Prevalence and impact of pain in diabetic neuropathy

M Geerts, GJJW Bours, R de Wit, SANT Landewé, A van Haarlem, NC Schaper*

Abstract

Background: Diabetic neuropathy (DNP) is a serious and common complication of diabetes mellitus, with a prevalence of around 30–50%.

Aims: To describe the prevalence, severity and medical treatment of painful DNP (PDNP) experienced by patients treated in secondary care; to determine quality of life (QoL) impact and the relationship between severity of pain and severity of DNP.

Methods: Cross-sectional, two-phase survey. First, a pain interview was conducted by telephone (219 DNP patients), which covered types of pain, location and duration. Secondly, 50 patients were visited at home. Patients completed the Brief Pain Inventory, the Short Form Health Survey (SF–36) and the Hospital Anxiety and Depression Scale.

Results: Prevalence of PDNP was 57.5%. Average and worst pain scores were 5.3±2.1 and 6.4±2.2, respectively (0–10 scale, 10 = worst pain imaginable). In 70% of patients, average pain was severe (score ≥5). Substantial interference by pain (score ≥4) was found in walking ability, sleep and normal activities. PDNP patients had a decreased QoL for all SF–36 domains ($p \leq 0.01$) except for health change. Moreover, symptoms of anxiety (36%) and depression (34%) were reported frequently. Medical treatment was prescribed in 46% of patients, in whom treatment was ineffective in 39%. Physical functioning scores were lower in patients with severe versus moderate DNP ($p \leq 0.01$).

Conclusions: The prevalence of severe PDNP was high. Severity of DNP was not related to pain severity. PDNP was associated with loss of QoL and with symptoms of anxiety and depression. A considerable proportion of patients did not have medical treatment and, if treatment was given, its impact was disappointing. Medical treatment of PDNP was unsatisfactory and clearly needs to be improved.

Eur Diabetes Nursing 2009; 6(2): 58–64

Key words

Diabetic neuropathy; pain severity; pain interference; anxiety; depression

Introduction

Diabetic neuropathy (DNP) is a serious and very common complication of diabetes mellitus, with a prevalence of around 30–50%.[1,2] Diabetic (large-fibre) polyneuropathy is a symmetrical and mostly chronic disorder of peripheral nerves, characterised by sensory and motor abnormalities, which affects mainly the distal lower extremities. By definition, polyneuropathy involves several nerves and can lead to sometimes painful sensory disorders and/or loss of strength. Neuropathic pain is known to affect patient functioning and quality of life (QoL).[3] Initial symptoms are few, and the first signs of painful DNP (PDNP) are typically characterised as sensory loss, pain or tingling in the hands, feet or legs. After a few years, these signs can be followed by muscle weakness in the legs and arms.

Although several epidemiological studies have investigated PDNP prevalence and incidence, very few studies have focused on disease severity and medical treatment in these patients. Chan *et al*[4] quoted a 7.5% prevalence rate for painful lower-limb symptoms in people with diabetes. More recently, Ziegler *et al*[5] reported that painful lower limb symptoms occur in 11.6% of type 1 and 32.1% of type 2 diabetic patients. Recent community-based studies of patients with diabetes suggest that the prevalence of PDNP is around 16–26%,[2] and in one study, 80% of the patients with PDNP had moderate or severe pain.[6] Benbow *et al*[7] demonstrated the negative impact of pain on patients with

Authors

M Geerts,[1] M–ANP, RN
GJJW Bours,[2,3] PhD, RN
R de Wit,[3,4] PhD, Professor
SANT Landewé,[5] MD
A van Haarlem,[1] RN
NC Schaper,[3,5] PhD, MD, Professor

[1]Department of Integrated Care, University Hospital Maastricht, The Netherlands
[2]Faculty of Health and Care, Zuyd University, Heerlen, The Netherlands
[3]School for Public Health and Primary Care (CAPHRI), Maastricht University, The Netherlands
[4]Department of Health Care and Nursing Science, Maastricht University, The Netherlands
[5]Department of Internal Medicine, Division of Endocrinology, University Hospital Maastricht, The Netherlands

