attention [108,109]:

- The appropriate and effective drug has to be tried and identified in each patient by carefully titrating the dose based on efficacy and side effects.
- Lack of efficacy should be judged only after 2–4 weeks of treatment using an adequate dose.
- A reduction of pain of 30–49% may be considered a "clinically relevant" response. A reduction of ≥50% may be considered a "robust" pain relief associated with important beneficial effects on sleep interference, fatigue, and depression as well as quality of life, function, and work.
- Because the evidence from clinical trials suggests only a maximum response of 50% for any monotherapy, analgesic combinations may be useful.
- Potential drug interactions have to be considered given the frequent use of polypharmacy in diabetic patients.

Table 8 – Consensus recommendations for pharmacotherapy of DSPN.

	Consensus voting scale	Level of agreement
Pathogenetically oriented pharmacotherapy 9.1 α-lipoic acid and benfotiamine have been approved for the treatment of symptomatic DSPN Pathogenetically oriented pharmacotherapyies but not by the FDA and EMA. 9.2 Pathogenetically oriented treatment with α-lipoic acid and benfotiamine may be used for the treatment of symptomatic DSPN, where available. 9.3 Pathogenetically oriented treatment with α-lipoic acid may also be used for the treatment of neuropathic deficits, where available [86]. 9.4 The evidence for α-lipoic acid is stronger than for benfotiamine.	9/strongly agree	20%
	8	13%
	7/agree	60%
	6	0%
	5/neutral	7%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**93%***
Gabapentinoids 10. 1 Gabapentin or pregabalin are considered 1st line analgesic treatments for painful DSPN. 10.2 Titration is usually more convenient with pregabalin compared to gabapentin.	9/strongly agree	67%
	8	20%
	7/agree	13%
	6	0%
	5/neutral	0%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**100%***
Antidepressants 11.1 Duloxetine and amitriptyline are considered 1st line analgesic treatments for painful DSPN. 11.2 If duloxetine is not tolerated, venlafaxine could be an option. 11.3 Doses used in the treatment of painful DSPN are usually lower than in depressed patients.	9/strongly agree	46%
	8	27%
	7/agree	20%
	6	0%
	5/neutral	7%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**93%***
Tramadol 12.1 Tramadol is considered 2nd line analgesic treatment for painful DSPN. 12.2 If tramadol is not available or effective, preferably oxycodone or tapentadol could be an option, other strong opioids might be used depending on the experience of the physician. Referral to specialists or centers with expertise in strong opioid use is recommended. **Strong opioids** 12.3 Strong opioids are considered 3rd line analgesic treatments for painful DSPN. 12.4 Risk for abuse, misuse, dependence and tolerance should be assessed at the start of treatment and regularly during follow-up. 12.5 Any treatment longer than 3 months should be regularly reevaluated.	9/strongly agree	40%
	8	20%
	7/agree	27%
	6	0%
	5/neutral	13%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**87%***
Topical analgesics 13.1 Topical analgesics such as capsaicin cream (0.025-0.075%) or patch (8%) may be used in the treatment of painful DSPN in clinical practice. 13.2 Capsaicin (8% patch) is considered 3rd line analgesic treatment for painful DSPN, whereas there is no evidence for the cream.	9/strongly agree	26%
	8	20%
	7/agree	47%
	6	7%
	5/neutral	0%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**93%***

Footnotes/abbreviations: *Ratings of ≤6 were considered as "disagreement" and ratings of ≥7 were considered as "agreement"; #A consensus was defined *a priori* based on ≥75% of participants agreeing with the statement; DSPN: diabetic sensorimotor polyneuropathy. EMA: European Medicine Agency; FDA: U.S. Food and Drug Administration.

