

EFFECTS OF DESIPRAMINE, AMITRIPTYLINE, AND FLUOXETINE ON PAIN IN DIABETIC NEUROPATHY

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Abstract Background. Amitriptyline reduces the pain caused by peripheral-nerve disease, but treatment is often limited by side effects related to the drug's many pharmacologic actions. Selective agents might be safer and more effective.

Methods. We carried out two randomized, double-blind, crossover studies in patients with painful diabetic neuropathy, comparing amitriptyline with the relatively selective blocker of norepinephrine reuptake desipramine in 38 patients, and comparing the selective blocker of serotonin reuptake fluoxetine with placebo in 46 patients. Fifty-seven patients were randomly assigned to a study as well as to the order of treatment, permitting comparison among all three drugs and placebo as the first treatment. The patients rated the degree of pain present each day using verbal descriptors, and they also assessed the extent of pain relief globally at the end of each treatment period.

Results. After individual dose titration, the mean daily doses of the drugs were as follows: amitriptyline, 105 mg; desipramine, 111 mg; and fluoxetine, 40 mg. There was

moderate or greater relief of pain in 28 of the 38 patients (74 percent) who received amitriptyline, 23 of the 38 patients (61 percent) who received desipramine, 22 of the 46 patients (48 percent) who received fluoxetine, and 19 of the 46 patients (41 percent) who received placebo. The differences in responses between amitriptyline and desipramine and between fluoxetine and placebo were not statistically significant, but both amitriptyline and desipramine were superior to placebo. Amitriptyline and desipramine were as effective in patients who were not depressed as in depressed patients, but fluoxetine was effective only in depressed patients.

Conclusions. Desipramine relieves pain caused by diabetic neuropathy with efficacy similar to that of amitriptyline, offering an alternative for patients unable to tolerate the latter. Blockade of norepinephrine reuptake is likely to mediate the analgesic effect of these antidepressant drugs in diabetic neuropathy. Fluoxetine, which blocks serotonin uptake, is no more effective than placebo for the relief of pain. (N Engl J Med 1992;326:1250-6.)

AMITRIPTYLINE reduces pain in patients with painful diabetic neuropathy or other neuropathic pain syndromes,¹⁻³ but treatment is often compromised by the sedation, urinary retention, or orthostatic hypotension caused by the drug. It has a wide range of pharmacologic actions, including inhibition of norepinephrine and serotonin reuptake and antagonism of muscarinic cholinergic, histamine H₁, and alpha-adrenergic receptors.⁴ Drugs that selectively affect the neurotransmitter systems responsible for pain relief might be useful substitutes for amitriptyline.

This study was designed to test the hypothesis that amitriptyline relieves neuropathic pain by blocking the reuptake of either norepinephrine or serotonin, neurotransmitters that are released by pain-modulating systems that descend from the brain stem to the spinal cord.⁵⁻⁷ Blocking the reuptake of these neurotransmitters prolongs their inhibitory action on the spinal cord neurons involved in transmitting pain.^{5,6} Amitriptyline may also have analgesic actions at other sites.^{8,9} Desipramine and fluoxetine were chosen as relatively specific blockers of the reuptake of norepinephrine and serotonin, respectively.^{4,10} Given previous placebo-controlled studies of each drug indi-

vidually,^{2,11-13} we expected that the efficacy of desipramine would be similar to that of amitriptyline. The effects of fluoxetine on pain have not been studied, but in two small previous studies, other serotonergic agents did not relieve neuropathic pain.^{14,15}

In patients with painful diabetic neuropathy we compared the proved effective treatments, amitriptyline and desipramine, to determine whether desipramine might replace amitriptyline as the drug of choice. In a concurrent trial, we compared fluoxetine with placebo, to determine whether fluoxetine has any analgesic activity.

