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ORIGINAL REPORT

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Neuropathic pain is not adequately treated in the older general population: Results from the KORA F4 survey

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Abstract

Purpose: We evaluated the pharmacological treatment of distal sensorimotor polyneuropathy (DSPN) among older subjects from the general population.

Methods: The study included subjects aged 61 to 82 years from the KORA F4 survey (2006-2008). DSPN was defined as the presence of bilaterally impaired foot-vibration perception and/or bilaterally impaired foot-pressure sensation. Pain intensity was assessed with the painDETECT questionnaire.

Results: From the included 1076 older persons, 172 (16%) persons reported pain in the lower extremities and DSPN was present in 150 (14%) subjects. Forty-eight people with pain in the lower extremities reported DSPN. Only 38% of the subjects with DSPN reporting an average pain level of ≥4 during the past 4 weeks received medical treatment, predominantly nonsteroidal anti-inflammatory drugs (NSAIDs 20% and opioids 12%). The medication of choice for neuropathic pain, antidepressants, anticonvulsants, and opioids was relatively being underused. However, opioids and neuropathy preparations were prescribed preferably for subjects with painful DSPN.

Conclusions: In the older general population, only a small proportion of subjects with painful DSPN receive analgesic pharmacotherapy. Although not recommended by guidelines for the treatment of neuropathic pain, NSAIDs were the most frequently used class of analgesic drugs.

KEYWORDS

aged, drug therapy, pain, pharmacoepidemiology, polyneuropathies

1 | INTRODUCTION

Distal sensorimotor polyneuropathy (DSPN) is common and associated with adverse effects on the health-related quality of life.[1-3] Distal sensorimotor polyneuropathy affects approximately one-third of the population with diabetes.[2] Management of DSPN is complex and so far unsatisfactory.[4,5] Of patients enrolled in a study from the UK (2004) with diabetes and chronic painful diabetic neuropathy, 12.5% (7/56) had never reported their symptoms to their treating physician and 39.3% (22/56) had never received any treatment for their painful symptoms.[6] At follow-up after 5 years, only 65% had ever received treatment for chronic painful diabetic neuropathy despite 96% (22/23) reporting pain to their physician.[7]

Treatment of painful DSPN should be tailored to individual requirements, taking into consideration present comorbidities, risk

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factors, and other aspects.[2] Guidelines for the treatment of painful neuropathies recommend antidepressants and anticonvulsants as the preferred medication for painful DSPN, and opioids are the second or third choice and add-on treatment for this condition.[8,9] Because of the lack of evidence from randomized controlled trials, current international guidelines for the treatment of painful DSPN state that there is no justification for using nonsteroidal anti-inflammatory drugs (NSAIDs) in this indication.[10] However, recent studies showed that patients with neuropathic pain more often use NSAIDs than medications with well-established efficacy.[11,12] So far, only a few studies have investigated to what extent evidence-based recommendations for painful polyneuropathy treatment are applied by the treating physicians, yet most of these prior studies were based mainly on patient groups and not on population-based samples suffering from DSPN.[13-17] Thus, the aim of the present study was to assess the characteristics and medical treatment of subjects with DSPN in men and women from the older general population.

2 | SUBJECTS, MATERIALS, AND METHODS

2.1 | The KORA F4 study

The present data are based on the KORA (Cooperative Health Research in the Region of Augsburg) F4 Study (2006-2008): This was a follow-up of the KORA S4 study, a population-based health survey conducted between 1999 and 2001. The S4 survey included 2656 subjects aged 55 to 74 years, who were living in the region of Augsburg, Germany, in 1999.[18] Of these, 1653 participated and 1353 completed an oral glucose tolerance test (OGTT) at baseline. This cohort was reexamined between 2006 and 2008 (F4 survey).[19,20] Of the initial 1353 subjects, a total of 1209 (89%) participated in the follow-up measurements. A total of 1076 participants aged 61 to 82 years with successful OGTT and complete follow-up data, including neurological testing, were included in this study (see Figure 1).

