Randomized, Placebo-Controlled Comparison of Amitriptyline, Duloxetine, and Pregabalin in Patients With Chronic Diabetic Peripheral Neuropathic Pain

Impact on pain, polysomnographic sleep, daytime functioning, and quality of life

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OBJECTIVE—Chronic diabetic peripheral neuropathic pain (DPNP) is difficult to treat, with treatment regimens often inadequate at controlling pain and limited by side effects and drug tolerance. Secondary parameters, such as quality of sleep and mood, may also be important for successful DPNP management. The objectives of this study were to compare the analgesic efficacy of pregabalin, amitriptyline, and duloxetine, and their effect on polysomnographic sleep, daytime functioning, and quality of life in patients with DPNP.

RESEARCH DESIGN AND METHODS—This was a double-blind, randomized, parallel group investigation of type 1 and 2 diabetic subjects with DPNP. Each treatment group had a single-blind, 8-day, placebo run-in followed by 14 days of lower-dose and 14 days of higher-dose medication. At the end of each dose titration period, subjective pain, sleep, and daytime functioning were assessed during a 2-day residential period.

RESULTS—All medications reduced pain when compared with placebo, but no one treatment was superior to any other. For sleep, pregabalin improved sleep continuity ($P < 0.001$), whereas duloxetine increased wake and reduced total sleep time ($P < 0.01$ and $P < 0.001$). Despite negative effects on sleep, duloxetine enhanced central nervous system arousal and performance on sensory motor tasks. There were no significant safety findings; however, there was a significantly higher number of adverse events in the pregabalin treatment group.

CONCLUSIONS—There was no significant difference in analgesic efficacy between amitriptyline, duloxetine, and pregabalin. However, there were significant differences in the secondary parameters, which may be of relevance when deciding the optimal treatment for DPNP.

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Chronic diabetic peripheral neuropathic pain (DPNP) is a common, debilitating, and distressing complication of diabetes (1). In addition to directly causing pain, it can also impair an individual's sleep, lower mood, and have a negative impact on daily activities, resulting in poor quality of life (2,3). In addition, the financial costs of chronic DPNP are substantial from both a direct healthcare cost and loss of productivity by the sufferers (4).

Chronic DPNP is often difficult to treat, with drug regimes often being inadequate at controlling pain and limited by side effects and the development of tolerance (5). First-line treatments for neuropathic pain include the tricyclic antidepressant amitriptyline, the selective serotonin and noradrenaline reuptake inhibitor duloxetine, and calcium channel α2 delta ligands such as pregabalin and gabapentin (6,7). Although amitriptyline has been shown to be efficacious in the treatment of neuropathic pain (8), its relative nonspecific mode of action may limit its use due a broad range of adverse effects (9). Duloxetine has been reported to be safe and effective in patients with DPNP (10), with a relatively low rate of adverse events (11). The anticonvulsant pregabalin has also been shown to be effective in the treatment of DPNP (12). Side effects associated with this agent include somnolence; however, it has been suggested that pregabalin's positive effect on sleep may lead to further improvement of pain and quality of life (13).

For patients with diabetes, sleep can be affected by a number of factors, including increased nocturia (14), sleep disordered breathing (15), periodic limb movements (PLMs) (16), and episodes of hyper- or hypoglycemia (17,18). In addition, for patients with DPNP, sleep may also be affected by pain (2,3,19).

Pregabalin has been shown to consistently improve subjective sleep in patients with DPNP (20), and studies in healthy volunteers suggest that this agent also enhances slow-wave sleep (21). The aim of this study was to assess the effects of three first-line treatments for DPNP on pain, sleep, cognitive function, and quality of life, and to investigate whether the

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improved restorative sleep seen in healthy individuals was replicated in patients with chronic DPNP.