METHODS

Patients

We recruited patients with painful diabetic neuropathy through advertisements in newspapers and diabetes newsletters. The inclusion criteria included the presence of diabetes mellitus with stable glycemic control as assessed by the patient's primary physician, signs of peripheral neuropathy not attributable to another cause, and three months or more of daily pain of at least moderate severity, the quality and location of which were consistent with the peripheral neuropathy (Table 1). The exclusion criteria included other pain more severe than the neuropathic pain, severe depression, postural hypotension, symptomatic coronary artery or peripheral vascular disease, and nephropathy (serum creatinine level, >150 μmol per liter). Previous treatment with the study drugs was not grounds for exclusion, whether or not the patients had obtained pain relief, nor was treatment with antihypertensive or diuretic drugs.

In patients taking antidepressants for the treatment of pain at the time of screening, such medications were stopped for at least three weeks before the base-line observations began. The patients were asked to discontinue the regular use of other analgesic drugs, but they were allowed up to one dose per day for severe pain. The study was approved by the Clinical Research Subpanel of the National

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Table 1. Characteristics of the Patients with Painful Diabetic Neuropathy.

CHARACTERISTIC	DESIPRAMINE-AMITRIPTYLINE (N = 54)	FLUOXETINE-PLACEBO (N = 54)
Sex (M/F)	33/21	31/23
Age (yr)		
Median	58	58
Range	20–84	25–84
Duration of diabetes (yr)		
Median	10	14
Range	1–30	1–60
Diabetes treatment (no. of patients)		
Insulin	33	33
Oral hypoglycemic drugs	19	19
Diet	2	2
Duration of pain (yr)		
Median	3	4
Range	½–12	½–12
Distribution of painful neuropathy (no. of patients)		
Distal symmetric		
Feet	29	24
Feet, legs	6	9
Feet, legs, hands	15	17
Proximal asymmetric		
Thigh	3	2
Thorax	1	2
Quality of pain (no. of patients)		
Burning	24	31
Pins and needles	16	16
Shooting	16	15
Aching	12	12
Jabbing	8	9
Sharp	8	5
Cramping	8	6
Tingling	8	7
Cold	7	2
Allodynia, or touch-evoked pain (no. of patients)	13	10
Previous treatment (no. of patients)		
Amitriptyline	28	25
Other tricyclic antidepressant drugs	8	11
Anticonvulsant drugs	8	11
Opioid analgesic drugs	10	6

Institute of Dental Research, and all the patients gave informed, written consent.

Treatments

After a one-week base-line period, the patients were assigned to either of two randomized, two-period crossover studies. One was a comparison of desipramine and amitriptyline and the other a comparison of fluoxetine and placebo. If there was no contraindication to any study drug, the patient underwent double-blind randomization to either study. Patients with medical contraindications or previous adverse reactions to a particular study drug were assigned to the other study. After completing one study, eligible patients were invited to enter the other study, after a three-week washout period.

Each study consisted of two six-week treatment periods separated by a two-week washout period. Although two weeks was insufficient for the complete elimination of all study drugs and their metabolites,^{16,17} the assessment of treatment efficacy was based on pain ratings during week 6 of treatment, allowing an additional five weeks for washout. The range of doses was 12.5 to 150 mg per day for desipramine and amitriptyline and 20 to 40 mg per day for fluoxetine. The drugs were administered in a single dose at 9 p.m., except in the patients who were nonrandomly assigned to the fluoxetine–placebo study, who were instructed to take their medication in

the morning. As in previous studies,^{2,11,12} benzotropine (0.125 to 1.5 mg per day) was used as the placebo, to mimic the dry mouth produced by desipramine and amitriptyline. This low dose of benzotropine has not caused any serious adverse reactions. During weeks 1 to 4 of each treatment period, a nurse clinician called each patient three times weekly to titrate doses of medication to the maximal dose or to the highest level at which side effects such as tiredness, headache, or orthostatic hypotension did not interfere with activities. This dose was maintained during weeks 5 and 6.