The data collection and procedures in the KORA F4 study are described in the Supporting Information S1 and in prior published work.[19]

2.2 | Definition of distal sensorimotor polyneuropathy

We defined the presence of clinical DSPN as bilateral impairment of foot-vibration perception and/or bilateral impairment of foot-pressure sensation. Vibration perception was assessed at the dorsal side of the left and right big toe, using a calibrated 64-Hz Rydel Seiffer tuning fork. Increased vibration perception threshold was calculated according to Martina et al.[20] Pressure sensation was measured at the dorsal side of the left and right big toe in between the nail fold and the metatarsophalangeal joint, using a 10-g monofilament (Twin-Tip, Heinsberg, Germany). Participants were asked to close their eyes during the test and to respond with "yes" each time the monofilament was sensed. No negative stimuli were tested. At least 8/10 correct responses were considered to indicate normal sensibility.[21] Less than 8 perceived applications indicated reduced sensibility, and in the case none of the applications were perceived, sensibility to touch was considered absent. Measurements of vibration perception and pressure sensation were performed by trained investigators under supervision of an experienced diabetologist,[22] and according to the practical guidelines for the diabetic foot from the American Diabetes Association and the International Diabetic Foot Working Group.[23,24] We have validated our clinical DSPN definition against nerve conduction studies as described elsewhere.[2]

2.3 | Definition of neuropathic pain

Neuropathic pain was assessed using the painDETECT questionnaire.[25] This validated 1-page questionnaire is specifically directed to neuropathic pain symptoms and is easily to be completed during a clinic visit. The painDETECT questionnaire comprises a total of 12 questions about the severity, course, and quality of pain. Pain intensity is to be rated on a 0 to 10 numerical rating scale (NRS) for 3 pain characteristics: current pain, strongest pain during the past 4 weeks, and average pain during the past 4 weeks. Common pain sites are then to be marked on a body diagram, and the participant is asked if pain radiates to other body regions (yes/no). Next, the participant is asked to choose 1 of 4 different pictures that best describes the course of the pain, and finally, the participant is asked about the quality of pain in the following categories: burning pain, spontaneous paraesthesias, mechanical allodynia, spontaneous pain attacks, thermal hyperalgesia, and numbness.

Using the marked pain site(s) on the body diagram of the painDETECT questionnaire, we defined pain locations for each participant. Bilateral pain in the feet was defined as having marked both the left and right foot in the body diagram, regardless of further locations being marked. Bilateral pain in the lower extremities was defined as having marked both left and right feet, ankles, lower legs, knees, and/or upper legs, regardless of further marked pain sites. Pain elsewhere was defined as any site on the body diagram being marked bilaterally except for both lower extremities.

2.4 | Definition of diabetes

Subjects were classified as having diabetes based on self-reported physician diagnosis of diabetes or use of antidiabetic medication (n = 173). A further 903 persons without known diabetes were successfully evaluated by a standard 75-g OGTT after an overnight fast of at least 10 hours.[26] Newly diagnosed diabetes, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and normal glucose tolerance (NGT) were defined according to the 1999 World Health Organization diagnostic criteria.[19,27] Subjects with new diagnosis of diabetes were grouped together with those having known diabetes. Subjects with IFG and IGT comprised the prediabetic group. In total, 564 subjects had normal glucose tolerance, 233 had diabetes, and 279 had prediabetes.