RESEARCH DESIGN AND METHODS

Subjects

Subjects 18 years of age and older with diabetes (type 1 or type 2) for at least 1 year and neuropathic pain of diabetic origin were invited to participate in the study. Subjects were recruited on the basis of symptoms suggestive of DPNP, including one or more of the following: dysesthesia, burning pain, cold or heat allodynia, shooting or lancinating pains, and hyperalgesia affecting both lower extremities at any level below the midthighs. A confirmation of DPNP was then made by means of a Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (22) score >12. Subjects were excluded if there was evidence of cognitive impairment (score of <25 on the Mini Mental State Exam), end-stage disease of a major system, evidence of a recurrent and/or severe hypoglycemic event (defined as hypoglycemia requiring help from a third party) in the last 3 years, or a recent cardiac or cerebral ischemic event. Pregnant or breast-feeding women and subjects with a history of dependence on or abuse of alcohol/recreational drugs were also excluded. Furthermore, subjects were not allowed to enter the study if they had been involved in another clinical trial within the previous 3 months.

Subjects were reimbursed for their time and inconvenience, and at the end of the study were provided with the study medication to which they had been randomized if this was requested. This trial was conducted according to ICH Good Clinical Practice guidelines at the Surrey Clinical Research Centre (Surrey CRC). The study received a favorable opinion from the Essex 1 Research Ethics Committee and University of Surrey Ethics Committee and was registered at clinicaltrials.gov. All participants supplied written informed consent before screening.

Procedures

The trial was a double-blind, randomized, parallel group investigation with an 8-day single-blind placebo run-in. Subjects were sequentially randomized into one of the three treatment arms (pregabalin, amitriptyline, or duloxetine). The randomization was provided by an independent statistician to ensure that groups were matched for age and sex where possible. Patients were stratified into four groups: males 18–59, females 18–59, males >60, and females >60 years of age. All participants were requested to stop taking their current pain medication (for the equivalent of at least five half-lives) before participating in the trial. For ethical reasons, subjects were allowed to continue taking opioids and nonsteroidal anti-inflammatory drugs during the study and were allowed to take paracetamol with a maximum dose of 4 g/day.

After the 8-day placebo run in, subjects were titrated through 14 days of lower-dose medication (amitriptyline 25 mg twice daily; duloxetine 60 mg every morning; pregabalin 150 mg twice daily) to 14 days of higher-dose medication (amitriptyline 25 mg every morning; 50 mg every night; duloxetine 60 mg twice daily; pregabalin 300 mg twice daily). At the end of each treatment period, subjects stayed at the Surrey CRC for a 48-h comprehensive assessment of polysomnographic (PSG) sleep, subjective pain, daytime functioning, and continuous glucose monitoring (CGMS System Gold Medtronic MiniMed, Inc.) (Fig. 1).

Outcomes

Primary outcome. The primary outcome was subjective pain as assessed by the Brief Pain Inventory (BPI).

Secondary outcomes. Quality of life was assessed using a short-form 36-item general health survey (SF-36) (23) at screening and again on the last day of treatment (day 36). Each residential visit was identical, with a PSG habituation night to familiarize patients with the environment, followed by a PSG assessment night. Subjects were trained and refamiliarized on the psychometric test battery the day after their habituation night, and baseline or treatment cognitive function and daytime sleepiness were assessed the following day.

Subjective pain was assessed by means of the BPI (24) and a visual analog scale adapted from the short-form McGill