Evaluation

The patients rated their pain in a diary once a day, choosing from a scale of 13 words that describe the intensity of pain. The words had been assigned magnitudes (Fig. 1) on the basis of ratio-scaling procedures that demonstrated good internal consistency, reliability, and objectivity.¹⁸ The scale has distinguished active from control interventions in studies of experimental^{19,23} and clinical^{2,11-13} pain. At the end of each treatment period, the patients made global ratings of their pain relief (complete, a lot, moderate, slight, none, or pain worse), as compared with the base-line level of pain preceding the trial of that pair of drugs, and their pain diaries were collected. The study physician examined the patients before and at the end of each treatment period. The patients continued to see their primary physicians for control of diabetes and for general medical care.

A psychiatrist interviewed each patient before treatment to determine whether he or she was depressed according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (third edition, revised) for major depressive episode and dysthymic disorder.²⁴ Before and at the end of each six-week treatment period, mood was assessed according to the Hamilton depression scale (21-item version).²⁵

Drug Concentrations

Serum concentrations of desipramine, amitriptyline, and fluoxetine and their major metabolites were determined in blood samples drawn within 24 hours after the last dose was given at the end of each treatment period. Desipramine, 2-hydroxydesipramine, amitriptyline, nortriptyline, and 10-hydroxynortriptyline were measured by reverse-phase high-performance liquid chromatography with a cyanopropyl column and ultraviolet detection at 254 nm after extraction from serum.²⁶ Fluoxetine and norfluoxetine were measured by gas-liquid chromatography (Wisconsin Analytical and Research Services, Madison).

Statistical Analysis

The verbal descriptors in the pain diary were converted to numerical equivalents.²⁰ For each pair of treatments the mean pain scores in week 6 were compared within patients by paired, two-tailed t-test. Period effects and interactions between treatment and period were examined for scores in week 6 by t-test.²⁷ On the basis of the variance from a previous study,² we calculated that a sample of 40 patients per paired crossover study would provide an 80 percent chance of detecting, at an alpha level of 0.05, a mean difference between treatments equivalent to approximately one third of the difference between mild and moderate pain. For patients randomized among all four possible treatments, the differences between week 6 and base-line pain with the study drugs were compared with the differences with placebo by one-way analysis of variance, followed by the one-tailed Dunnett's test.

RESULTS

Fifty-seven patients were randomly assigned to a study; among them, 29 were assigned to the desipramine–amitriptyline study and 28 to the fluoxetine–placebo study. Seventeen additional patients were nonrandomly assigned to the fluoxetine–placebo study because of contraindications to amitriptyline