The most recent guidelines for pharmacotherapy of painful DSPN specifically and neuropathic pain in general are summarized in Table 1. These recommendations vary considerably depending on their trial selection criteria and methodology used. In summary, the most frequently recommended drug classes for the treatment of painful DSPN include α2δ subunit ligands (pregabalin, gabapentin), serotonin and norepinephrine reuptake inhibitors (preferably duloxetine), and tricyclic antidepressants (preferably amitriptyline). While some of these guidelines claim a high strength of evidence (SOE) for their recommendations of 1st choice agents, a recent systematic review concluded that the SOE for reducing pain associated with DSPN is moderate for the serotonin noradrenaline reuptake inhibitors (SNRI) duloxetine and venlafaxine and is low for tricyclic antidepressants (TCA) and anticonvulsants pregabalin, and oxcarbazepine, whereas gabapentin was not recommended at all [101]. For example, 8 out of 15 trials that evaluated the efficacy of pregabalin in painful DSPN failed to demonstrate significantly more pain reduction with this drug than with placebo, and gabapentin was rated as ineffective [101]. Likewise, in the Comparative Effectiveness Review Number 187 prepared for the Agency for Healthcare Research and Quality (U.S.), the only class with moderate strength of evidence for reducing pain associated with DSPN was SNRI, while pregabalin and oxcarbazepine, atypical opioids, botulinum toxin, and α-lipoic acid were more effective than placebo albeit with low SOE [93]. Since the strength of evidence derived from systematic reviews, on which recommendations for pharmacotherapy of painful DSPN are based, is highly variable, efforts should be made toward harmonizing these guidelines to prevent the treating physician from making wrong decisions.

6.3.1. *Gabapentinoids*

Pregabalin is the most frequently studied drug in DSPN. In contrast to gabapentin, it shows a linear, dose-dependent absorption in the therapeutic dose range and a more rapid onset [2]. Pregabalin and gabapentin may be used in patients with impaired liver and autonomic nervous system function and at markedly reduced doses also in patients with renal dysfunction. However, their use is associated with weight gain, oedema, and central nervous adverse effects such as somnolence or dizziness (Table 7). They should be used with caution in patients taking pioglitazone or those with congestive heart failure and NYHA class III or IV. A pooled trial analysis showed that the risk for adverse events was associated with increasing pregabalin dose but not older age [110]. An earlier meta-analysis reported that treatment with pregabalin improved neuropathic pain in patients with painful DSPN in a dose-dependent manner, with 600 mg/day being more effective than 300 mg/day [111]. A recent Cochrane review concluded that pregabalin shows efficacy in painful DSPN, whereby some people will derive substantial benefit with pregabalin, more will have moderate benefit, and many will have no benefit or will discontinue treatment [103]. Furthermore, the aforementioned recent systematic reviews suggested a low strength of evidence for pregabalin [93,101]. Another Cochrane review concluded that gabapentin at doses of 1800–3600 mg daily (1200 mg to 3600 mg gabapentin encarbil) can provide good levels of pain relief to some people with painful DSPN. Around 3 to 4 out of 10 participants with neuropathic pain achieved ≥50% pain relief with gabapentin, compared with 1 to 2 out of 10 for placebo. Over half of those treated with gabapentin will not have worthwhile pain relief but may experience adverse events [99]. In the COMBO-DN study, pregabalin (300 mg/day) was less effective in painful DSPN than duloxetine (60 mg/day), although there was no difference at maximum doses of each (pregabalin 600 mg/day and duloxetine 120 mg/day) [112]. The consensus recommendations on the use of gabapentinoids are summarized in Table 8. A recent meta-analysis suggested that misuse and abuse of gabapentinoids represents a growing problem in the U.S. and in Europe. Hence, cautious use in populations at risk and monitoring for signs of misuse or abuse is needed [113].

6.3.2. *Tricyclic antidepressants (TCA)*

The putative mechanisms of pain relief by antidepressants include the inhibition of norepinephrine and/or serotonin reuptake at synapses of central descending pain control systems and the antagonism of N-Methyl-D-Aspartate receptor. Among TCA, amitriptyline is more widely used in painful DSPN than nortriptyline, imipramine, and desipramine [98,104]. The most frequent adverse events of TCA include fatigue, dry mouth, and weight gain. TCA are contraindicated in patients with orthostatic hypotension, prostate hyperplasia, closed-angle glaucoma, unstable angina, recent (<6 months) myocardial infarction, heart failure, history of ventricular arrhythmias, significant conduction system disease, and long QT syndrome. Anticholinergic side effects may aggravate cardiovascular and colonic autonomic neuropathy (Table 7) and doses >100 mg should be avoided in elderly. Table 8 summarizes the consensus recommendations for the treatment with amitriptyline.

