Does Treatment With Duloxetine for Neuropathic Pain Impact Glycemic Control?

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OBJECTIVE — We examined changes in metabolic parameters in clinical trials of duloxetine for diabetic peripheral neuropathic pain (DPNP).

RESEARCH DESIGN AND METHODS — Data were pooled from three similarly designed clinical trials. Adults with diabetes and DPNP ($n = 1,024$) were randomized to 60 mg duloxetine q.d., 60 mg b.i.d., or placebo for 12 weeks. Subjects ($n = 867$) were re-randomized to 60 mg duloxetine b.i.d. or routine care for an additional 52 weeks. Mean changes in plasma glucose, lipids, and weight were evaluated. Regression and subgroup analyses were used to identify relationships between metabolic measures and demographic, clinical, and electrophysiological parameters.

RESULTS — Duloxetine treatment resulted in modest increases in fasting plasma glucose in short- and long-term studies (0.50 and 0.67 mmol/l, respectively). A1C did not increase in placebo-controlled studies; however, a greater increase was seen relative to routine care in long-term studies (0.52 vs. 0.19%). Short-term duloxetine treatment resulted in mean weight loss (−1.03 kg; $P < 0.001$ vs. placebo), whereas slight, nonsignificant weight gain was seen in both duloxetine and routine care groups with longer treatment. Between-group differences were seen for some lipid parameters, but these changes were generally small. Metabolic changes did not appear to impact improvement in pain severity seen with duloxetine, and nerve conduction was also not significantly impacted by treatment.

CONCLUSIONS — Duloxetine treatment was associated with modest changes in glycemia in patients with DPNP. Other metabolic changes were limited and of uncertain significance. These changes did not impact the significant improvement in pain observed with duloxetine treatment.

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Neuropathy is the most common diabetic microvascular complication, affecting up to 50% of all individuals with diabetes (1). Substantial morbidity is associated with diabetic peripheral neuropathy (DPN), which is the leading risk factor for diabetic foot complications and nontraumatic amputations. Though these late complications frequently occur in the insensate foot, symptomatic DPN also significantly impacts quality of life (2,3). Estimates of the prevalence of diabetic peripheral neuropathic pain (DPNP) vary from 3% to >20% (4).

For many agents, the data supporting effectiveness is limited. In addition, nearly all treatments are associated with safety or tolerability issues. One category of side effects common to a number of the antidepressant and anticonvulsant drugs is related to metabolic changes. Weight gain is seen with tricyclic antidepressants (TCAs) (5) and anticonvulsants (e.g., valproate, gabapentin, pregabalin) (6). Changes in plasma glucose have also been reported with TCAs (7,8) and phenytoin (9), and dyslipidemia can be seen with carbamazepine (10).

Duloxetine has demonstrated efficacy in several large clinical trials of DPNP (11–13) and is one of only two drugs to have received regulatory approval for the treatment of this condition. As a selective reuptake inhibitor of both norepinephrine and serotonin, it shares some features with secondary amine TCAs such as nortriptyline. However, it differs from TCAs in some aspects, including the lack of interaction with acetylcholine receptors in vitro. In clinical trials of major depressive disorder, duloxetine was not associated with weight gain; however, other metabolic parameters, such as fasting glucose and lipids, were not tested (14).

The clinical trials of duloxetine for DPNP provide a large database to evaluate potential metabolic effects of duloxetine in patients with diabetes. The current study examined pooled data from both short- and long-term studies to assess changes in weight, glycemia, and plasma lipids and to test for relationships between metabolic changes and baseline clinical factors, as well as the analgesic response to duloxetine treatment.

RESEARCH DESIGN AND METHODS

— Three randomized trials (each with a 12-week, double-blind, placebo-controlled acute phase and a 52-week, open-label extension phase) were included in these analyses. Entry criteria and study designs were nearly identical for these large, phase-three clinical trials, and details of these studies have been previously published (11–13). Briefly, patients were adults with type 1 or type 2 diabetes and with bilateral peripheral

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Data from this study were previously published in abstract form in 2004, specifically as "The safety of duloxetine in the long-term treatment of diabetic neuropathic pain" at the 20th Annual Meeting of the American Academy of Pain Medicine in Orlando, Florida, and as "Duloxetine at doses of 60 mg QD and 60 mg BID is effective treatment of diabetic neuropathic pain" at the 56th Annual Meeting of the American Academy of Neurology in San Francisco, California.