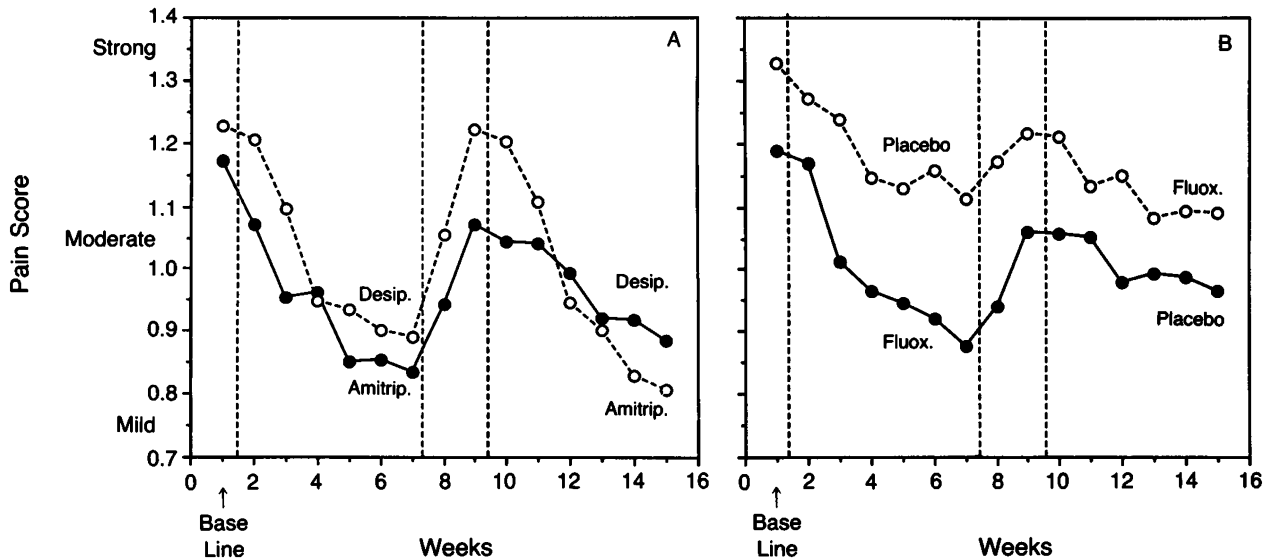


Figure 1. Intensity of Pain Caused by Diabetic Neuropathy during Treatment with Amitriptyline and Desipramine in 38 Patients (Panel A) and during Treatment with Fluoxetine and Placebo in 46 Patients (Panel B).

The mean weekly values of the descriptors of pain intensity are plotted; three of the actual descriptors (strong, moderate, and mild) used in the diary are shown in their equivalent positions on the ordinate. Each curve represents a single group receiving sequential treatments. The central vertical lines distinguish the two six-week treatment periods from the intervening two-week washout period. There was no statistically significant difference between the effects of amitriptyline and desipramine, but both were significantly more effective than placebo in the subgroup of patients who were randomized among all four initial treatments (Fig. 2). There was no significant difference between the effects of fluoxetine and placebo.

or desipramine. Five additional patients entered the desipramine–amitriptyline study after the fluoxetine–placebo study had filled. After completion of their initial study, 20 patients who had received fluoxetine and placebo then entered the desipramine–amitriptyline study, and 9 who had received desipramine and amitriptyline then entered the fluoxetine–placebo study. The clinical characteristics of the patients in each study were similar (Table 1). Thirty-eight patients completed the desipramine–amitriptyline study, and 46 completed the fluoxetine–placebo study. Because of adverse effects or voluntary withdrawal, 16 patients did not complete the desipramine–amitriptyline study and 8 patients did not complete the fluoxetine–placebo study.

Effects of Treatment

Relief of Pain

Figure 1 shows the weekly mean scores from the pain diaries and Table 2 the global pain-relief ratings for the patients who completed at least one study, including those who were randomly assigned and those who were not. The magnitude and statistical significance of the paired comparisons between desipramine and amitriptyline or fluoxetine and placebo within patients were similar whether we restricted the comparison to patients randomly assigned to either study or included patients who were nonrandomly assigned.

In the desipramine–amitriptyline study (Fig. 1A) there was a steady decline in pain during the four weeks of dose titration with either drug, and slight

additional relief of pain during weeks 5 and 6. The pain returned after either drug was discontinued, and then declined during treatment with the other drug. There were no statistically significant differences in pain scores between the amitriptyline and desipramine periods. For all 38 patients who completed the desipramine–amitriptyline study, the mean difference in diary scores during the last week of treatment favored amitriptyline by 0.07 unit (95 percent confidence interval, -0.04 to 0.18), where 0.35 unit was the difference between moderate and mild pain.²⁰ This difference was not statistically significant (P = 0.21 by two-tailed paired t-test). Using the global descriptors of pain relief (Table 2), 74 percent of the patients

Table 2. Global Ratings of Relief of Pain in Patients with Painful Diabetic Peripheral Neuropathy.*