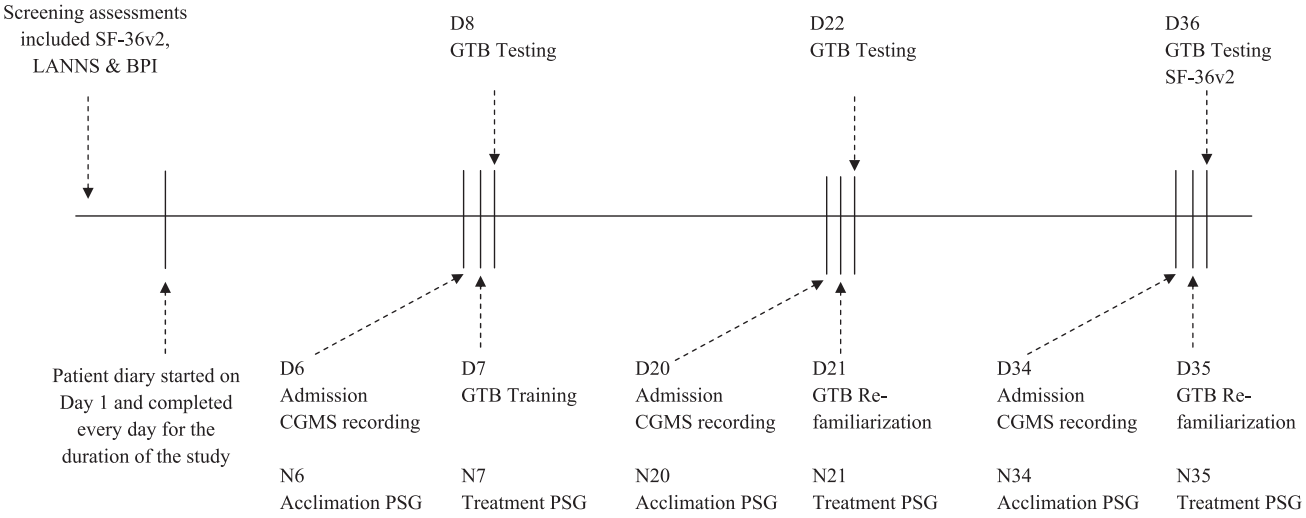

Figure 1—*A schematic illustrating the timing of the main study procedures. CGMS, continuous glucose monitoring system; GTB, Guildford test battery (CFF, CRT, CTT, Stroop test, Sternberg short-term memory scanning task, DSST, word recall, Leeds Sleep Evaluation Questionnaire, and linear analog scales). GTB training was at 10:00, 13:00, and 16:00 on day 7, 21, and 35. GTB testing was at 08:00, 10:00, 13:00, and 16:00 on day 8, 22, and 36.*

Pain Questionnaire (25). Subjective sleep, mood, and daytime sleepiness were assessed by the following visual analog scales: Leeds Sleep Evaluation Questionnaire (26), Linear Analog Rating Scale (27), and Karolinska Sleepiness Scale (28).

PSG sleep records were manually staged according to Rechtschaffen and Kales criteria (29). For clinical sleep variables (PLMs and apnea/hypopnea index [AHI]), only placebo and higher-dose (period three) records were manually staged. Psychomotor performance and cognitive functioning were assessed by means of psychometric test battery including the following: sensori-motor and psychomotor speed (continuous tracking task [CTT] [27] and choice reaction time task [CRT] [27]); central nervous system (CNS) arousal and information processing tasks (critical flicker fusion [CFF] [27], Stroop task, and digit symbol substitution test [DSST] [30]); and working and explicit memory tasks (immediate and delayed word recall [31] and Sternberg short-term memory scanning task [STM] [32]).

Statistical analysis

No reliable data were available to enable a formal calculation of the sample size of patients needed for an 80% power to show a statistically significant (5% level, double sided) difference between treatments on the primary end point of subjective pain (BPI). However, comparable single-site studies investigating amitriptyline and gabapentin (a compound closely related to pregabalin) in DPNP successfully used ~30 patients for each comparison (9,33).

The main analysis was performed according to a preplanned statistical analysis plan. The safety population was defined as consisting of the set of those subjects who were randomized onto the trial, and received at least one administration of study medication. This population was used for the summary of safety data and baseline characteristics. The evaluable population was defined as consisting of those subjects who completed the study. The dataset was analyzed in a linear mixed model. The observations were the dependent variable, and fixed effect was treatment with visits being a repeated measure. Subjects were added as a random effect. Additional independent covariates included BMI and age. Statistical significance level was set to 5% ($P < 0.05$). All analyses were performed with SAS PROC MIXED 9.1 software.

RESULTS—A total of 104 subjects with both type 1 and 2 diabetes were screened between February 2007 and March 2009, and 83 were enrolled and randomized. Follow-up visits took place between April 2007 and May 2009. A total of 65 subjects (78%) completed all treatment periods and were considered the evaluable population used for the main analysis. Table 1 shows the demographic characteristics of all subjects randomized to the trial. Twenty seven were randomized to pregabalin, 28 to duloxetine, and 28 to amitriptyline. All subjects were Caucasian, and an equal number of males ($n = 19$) and females ($n = 9$) were randomized to each treatment arm except in the pregabalin arm (females, $n = 8$). Mean BMI and mean age were similar across all three treatment groups.