2.5 | Medication use and definition of pain treatment

Information on medication use (up to 7 days prior to the interview by recording every medication package with the information that a physician prescribed or advised this for neuropathic pain) was gathered during a standardized interview. All pharmaceutical data were coded using the Anatomical Therapeutic Chemical index.[28]

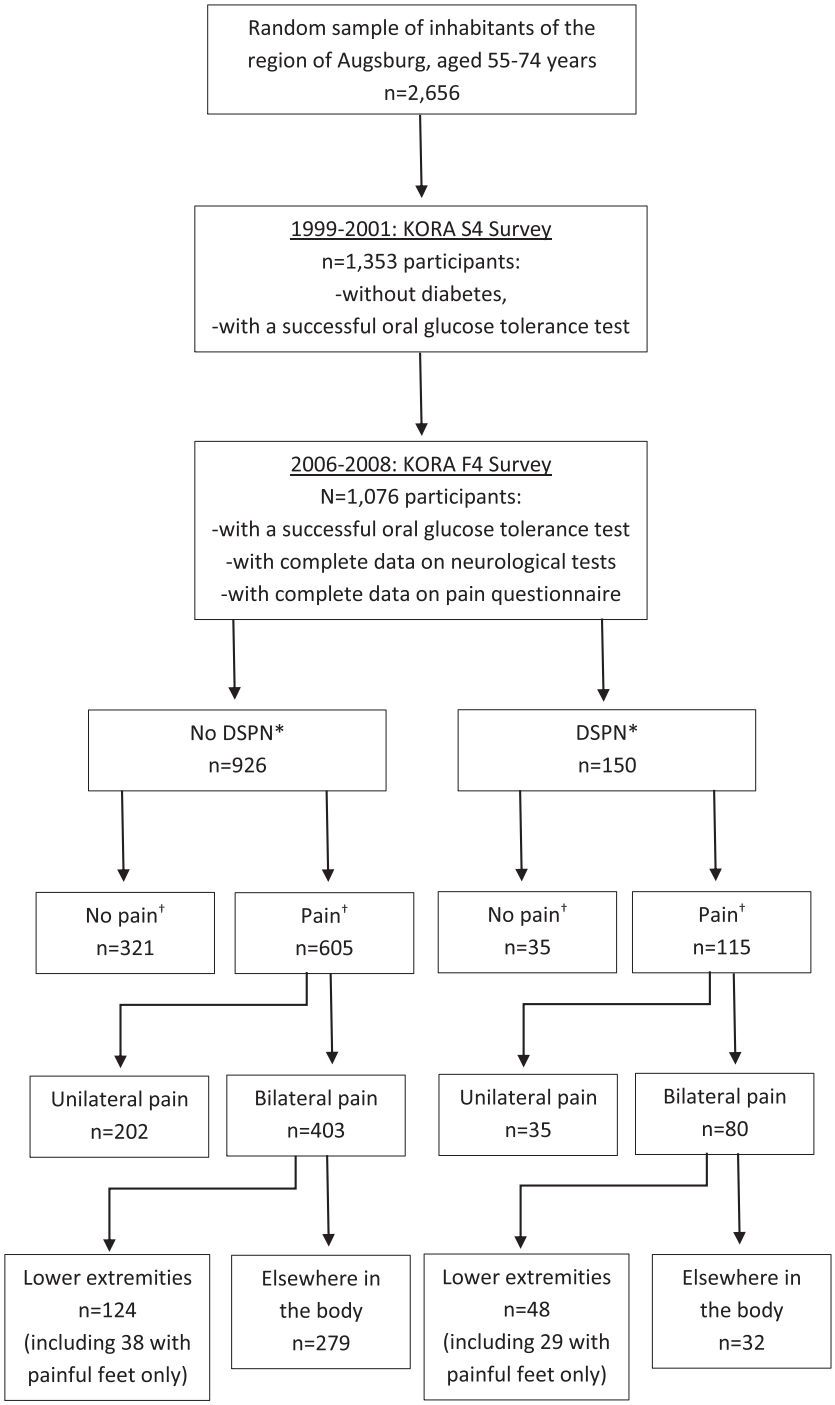

FIGURE 1 Flow chart of the study population. KORA, the Cooperative Health Research in the Augsburg Region; DSPN, distal sensorimotor polyneuropathy. *The presence of DSPN was defined as bilateral impairment of foot-vibration perception and/or bilateral impairment of foot-pressure sensation. †Having pain was defined using as scoring the average level of pain during the preceding 4 weeks on a numerical rating scale anywhere from 1 to 10 (painDETECT questionnaire). Subsequently, having no pain was defined as a pain level that was reported as being "0"