Abbreviations: BPI, brief pain inventory; DPN, diabetic peripheral neuropathy; DPNP, DPN pain; FPG, fasting plasma glucose; TCA, tricyclic antidepressant.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Baseline characteristics of patients in pooled DPNP studies*

	Acute studies		Extension studies	
	Duloxetine	Placebo	Duloxetine	Routine care
n	685	339	580	287
Age (years)	59.7	60.1	59.4	59.2
Male (%)	42.9	46.6	55.7	56.4
Caucasian (%)	85.4	85.8	86.0	83.3
Type 2 diabetes (%)	87.7	89.4	87.4	87.8
Duration of DPN (years)	4.04	3.85	4.09	3.52
Smoking (%)	14.0	13.9	13.4	13.6
FPG (mmol/l)	9.75	10.09	10.18	10.67
A1C (%)	7.81	7.86	7.74	7.90
Triglycerides (mmol/l)	2.70	2.28	2.44	2.46
LDL cholesterol (mmol/l)	2.95	2.93	3.01	3.02
HDL cholesterol (mmol/l)	1.19	1.21	1.21	1.23
Total cholesterol (mmol/l)	5.24	5.14	5.26	5.34
Weight (kg)	94.29	95.03	92.99	94.88
Pain severity (0–10 scale)	5.90	5.70	NA	NA

neuropathic pain of at least moderate severity. Peripheral neuropathy was confirmed with the Michigan Neuropathy Screening Instrument (15). Entry A1C >12% and major depressive disorders were among the exclusion criteria.

Patients analyzed for this study were randomized to placebo or 60 mg duloxetine q.d. or 60 mg b.i.d. during the acute phase of treatment. Patients completing 12 weeks of treatment were then rerandomized (2:1) to 60 mg duloxetine b.i.d. or routine care. In one of the studies, some patients were also randomized to 20 mg duloxetine q.d. This dose is not approved for treatment of DPNP, and those patients were not included in the analysis of the acute studies (but were included in the extension-phase data analysis if they entered the extension phase). Only acetaminophen was allowed as adjuvant pain therapy in all patients during the acute phase and in duloxetine-treated patients during the extension phase. Investigators were not restricted in their choice of treatments for the routine care group, including allowance for combination therapy. No specific directions were included in the study protocols with regard to management of diabetes or dyslipidemia, nor were there any specific dietary or physical exercise instructions.

Fasting glucose, lipids, A1C, and other clinical chemistries were determined by standard techniques at a central laboratory (Covance Laboratories, Princeton, NJ). Diabetes-related adverse events were determined from unsolicited reports to investigators, which were then identified using a search for diabetes-related MedRA terms. A history of hypoglycemic events was taken from patients at each visit. Patients kept a daily diary of average pain severity during the acute-phase studies (0–10 scale), which was then averaged on a weekly basis. Interference of pain with daily activities was measured using the brief pain inventory (BPI) interference scale (16). Nerve conduction studies were performed in two of three studies at baseline and at the conclusion of both the acute and extension phases using the NC-stat automated nerve conduction testing system (NeuroMetrix, Waltham, MA). Parameters measured included peroneal A wave (presence or absence), deep peroneal F wave latency, ulnar F wave latency, ulnar distal sensory latency, and deep peroneal compound action potential amplitude. All were studied in the nondominant extremities. Electrophysiology measures from extension-phase studies were reported by study and were not pooled for the current analysis. Some of these nerve conduction results have been previously reported (17).

Statistical analyses

Unless otherwise noted, the current analyses included all subjects who received at least one dose of treatment and had at least one postbaseline measurement. Mean changes from baseline to last observation carried forward in weight, fasting glucose, A1C, and electrophysiology measures were assessed using an ANCOVA model that included baseline measure, treatment, and study. Other laboratory measures were examined using an ANOVA model with terms for treatment and study. Raw values were used for the analysis of fasting glucose, A1C, weight, and electrophysiology measures, and rank-transformed data were used for other laboratory analytes. The change from baseline to last observation carried forward in fasting glucose and A1C were also analyzed using subgroups based on baseline BMI (<30 and ≥30 kg/m^2), A1C level (≤8 and >8%), and change in status of peroneal F wave (same, better, and worse) using an ANCOVA model with terms for treatment, subgroup, study, and subgroup-by-treatment interaction, with baseline score as a covariate. Analysis of the primary efficacy variable (24-h average pain severity) and one of the secondary efficacy variables (BPI interference) was performed using subgroups based on baseline A1C level (≤8 and >8%) and baseline peroneal F wave (presence or absence), as well as the same ANCOVA model terms as previously listed. Categorical data (categorical change in fasting glucose and A1C, diabetes-related adverse events, significant hypoglycemic episode, and shift of status in electrophysiology measures) were assessed using the Cochran-Mantel-Haenszel test to adjust for study. Pearson's correlation coefficients (*r*) were calculated to evaluate correlations between the continuous variables of pain severity score and metabolic parameters. Data for all subjects were used for correlations between two baseline variables, but only data from duloxetine-treated patients were used when either variable in the correlation involved change during treatment. No adjustments were made for multiple comparisons.