Pain

The primary outcome of subjective pain showed no significant difference between the treatment groups. Amitriptyline, duloxetine, and pregabalin reduced BPI severity, BPI interference, and visual analog scale pain when compared with placebo baseline, with no one treatment showing superiority to another (Table 2).

Subjective sleep

Subjects in the pregabalin arm had improved ease of getting to sleep and improved quality of sleep at day 36, compared with placebo baseline; however, there was no significant difference between treatments on any of the subjective sleep components.

PSG sleep

Sleep continuity. There was a significant treatment by visit effect on measures of sleep continuity with duloxetine significantly showing worse effect than pregabalin and amitriptyline (pregabalin and amitriptyline not statistically distinguishable). Compared with placebo baseline, duloxetine (60 and 120 mg) worsened sleep through reduced sleep efficiency (SE) ($P < 0.0001$ and $P < 0.05$, respectively), reduced total sleep time (TST) ($P < 0.0001$ and $P < 0.05$, respectively), and increased wake after sleep onset (WASO) ($P < 0.01$). In contrast, compared with placebo baseline, pregabalin (600 mg) significantly increased SE and TST and reduced WASO ($P < 0.01$ for all). Amitriptyline (50 and 75 mg) had no significant effect on SE and TST but did, at the higher dose (75 mg), reduce WASO ($P < 0.05$) (Table 3).

Sleep architecture. There was no significant treatment by visit effect on non-rapid eye movement (non-REM) sleep (Table 3).

For REM sleep, there was a significant difference between treatments, with clear

Table 1—*Basic demography of randomized patients*

	Pregabalin	Duloxetine	Amitriptyline	All
	$n = 27$	$n = 28$	$n = 28$	$n = 83$
Sex (n)				
Male	19	19	19	57
Female	8	9	9	26
Age (years)	66.3 (7.5)	65.0 (9.6)	64.2 (9.6)	65.1 (8.9)
BMI (kg/m^2)	32.1 (5.2)	32.0 (5.5)	31.9 (5.6)	32.0 (5.4)
Cholesterol (mmol/L)*	5.7 (0.9)	4.3 (1.1)	4.2 (1.2)	4.2 (1.1)
HDL (mmol/L)*	1.2 (0.4)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)
LDL (mmol/L)*	1.8 (0.8)	2.0 (0.8)	1.8 (0.9)	1.9 (0.8)
Triglycerides (mmol/L)*	2.5 (1.4)	2.4 (2.0)	2.8 (1.5)	2.6 (0.6)
HbA_{1c} (%)	7.7 (1.6)	7.9 (1.5)	8.2 (1.4)	7.9 (1.5)
Duration of diabetes (years)	15.2 (16.6)	13.8 (8.7)	13.8 (8.7)	14.2 (11.8)
Type of diabetes (n)				
Type 1	5	4	2	11
Type 2	22	24	26	72
Diabetes treatment (n)				
Insulin	14	18	20	52
Diabetes medication	10	9	8	27
Diet only	3	1	0	4
Ethnicity (n)				
Caucasian	27	28	28	83

Data are means (SD) unless otherwise indicated and are derived from the screening visit. *Only post-study values were available.

Table 2—*Patients' general well-being through subjective assessments and daytime performance measures*