DRUG	PAIN RELIEF AT END OF TREATMENT PERIOD						TOTAL OF COMPLETE, A LOT, AND MODERATE
	COM- PLETE	A LOT	MODER- ATE	SLIGHT	NONE	PAIN WORSE	
	percent of patients						
Amitriptyline	13	34	26	11	16	0	74†
Desipramine	11	29	21	13	21	5	61
Fluoxetine	2	26	20	17	31	4	48
Placebo	0	22	19	22	28	9	41

*Data are from all patients who completed a study; 38 patients completed the amitriptyline–desipramine study, and 46 the fluoxetine–placebo study. There was no significant difference between amitriptyline and desipramine or between fluoxetine and placebo by two-tailed, paired Wilcoxon signed-rank test.

†Total does not equal the sum of the components because of rounding.

reported moderate or greater relief during treatment with amitriptyline, as compared with 61 percent during treatment with desipramine (*P* not significant by two-tailed paired Wilcoxon signed-rank test). There were no significant period or carry-over effects. The degree of pain relief was similar in patients with the various qualities of pain listed in Table 1.

In the fluoxetine–placebo study (Fig. 1B), there was a moderate decrease in pain during the first period of treatment with either fluoxetine or placebo, but both treatments had minimal effects during the second period. There were no statistically significant differences between fluoxetine and placebo. For the 46 patients who completed this study, the mean difference in pain scores during the last week of treatment favored fluoxetine by 0.05 unit (95 percent confidence interval, -0.06 to 0.17 ; *P* = 0.34 by two-tailed paired *t*-test). Using the global descriptors of pain relief (Table 2), 48 percent of the patients reported moderate or greater relief during treatment with fluoxetine, as compared with 41 percent during treatment with placebo (*P* not significant by two-tailed paired Wilcoxon signed-rank test). There were no significant period or carry-over effects.

The results of intention-to-treat analyses were similar to those of the analyses described above. Similarly, excluding patients in whom insomnia developed with fluoxetine or desipramine did not alter the results.

Figure 2 shows the changes in the intensity of pain during the first treatment period in the 52 patients for whom random assignment to either study arm permitted statistical comparison among all four treatments. The mean (\pm SE) pain-diary scores decreased by 0.47 ± 0.09 unit in the 12 patients who received amitriptyline, 0.45 ± 0.12 unit in the 13 patients who received desipramine, 0.35 ± 0.11 unit in the 12 patients who received fluoxetine, and 0.15 ± 0.07 unit in the 15 patients who received placebo. The decreases in pain were significantly larger in the patients given amitriptyline or desipramine than in those given placebo (*P* < 0.05 by one-tailed Dunnett's test), but not significantly larger than the decrease in the patients given fluoxetine.

Mood and Pain Relief

The psychiatrist diagnosed depression in 15 of the 54 patients who entered the amitriptyline–desipramine study and in 16 of the 54 who entered the fluoxetine–placebo study; the mean (\pm SD) scores on the Hamilton scale in the subgroups of patients who were depressed were 15 ± 5 and 17 ± 6 , respectively. The Hamilton scores improved significantly during treatment with fluoxetine or amitriptyline (*P* < 0.05), but not during treatment with desipramine or placebo.

Among the patients who were depressed, the decrease in pain score was larger in those who received fluoxetine than in those who received placebo (Table 3). The changes in these patients accounted for the nonsignificant trend toward greater improvement