National and international guidelines were used to identify medication recommended for treatment of neuropathic pain.[29-32]

Anatomical Therapeutic Chemical-coded variables for the following drug class were built (see also Supporting Information S2):

- Antidepressants
- Anticonvulsants
- Opioids
- NSAIDs (only included if a physician prescribed or advised NSAIDs for neuropathic pain and without over-the-counter medication)
- Muscle relaxants
- Analgesics (only included if a physician prescribed or advised analgesics for neuropathic pain and without over-the-counter medication)
- Neuropathy preparations
- Topical agents

2.6 | Clinical chemical measurements

A fasting venous blood sample was obtained from all study participants while sitting. All parameters were measured immediately. Blood

glucose was analyzed using a hexokinase method (GLU Flex, Dade Behring). Total serum cholesterol analyses were carried out using a CHOD-PAP method (Dade Behring). Serum creatinine was determined using a modified kinetic Jaffé reaction.[19] HbA1c was measured with a reverse-phase cation exchange high-pressure liquid chromatography (HPLC) method (Menarini analyzer HA 8160).

2.7 | Statistical analysis

Statistical analysis was carried out with the STATA statistical software package (Version 11, StataCorp LP, USA). Follow-up characteristics were presented as means ± SD for normally distributed variables and as median (interquartile range) for variables without a normal distribution. Age-adjusted and sex-adjusted differences in characteristics were evaluated using analysis of variance ANOVA for the following subgroups within the total study sample: (1) participants with DSPN and an average NRS pain level during the preceding 4 weeks <4 versus participants with DSPN and an average NRS pain level during the preceding 4 weeks ≥4; (2) participants with DSPN and bilateral pain in the feet, participants with DSPN and bilateral pain in the lower extremities (including the feet) versus participants with DSPN and bilateral pain elsewhere in the body; and (3) participants without DSPN but with an average NRS pain level during the preceding 4 weeks ≥4 and bilateral pain in the lower extremities versus participants with DSPN and an average NRS pain level during the preceding 4 weeks ≥4 and bilateral pain in the lower extremities. For log-normal variables, ANOVA was performed on a log scale. The level of statistical significance for 2-sided testing was set uniformly at $\alpha < 0.05$. To reduce the chances of obtaining false-positive results because of performing multiple pairwise tests, we additionally applied a Bonferroni correction. With 28 different characteristics examined, a corrected *P* value <.002 was required.

3 | RESULTS

A flow chart of the study population is presented in Figure 1. From the population-based sample including 1076 persons aged 61 to 82 years, DSPN was present in 150 (14%) subjects. Of the participants with DSPN, 115 reported to have pain (pain level between 1 and 10), 80 of whom reported to have bilateral pain. Of the participants without DSPN, 124 reported bilateral pain in the lower extremities. A subsequent 48 participants had bilateral pain in the lower extremities, including 29 people with pain in the feet only. The demographic and clinical data as well as the medication use of subjects with DSPN (n = 150) and an average NRS pain level during the preceding 4 weeks <4 in comparison to subjects with DSPN and an average NRS pain level during the preceding 4 weeks ≥4 are shown in Table 1 (location of pain was not taken into account). Altogether 38% of older subjects with DSPN who reported an average pain level of ≥4 during the past 4 weeks received medical treatment. Subjects with NRS ≥4 (a higher pain level) had significantly more often additional neurological disease than those with NRS <4. No significant differences between the groups were noted for age, sex, systolic and diastolic blood pressure, alcohol consumption, smoking, physical activity, body mass index, prediabetes, diabetes, fasting and 2-hour glucose levels, HbA1c levels, total cholesterol, and creatinine values. Persons with NRS pain level ≥4 more often reported the use of NSAIDs (20%) and opioids (12%) in comparison with persons with NRS <4, but these differences were not statistically significant after Bonferroni correction ($P < .002$). The groups did not differ regarding the treatment with antidepressants, anticonvulsants, muscle relaxants, analgesics, neuropathy preparations, and topical preparations (Table 1).