***Correspondence to:**
M Geerts, M–ANP, RN, University Hospital Maastricht, Department of Integrated Care, PO Box 5800, 6202 AZ Maastricht, The Netherlands
e-mail: m.geerts@mumc.nl

Received: 29 July 2008
Accepted in revised form: 6 November 2008

DNP, and found a strong relationship between chronic pain and poor sleep quality, which was thought likely to be due to the worsening of pain symptoms at night. Galer *et al*[8] found that over half of the patients whom they studied reported that pain interfered substantially with one or more aspects of their QoL (namely mobility, employment, sleep, enjoyment of life and recreational and social activities).

The medical treatment of PDNP depends on a two-pronged approach: optimal metabolic control and medical treatment of pain symptoms.[9] Neuropathic pain is difficult to treat as it does not respond to traditional analgesics, and most experts advise tricyclic antidepressants, anticonvulsants and opioids for the medical management of PDNP.[2] However, treatment is often inadequate and limited by the adverse systemic effects of currently available medicines. The pathogenesis of pain in patients with DNP is complex, and both central and peripheral mechanisms are probably involved.

Moreover, a systematic approach is necessary to diagnose and quantify neuropathic pain, and subsequently to evaluate and adapt the medical treatment.[10] Most of the symptoms of PDNP seem to be related to small-fibre damage but, unfortunately, small-fibre neuropathy is difficult to diagnose in routine clinical practice. Direct examination of intra-epidermal nerve fibres (IENF) in skin biopsies showed that IENF density was reduced in diabetic neuropathy, and that there was a progressive loss of small fibres which paralleled the severity of the neuropathy.[11] Therefore, it seems likely that patients with more severe DNP suffer more severe pain.

Methods

Study aims

The aims of the study were to describe the prevalence, severity and medical treatment of PDNP in patients treated in secondary care, and to determine the QoL impact and the relationship between severity of pain and severity of DNP.

Study design

The study consisted of a cross-sectional survey of patients who met criteria for DNP, as assessed by a clinical neurological examination (Valk score) at the University Hospital, Maastricht.[12] Neuropathic pain was defined as the presence of painful symptoms (burning, tingling, lancinating) in legs and/or feet, with a duration of >1 month on ≥4 days per week. All materials relating to the study, including the informed consent forms, were approved by the Medical Ethics Committee of the University Hospital of Maastricht in July 2006. All participants gave informed consent.

The study consisted of two phases. First, a pain interview was conducted by telephone in patients with DNP. Then, to determine the impact of pain, a convenient sample of patients with PDNP were visited at home.

The telephone interview included items relating to types of pain, location, severity and duration; these data were collected in an Excel® database. Following the telephone interview phase, a series of consecutive patients with PDNP were approached for the home visit, during which they were asked to complete three validated questionnaires, described below.

Patients

The study involved patients registered at a university hospital that takes part in a diabetes disease management programme, in which there is close co-operation between hospital-based specialists and community-based general practitioners. Patients with multiple complications are treated in the diabetes clinic at the hospital; other patients are treated by a general practitioner. Regardless of severity of DNP, all patients with this condition are referred to a podiatrist for standardised clinical neurological examination and preventative foot care. All patients with DNP who were treated by the podiatrist at the university hospital were then selected for a telephone interview.

Measures

More extensive evaluation was performed during the subsequent home visit, using several questionnaires that patients completed independently (although if necessary the questionnaires were completed by the researcher on an interview basis). The average time needed for the home visit was one hour, and visits took place between October 2006 and April 2007. Patients' data (including demographic, sociodemographic and medical data) were extracted from electronic patient records.