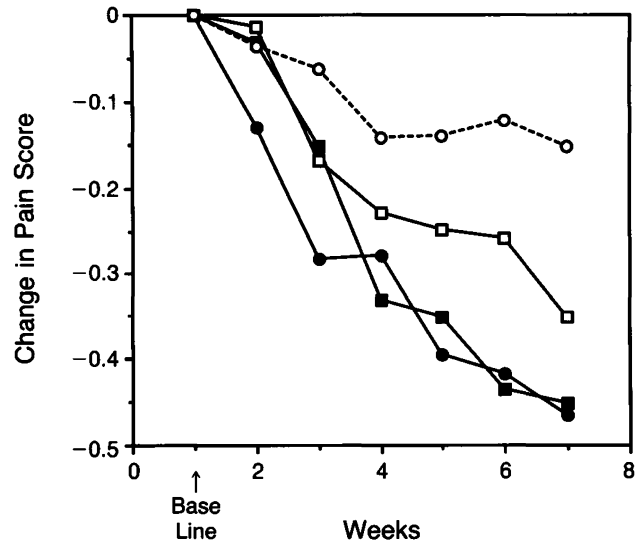


Figure 2. Mean Change from Base Line in the Intensity of Pain Caused by Diabetic Neuropathy during the First Treatment Period in 12 Patients Who Received Amitriptyline (●), 13 Who Received Desipramine (■), 12 Who Received Fluoxetine (□), and 15 Who Received Placebo (○).

A decrease of 0.35 unit is equivalent to a reduction from moderate to mild pain. Amitriptyline and desipramine, but not fluoxetine, were significantly superior to placebo (*P* < 0.05 by one-tailed Dunnett's test). Although there appeared to be a trend toward a difference between fluoxetine and placebo in this subgroup of patients, the randomized comparison of fluoxetine and placebo (Fig. 1) comprised almost four times as many patients and is probably the more reliable estimate.

with fluoxetine than with placebo in all 46 patients who completed the study. Amitriptyline and desipramine reduced pain by similar amounts in both depressed and nondepressed patients.

Drug Doses, Serum Concentrations, and Pain Relief

The mean (\pm SD) daily drug doses during week 6 were 105 ± 37 mg in the patients who received amitriptyline, 111 ± 39 mg in those who received desipramine, 40 mg in those who received fluoxetine (except one who took 20 mg per day), and 1.3 ± 0.2 mg of

Table 3. Pain Relief and Depression in Patients with Painful Diabetic Neuropathy.

PATIENT GROUP	DECREASE IN PAIN SCORE*			
	FLUOXETINE	PLACEBO	AMITRIPTYLINE	DESIPRAMINE
	<i>mean (\pmSE)</i>			
All patients	0.27 ± 0.06	0.22 ± 0.06	0.38 ± 0.06	0.31 ± 0.06
Depressed	$0.34 \pm 0.11^\dagger$	0.13 ± 0.09	0.36 ± 0.09	0.27 ± 0.11
Not depressed	0.25 ± 0.06	0.25 ± 0.07	0.39 ± 0.08	0.33 ± 0.07

*Pain scores represent decreases from base line to the last week of the treatment. A decrease in pain score of 0.35 unit corresponds to a decrease from moderate to mild pain. The results are from all 46 patients who completed the fluoxetine–placebo study (13 depressed and 33 not depressed) and all 38 patients who completed the amitriptyline–desipramine study (10 depressed and 28 not depressed).

†Pain relief was significantly greater with fluoxetine than with placebo in depressed patients (*P* = 0.03 by two-tailed paired *t*-test). None of the other differences between fluoxetine and placebo or amitriptyline and desipramine were statistically significant.

benztropine in those who received placebo. There were no significant correlations between relief of pain and the dosage or serum concentration of amitriptyline, desipramine, or fluoxetine (Fig. 3), the serum concentrations of their respective active metabolites (nortriptyline and 10-hydroxynortriptyline, 2-hydroxydesipramine, and norfluoxetine), or the sum of the serum concentrations of each parent drug and its active metabolites.

Adverse Effects

Symptoms possibly related to study drugs caused seven patients to drop out while receiving amitriptyline (confusion in two patients and orthostatic hypotension, fatigue, malaise, hypomania, and rash in one patient each). Similarly, seven patients dropped out while receiving desipramine (because of rash in three and orthostatic hypotension, bundle-branch block, tremor, and fever in one each). Three patients dropped out while receiving fluoxetine (because of orthostatic hypotension, rash, and headache, respectively), and two patients dropped out while receiving placebo (because of fatigue and chest pain, respectively). Table 4 shows the relative frequency of common side effects during the administration of each drug. Drug-related insomnia required rescheduling the administration of fluoxetine and desipramine to the morning in seven and five patients, respectively, and probably weakened the double-blind conditions for these patients. Other side effects occurred more commonly with a particular drug, but occasionally with all drugs.