Table 2 shows the comparison of the characteristics and medical treatment between subjects with DSPN and NRS pain level >0 in the feet (n = 29) or in the entire lower limbs (n = 48) versus pain elsewhere (n = 32). No significant differences regarding the characteristics and blood parameters were found between the groups. There was no difference in drug treatment between the 3 groups shown in Table 2. Altogether, NSAIDs were used most, while antidepressants and anticonvulsants being the treatments of first choice recommended by guidelines were relatively underused compared to NSAIDs and opioids.

Table 3 shows the comparison of characteristics and medical treatment between subjects with an average NRS pain intensity in the lower limbs during the past 4 weeks >0 stratified by the presence or absence of DSPN. As to be expected, subjects with DSPN were taller than those without DSPN, were more often male and had higher HbA1c levels, less often a normal glucose tolerance as well as more often diabetes and neurological disease. Regardless of whether DSPN was present or not, NSAIDs were the most frequently used medication. Antidepressants and anticonvulsants were used relatively infrequently, while opioids and neuropathy preparations were significantly more often prescribed in subjects with DSPN compared to those without DSPN.

4 | DISCUSSION

The present population-based study showed that only 38% of older subjects with DSPN who reported an average pain level of ≥4 during the past 4 weeks received medical treatment. Receiving treatment was independent of the location and type of the pain. Nonsteroidal anti-inflammatory drugs appeared to be the most frequently used class of medication in subjects with painful DSPN, although current international guidelines do not recommend NSAIDs for the treatment of neuropathic pain.[2,8,29] Drug classes of choice for neuropathic pain such as antidepressants and anticonvulsants were relatively being underused. However, our study found that not NSAIDs but opioids and neuropathy preparations were prescribed preferentially in subjects with pain in the lower extremities and with the presence of DSPN. This might indicate that NSAIDs are not predominantly used for painful DSPN but rather used for other comorbidities with pain symptoms. Earlier studies reported a considerable proportion of NSAID use in control patients who did not have neuropathic pain.[11,12]

So far, only a few studies have investigated whether and to what extent evidence-based recommendations for neuropathic pain treatment are applied by physicians.[13,14,16,17] A recent study based on data from the General Practice Research Database (GPRD) in the UK including 5920 patients with post-herpetic neuralgia (PHN), 5340 with painful diabetic neuropathy (PDN), and 185 with phantom limb pain

TABLE 1 Comparison of characteristics and medical treatment between subjects with DSPN and an average pain level during the preceding 4 weeks <4 (on a 0-10 Likert scale) and subjects with DSPN and an average pain level during the preceding 4 weeks ≥4

	DSPN[a] and Average Pain[b]		
	<4	≥4	*P* Value[e]
Characteristics			
N	84	66	
Age (years)	71.7 ± 5.9	72.3 ± 5.6	.596
Sex (% men)	60	65	.529
Height (cm)	168 ± 8.6	168 ± 9.4	.220
Body mass index (kg/m^2)	28.8 ± 4.8	29.5 ± 4.2	.278
Waist circumference (cm)	100 ± 13.0	103 ± 12.3	.142
Systolic blood pressure (mm Hg)	126 ± 17.3	130 ± 22.5	.226
Diastolic blood pressure (mm Hg)	72.2 ± 10.2	70.8 ± 12.0	.533
Hypertension (% yes)	60	74	.071
Smoking (% yes)	5	8	.101
High alcohol consumption (% yes)[c]	15	14	.522
Low physical activity (% yes)	54	68	.086
Normal glucose tolerance (% yes)	46	35	.178
Prediabetes (% yes)	25	29	.335
Diabetes (% yes)	29	36	.329
Presence of neurological disease (% yes)	18	45	<.001
Blood concentrations			
Fasting glucose (mg/dL)[d]	97.3 ± 9.9	99.9 ± 14.8	.263
2-Hour glucose (mg/dL)[d]	127 (95-155)	133 (114-168)	.178
Hb1Ac (%)	5.9 ± 0.7	6.0 ± 0.9	.357
Total cholesterol (mg/dL)	207 (182-238)	198 (176-227)	.323
Creatinine (mg/dL)	0.9 (0.8-1.1)	1.0 (0.9-1.2)	.137
Medication use			
Antidepressants (%)	6	9	.460
Anticonvulsants (%)	1	3	.416
Opioids (%)	1	12	.004
NSAIDs (%)	7	20	.024
Muscle relaxants (%)	1	3	.323
Analgesics (%)	0	2	.272
Neuropathy preparations (%)	4	2	.416
Topical agents (%)	0	0	-