DNP was diagnosed by standardised neurological testing, consisting of an examination of sensory function (pinprick, light touch, vibration and position sense), tendon reflexes and muscle strength in the lower extremities.[12] This clinical scoring system corresponds well with the results of neurophysiological examination, and has acceptable sensitivity and specificity for the diagnosis of DNP when a cut-off point of more than 4 is used.[12] Patients were diagnosed with moderate DNP if their Valk scores were between 5 and 14; they were diagnosed with severe DNP if they had Valk scores between 15 and 33.[12]

Pain was measured with the Brief Pain Inventory (BPI).[13] The BPI is a patient-rated instrument that measures severity of pain on 0–10 scales (0 = no pain; 10 = pain as bad as you can imagine) and assesses its interference with seven

functional areas, using 0–10 interference scales (0 = does not interfere; 10 = completely interferes). Several studies demonstrate the validity and reliability of the BPI for chronic pain measurement[14–16] and PDNP evaluation.[13]

Patients' general health condition was measured with the 36-Item Short Form Health Survey (SF–36), which includes scales for physical functioning, mental health and general health perception. The maximum score in each domain is 100: higher scores indicate greater well-being.[17] The SF–36 has been found in a number of studies to be a valid and reliable measure of QoL.[18] The impact of PDNP on QoL was assessed by comparing the QoL in our study population with that of a healthy, age- and gender-matched Dutch reference population.[19]

The impact of PDNP on anxiety and depression was assessed using the Hospital Anxiety and Depression Scale (HADS), which consists of two subscales: one measuring anxiety (HADS–A) and the other measuring depression (HADS–D). Higher scores indicate more symptoms of anxiety and depression. The HADS has shown good reliability and validity.[20–23]

Data analysis

Descriptive statistics were used to describe the demographics of the study population. Quantitative variables were described as mean±SD, using percentages for the BPI. Missing values were adjusted by using the BPI/HADS/SF–36 average scores of the mean subscales. Missing values were scored using personal scale average, if the respondent had answered at least half of the items. The two-tailed *t*-test was used to objectify the differences between the study research groups with moderate and severe DNP and the impact of PDNP against the general population. P-values ≤0.05 were considered to be statistically significant. All analyses used the SPSS statistical program, version 12.01 (SPSS Inc., USA).

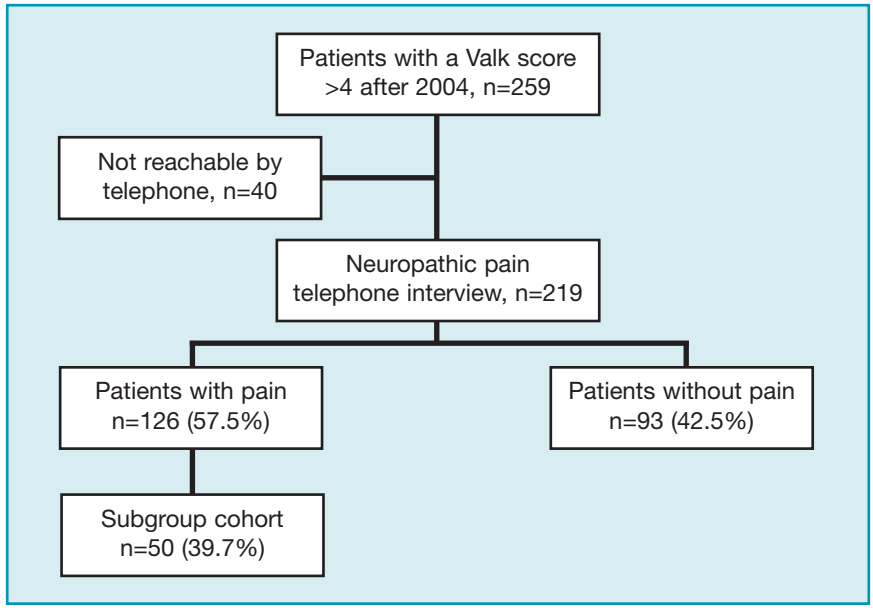

Figure 1. Patient selection for interview and questionnaire-based trial of patients with diabetic neuropathy. Valk score, score of standardised clinical neurological examination

Results

Results are presented as mean±SD. Figure 1 shows the process used to select the study population. In total, 219 patients with DNP were interviewed; 15% of these patients could not be reached (Figure 1). All patients agreed to participate in the telephone interview, 57.5% (n=126) of whom reported pain. A subgroup participated in the home visit and completed questionnaires (Figure 1).