Path analysis was used to test whether the change in 24-h average pain severity depends on the change in fasting glucose, A1C, or individual lipid parameters—versus the alternative that the reduction in 24-h average pain severity is due to a direct analgesic effect of the treatment and is independent of the treatment effect on metabolic parameters.

RESULTS — Pooled analysis from the three studies included 685 duloxetine-treated patients from the acute studies and 580 patients treated with 60 mg duloxetine b.i.d. in extension-phase studies. Baseline demographics are listed in Table 1. Type 2 diabetes predominated in all treatment groups, and mean baseline A1C was very similar between treatment groups in both acute and extension-phase studies. Leading medications used in the routine care group during the extension

Table 2—*Mean changes in metabolic and pain parameters in pooled DPNP studies*

	Acute studies			Extension studies		
	Duloxetine	Placebo	*P*	Duloxetine	Routine care	*P*
n	685	339		580	287	
FPG (mmol/l)	0.50	−0.11	0.064	0.67	−0.64	<0.001
A1C (%)	−0.09	−0.07	0.766	0.52	0.19	<0.001
Triglycerides (mmol/l)	−0.19	0.07	0.106	0.05	0.00	0.854
LDL cholesterol (mmol/l)	0.08	−0.02	0.075	0.02	−0.09	0.068
HDL cholesterol (mmol/l)	0.03	0.00	0.008	−0.01	−0.08	0.002
Total cholesterol (mmol/l)	0.07	−0.03	0.090	0.06	−0.16	0.005
Weight (kg)	−1.03	0.03	<0.001	0.31	0.49	0.531
Pain severity (0–10 scale)	−2.70	−1.64	<0.001	NA	NA	

phase were gabapentin (48%), venlaxafine (17%), and amitriptyline (15%). On average, patients reported moderately severe pain before treatment (Table 1), as measured using the Likert scale (18).

Metabolic changes in acute and long-term studies

Mean changes in glycemic parameters, plasma lipids, and weight are listed in Table 2. In the short-term (12-week) studies, duloxetine-treated patients experienced a modest increase in mean fasting plasma glucose (FPG), whereas a small decrease was seen in the placebo group (0.5 vs. −0.11 mmol/l; $P = 0.064$ for comparison; $P = 0.002$ for change from baseline in duloxetine group). The increase was higher in the group receiving duloxetine twice daily (0.55 mmol/l) compared with the once-daily group (0.46 mmol/l), but the difference was not statistically significant. These changes were not associated with a significant increase in A1C in the duloxetine group. Instead, a small statistically significant decrease in A1C was observed during duloxetine treatment (−0.09%; $P = 0.013$). An increase in FPG was also seen during duloxetine treatment in extension studies (0.67 mmol/l), whereas the routine care experienced a decline (−0.64 mmol/l). A1C increased in both the duloxetine and routine care groups; however, the change was significantly larger in the duloxetine group (0.52 vs. 0.19%; $P < 0.001$). These glycemic changes varied somewhat between studies, but it did not appear that any single study was overly influential regarding these findings. In particular, A1C changes in the long-term studies were consistent.

Subgroup analyses of glucose change were also performed as a function of baseline A1C and baseline BMI. FPG increases were significantly greater in patients with baseline A1C <8% during acute studies (between subgroups $P < 0.001$). However, relative FPG change between treatment groups was similar regardless of baseline glycemic control (subgroup-by-therapy $P = 0.843$). The BMI categories used were not predictive of treatment-specific, or of overall, FPG change in the acute studies (*P* values for subgroup and subgroup-by-therapy, both >0.79). Therefore, the presence of obesity was not predictive of change in glycemic parameters in these studies, but a higher baseline A1C was inversely related to glycemic change during duloxetine treatment.

Similar results were observed in subgroups with different baseline A1C values in the extension studies. A1C changes were inversely related to pretreatment A1C levels in both duloxetine and routine care groups, and the therapy-by-subgroup interaction was not significant ($P = 0.765$). However, when comparing glycemic categories at baseline and end point (<7, 7–8, and >8%), more duloxetine-treated patients shifted to higher categories, and fewer improved categories, than with routine care. Treatment groups did not differ in the number of diabetes-related adverse events or in the frequency of hypoglycemic events in either short-term or extension-phase studies.