Data are presented as mean ± sd or as median (interquartile range).

Hb1Ac, glycosylated hemoglobin A.

[a]Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

[b]Extracted from the painDETECT questionnaire. Pain intensity ≥4 is generally considered as clinically relevant and in requirement of treatment (location of pain was not taken into account).

[c]For women ≥20 g/day and for men ≥40 g/day.

[d]Subjects with known diabetes were excluded because of inadequate fasting, based on 65 subjects with DSPN and an average pain <4 during the preceding 4 weeks and 46 subjects with DSPN and an average pain ≥4 during the preceding 4 weeks.

[e]Considering adjustment for multiple testing using the Bonferroni method, only *P* values <.002 were considered to be statistically significant.

(PLP) found that an antidepressant or an antiepileptic was prescribed as part of a first-line treatment for 57.0% of patients with PHN, 70.5% of the PDN cohort, and 61.1% of the PLP cohort; amitriptyline and gabapentin were the 2 most commonly prescribed drugs.[15] The authors concluded that "while use of licensed antiepileptics increased, prescribing of therapy with little evidence of efficacy in neuropathic pain is still common and consequently treatment was often not in-line with current guidance".[15] Very recently, a study from the United States could show that in patients with newly diagnosed diabetic peripheral neuropathy, pain most commonly were treated with anticonvulsants, but many patients received less than the recommended dose of prescribed medication. Furthermore, the adherence was suboptimal, and the discontinuation rates were high for all treatments.[33]

In concordance with our data about NSAID use of around 20% depending on type and severity of pain, a study conducted in US patients with postherpatic neuralgia reported that 17.9% used NSAIDs.[34] Furthermore, in a study including patients with diabetes with painful peripheral neuropathy, 46.7% used NSAIDs[35] which were

TABLE 2 Comparison of characteristics and medical treatment between subjects with DSPN and pain in the feet or the whole lower extremities versus pain elsewhere in the body

	DSPN[a] and Bilateral Pain[b]		
	Feet	Lower Extremities	Elsewhere
Characteristics			
N	29	48	32
Age (years)	71.7 ± 5.7	71.3 ± 5.5	71.9 ± 6.2
Sex (% men)	69	65	60
Height (cm)	170 ± 8.7	169 ± 8.9	167 ± 10.6
Body mass index (kg/m^2)	29.8 ± 4.1	30.3 ± 5.1	29.7 ± 4.2
Waist circumference (cm)	104 ± 12.7	104 ± 13.9	103 ± 10.5
Systolic blood pressure (mm Hg)	130 ± 25.5	128 ± 21.9	133 ± 19.6
Diastolic blood pressure (mm Hg)	71.6 ± 14.5	70.8 ± 12.6	73.3 ± 9.7
Hypertension (% yes)	69	73	59
Smoking (% yes)	3	6	3
High alcohol consumption (% yes)[c]	17	15[e]	16
Low physical activity (% yes)	62	60	68
Normal glucose tolerance (% yes)	28	38	34
Prediabetes (% yes)	34	23	28
Diabetes (% yes)	38	40	38
Blood concentrations			
Fasting glucose (mg/dL)[d]	98.0 ± 12.9	96.2 ± 12.5	102 ± 12.5
2-Hour glucose (mg/dL)[d]	142 (106-170)	129 (97-163)	135 (112-168)
Hb1Ac (%)	6.1 ± 1.2	6.1 ± 1.1	6.0 ± 0.6
Total cholesterol (mg/dL)	204 (190-236)	207 (186-240)	212 (180-243)
Creatinine (mg/dL)	1.0 (0.9-1.2)	1.1 (0.9-1.2)	0.9 (0.8-1.1)
Medication use			
Antidepressants (%)	10	8	9
Anticonvulsants (%)	7	4	0
Opioids (%)	14	13	9
NSAIDs (%)	17	23	9
Muscle relaxants (%)	3	4	0
Analgesics (%)	3	2	0
Neuropathy preparations (%)	7	6	3
Topical preparations (%)	0	0	0