Table 1 details the characteristics of the subgroup of patients who completed questionnaires. Of these 50 patients, 24 had moderate DNP and 26 had severe DNP, based on

Characteristic	Moderate DNP Valk score 5–14 (n=24)	Severe DNP Valk score 15–33 (n=26)	Total (n=50)	p-value
Female, n (%)	13 (54.2)	9 (34.6)	22 (44.0)	ns
Male, n (%)	11 (48.8)	17 (65.4)	28 (56.0)	ns
Mean age, SD (years)	66.6±9.1	64.7±8.8	65.6±8.9	ns
Type 1 DM, n (%)	0 (0.0)	3 (11.5)	3 (6.0)	ns
Type 2 DM, n (%)	24 (100.0)	23 (88.5)	47 (94.0)	ns
Mean HbA_{1c} (%)	8±1.0	7.7±1.3	7.8±1.2	ns
HbA_{1c} <7%, n (%)	4 (16.7)	10 (38.5)	14 (28.0)	ns
HbA_{1c} 7–8.5, n (%)	15 (62.5)	10 (38.5)	25 (50.0)	ns
HbA_{1c} >8.5, n (%)	5 (20.8)	6 (23.0)	11 (22.0)	ns
Mean Valk score	9.5±2.7	19.2±3.6	14.6±5.8	0.00

DNP, diabetic neuropathy; DM, diabetes mellitus; Valk score, score of standardised clinical neurological examination; ns, not significant

Table 1. Sociodemographic and medical data obtained from 50 patients with painful diabetic neuropathy

	Moderate DNP Valk score 5–14 (n=24)	Severe DNP Valk score 15–33 (n=26)	Total (n=50)	p-value
Results, BPI (mean±SD)				
Worst pain in last 24 hours	6.4±2.6	6.4±1.9	6.4±2.2	0.96
Least pain in last 24 hours	3.0±2.4	3.7±2.1	3.4±2.3	0.32
Average pain	5.2±2.2	5.3±1.9	5.3±2.1	0.87
Current pain	3.6±2.7	3.9±2.8	3.8±2.7	0.66
Subscale on pain severity	4.6±2.0	4.8±1.7	4.7±1.9	0.63
Location of pain, n (%)				
Legs, symmetric	6 (25.0)	9 (34.6)	15 (30.0)	0.27
Feet, symmetric	14 (58.3)	13 (50.0)	27 (54.0)	0.47
Pain complaints not symmetric	4 (16.7)	4 (15.4)	8 (16.0)	–
Interference in functional domains (mean±SD)				
Walking ability	4.5±3.3	5.6±2.7	5.1±3.0	0.21
Sleep	4.9±3.7	4.5±2.9	4.7±3.3	0.86
Normal work	3.7±3.0	4.9±2.9	4.3±3.0	0.22
General activity	3.6±2.6	4.6±2.6	4.1±2.6	0.15
Mood	3.3±2.6	3.4±2.7	3.3±2.6	0.07
Enjoyment of life	2.5±2.7	3.4±3.0	3.0±2.8	0.73
Relations with others	1.6±2.3	3.1±3.1	2.4±2.9	0.28
Subscale on pain interference	3.4±2.1	4.2±2.2	3.8±2.2	0.21
Medication, n (%)				0.98
No medication	13 (54.1)	14 (53.8)	27 (54.0)	–
Paracetamol +/- codeine	5 (20.8)	7 (26.9)	12 (24.0)	–
Neuropathic pain treatment, n (%)				
Antidepressants	4 (16.7)	2 (7.7)	6 (12.0)	–
Opioids	1 (4.2)	2 (7.7)	3 (6.0)	–
Anti-epileptics	0 (0.0)	1 (3.9)	1 (2.0)	–
Other	1 (4.2)	0 (0.0)	1 (2.0)	–
Pain reduction in patients with medication, n (%)	**(n=11)**	**(n=12)**	**(n=23)**	0.51
<30% pain reduction	6 (54.5)	3 (25.0)	9 (39.0)	–
Between 40% and 70% pain reduction	3 (27.3)	8 (66.7)	11 (48.0)	–
>80% pain reduction	2 (18.2)	1 (8.3)	3 (13.0)	–

