Randomised, 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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Abstract

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 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, randomised, 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 lower dose and 14 days higher dose medication. At the end of each dose titration period subjective pain, sleep and daytime functioning were assessed during a two-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 ($P < 0{\cdot}001$) whereas duloxetine increased wake and reduced total sleep time ($P < 0{\cdot}01$ and $P < 0{\cdot}001$). Despite negative effects on sleep, duloxetine enhanced CNS 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.

Introduction

Chronic diabetic peripheral neuropathic pain (DPNP) is a common, debilitating and distressing complication of diabetes mellitus.[1] In addition to directly causing pain, it also can impair an individuals' 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 (TCA) amitriptyline, the selective serotonin and noradrenaline reuptake inhibitor (SNRI) duloxetine, and calcium channel alpha 2 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 non-specific 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[16], and episodes of hyper or hypo-glycaemia.[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 improved restorative sleep seen in healthy individuals was replicated in patients with chronic DPNP.

Research Design and Methods

Subjects

Subjects aged 18 years and above, with diabetes mellitus (type 1 or type 2) for at least one 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- dysaesthesia, burning pain, cold or heat allodynia, shooting or lancinating pains and hyperalgesia affecting both lower extremities at any level below the mid-thighs. 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 (MMSE)), end stage disease of a major system, evidence of a recurrent and/or severe hypoglycaemic event, (defined as hypoglycaemia requiring help from a third party), in the last 3 years, or a recent cardiac or cerebral ischaemic 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 three 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-GCP guidelines at the Surrey Clinical Research Centre (Surrey CRC), Faculty of Health and Medical Sciences, University of Surrey, UK. The study received a favourable opinion from the Essex 1 Research Ethics Committee and

University of Surrey Ethics Committee and was registered at clinicaltrials.gov, with registration number NCT00370656. All participants supplied written informed consent before screening.

Procedures

The trial was a double-blind, randomised, parallel group investigation with an eight day single-blind placebo run in. Subjects were sequentially randomized into one of the three treatment arms (pregabalin, amitriptyline, or duloxetine). The randomisation was provided by an independent statistician to ensure that groups were matched for age and gender where possible. Patients were stratified into four groups: males 18-59 yrs; females 18-59 yrs; male >60 yrs; females >60 yrs. 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 non-steroidal anti-inflammatory drugs during the study and were allowed to take paracetamol with a maximum dose of 4 g /day.

After the eight-day placebo run in, subjects were titrated through 14 days of lower dose medication (amitriptyline 25 mg bd; duloxetine 60 mg om; pregabalin 150 mg bd) to 14-days of higher dose medication (amitriptyline 25 mg om, 50 mg on; duloxetine 60 mg bd; pregabalin 300 mg bd). At the end of each treatment period subjects were resident at the Surrey CRC for a 48 hour comprehensive assessment of polysomnographic (PSG) sleep, subjective pain, daytime functioning and continuous glucose monitoring (CGMS® System Gold™ Medtronic MiniMed, Inc. (figure 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 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 re-familiarised 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 Brief pain inventory (BPI)[24] and a visual analogue scale adapted from the Short Form McGill Pain Questionnaire.[25]

Subjective sleep, mood and daytime sleepiness were assessed by the visual analogue scales: Leeds Sleep Evaluation Questionnaire (LSEQ)[26], Linear Analogue Rating Scales (LARS)[27], and Karolinska Sleepiness Scale (KSS).[28]

PSG sleep records were manually staged according to Rechtschaffen and Kales criteria.[29] For clinical sleep variables (periodic limb movements and apnoea / hypopnoea index), 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:-

Sensori-motor and psychomotor speed: Continuous Tracking task, CTT,[27] and Choice Reaction Time task, CRT.[27]

CNS arousal and information processing tasks: Critical Flicker Fusion, CFF [27], Stroop task and Digit Symbol Substitution Test, DSST.[30]

Working and explicit memory tasks: Immediate and Delayed Word Recall [31] and Sternberg's 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 statistical significant (5%-level, double-sided) difference between treatments on the primary endpoint of subjective pain (BPI). However, comparable single-site studies investigating amitriptyline and gabapentin (a compound closely related to pregabalin) in DPNP successfully used around 30 patients for each comparison.[9, 33]

The main analysis was done according to a pre-planned statistical analysis plan. The safety population was defined as consisting of the set of those subjects who were randomised 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 data set was analysed 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 body mass index (BMI) and age. Statistical significance level was set to 5% ($p < 0.05$). All analyses were done with SAS® PROC MIXED 9.1 software.