Duloxetine-treated patients experienced a small decrease in triglycerides and small increases in HDL, LDL-C, and total cholesterol during acute studies. Only the HDL cholesterol change was significantly different from placebo. During extension studies, the direction of change in triglycerides and HDL cholesterol was reversed in the duloxetine group, but changes remained small in magnitude. Routine care was associated with significantly greater declines in total and HDL cholesterol (−0.16 vs. +0.06 mmol/l, $P = 0.005$ and −0.08 vs. 0.01 mmol/l, $P = 0.002$, respectively). Weight decreased in duloxetine patients during acute studies, unrelated to dose (−1.03 kg; $P < 0.001$ vs. placebo), and a negative correlation between weight change and baseline weight was observed ($r = -0.27$; $P < 0.001$). No other significant between-group changes were observed.

Relationships between pain and metabolic parameters

We evaluated potential relationships between pain severity and demographic and metabolic parameters using correlational, subgroup, and regression (path) analyses. Mean baseline pain levels were significantly higher in females and in non-Caucasians but did not differ significantly based on age (<65 or >65 years), type of diabetes (1 or 2), duration of neuropathy (<2 or >2 years), or smoking status (data not shown). Among the measured metabolic parameters, baseline BMI and triglyceride levels were positively but weakly correlated with baseline pain severity ($r = 0.09$, $P < 0.001$ and $r = 0.07$, $P = 0.026$, respectively). Other baseline lipid values and A1C were not correlated with pain scores. Importantly, changes in metabolic parameters appeared to have little or no impact on the improvement in pain severity during duloxetine treatment. Only change in LDL and total cholesterol were significantly correlated with change in pain severity, but these correlations were weak ($r = -0.10$, $P < 0.05$ and $r = -0.13$, $P < 0.05$, respectively). Furthermore, path analysis suggests that <2% of the treatment effect on neuropathic pain could be attributed to changes in weight, FPG, A1C, or individual lipid parameters. Improvements in BPI interference scores during duloxetine treatment were also independent of changes in these metabolic measures.

Relationships between measures of nerve function and metabolic parameters

We examined potential relationships of baseline electrophysiology measures with pain severity or metabolic parameters. Only ulnar F wave latency was weakly, but significantly, correlated with baseline pain severity ($r = -0.09$; $P = 0.048$). Focusing on lower-extremity nerve function, significant inverse correlations were observed between baseline peroneal F wave latency and baseline LDL cholesterol ($r = 0.19$; $P < 0.001$), HDL cholesterol ($r = -0.26$; $P < 0.001$), and total

Table 3—*Mean electrophysiology measures in extension-phase studies*

	Duloxetine (n = 73)			Routine care (n = 40)		
	Baseline	End point	Change	Baseline	End point	Change
Study HMAVa						
Ulnar F wave (ms)	31.66	31.73	0.07	31.33	31.60	0.27
Ulnar distal sensory latency (ms)	3.37	3.42	0.05	3.42	3.44	0.01
Peroneal F wave (ms)	58.35	58.86	0.51	59.76	60.83	1.07
Peroneal CMAP (mV)	1.29	1.20	−0.09	1.30	1.21	−0.10
	Duloxetine (n = 118)			Routine care (n = 49)		
Study HMAVb						
Ulnar F wave (ms)	29.84	30.03	0.19	30.98	31.26	0.28
Ulnar distal sensory latency (ms)	3.32	3.29	−0.03	3.38	3.31	−0.07
Peroneal F wave (ms)	56.31	56.54	0.23	54.72	56.43	1.71*
Peroneal CMAP (mV)	1.47	1.44	−0.03	1.46	1.40	−0.06

Data are mean values from the two 12-month extension-phase studies in which electrophysiology parameters were measured. Only those patients that had baseline and postbaseline measurements in the same limb are included. For some parameters, the number of patients with measurements may be less than what is listed (n) if not all measurements were completed or if different limbs were used at baseline and end point. *P = 0.05 compared with the duloxetine group. No other between-group differences reached statistical significance. CMAP, compound muscle action potential.

cholesterol (r = −0.15; P = 0.002). No significant correlations were seen between this parameter and baseline BMI, A1C, or triglycerides ($P > 0.1$ for all). No differences were seen in acute studies between duloxetine and placebo groups with respect to change in any of the measured electrophysiology parameters. Neither group showed evidence of a decline in nerve conduction velocities using mean change analyses or categorical analyses using a priori-defined cutoffs (data not shown). In two extension-phase trials, nerve conduction testing was completed in 191 duloxetine-treated patients and 89 patients receiving routine care. Changes in nerve conduction velocities and amplitudes were generally small and not significantly different between treatment groups (Table 3). The routine care group did show a slightly greater slowing of peroneal F wave conduction, but this barely reached statistical significance. Given the small changes in the measured electrophysiology parameters during the course of these studies, we did not test for correlations between changes in metabolic parameters and change in nerve conduction.

