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Dextromethorphan and Memantine in Painful Diabetic Neuropathy and Postherpetic Neuralgia

Efficacy and Dose–Response Trials

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Background: There are few repeated dose-controlled trials of *N*-methyl-D-aspartate glutamate receptor antagonists in patients with neuropathic pain. The authors sought to evaluate two low-affinity *N*-methyl-D-aspartate antagonists using a novel two-stage design.

Methods: The authors studied patients with painful diabetic neuropathy (DN) and postherpetic neuralgia (PHN) in two crossover trials: (1) efficacy trial (dextromethorphan *vs.* memantine *vs.* active placebo [lorazepam]) and (2) dose–response trial of the preferred active drug in responders from the first study (0% *vs.* 25% *vs.* 50% *vs.* 100% of each patient's maximally tolerated dose). Pain intensity was measured on a 20-point scale.

Results: Nineteen of 23 DN patients and 17 of 21 PHN patients completed the efficacy trial. Median doses for DN and PHN were 400 and 400 mg/day dextromethorphan, 55 and 35 mg/day memantine, and 1.8 and 1.2 mg/day lorazepam. In the efficacy trial, among patients with DN, dextromethorphan reduced pain intensity by a mean of 33% from baseline, memantine reduced pain intensity by a mean of 17%, and lorazepam reduced pain intensity by a mean of 16%; the proportions of subjects achieving greater than moderate pain relief were 68% with dextromethorphan, 47% with memantine, and 37% with lorazepam. Mean reductions in pain intensity in patients with PHN were 6% with dextromethorphan, 2% with memantine, and 0% with lorazepam. No comparison with placebo reached statistical significance in the efficacy trial. In the 10 DN subjects who responded to dextromethorphan, there was a significant dose–response effect on pain intensity ($P = 0.035$), with the highest dose significantly better than that of lorazepam ($P = 0.03$).

Conclusions: Dextromethorphan is effective in a dose-related fashion in selected patients with DN. This was not true of PHN, suggesting a difference in pain mechanisms. Selective approaches to pain-relevant *N*-methyl-D-aspartate receptors are warranted.

ANIMAL studies in many laboratories[1-6] have shown that antagonists of the *N*-methyl-D-aspartate (NMDA) glutamate receptor reduce pain after nerve injury. Randomized controlled clinical trials have demonstrated that the acute single-dose administration of spinal and systemic NMDA glutamate receptor antagonists in patients with chronic neuropathic pain reduces spontaneous pain and hyperalgesia.[7-11] In contrast, four randomized trials of chronic oral administration have had equivocal results. Dextromethorphan appeared to reduce the symptoms of painful diabetic neuropathy (DN) but not postherpetic neuralgia (PHN)[12] or orofacial neuralgia.[13] Memantine was not effective in PHN[14] or neuropathic pain caused by amputation or surgery.[15]

The positive results shown in previous trials of NMDA receptor antagonists in human subjects[7-11] may have been influenced by biases that could have compromised internal validity, such as insufficient power and the potential for unblinding caused by side effects. Moreover, studies that titrate each subject to maximally tolerated doses (MTDs) provide no information on dose–response. In the current study, we enrolled enough subjects to achieve sufficient statistical power to detect a moderate effect and sought to maintain blinding by including a small dose of lorazepam in each placebo capsule, and prospectively assessed dose–response in a follow-up randomized crossover trial in responders.

We evaluated two low-affinity NMDA receptor antagonists: dextromethorphan and memantine. The antitussive dextromethorphan, the *d*-isomer of levorphanol, and its O-demethylated metabolite dextrorphan both antagonize voltage-dependent calcium channels and NMDA receptor–operated channels.[16] The antiparkinsonian agent memantine is a 1-amino-3,5-dimethyl-adamantane derivative.[17] In animal models, memantine reduces hyperalgesia[18-20] and has been noted to cause fewer adverse effects than ketamine.[21]

Materials and Methods

Subjects

The two studies were performed at a single site (Clinical Center, National Institutes of Health, Bethesda, Maryland) after obtaining informed consent from patients and approval from the National Institute of Dental Research

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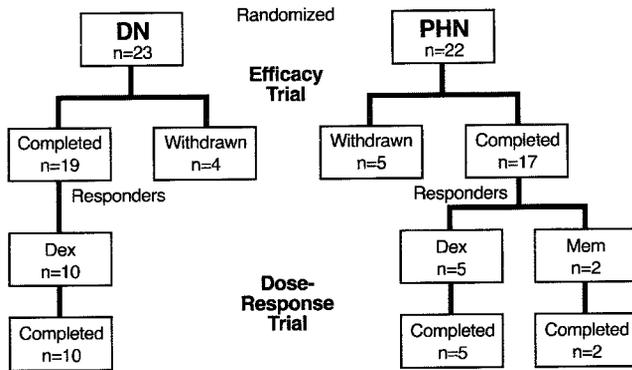
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Fig. 1. Profile of the serial efficacy and dose–response trials conducted in cohorts of patients with painful diabetic neuropathy (DN) and postherpetic neuralgia (PHN). Dex = dextromethorphan; Mem = memantine.