Task	Treatment by visit effect	Pregabalin, mean (SE)			Duloxetine, mean (SE)			Amitriptyline, mean (SE)		
		Plc	Low dose	High dose	Plc	Low dose	High dose	Plc	Low dose	High dose
Subjective pain and QoL										
n		24	21	19	23	23	23	27	24	23
BPI severity	NS	3.1 (0.4)	2.3* (0.4)	2.4 (0.4)	3.4 (0.5)	2.5** (0.4)	2.2* (0.4)	3.5 (0.4)	2.7* (0.4)	2.6 (0.4)
BPI interference on sleep	NS	3.1 (0.5)	2.7** (0.6)	2.9* (0.7)	3.9 (0.7)	3.3* (0.7)	2.5** (0.6)	3.8 (0.5)	2.7** (0.6)	2.0** (0.5)
VAS	NS	16.8 (2.0)	13.5* (2.1)	13.2 (1.7)	23.3 (2.5)	16.3** (2.3)	13.2*** (2.2)	29.6 (2.3)	22.3** (2.1)	23.6 (2.4)
SF-36 mental component summary	NS	52.8 (9.3)		52.4 (10.0)	50.2 (9.0)		51.0 (8.8)	51.1 (7.3)		51.7 (8.0)
SF-36 physical component summary	NS	34.2 (8.2)		31.1 (10.9)	37.8 (10.0)		36.6 (9.4)	39.5 (9.3)		38.5 (8.8)
Cognitive functioning										
n		25	21	17	21	20	23	26	23	23
CTT MD	$P < 0.01$	14.0 (0.6)	16.8** (1.4)	19.6*** (1.7)	17.0 (1.4)	15.1 (1.0)	15.0 (1.1)	16.6 (1.0)	16.1 (0.9)	16.7 (1.2)
CRT TRT	$P < 0.05$	871.7 (30.4)	768.6 (19.5)	780.8 (17.1)	812.6 (75.8)	752.4*** (13.5)	726.5*** (12.5)	808.1 (15.2)	773.9** (14.7)	750.3** (13.6)
CFF	$P < 0.001$	27.1 (0.3)	27.4 (0.2)	26.9* (0.2)	28.0 (0.3)	30.0*** (0.3)	30.1*** (0.3)	27.2 (0.2)	26.8 (0.3)	27.2 (0.2)
Stroop VR	NS	68.6 (0.4)	68.2 (0.7)	68.5 (0.5)	67.2 (0.8)	70.1* (0.2)	69.8* (0.2)	68.2 (0.5)	68.7 (0.6)	69.2 (0.4)
DSST correct	NS	28.6 (0.8)	32.1 (0.9)	32.1 (0.9)	29.1 (0.9)	31.3** (0.9)	32.0** (0.9)	27.7 (0.9)	29.9*** (1.1)	31.3*** (1.2)
STM RT	NS	838.6 (13.9)	768.3*** (15.5)	795.6 (20.8)	911.6 (14.2)	860.8*** (12.7)	829.7*** (12.7)	845.2 (17.2)	800.2*** (14.5)	771.4*** (14.2)
IWR correct	NS	7.0 (0.2)	7.5 (0.3)	7.3 (0.3)	7.5 (0.4)	7.5 (0.3)	7.6 (0.3)	6.3 (0.3)	6.0 (0.3)	5.4** (0.3)
DWR correct	NS	2.7 (0.2)	3.4 (0.3)	3.2 (0.3)	4.1 (0.3)	4.3 (0.3)	4.1 (0.3)	3.0 (0.3)	2.5 (0.3)	2.3* (0.2)

Subjective assessments included the mean pain scores for BPI pain severity, BPI pain interference on sleep and visual analog scale, as well as quality of life (QoL) (SF-36) changes. There was no significant treatment by time effects for any of the pain variables or on SF-36 scores. Cognitive function assessment included the following: CFF, CRT, CTT, DSST, delayed word recall (DWR), immediate word recall (IWR), reaction time (RT), STM, TRT, and valid responses (VR). *n*, number of records included in the analysis. Treatment by visit effect is detailed where a significant difference between treatments was observed. Individual treatments (low and high dose) were compared with placebo baseline. MD, mean deviation; Plc, placebo; VAS, visual analog scale. $^*P < 0.05$. $^{**}P < 0.01$. $^{***}P < 0.001$.

evidence that loss of REM sleep (reduced REM duration, % REM, and REM cycles) was more pronounced in the duloxetine treatment group compared with pregabalin and amitriptyline (the latter two not statistically distinguishable) ($P < 0.01$, $P < 0.05$, and $P < 0.0001$, respectively) (Table 3).

Clinical sleep

There was a significant treatment by visit effect for PLMs per hour of sleep ($P < 0.001$) and AHI ($P < 0.0001$) (Table 3). Pregabalin (600 mg) significantly reduced PLM index compared with placebo baseline ($P < 0.001$), whereas duloxetine ($P < 0.05$) and amitriptyline ($P < 0{\cdot}01$) increased PLM index (the latter two not statistically distinguishable) (Table 3).