DNP, diabetic neuropathy; BPI, Brief Pain Inventory

Table 2. Pain and pain treatment described by 50 patients with painful diabetic neuropathy who completed questionnaires

the standardised neurological examination.

Severity of and interference by pain

Table 2 details the pain and pain treatment scores. The mean average and worst pain scores of the study population were 5.3±2.1 and 6.4±2.2, respectively. Patients' current pain score (pain score at the time of the interview) was 3.8±2.7. Pain substantially interfered (defined as scores ≥4) with walking ability, sleep and normal activities. The mean pain severity and pain interference composite scores for the study population were 4.7±1.9 and 3.8±2.2, respectively. No significant differences in pain or medical treatment were observed between the groups with moderate and severe DNP (Table 2).

Pain treatment

Medical treatment was given to 46% of the patients. The most commonly prescribed treatment was paracetamol, with or without codeine, followed by antidepressants (Table 2). Only a minority (20%) of the patients were being treated with antiepileptics or opioids. In 39% of the patients, medical treatment was ineffective. There were no significant

	Healthy reference population[19] (n=118)	Moderate DNP Valk score 5–14 (n=24)	Severe DNP Valk score 15–33 (n=26)	p-value	Total (n=50)	p-value*
Results for SF–36 (mean±SD)						
Physical functioning	66.7±26.0	62.7±25.6	40.4±27.6	0.01	51.1±28.7	0.00
Social functioning	83.2±23.7	75.0±25.3	60.0±31.9	ns	67.0±29.6	0.00
Role physical	69.1±42.5	56.3±38.5	40.4±40.0	ns	48.0±39.7	0.00
Role mental	82.9±33.8	56.9±44.5	53.8±44.3	ns	55.3±44.0	0.00
Mental health	75.9±17.3	66.7±18.3	67.7±24.2	ns	67.2±21.3	0.01
Vitality	64.2±22.0	49.2±16.3	50.6±21.9	ns	49.9±19.2	0.00
Bodily pain	74.8±28.0	53.7±23.3	50.5±22.5	ns	52.0±22.7	0.00
General health profile	60.1±23.9	47.3±17.6	43.2±23.1	ns	45.2±20.5	0.00
Health change	46.8±20.5	46.9±17.0	44.2±21.6	ns	45.5±19.4	ns
Results for HADS						
Anxiety in patients, n (%)	–	(n=24)	(n=26)	–	(n=50)	ns
None (≤7)	–	15 (62.5)	17 (65.4)	–	32 (64)	–
Moderate (8–10)	–	6 (25.0)	4 (15.4)	–	10 (20)	–
Severe (>11)	–	3 (12.5)	5 (19.2)	–	8 (16)	–
Depression in patients, n (%)						ns
None (≤7)	–	15 (62.5)	18 (36.0)	–	33 (66)	–
Moderate (8–10)	–	8 (16.0)	4 (8.0)	–	12 (24)	–
Severe (>11)	–	1 (2.0)	4 (8.0)	–	5 (10)	–
Mean score on subscales (mean±SD)						
Anxiety	–	7.0±3.5	6.7±4.3	–	6.8±3.9	ns
Depression	–	5.9±3.1	6.1±4.2	–	6.0±3.7	ns

Normal scores of a healthy Dutch population aged 65–75 years[19]
*p≤0.01 indicate significant differences in PDNP patients versus healthy reference population
DNP, diabetic neuropathy; PDNP, painful diabetic neuropathy; SF–36, Study 36-Item Short Form Health Survey; HADS, Hospital Anxiety and Depression Scale; ns, not significant

Table 3. Quality of life and mental functioning findings in 50 patients with painful diabetic neuropathy who completed questionnaires

differences in pain scores between patients treated with or without medical treatment (data not shown).