DISCUSSION

We found that the efficacy of desipramine was similar to that of amitriptyline, the standard therapy for the relief of pain caused by diabetic neuropathy. The superiority of both amitriptyline and desipramine to placebo in the subgroup of patients randomized among all four regimens demonstrates the sensitivity

Table 4. Side Effects of Amitriptyline and Desipramine in 38 Patients and of Fluoxetine and Placebo in 46 Patients.

SIDE EFFECT*	AMITRIPTYLINE	DESIPRAMINE	percent of patients	
			FLUOXETINE	PLACEBO (BENZTROPINE)
Dry mouth	63	32	11	35
Tiredness	34	34	13	17
Headache	21	11	24	9
Constipation	8	21	2	7
Insomnia	—	13	15	—
Orthostatic symptoms	5	3	2	—
Palpitations	13	3	2	—
Increased sweating	11	13	11	2
Lightheadedness	8	11	—	—
Any side effect	81	76	63	68
Dose-limiting side effect†	71	63	41	41

*Reports of side effects were elicited weekly by telephone, with use of a symptom checklist; only reports of moderate or greater severity are included.

†Values indicate the percentage of patients who did not reach the maximal planned dosage because of side effects.

of the study methods to differences in treatment efficacy.^{28,29} As in previous studies,^{2,3,11,13} both drugs were as effective in patients with normal mood as in depressed patients, suggesting that the relief of pain was not mediated solely through a change in mood. Although the frequency of most side effects except dry mouth and insomnia was similar during the four regimens, sedation and anticholinergic effects are usually more prominent with amitriptyline than with desipramine.^{30,31} Desipramine may therefore be a useful alternative in patients unable to tolerate the side effects of amitriptyline. Because the pain scores and the global ratings of pain relief favored amitriptyline slightly, we recommend that amitriptyline remain the treatment of choice for patients in whom sedative and anticholinergic effects are unlikely to pose hazards.

Fluoxetine had no greater analgesic effect than pla-

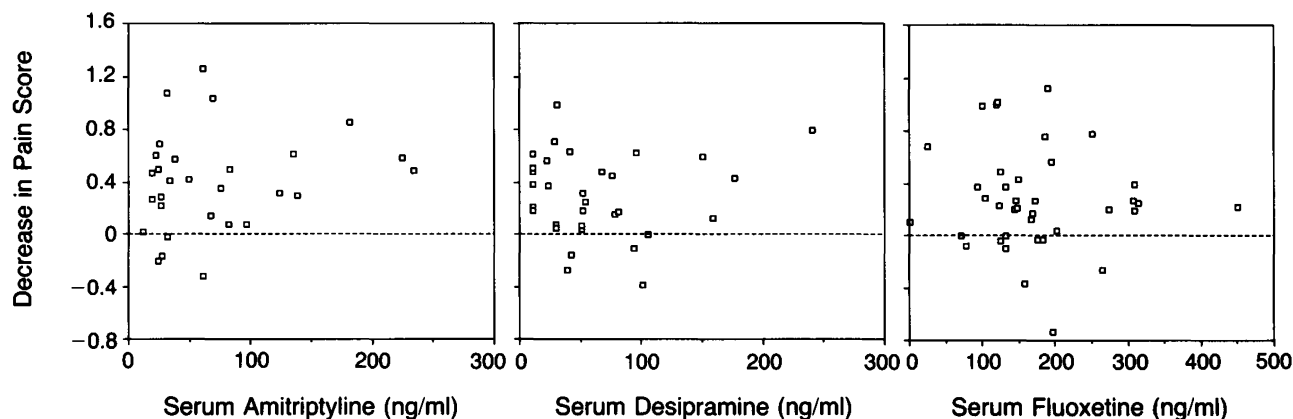


Figure 3. Decrease in Pain Score According to Serum Concentration of Amitriptyline, Desipramine, or Fluoxetine in Patients with Painful Diabetic Neuropathy.