6.3.3. *Serotonin noradrenaline reuptake inhibitors (SNRI)*

Seven RCTs confirmed that duloxetine reduces neuropathic pain effectively and to a clinically meaningful degree in patients with painful DSPN. Systematic reviews consistently reported efficacy with moderate strength of evidence [93,101,106]. Pain severity but not variables related to diabetes or neuropathy has been identified to predict the effect size of duloxetine in painful DSPN [114]. Benefits include a favorable effect on concomitant depression, a frequent comorbidity in patients with painful DSPN [115], and unlike TCAs and gabapentinoids, the drug does not cause weight gain. However, duloxetine has to be avoided in patients with significant renal or hepatic disease, and most frequent adverse events include somnolence, headache, and nausea (Table 7). Blood pressure should be monitored during the treatment and the risk of bleeding should be considered in patients under anticoagulants. When discontinuing treatment with duloxetine, the potential of withdrawal symptoms ranging from 6 to 55% in RCTs and open trials, should be considered [116]. Consensus recommendations for duloxetine are given in Table 8.

6.3.4. *Opioids*

The best studied opioids in painful DSPN are tramadol (weak opioid agonist and SNRI), oxycodone (μ opioid agonist), and

tapentadol (μ opioid agonist and SNRI). However, Cochrane reviews concluded that only limited evidence is available from small studies using oxycodone and tramadol in painful DSPN [105,117]. Frequent adverse events include somnolence, headache, and nausea (Table 7). Since tramadol and tapentadol have serotonin reuptake inhibitor properties, these agents should not be combined with serotonergic drugs (caveat: serotonin syndrome). In a recent meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo [118]. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality. Opioids were associated with less pain relief during longer trials possibly due to opioid tolerance or opioid induced hyperalgesia [118]. The European clinical practice recommendations on opioids for chronic noncancer pain recently suggested to first optimize established non-pharmacological treatments and non-opioid analgesics and only thereafter to consider opioid treatment if established non-pharmacological treatments or nonopioid analgesics are not effective and/or not tolerated and/or contraindicated [119]. In a retrospective population-based cohort study, adverse outcomes were more common among patients with polyneuropathy (68% with diabetes) receiving long-term (≥90 days) compared with short-term (<90 days) opioid therapy, including depression, impaired functional status, opioid dependence, and opioid overdose [120], supporting a limitation of treatment duration for opioids to 3 months whenever possible. Opioid dependence (addiction or opioid use disorders) describes a maladaptive pattern of substance use with behavioural changes constituting one of the most important substance use disorders contributing to substantial morbidity and premature mortality [121]. Hence, prevention of harm due to opioids is an important aspect in clinical practice [121]. Consensus recommendations for the use of opioids are given in Table 8.

6.3.5. *Topical analgesics*

Topical analgesic therapy may be an alternative option to systemic pharmacotherapy, as it is associated with lower rates of side effects and has lower potential for drug interactions. Capsaicin, a highly selective agonist of transient receptor potential vanilloid-1 (TRPV1), is authorized as an 8% dermal patch for the treatment of peripheral neuropathic pain [122], yet should not be used in active skin lesions. In one RCT in patients with painful DSPN, capsaicin 8% patch applied for 30 min provided modest relief of pain within 3 months [107]. Application requires trained staff and suitable infrastructure and can be repeated every 2–3 months where appropriate (Table 7). A Cochrane Review focusing on topical low-dose (0.025–r0.075%) capsaicin treatment summarized that no conclusions could be drawn due to insufficient data [123]. Table 8 lists the consensus recommendations for topical analgesic treatment with capsaicin.

Lidocaine 5% patch is being used in patients with neuropathic pain due to postherpetic neuralgia [124], but has not been adequately studied in those with painful DSPN.

6.3.6. *Other interventions*

Simple analgesics (e.g. ibuprofen, diclofenac, paracetamol) do not constitute appropriate treatment options for painful DSPN. As concerns cannabis-based medicine, the potential benefits in chronic neuropathic pain might be outweighed by their potential harms [125], and treatment of neuropathic pain due to DSPN with the cannabinoid compound Sativex was not effective [126,127].