Impact on QoL, anxiety and depression

The impact of PDNP on QoL is presented in Table 3. Compared with patients who had moderate DNP, those suffering with severe DNP had lower SF–36 scores in all domains. A significant difference was found in physical functioning (p≤0.01). Moderate-to-severe symptoms of anxiety were reported by 36% of the PDNP patients and moderate-to-severe symptoms of depression by 34% of these patients. Mean scores for symptoms of anxiety and depression were 6.8±3.9 and 6.0±3.7 (Table 3). No differences were observed between patients with moderate and severe DNP.

Impact of pain severity

To determine the effect of pain severity on anxiety, depression and QoL, patients were divided into two groups, based on the average pain scores of the BPI (≤4 and ≥5; Table 4). In 70% of patients, average pain was severe (score ≥5). Research has shown that physical function loss is to be expected with a pain score ≥4. As expected, patients with high average pain scores were more likely to suffer from anxiety and depression (both p≤0.05); these patients also had poorer scores for social functioning and general health profile (both p≤0.05) compared with low pain-scoring patients.

Discussion

The present study aimed to describe the prevalence, severity and medical treatment of PDNP in patients treated in secondary care. Moreover, we explored whether pain symptoms were related to DNP severity. Over half of our patients with DNP had moderate-to-severe

pain – results that are in line with another study.[24] The prevalence of severe PDNP in our study was high, but the severity of pain was not related to the severity of large-fibre DNP. Many patients had not received a diagnosis of neuropathic pain. The scores for pain interference with daily functioning were lower than the pain severity scores, suggesting that our patients were able to limit the negative effects of pain on their daily lives.

It is remarkable that over half of the patients we studied had not been prescribed any medical treatment. Moreover, if prescribed, medical treatment was ineffective in a large proportion (39%). These results are in line with those of other studies which show that many patients with severe pain are treated inadequately.[6,25–27] Patients often have multiple comorbidities, but there is often insufficient time to address neuropathic pain. Moreover, it seems likely that both patient and doctor do not always associate painful symptoms in the legs with PDNP.

Findings of the current study also emphasise the complex interaction between DNP and QoL. The high prevalence of painful symptoms and their negative effect on QoL in patients with DNP are in line with those of previous studies.[5–6,28] In comparison with an earlier study by Currie *et al* concerning QoL in DNP patients without pain,[28] our patients reported an even poorer QoL. Our results indicate that loss of QoL in DNP is not purely related to the presence or absence of pain: even painless DNP was clearly associated with several determinants of QoL, particularly with impairments in physical functioning. The reported impairments in physical functioning are probably related to disabilities such as unsteadiness and muscle weakness,[29,30] and these symptoms need to be addressed (they also need to be addressed when treating patients with PDNP).

Variables (mean±SD)	Pain score ≤4 (n=15)	Pain score ≥5 (n=35)	p-value
HADS			
Anxiety	4.9±2.6	7.6±4.1	0.03
Depression	4.5±2.8	6.7±3.8	0.03
SF–36			
Physical functioning	60.7±27.6	47.0±28.5	ns
Social functioning	80.0±10.4	61.4±33.4	0.04
Role physical	51.7±35.9	46.4±41.6	ns
Role mental	66.7±41.8	50.5±44.6	ns
Mental health	73.9±18.8	64.2±21.9	ns
Vitality	55.0±18.8	47.6±19.2	ns
Bodily pain	66.4±15.4	45.7±22.7	0.00
General health profile	53.3±14.8	41.6±21.8	0.04
Health change	50.0±16.4	43.6±20.4	ns