Data are presented as mean ± SD or as median (interquartile range).

OGTT, oral glucose tolerance test; AMI, acute myocardial infarction; Hb1Ac, glycosylated hemoglobin A; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a]Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

[b]As reported on the painDETECT questionnaire. Only bilateral appearance of pain was taken into consideration.

[c]For women ≥20 g/day and for men ≥40 g/day.

[d]Subjects with known diabetes were excluded because of inadequate fasting, based on 27 subjects with DSPN and pain elsewhere and on 33 subjects with pain in the feet calves.

[e]*P* value for the comparison with subjects with DSPN and bilateral pain elsewhere in the body <.05.

also specifically prescribed for pain treatment in 43% out of 602 patients with peripheral or central neuropathic pain in a study conducted in 6 European countries.[36]

The findings of this study are in line with prior findings from studies mainly focusing on patients with neuropathic pain showing that NSAIDs or other therapies with little evidence of efficacy in neuropathic pain are more frequently used in this indication than drugs recommended by current clinical guidelines[2,15] and extend the current knowledge regarding the treatment of DSPN in older men and women from the general population.

Treatment of painful DSPN remains a considerable challenge for the treating physicians.[8] Patients with neuropathic pain frequently have other medical problems and comorbidities, and therefore, many receive polypharmacotherapy in addition to analgesics.[16] Some of the comorbidities, such as diabetes, may be etiologically related to neuropathic pain, while others are not. Thus, a main limitation of the present study is that we cannot distinguish whether the medications were used for the treatment of DSPN or for pain associated with other conditions or were used only for other indications such as anticonvulsants for epilepsy. Some medications designated as "pain-

TABLE 3 Comparison of characteristics and medical treatment between subjects with pain in the lower extremities and an average pain intensity during the past 4 weeks >0, according to the presence or absence of DSPN[a]

	Average Pain Level During Preceding 4 weeks >0 and Bilateral Pain in the Lower Extremities		
	No DSPN[a]	DSPN[a]	*P* Value[d]
Characteristics			
N	124	48	
Age (years)	70.8 ± 5.9	71.3 ± 5.5	.791
Sex (% men)	39	65	.002
Height (cm)	163 ± 8.6	169 ± 8.9	.009
Body mass index (kg/m^2)	29.9 ± 5.1	30.3 ± 5.1	.659
Waist circumference (cm)	99.7 ± 12.9	104 ± 13.9	.457
Systolic blood pressure (mm Hg)	124 ± 21.0	128 ± 21.9	.535
Diastolic blood pressure (mm Hg)	72.4 ± 10.3	70.8 ± 12.6	.235
Hypertension (% yes)	65	73	.574
Smoking (% yes)	9	6	.606
High alcohol consumption (% yes)[b]	15	15	.280
Low physical activity (% yes)	51	60	.317
Normal glucose tolerance (% yes)	56	38	.043
Prediabetes (% yes)	23	23	.550
Diabetes (% yes)	21	40	.021
Presence of neurological disease (% yes)	19	42	.002
Blood concentrations			
Fasting glucose (mg/dL)[c]	97.2 ± 10.5	96.2 ± 12.5	.369
2-Hour glucose (mg/dL)[c]	117 (97-138)	129 (97-163)	.314
Hb1Ac (%)	5.8 ± 0.6	6.1 ± 1.1	.035
Total cholesterol (mg/dL)	219 (196-245)	207 (186-240)	.193
Creatinine (mg/dL)	0.9 (0.8-1.1)	1.1 (0.9-1.2)	.057
Medication use			
Antidepressants (%)	6	8	.713
Anticonvulsants (%)	3	4	.814
Opioids (%)	3	13	.005
NSAIDs (%)	19	23	.848
Muscle relaxants (%)	2	4	.135
Analgesics (%)	2	2	.939
Neuropathy preparations (%)	0	6	.014
Topical preparations (%)	0	0	-