People with diabetes are at risk of developing vitamin D, vitamin B12 and/or other vitamin B deficiencies (see Table 3, differential diagnosis) [65,128–130]. In patients with deficient status, these vitamins should be supplemented. Vitamin B12 supplementation in deficient patients with DSPN has been shown to be effective in reducing neurophysiological parameters, pain intensity, and sudomotor function [131]. Excessive vitamin B6 ingestion may cause neurotoxicity [132–135]. Magnesium as a natural calcium antagonist, is known to block the N-methyl-D-aspartate (NMDA) receptor excitability and is of importance for nerve impulse conduction [136]. Evidence suggests that diabetes and DSPN are associated with reduced magnesium levels [137–139]. Symptoms such as paraesthesias and numbness have been described in magnesium deficiency [140,141]. Therefore, magnesium substitution may be relevant in diabetes patients with magnesium deficiency, but further studies are needed to draw general conclusions.

6.3.7. *Analgesic combination treatment*

Overall, only 50% of subjects with painful DSPN respond to analgesic monotherapy [31,109]. Therefore, combination pharmacotherapy is required in patients who have only partial response or in whom the drug cannot be further titrated due to intolerable side effects. There is agreement that patients should be offered the available therapies in a stepwise fashion. Effective pain treatment considers a favorable balance between pain relief and side effects without implying a maximum effect. Synergistic interactions of drug combinations might provide superior analgesia and fewer side-effects than monotherapy by targeting multiple mechanisms [31,109]. Although the evidence suggesting that combination therapy is superior to monotherapy is limited [142–144], patients who cannot tolerate higher doses or do not respond with sufficient pain relief may benefit from combination pharmacotherapy, in particular from combinations of gabapentinoids and antidepressants [145–147]. In the COMBO-DN study, titration to high-dose monotherapy with either pregabalin (300 mg BID) or duloxetine (60 mg BID) in non-responders with painful DSPN was equally effective as the combination of both (300 mg/day and 60 mg/day) over 8 weeks [112]. The OPTION-DM trial, that has just concluded has examined if two drug combination treatments (duloxetine, pregabalin and amitriptyline) provide additional analgesia than monotherapy (Selvarajah et al. trials). The advantages and disadvantages of the various drugs and drug classes used for treatment of painful DSPN under consideration of the various comorbidities and complications associated with diabetes as well as potential drug interactions are summarized in Table 9 [148].

6.3.8. *Non-pharmacological treatment*

Because there is no entirely satisfactory pharmacotherapy of painful DSPN, non-pharmacological treatment options such

Table 9 – Differential therapy of DSPN taking into account comorbidities and interactions (modified from Ziegler et al. [148]).

Drug/class	Duloxetine	Gabapentinoids (Pregabalin/ gabapentin)	Tricyclic antide pressants	Opioids	Capsaicin patch 8%	α-lipoic acid / benfotiamine
Depression	+[a]	±[a]	+	±	±	±
Generalized anxiety disorder	+	+	+	+	±	±
Insomnia	+	+	+	+	+	±
Autonomic neuropathy	±	±	↓[b]	↓[c]	±	+[d]
Obesity	±	↓	↓	±	±	±
Coronary heart disease	±	±	↓	±	±	±
Fasting blood sugar level	(↓)	±	(↓)	±	±	(+)[d]
Liver failure	↓	±	Dose adjustment[e]	Dose adjustment[e]	±	±
Severe renal insufficiency	↓	Dose adjustment	Dose adjustment[e]	Dose adjustment[e]	±	±
Interactions	↓	±	↓	±	±	±
Pathogenetically oriented therapy	No	No	No	No	No	Yes

Footnotes/abbreviations: + favorable effects, (+) limited evidence for favorable effects; ↓ unfavorable effects, (↓) limited evidence for unfavorable effects; ± no relevant effects; [a] Additional anxiolytic effect in generalized anxiety disorder (GAD); [b] Caution in micturition disorders or cardiovascular autonomic neuropathy due to anticholinergic side effects; [c] Caution due to slowing of gastrointestinal transit in gastrointestinal neuropathy; [d] Applies to α-lipoic acid only; [e] Depending on the single agent; DSPN: diabetic sensorimotor polyneuropathy.