Role of the funding source

The funding source was a research investigator led grant from Pfizer Ltd. Pfizer did not participate in data collection, data analysis, data interpretation or writing of the report.

Results

A total of 104 subjects with both type 1 and 2 DM were screened between Febuary 2007 and March 2009, and 83 enrolled and randomised. 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 randomised to the trial. Twenty-seven were randomised 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 randomised 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 VAS 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 mg and 120 mg) worsened sleep through reduced sleep efficiency (SE) ($P < 0{\cdot}0001$ and $P < 0{\cdot}05$, respectively), reduced total sleep time (TST) ($P < 0{\cdot}0001$ and $P < 0{\cdot}05$, respectively and increased wake after sleep onset (WASO) ($P < 0{\cdot}01$). In contrast, compared with placebo baseline pregabalin (600 mg) significantly increased SE and TST and reduced WASO ($P < 0{\cdot}01$ for all). Amitriptyline (50 mg and 75 mg) had no significant effect on SE and TST but did, at the higher dose (75 mg), reduce WASO ($P < 0{\cdot}05$) (Table 3).

Sleep Architecture

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

For rapid eye movement (REM) sleep there was a significant difference between treatments with clear 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) ($P < 0{\cdot}01$, $P < 0{\cdot}05$ and $P < 0{\cdot}0001$, respectively) (Table 3).

Clinical Sleep

There was a significant treatment by visit effect for periodic limb movements (PLM) per hour of sleep ($P < 0{\cdot}001$) and apnoea hypopnoea index (AHI) ($P < 0{\cdot}0001$) (Table 3).

Pregabalin (600 mg) significantly reduced PLM index compared with placebo baseline ($P < 0{\cdot}001$) whereas duloxetine ($P < 0{\cdot}05$) and amitriptyline ($P < 0{\cdot}01$) increased PLM index (the latter two not statistically distinguishable) (Table 3).

For apnoeas and hypopnoeas, pregabalin significantly increased AHI compared with placebo baseline ($P < 0{\cdot}001$). Duloxetine and amitriptyline had no distinguishable effect on AHI. Pregabalin also increased the number of oxygen desaturations / hr ($\geq 4\%$) ($P < 0{\cdot}001$) but did not affect mean nocturnal oxygen saturation (Table 3).

Daytime function

There was no significant treatment by visit effect on memory tasks (STM, IWR, DWR) (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 (TRT) reaction time (RRT: $P < 0{\cdot}0001$ and $P < 0{\cdot}05$; TRT: $P < 0{\cdot}0001$ and $P < 0{\cdot}01$, 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 ($P < 0{\cdot}0001$ 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 ($P < 0{\cdot}01$) task, with pregabalin (300 mg 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 between treatment groups on subjective measures of mood, co-ordination and sedation (LARS and KSS) and no change on 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 mg and 120 mg) was associated with a small but significant decrease in nocturnal blood glucose (mean, $P < 0{\cdot}01$ and area under the curve, AUC, $P < 0{\cdot}05$) (Table 3). Pregabalin (600 mg only) was associated with a small but significant increase in nocturnal blood glucose (mean, $P < 0{\cdot}01$, AUC $P < 0{\cdot}05$ and % measurements > 15 mmol / L, $P < 0{\cdot}01$) (Table 3).

No changes of note were seen in vital signs, biochemistry parameters or ECGs. There were no clinically significant changes in haematology 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 non-fatal 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 ($P < 0{\cdot}0001$) with a causal relationship to 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 (eleven pregabalin, eight amitriptyline, and six duloxetine).

Discussion

The three study medications, amitriptyline, duloxetine and pregabalin, all reduced subjective pain with no one drug being superior to another over the four-week, dose titration period. Subjective pain ratings (BPI severity) showed approximately 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 which 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 SNRIs and selective serotonin reuptake inhibitors (SSRIs) 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 mg 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 periodic limb movements 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 apnoea hypopnoea index and increase in oxygen desaturations with pregabalin during sleep. This clinical finding has not been reported previously although Saletu-Zhylarz et al., (2006) did report an increase in snoring index.[40] It should be noted that there was a relatively low incidence of sleep apnoea 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 following 28 days of treatment. All 3 treatments (pregabalin for generalised anxiety disorder, 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 (POMS) 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 haematological changes with amitriptyline (platelet count reducing from 253,000 to 87,000 x 10^9 / L), reinforcing the need for care when prescribing the tricylcic 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 suggested 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, glycaemic control, and quality of life during long term treatment.