CONCLUSIONS — This analysis summarizes changes in metabolic parameters during three registration trials of duloxetine for DPNP. Briefly, we observed modest increases in FPG during both short- and long-term treatment with duloxetine. This was associated with a modest increase in A1C only in the longer-term studies, which was statistically greater than the increase seen in a routine care group. There were also some between-group differences in lipid parameters in both placebo-controlled and routine care–controlled studies, but these tended to be small.

It is unclear how duloxetine might affect glucose homeostasis, but similar effects have been reported for some TCAs. For example, nortriptyline significantly increased glucose levels in mice (7), and a detrimental effect on glycemic control in humans has also been suggested (8). Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (19). While nortriptyline shares these attributes, it also has other pharmacological properties not seen with duloxetine (e.g., cholinergic antagonism) (19,20). The role of serotonin in glucose homeostasis is uncertain. Both inhibition and stimulation of insulin secretion have been observed with serotonergic agonists (21,22). Interestingly, the selective serotonin reuptake inhibitor fluoxetine improved insulin sensitivity in obese humans (23), and the serotonergic anxiolytic buspirone reduced glucose-induced hyperglycemia in mice (24). On the other hand, increased noradrenergic effects may be important, as catecholamines can promote hyperglycemia through multiple mechanisms (e.g., inhibition of insulin secretion, stimulation of gluconeogenesis, decrease in insulin sensitivity) (25,26). Finally, it has been reported that hypothalamic infusion of norepinephrine plus serotonin impairs glucose-stimulated insulin release in rodents (27). Thus, an additive effect of both neurotransmitters is possible.

Weight change was not associated with glycemic changes during duloxetine treatment. Mean weight loss was seen with short-term duloxetine treatment. Furthermore, weight change was inversely correlated with baseline weight in these studies, such that greater degrees of weight loss were seen in patients with higher baseline weights. In contrast, small, nonsignificant weight gain was seen in extension studies. This weight increase was based on a new baseline established after re-randomization from the acute studies, making it difficult to quantify the long-term weight effects of duloxetine. Nonetheless, weight change with up to 15 months of treatment appears to be small. Long-term comparative studies with anticonvulsants used for DPNP would be of interest, as weight gain is a common effect of many agents in this class (28).

Hyperglycemia is known to have detrimental effects on nerve function and on painful symptoms in DPN (4). The modest metabolic changes observed in this study did not impact pain relief during duloxetine treatment, and no decline in neurological function was detected during these studies. It is interesting that baseline glycemic control was not correlated with pain severity; however, limiting the entry A1C (≤12%) may have limited our ability to see an association. Likewise, duration of diabetes or DPN and measures of nerve conduction were not correlated with reported pain in patients entering these studies. Baseline triglycerides and BMI were significantly

correlated with baseline pain intensity, but this association was weak. Among other baseline characteristics, female patients reported a significantly higher baseline pain severity. Sex differences in pain perception have been previously reported (29,30), but the mechanisms underlying these differences remain to be defined.

The current study has a number of limitations. Importantly, the trials included in this analysis were not initially designed to evaluate the impact of treatment on glycemic control or other metabolic parameters. For example, investigators were not given specific instructions on glycemic targets and were allowed to adjust glucose- and lipid-lowering therapies during the course of these trials. Likewise, the routine care group in extension studies included a number of different treatments for diabetic neuropathic pain, which may have divergent effects on some of the parameters we have analyzed. For these reasons, the current study does not allow definitive conclusions about the metabolic effects of duloxetine or other medications utilized in these studies.

Obviously, the patients included in these trials reflect a selected study population, and this may limit the generalizability of our findings. For example, this may explain some of the differences between our results and those of epidemiological studies that have looked at relationships between metabolic parameters and nerve function or pain symptoms (rev. in 1). Nonetheless, these trials provide a large database that is likely representative of the broader DPNP population We hope that the findings reported here will help clinicians make informed decisions regarding the risks and benefits of duloxetine in patients seeking relief from painful diabetic neuropathy.

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