Table 10 – Consensus recommendations for combination pharmacotherapy and non-pharmacological treatment in DSPN.

	Consensus voting scale	Level of agreement
Combination pharmacotherapy 14.1 In clinical practice different treatment approaches may be combined. 14.2 Possible combinations include a mix of different analgesic treatments (mainly antidepressants + gabapentinoids, or combinations with opioids as 3rd choice), analgesics plus pathogenetically oriented treatments (mainly antidepressants or gabapentinoids + α-lipoic acid or benfotiamine) as well as a mix of different pathogenetically oriented treatments (mainly α-lipoic acid + benfotiamine). 14.3 There is limited evidence in support of analgesic combinations compared to monotherapie	9/strongly agree	27%
	8	33%
	7/agree	27%
	6	0%
	5/neutral	13%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**87%***
Non-pharmacological treatment 15.1 Non-pharmacological treatment options such as psychological support, behavioral treatment, acupuncture, physical measures, transcutaneous electrical and electromagnetic stimulation (TENS, FREMS) may be used. 15.2 Electrical spinal cord stimulation may be indicated in patients resistant to pharmacotherapies, but should be done in specialized units. 15.3 Evidence supporting the efficacy of non-pharmacological treatments in DSPN is limited.	9/strongly agree	73%
	8	7%
	7/agree	20%
	6	0%
	5/neutral	0%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement Consensus endorsed#	**100%***

Footnotes/abbreviations: *Ratings of ≤6 were considered as "disagreement" and ratings of ≥7 were considered as "agreement"; . #A consensus was defined *a priori* based on ≥75% of participants agreeing with the statement; DSPN: diabetic sensorimotor polyneuropathy; TENS: transcutaneous electrical nerve stimulation; FREMS: frequency-modulated electromagnetic neural stimulation.

as psychological support, physical measures, transcutaneous electrical nerve or muscle stimulation, and acupuncture should always be considered despite the relatively low level of evidence [91]. In patients with refractory painful DSPN, spinal cord stimulation leads to pronounced pain relief and improved quality of life [149–151]. This invasive treatment option should be reserved for patients who do not respond to analgesic combination pharmacotherapy (Table 10).

Fig. 2 shows the consensus recommendation of the algorithm for the choice of treatment options for DSPN in clinical practice.

The consensus recommendation of the algorithm for analgesic mono- and combination-pharmacotherapy and non-pharmacological treatment options in painful DSPN in clinical practice is illustrated in Fig. 3.

7. Influence of COVID-19 pandemic and lockdown situation

Coronavirus disease 2019 (COVID-19) has brought several challenges in the management of people with diabetes. Nationwide studies in England and South Korea show that type 1 and type 2 diabetes are independently associated with worse clinical outcomes as well as with a significantly increased risk of in-hospital mortality with COVID-19 compared to people without diabetes [152,153]. Conversely, the COVID-19 pandemic interferes with diabetes care in several aspects: first, lock-down situations have reduced access to routine check-ups, screenings and educational programs; and second, diabetes health care professionals have been shifted to the care of COVID-19 patients [154]. A survey among 1829 diabetes nurses across Europe confirmed that psychological as well as physical problems, including acute hyperglycemia, and foot complications were perceived to have increased "a lot" in patients with diabetes [154]. A recent retrospective review of patients necessitating a consultation at the surgery service in 2020 confirmed an amputation risk that was 10.8 times higher during the pandemic versus before the pandemic. Additionally, the severity of infections and the risk of requiring a major amputation increased [155].

Virtual consultations with diabetes patients via telephone, e-mail or video consultations have increased during the COVID-19 pandemic [154,156]. Telemedicine has been proven effective in general diabetes care [157,158], especially in patients with high HbA1c (≥9%) to deliver more frequent consultations and in this way achieve greater improvement [157]. The use of telemedicine during the COVID-19 pandemic is in general well-received by the patients [159–161]. The majority of patients judged the remote visits as "useful" [160] and rated their experience as "just as good as" or "better than" their traditional face-to-face experience, yet 35% complained about the fact that a physical examination could not be performed [159]. Notably, patients seemed to be worried more about diabetic foot syndrome than COVID-19 [160]. As the implementation of remote monitoring for patients with chronic conditions increases, questions about the appropriate usage of this care model arise. It has recently been highlighted that clinical studies are urgently needed to identify which patients will benefit and which technologies are most useful and effective [161,162].