For apneas and hypopneas, pregabalin significantly increased AHI compared with placebo baseline ($P < 0.001$). Duloxetine and amitriptyline had no distinguishable effect on AHI. Pregabalin also increased the number of oxygen desaturations per hour (≥4%) ($P < 0.001$) but did not affect mean nocturnal oxygen saturation (Table 3).

Daytime function

There was no significant treatment by visit effect on memory tasks (STM, immediate word recall, and delayed word recall) (Table 2). There was a significant difference between treatments and improved daytime performance for duloxetine and amitriptyline. Duloxetine and amitriptyline improved reaction time on the psychomotor CRT task, with reduced recognition (RRT) and total reaction time (TRT) (RRT: $P < 0.0001$ and $P < 0.05$; TRT: $P < 0.0001$ and $P < 0.01$, respectively, for both low and higher dose). There was also evidence that duloxetine improved CNS arousal and information processing ability with an increased CFF threshold ($P < 0.0001$ at both doses) (Table 2). There was, however, no evidence of improved information processing ability on the DSST and Stroop task (Table 2).

There was evidence of impairment of daytime functioning with pregabalin on the sensori-motor CTT ($P < 0.01$) task, with pregabalin (300 and 600 mg) increasing tracking error compared with duloxetine and amitriptyline.

Quality of life and subjective daytime ratings

There was no significant treatment by visit effect on any quality of life component (SF-36) or SF-36 summary score (Table 2). There were no differences

Table 3—*Assessment of PSG sleep and nocturnal blood glucose*

		Pregabalin, mean (SE)			Duloxetine, mean (SE)			Amitriptyline, mean (SE)		
	Treatment by visit effect	Plc	Low dose	High dose	Plc	Low dose	High dose	Plc	Low dose	High dose
PSG sleep										
n		25	21	17	21	20	23	27	23	23
TST (min)	$P < 0.001$	371.6 (11.8)	380.6 (9.1)	410.3** (10.2)	381.4 (9.4)	338.1**** (12.1)	356.6* (13.8)	368.6 (8.9)	378.3 (12.0)	393.8 (10.9)
SE (%)	$P < 0.001$	77.3 (2.5)	79.2 (1.9)	85.4** (2.1)	79.4 (2.0)	70.4**** (2.5)	74.2* (2.9)	76.7 (1.9)	78.7 (2.5)	82.0 (2.3)
WASO (min)	$P < 0.01$	90.9 (11.8)	81.8 (8.8)	57.2** (10.3)	85.6 (9.0)	120.2** (11.0)	100.5 (12.8)	91.0 (9.4)	78.8 (12.2)	66.6* (10.8)
Duration of non-REM sleep (min)	$P = 0.0526$	291.5 (10.6)	319.0** (8.9)	348.3**** (10.1)	298.0 (9.6)	303.3 (10.7)	326.7* (12.6)	291.6 (7.4)	328.6**** (10.0)	343.6**** (9.3)
Duration of REM (min)	$P < 0.01$	80.1 (6.0)	61.6** (6.8)	62.0** (6.9)	83.4 (7.5)	34.8**** (5.2)	29.9**** (5.7)	77.0 (5.2)	49.7**** (6.5)	50.2**** (5.4)
Number of REM periods	$P < 0.0001$	3.3 (0.2)	2.8* (0.3)	3.1 (0.3)	3.8 (0.3)	1.5**** (0.2)	1.8**** (0.2)	3.7 (0.2)	2.7*** (0.3)	2.3**** (0.2)
PLM index (PLMs/hour of sleep)	$P < 0.001$	19.7 (4.5)		12.0** (4.1)	16.2 (3.6)		24.4* (6.2)	16.2 (4.6)		19.9** (4.9)
AHI	$P < 0.0001$	5.8 (1.6)		11.9*** (3.5)	3.7 (0.8)		2.3 (0.6)	3.6 (0.8)		2.9 (0.9)
Mean number of desaturations (>4%/hour of sleep)	$P < 0.0001$	3.9 (1.0)		10.2*** (3.2)	2.9 (0.7)		1.9 (0.6)	2.8 (0.6)		2.3 (0.7)
Blood glucose										
n		24	21	17	21	20	23	27	23	23
Mean nocturnal blood glucose (mmol/L)	$P < 0.01$	7.1 (0.4)	7.4 (0.6)	8.7** (0.7)	8.1 (0.5)	6.8** (0.4)	7.0* (0.4)	8.3 (0.4)	7.5 (0.5)	7.9 (0.4)
Nocturnal glucose: AUC mmol/L × min	$P < 0.05$	3,395.3 (188.1)	3,518.0 (308.2)	4,185.1* (317.2)	3,844.3 (234.9)	3,253.6** (183.5)	3,361.5* (190.2)	3,959.9 (173.4)	3,620.0 (233.7)	3,802.6* (178.7)
Mean % of nocturnal glucose levels >15.0 mmol/L	$P < 0.05$	0.0 (0.0)	5.5* (3.8)	3.2** (2.3)	0.9 (0.9)	0.9 (0.9)	0.1 (0.1)	0.3 (0.2)	0.8 (0.8)	0.6 (0.6)