HADS, Hospital Anxiety and Depression Scale; SF–36, 36-Item Short Form Health Survey; ns, not significant

Table 4. Differences in pain perception, physical and mental functioning in 50 patients with painful diabetic neuropathy who completed questionnaires

Treatment of PDNP requires a plan that should include psychosocial factors, glucose control and, if necessary, medical treatment.[2,31] As described in another study,[27] one in three of our patients had anxiety; listening to the patient and explaining the cause of the pain can help to reduce this anxiety. Moreover, both anxiety and depression were associated with pain severity. Consequently, medical treatment should aim to reduce pain and also alleviate anxiety and depression.

Although one might intuitively expect it, we did not observe an association between severity of DNP and pain severity. In a recent study, loss of epidermal small fibres correlated with severity of large-fibre neuropathy and presence of neuropathic pain.[32] However, in this study the correlation between epidermal nerve density and large-fibre neuropathy was relatively weak (r=0.5), which probably explains the lack of association between pain and the neurological examination.

Strengths and limitations

The strength of our study was the high response rate – patients were telephoned and then visited at home, and so did not need to attend the hospital.

There are several limitations to our study: only patients with large-fibre neuropathy were included, the number of subjects was relatively small and the study design was cross-sectional. Moreover, it was not population based, but performed in people with DNP. We recommend repeating this research in a larger population with a longer follow-up period. Further research may be necessary to follow the course of patients with PDNP and to evaluate the impact of various medical treatments.

Neuropathic pain is often observed in patients with diabetes, irrespective of the severity of the neurological abnormalities on clinical examination, which is associated with a marked loss of QoL. However, in our study population, PDNP was frequently undiagnosed; even if it was treated, most patients received ineffective medication. These results suggest that there is still considerable

room for improvement in the medical treatment of PDNP.

Recommendations for practice

All people with diabetes should be screened regularly for pain using a specialist instrument such as the BPI. The introduction of a standardised screening instrument and a dedicated clinic for patients with PDNP may help to reduce the level of under-treatment. After screening and a relatively simple diagnostic evaluation, pain complaints should be treated on the basis of a strict pain protocol that also encompasses aspects such as disturbed sleep, anxiety and depression.