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Dr J, Boyle 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.

Authors' contributions

J Boyle wrote the manuscript, contributed to the study design and interpretation of the data

M. Eriksson co-wrote the manuscript, contributed to the study design and data interpretation and was responsible for data collection and analysis

L. Gribble reviewed the manuscript, contributed to the study design and was responsible for data collection

R Gouni reviewed the manuscript and was responsible for data collection,

S. Johnsen reviewed the manuscript and was responsible for the statistical analysis of the clinical trial data

D Kerr reviewed the manuscript, contributed to the study design and interpretation of the data

D. Coppini reviewed the manuscript, contributed to the study design interpretation of the data

Conflicts of interest

J Boyle has received an honorarium to present the research findings internally to a Pfizer consultancy board

M. Eriksson has no conflicts of interest

L. Gribble has no conflicts of interest

R Gouni has no conflicts of interest

D Kerr has received consultancy fees and honoraria from Lilly, NovoNordisk, Abott Diabetes Care and Roche, companies providing medicines and monitoring equipment used by subjects in this study

D Coppini has no conflicts of interest

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Table 1

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

Table 1 shows basic demography of randomised patients. Data is derived from the screening visit except for values marked * where only post study values were available.

Table 2

Task	Treatment by Visit Effect	Pregabalin			Duloxetine			Amitriptyline		
		Mean (SE)			Mean (SE)			Mean (SE)		
		Plc	Low dose	High dose	Plc	Low dose	High dose	Plc	Low dose	High dose
Subjective Pain & 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)
SF36 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)
SF36 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)

Table 2 shows patients' general well-being through subjective assessments and daytime performance measures.

Subjective assessments included the mean pain scores for Brief Pain Inventory (BPI) pain severity, BPI pain interference on sleep and visual analogue 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: CTT = Continuous tracking test; CFF = Critical flicker fusion; CRT = Choice reaction time; TRT = Total reaction time; VR = Valid responses; STM = Sternberg short-term memory scanning task; RT = reaction time; DSST = Digit symbol substitution test; IWR = Immediate word recall; DWR = Delayed word recall.

N = number of records included in the analysis. Treatment by visit effect is detailed where a significant difference between treatments was observed. NS means that there was no significant difference between the three treatment groups.

Individual treatments (low and high dose) were compared with placebo baseline. Where there was a significant change in time from placebo baseline this is shown as an asterix against individual treatment means. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ and **** $P < 0.0001$

Table 3

		Pregabalin			**Duloxetine**			**Amitriptyline**		
	Treatment by Visit Effect	Mean (SE)			Mean (SE)			Mean (SE)		
		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)
PLMS Index (PLM / 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 (minsmmol / L)	**P < 0.05**	3395.3 (188.1)	3518.0 (308.2)	4185.1* (317.2)	3844.3 (234.9)	3253.6** (183.5)	3361.5* (190.2)	3959.9 (173.4)	3620.0 (233.7)	3802.6* (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)

Table 3 shows assessment of polysomnographic (PSG) sleep and nocturnal blood glucose. PSG sleep continuity and sleep architecture variables included: TST = Total sleep time; SE% = Sleep efficiency; WASO = Wake after sleep onset; REM = Rapid eye movement. Clinical sleep variables included AHI = Apnoea hypopnoea index and PLMS = Periodic Limb Movements. Nocturnal blood glucose measurements included mean and AUC = Area under the curve.

N = number of records included in the analysis. Treatment by visit effect is detailed where a significant difference between treatments was observed. NS means that there was no significant difference between the three treatment groups.

Individual treatments (low and high dose, where applicable) were compared with placebo baseline. Where there was a significant change in time from placebo baseline this is shown as an asterix against individual treatment means. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ and **** $P < 0.0001$

Figure Legends

Figure 1: A Schematic diagram illustrating the timing of the main study procedures. BPI = Brief Pain Inventory, CGMS = Continuous Glucose Monitoring System, GTB = Guildford Test Battery (Continuous tracking test; Critical flicker fusion; Choice reaction time; Stroop Test; Sternberg short-term memory scanning task; DSST = Digit symbol substitution test; Word Recall; Leeds Sleep Evaluation Questionnaire and Linear Analogue Scales), PSG = Polysomnography.

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.