PSG sleep continuity and sleep architecture variables included are as follows: REM, SE %, TST, and WASO. Clinical sleep variables included the following: AHI and PLMs. Nocturnal blood glucose measurements included mean and AUC. *n*, number of records included in the analysis. Treatment by visit effect is detailed where a significant difference between treatments was observed. Individual treatments (low and high dose, where applicable) were compared with placebo baseline. Plc, placebo. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$. ****$P < 0.0001$.

between treatment groups for subjective measures of mood, coordination, and sedation (Linear Analog Rating Scale and Karolinska Sleepiness Scale), and no change for any of these variables with time.

Safety

There was no overall significant treatment by visit effect for overall blood glucose, but there were significant differences between treatments on nocturnal glucose. Duloxetine (60 and 120 mg) was associated with a small but significant decrease in nocturnal blood glucose (mean, $P < 0.01$, and area under the curve [AUC], $P < 0.05$) (Table 3). Pregabalin (600 mg only) was associated with a small but significant increase in nocturnal blood glucose (mean, $P < 0.01$; AUC, $P < 0.05$; and % measurements >15 mmol/L, $P < 0.01$) (Table 3).

No changes of note were seen in vital signs, biochemistry parameters, or electrocardiograms. There were no clinically significant changes in hematology parameters except that one patient experienced a fall in platelet count, which may have been due to amitriptyline treatment.

There were six serious adverse events (SAEs), one death and five nonfatal SAEs. None of the SAEs were considered to be related to study medication. Ten subjects withdrew prematurely as a result of an adverse event (six from the pregabalin treatment group, three from the duloxetine group, and one from the amitriptyline group). Subjects in the pregabalin treatment group recorded the highest number of treatment-emergent adverse events ($P < 0.0001$) with a causal relationship with study drug. These events were related to general and nervous system disorders and specifically fatigue, dizziness, and somnolence. Twenty-five subjects asked to continue with their medication at the end of the trial (11 pregabalin, 8 amitriptyline, and 6 duloxetine).

CONCLUSIONS—The three study medications, amitriptyline, duloxetine, and pregabalin, all reduced subjective pain with no one drug being superior to another over the 4-week, dose titration period. Subjective pain ratings (BPI severity) showed ~50% improvement, in line with previous studies (8,12).

Daytime performance measures showed no evidence of cognitive impairment during treatment, with the exception of increased tracking error on a divided attention task (CTT) with pregabalin. Previous studies have indicated that use of amitriptyline may be limited by its effects on daytime functioning, in particular aspects of memory function that are disrupted even after long-term dosing (34). The study reported here suggests that there is limited evidence for cognitive function being compromised with amitriptyline treatment, and all three treatments were relatively well tolerated. The change in tracking (CTT) performance with pregabalin replicated a similar finding reported previously in healthy volunteers (35) and supports current clinical evidence that daytime effects from pregabalin treatment are limited. There was evidence that duloxetine improved attention-based tasks and sensori-motor performance. Similar improvements with selective serotonin and noradrenaline reuptake inhibitors and selective serotonin reuptake inhibitors in mental processing speed have been observed in both patients with depression and healthy volunteers (36), possibly reflecting CNS activation.