The management of patients with diabetic foot ulcers presents a unique challenge in the COVID-19 pandemic era because of the frequent need for "face-to-face" consultations

Table 11 – Consensus recommendations for the examination and management of DSPN during the COVID-19 pandemic and lockdown situation.

	Consensus voting scale	Level of agreement
16.1. Remote visits are becoming increasingly important, especially during the COVID-19 pandemic and lock-down situations. 16.2 Assessment of neuropathic symptoms via patient interview and completion of appropriate questionnaires and scores as well as access to electronic patient records constitute essential parts of remote visits. 16.3 Treatment of neuropathic symptoms may be initiated and adjusted via remote consultations. 16.4 Personal follow-up visits remain indispensable for all patients, especially for those at risk of foot ulceration. 16.5 As up to 50% of cases with DSPN may be asymptomatic [2], a high proportion of patients cannot be captured via remote visits and an appropriate examination by physicians is needed.	9/strongly agree	67%
	8	20%
	7/agree	13%
	6	0%
	5/neutral	0%
	4	0%
	3/disagree	0%
	2	0%
	1/strongly disagree	0%
	Overall agreement **Consensus endorsed#**	**100%***

Footnotes/abbreviations: *Ratings of ≤6 were considered as "disagreement" and ratings of ≥7 were considered as "agreement"; #A consensus was defined *a priori* based on ≥75% of participants agreeing with the statement; DSPN: diabetic sensorimotor polyneuropathy.

for wound care [156]. Strategies for risk stratification, management of diabetic foot problems and prevention of hospital admission have been described [156,163,164].

Although consensus guidelines and recommendations for pain management of patients with chronic pain have been released by pain medicine specialists [165–167], no data or experiences have been published concerning the screening of diabetes patients for DSPN or the management of patients with DSPN during the COVID-19 pandemic and lockdown situations. In the routine care of diabetes patients it is important to keep in mind the need for thorough examination of the feet [156]. Patients with asymptomatic DSPN might not be diagnosed with the condition and those who have "lost the gift of pain" are less likely to seek help when needed [156]. The consensus recommendations for COVID-19 pandemic and lockdown situation are summarized in Table 11.

8. Strengths and limitations

Strengths of the present consensus recommendations include (1) the holistic view on the treatment of DSPN, including pathogenetically oriented and symptomatic treatment approaches, (2) the use of a structured consensus finding process applying the Delphi methodology, (3) detailed recommendations for the screening and diagnosis in clinical practice, and (4) recommendations owed to the current topic of COVID-19 pandemic. This consensus report has also some limitations. (1) Not all relevant topics could be discussed in depth and were beyond the scope of the panel discussion such as pharmacoresistant neuropathic pain and (2) not all geographical regions were represented by the panel, as for example experts from Latin America or Australia did not participate.

9. Conclusions

The increasing burden of diabetes and its complications including DSPN constitute important public health challenges both at regional and global levels. While progress has been made over the last decades in understanding the pathophysiology of DSPN, the condition still remains poorly diagnosed and treated. Hence, effective strategies to improve these deficiencies need to be pursued. To reduce the burden resulting from DSPN and its sequela, adequate consideration and implementation of strategies aimed at early detection and prevention of the condition in national diabetes plans is imperative. Since the efficacy of available treatments for DSPN is limited, optimizing the therapeutic armamentarium to combat DSPN remains an area of substantial unmet medical need. The evidence for interventions in DSPN, as derived from systematic reviews on which recommendations are based, is often inconclusive. Therefore, therapeutic algorithms need to be harmonized and constantly updated to foster suitable and efficacious treatments in everyday routine. Here we provide recommendations and algorithms for screening, diagnosis, and treatment of DSPN in clinical practice.

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Author Contributions

DZ wrote the manuscript. DZ, ST, VS, IG, JK, BM, EM, GR, KTN, AOS, TT, TV, RF, PK, and AJMB contributed to the discussion and reviewed and edited the manuscript. All authors approved the final manuscript.

Declaration of Competing Interest

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Appendix A. Supplementary data

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