Data are presented as mean ± sd or as median (interquartile range).

OGTT, oral glucose tolerance test; AMI, acute myocardial infarction; Hb1Ac, glycosylated hemoglobin A; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a]Defined as the presence of an impaired bilateral foot-vibration perception and/or an impaired bilateral foot-pressure sensation.

[b]For women ≥20 g/day and for men ≥40 g/day.

[c]Subjects with known diabetes were excluded because of inadequate fasting, based on 103 subjects without DSPN and 32 subjects with DSPN.

[d]Considering adjustment for multiple testing using the Bonferroni method, only *P* values <.002 were considered to be statistically significant.

related" also may be used to treat conditions that are frequently associated with pain (eg, antidepressants for the treatment of depression). Furthermore, it is possible that individuals with DSPN who had "mixed" neuropathic and musculoskeletal pain have used preferably NSAIDs to treat the latter pain component. Unfortunately, we had no information for which indication the NSAIDs were prescribed. Another limitation is that there is no general consensus on the diagnostic criteria for painful DSPN for use in epidemiological studies. Also, we cannot rule out that our definition of clinical DSPN allowed for the inclusion of subjects with causes of neuropathy other than chronic hyperglycemia. However, we previously validated our clinical DSPN definition which showed an excellent diagnostic performance.[22]

A large number of Cochrane reviews give an overview of the evidence situation for the treatment of neuropathic pain. In these studies, individual substance classes used in the treatment of neuropathic pain, such as NSAIDs,[37] other analgesics,[38] opioids,[39] or other medications,[40-42] were examined. These investigations highlight the lack of any nouns evidence. In addition, these comprehensive reviews certify the limitations and biases regarding the methodology of the studies and also the heterogeneity in pain conditions. Further randomized

controlled trials are needed to establish unbiased estimates of efficacy and safety of drugs or drug combinations, which are used for the treatment of neuropathic pain.

The strength of the study is the inclusion of a large number of individuals randomly drawn from the general population and the availability of data on lifestyle and multiple metabolic risk factors. A further strength is the standardized assessment of all drugs used by the participants within the last 7 days before the examination including over-the-counter drugs.

In conclusion, in the older general population, only a small proportion of subjects with DSPN receive analgesic pharmacotherapy. Although not recommended by international guidelines for the treatment of neuropathic pain, NSAIDs were the most frequently used class of analgesic agents in persons with DSPN, while drug classes of choice such as antidepressants and anticonvulsants tended to be underused.

ETHICS STATEMENT

The investigations were carried out in accordance with the Declaration of Helsinki and included written informed consent from all participants. All study methods were approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany).

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CONFLICT OF INTEREST

None known.

AUTHOR'S CONTRIBUTIONS

C.M. participated in the conduct of the study, collected the data, interpreted the results, and wrote the manuscript. B.W.C.B. participated in the conduct of the study and conducted the statistical analysis. M.H. participated in the conduct of the study and collected the data. U.A., B.K., C.H., I-M. R.-E., and W.R. participated in the conduct of the study. D.Z. participated in the conduct of the study and interpreted the results. All authors reviewed, edited, and approved the submitted manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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