There were no significant correlations between the decrease in pain score and the serum concentration of amitriptyline, desipramine, fluoxetine, or any of their active metabolites.

cebo except in the minority of patients who were depressed. The finding that amitriptyline and desipramine were superior to placebo increases the likelihood that fluoxetine was ineffective. Other doses of fluoxetine might have been more effective, but we found the relief of pain to be no greater in patients who had serum concentrations of fluoxetine or norfluoxetine that were higher or lower than the mean. In contrast to its lack of effect in patients with normal mood, fluoxetine decreased the level of pain in the 13 depressed patients, underscoring the importance of recognizing depression in patients with chronic pain.³²

Unlike previous studies in which there was a positive correlation between pain relief and the dose of amitriptyline (up to 150 mg per day),^{2,13} this study found no correlation between pain relief and drug dose or serum concentrations of amitriptyline, desipramine, or their active metabolites. These results allow only the conclusion that doses of desipramine or amitriptyline ranging from 75 to 150 mg per day are likely to be effective.

The efficacy of desipramine in relieving pain supports the hypothesis that a blockade of the reuptake of norepinephrine mediates much or all of the analgesia produced by tricyclic compounds in patients with neuropathic pain. In fact, virtually all the antidepressant drugs that have relieved neuropathic pain in placebo-controlled trials — amitriptyline,^{2,3,13} desipramine,^{11,12} nortriptyline,³³ imipramine,³⁴ and clomipramine³⁵ — block the reuptake of norepinephrine or have an active metabolite that does so.³⁶ Fluoxetine, the selective blocker of serotonin reuptake, was ineffective in this study, suggesting that serotonin is not the primary mediator of amitriptyline analgesia. Watson and Evans¹⁴ came to a similar conclusion after finding that zimeldine, which blocks the reuptake of serotonin, did not relieve postherpetic neuralgia in any of 13 patients who subsequently responded to amitriptyline. The single exception to this pattern is a recent report by Sindrup et al.³⁷ that paroxetine, which blocks the reuptake of serotonin, reduced symptoms more than did placebo in 14 of 20 patients with diabetic neuropathy. In their study, paroxetine was less effective than imipramine, which blocks the reuptake of both norepinephrine and serotonin.^{4,38} Perhaps the blockade of serotonin reuptake is no more than weakly analgesic by itself, but augments the analgesic effect of blocking the reuptake of norepinephrine.³⁹ This could account for the moderate trend toward more pain relief with amitriptyline, which blocks the reuptake of serotonin as well as norepinephrine,^{4,38} than with desipramine.

Other mechanisms might contribute to the relief of pain produced by amitriptyline and desipramine. Amitriptyline and, to a lesser extent, desipramine (but not fluoxetine) block histamine H₁, alpha₁-adrenergic, and muscarinic cholinergic receptors.^{4,40} Antihistamines are known to be effective in patients with postoperative and musculoskeletal pain, but there are no

controlled studies in patients with neuropathic pain.⁴¹ Alpha₁-adrenergic antagonists have been reported to be effective in some patients with neuropathic pain.⁴² Because benzotropine had far less efficacy than desipramine at doses that produced similar side effects, an anticholinergic mechanism of analgesia appears unlikely. The results of this study suggest two additional steps toward more selective drug treatment of neuropathic pain — the development of blockers of norepinephrine reuptake that are free of alpha₁-adrenergic or histamine antagonism, and clinical trials of antihistamine H₁ drugs.

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