Conflict of interest statement:
None

References

1. Jude E, Boulton AJM. End stage complications of diabetic neuropathy. *Diab Rev* 1999; **7:** 395–410.
2. Jude EB, Schaper NC. Treating painful diabetic polyneuropathy. *BMJ* 2007; **335:** 57–58.
3. Meyer-Rosberg K, Kvarnstrom A, Kinnman E, *et al.* Peripheral neuropathic pain: a multidimensional burden for patients. *Eur J Pain* 2001; **5:** 379–389.
4. Chan AW, MacFarlane IA, Bowsher DR, *et al.* Chronic pain in patients with diabetes mellitus: comparison with non-diabetic population. *The Pain Clinic* 1990; **3:** 147–159.
5. Ziegler D, Gries AF, Spuler M, *et al.* The epidemiology of diabetic neuropathy. *J Diabetes Complicat* 1992; **6:** 49–57.
6. Daousi C, MacFarlane IA, Woodward A, *et al.* Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med* 2004; **21:** 976–982.
7. Benbow SJ, Wallymahmed ME, MacFarlane A. Diabetic peripheral neuropathy and quality of life. *Q J Med* 1998; **91:** 733–737.
8. Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. *Diabetes Res Clin Pract* 2000; **47:** 123–128.
9. Low P, Dotson R. Symptom treatment of painful neuropathy. *JAMA* 1998; **280:** 1863–1864.
10. Barbano RL, Herrmann DN, Hart-Gouleau S, *et al.* Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy. *Arch Neurol* 2004; **61:** 914–918.
11. Polydefkis M, Hauer P, Sheth S, *et al.* The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. *Brain* 2004; **127:** 1606–1615.
12. Valk GD, de Sonaville JJ, van Houtum WH, *et al.* The assessment of diabetic polyneuropathy in daily clinical practice: reproducibility and validity of Semmes Weinstein monofilaments examination and clinical neurological examination. *Muscle Nerve* 1997; **20:** 116–118.
13. Zelman DC, Gore M, Dukes E, *et al.* Validation of a modified version of the Brief Pain Inventory for painful diabetic peripheral neuropathy. *J Pain Symptom Manage* 2005; **29:** 401–410.
14. Keller S, Bann CM, Dodd SL, *et al.* Validity of the Brief Pain Inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 2004; **20:** 309–318.
15. Dworkin RH, Backonja M, Rowbotham MC, *et al.* Advances in neuropathic pain: diagnosis, mechanisms and treatment recommendations. *Arch Neurol* 2003; **60:** 1524–1534.
16. Dworkin R, Nagasako E, Galer B. Assessment of neuropathic pain. *Handbook of Pain Assessment.* New York: Guilford Press, 2002; 519–548.
17. Health Science Program RAND 36-item Health Survey i.o. Santa Monica, CA: RAND, 1992. www.rand.org/pubs/reprints/RP247/ [accessed 17 July 2009].
18. Clouet F, Excler-Cavailher G, Christophe B, *et al.* Type 2 diabetes and short form 36-items health survey. *Diabetes Metab* 2001; **27:** 711–717.
19. van der Zee KI, Sanderman R. *Het meten van de algemene gezondheidstoestand met de RAND–36: een handleiding.* Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken, 1993; 9–14 (in Dutch).
20. Bjelland I, Dahl A, Haug T, *et al.* The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52:** 69–77.
21. Johnston M, Pollard B, Hennessey P. Construct validation of the Hospital Anxiety and Depression Scale with clinical populations. *J Psychosom Res* 2000; **48:** 579–584.
22. Spinhoven P, Ormel J, Sloekers P, *et al.* A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychological Med* 1997; **27:** 363–370.
23. Croon EM de, Nieuwenhuijsen K, Hugenholtz NIR, *et al.* Drie vragenlijsten voor diagnostiek van depressie en angststoornissen. *TBV* 2005; **13:** 98–103 (in Dutch).
24. Gore M, Brandenburg NA, Hoffman DL, *et al.* Burden of illness in painful diabetic peripheral neuropathy: the patients' perspectives. *J Pain* 2006; **7:** 892–900.
25. Toelle T, Xu X, Sadosky AB. Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns. *J Diabetes Complicat* 2006; **20:** 26–33.
26. Wit R de, Dam F van, Loonstraa S, *et al.* The Amsterdam Pain Management Index compared to eight frequently used outcome measures to evaluate the adequacy of pain treatment in cancer patients with chronic pain. *Pain* 2001; **91:** 339–349.
27. Gore M, Brandenburg N, Dukes E, *et al.* Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression and sleep. *J Pain Symptom Manage* 2005; **30:** 374–385.
28. Currie CJ, Poole CD, Woehl A, *et al.* The health-related utility and health-related quality of hospital-treated subjects with type 1 or type 2 diabetes with particular reference to differing severity of peripheral neuropathy. *Diabetologia* 2006; **49:** 2272–2280.
29. Vileikyte L, Leventhal H, Gonzalez JS, *et al.* Diabetic peripheral neuropathy and depressive symptoms: the association revisited. *Diabetes Care* 2005; **28:** 2378–2383.
30. Andreassen CS, Jakobsen J, Andersen H. Muscle weakness: a progressive late complication in diabetic distal symmetric polyneuropathy. *Diabetes* 2006; **55:** 806–812.
31. Jensen TS, Backonja MM, Hernández Jiménez S, *et al.* New perspectives on the management of diabetic peripheral neuropathic pain. *Diabetes Vasc Dis Res* 2006; **3:** 108–119.
32. Sorensen L, Molyneaux L, Yue DK. The relationship among pain, sensory loss, and small nerve fibers in diabetes. *Diabetes Care* 2006; **29:** 883–887.