PSG sleep examination gave further support to a CNS-activating effect of duloxetine as both the 60- and 120-mg dose reduced total sleep time, increased the amount of wake, increased time to fall asleep, and substantially disrupted REM sleep. In contrast, sleep continuity was promoted by pregabalin (600 mg) and unchanged with amitriptyline. The signature changes in sleep seen with duloxetine have previously been reported; although the alerting effect has been associated more with evening dosing (37). Despite previous literature suggesting that amitriptyline promotes sleep initiation and sleep continuity (38), our results indicated little impact of amitriptyline on sleep in patients with DPNP. In line with previous reports, pregabalin improved sleep continuity, reducing wake after sleep onset.

The sleep fragmentation seen with duloxetine is concerning. It is widely believed that poor sleep may worsen pain, and although duloxetine has good analgesic efficacy, its effectiveness may be limited by this physiological effect. In addition to a direct effect on sleep, there was also evidence that PLMs were significantly increased under duloxetine and amitriptyline, a finding often reported for antidepressant drugs (39). Pregabalin, on the other hand, significantly reduced PLM. One clinical finding that requires further investigation was the apparent increase in AHI and increase in oxygen desaturations with pregabalin during sleep. This clinical finding has not been reported previously; although Saletu-Zhylarz et al. (40) did report an increase in snoring index. It should be noted that there was a relatively low incidence of sleep apnea in the patient population, and overall the increase in AHI was numerical rather than increasing clinical severity.

As significant changes in sleep and daytime functioning were observed, it was perhaps surprising to find that there were no significant improvements in mental health, as assessed by the SF-36, after 28 days of treatment. All three treatments (pregabalin for generalized anxiety disorder and duloxetine and amitriptyline for depression) are indicated for affective disorders and it has been well documented that DPNP is associated with low mood, depression, and anxiety (2,3). Although the SF-36 had been a tool used in previous DPNP studies (10), it is possible that this measure was not sensitive enough to assess changes in mood over a short, 4-week period. Mood scales, such as Profile of Mood States, might be a more appropriate measure to detect subtle changes in mood state over a shorter period of time.

Overall, all three treatments were well tolerated with no significant laboratory or safety findings. There was no indication of changes in HDL values with duloxetine as has been reported by other authors (11). One patient had clinically significant hematological changes with amitriptyline (platelet count reducing from 253,000 to 87,000 $\times$ 10^9/L), reinforcing the need for care when prescribing the tricyclic antidepressant in older adults. In general, all adverse events were in line with those previously reported; however, there was a significantly higher number of adverse events reported in the pregabalin treatment group, in particular, those related to nervous system disorders such as fatigue, somnolence, and dizziness. Although patients reported a higher number of adverse events with pregabalin, and this should be considered when prescribing pregabalin to DPNP patients, it should be noted that a higher proportion of patients requested to continue with pregabalin treatment at the end of the study, suggesting that the adverse events did not interfere significantly with their activities of daily living.

In conclusion, amitriptyline, duloxetine, and pregabalin were equally effective

analgesic medications in patients with DPNP. Pregabalin promoted sleep, whereas duloxetine increased sleep fragmentation and substantially reduced REM sleep. Daytime function was relatively unaffected by drug treatment, and all three drugs were well tolerated. In this short, 28-day dosing study, there was no evidence of improved quality of life (SF-36) even with the sleep enhancement observed with pregabalin. Further longer-term studies, with more sensitive measures of assessment, may help establish the effect of sleep changes seen with pregabalin and duloxetine on pain, glycemic control, and quality of life during long-term treatment.

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J.B. wrote the manuscript, contributed to the study design, and interpreted data. M.E.V.E. cowrote the manuscript, contributed to the study design, and collected, analyzed, and interpreted data. L.G. reviewed the manuscript, contributed to the study design, and collected data. R.G. reviewed the manuscript and collected data. S.J. reviewed the manuscript and performed statistical analysis of the clinical trial data. D.V.C. and D.K. reviewed the manuscript, contributed to the study design, and interpreted data. J.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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