Institutional Review Board. Patients with painful distal symmetric diabetic polyneuropathy and PHN were recruited nationwide using written announcements in newspapers, patient association newsletters, and direct referrals. Inclusion criteria included: adults aged greater than 18 yr with at least moderate pain for at least 50% of the day for a minimum of 3 months caused by either PHN or DN; previously failed trial of a tricyclic antidepressant for at least 2 weeks or the development of intolerable side effects; for diabetics, stable glucose control as determined by glycosylated hemoglobin of less than 13% on screening evaluation; stable analgesic regimen for 2 weeks (consisting of no more than two analgesics, including tricyclic antidepressants, anticonvulsants, or use of low-potency short-acting opioids no more than four times daily). Exclusion criteria included: presence of another type of pain as severe as that caused by PHN–DN; pregnancy or breast feeding; hepatic or renal dysfunction; significant cardiac disease; signs or symptoms of any central neurologic disorder; diagnosis of angle-closure glaucoma; severe psychological disorder requiring treatment; concurrent use of monoamine oxidase inhibitors or phenothiazines; history of hypersensitivity or intolerance to dextromethorphan or structural analogs of memantine (amantadine and rimantadine); and long-term alcohol or drug abuse.

Study Design, Randomization, and Treatments

Patients were offered sequential participation in two randomized, placebo-controlled, double-blinded trials (fig. 1): (1) efficacy trial: a three-period, three-treatment balanced Latin square design comparing the MTD of dextromethorphan and of memantine to an active placebo (lorazepam); and (2) dose–response trial: a four-period four-treatment Latin square design in "responders" comparing 25, 50, and 100% of the MTD determined in the first study to active placebo (lorazepam). Responders were defined as those who demonstrated at least moderate pain relief with active drug that surpassed

placebo on a pain-relief category scale consisting of the following phrases: complete relief, a lot of relief, moderate relief, slight relief, no relief, and pain worse.

Randomization was performed by the Pharmaceutical Development Service (Clinical Center, National Institutes of Health). Dextromethorphan, memantine, and lorazepam were dispensed as externally identical capsules. In both trials, to facilitate finer dose titration, each patient received medications in two dosages, which were used in various combinations during the escalation. Each treatment period consisted of a 7-week titration period to MTD followed by a 2-week maintenance period. The high- and low-dosage strengths were as follows: 100 and 30 mg dextromethorphan, 6.0 and 1.8 mg memantine, and 0.2 and 0.06 mg lorazepam. Medications were administered four times daily. The targeted maximal daily doses were 960 mg dextromethorphan, 58 mg memantine, and 2 mg lorazepam.

In the dose–response trial, there were three NMDA antagonist treatment periods and one active placebo period. In the NMDA antagonist period, patients were given the favored drug, again in two dosage strengths, with each capsule containing either 25, 50, or 100% of the doses of dextromethorphan or memantine listed above. During the active placebo period, lorazepam capsules were dispensed in the original strength, 0.2 and 0.06 mg. In each period, patients were titrated to the number of capsules that they took during the period of the favored NMDA antagonist in the efficacy study.

During both trials, a nurse blinded to the study drug called each patient approximately twice weekly to assess side effects and titrate the medication. A 1-week baseline period preceded each clinical trial. In each trial, treatment periods were separated and followed by a 2-week washout period.

Endpoints

The primary endpoint was the mean of the pain intensity ratings during the last week of each treatment period. Pain intensity was rated on the Gracely Box Scale for pain intensity, in which 13 words describing pain intensity are placed along a vertical stack of boxes containing the numbers 0 to 20. The words are spaced according to magnitudes determined on the basis of ratio-scaling procedures that demonstrated good internal consistency, reliability, and objectivity.[22] Subjects were asked to rate their pain intensity five times daily, each rating representing the mean pain intensity since the last rating. Secondary endpoints were reported by each subject on the last day of each maintenance period and included (1) pain relief (category rating), (2) intensity of allodynia over the last week of treatment (Gracely Scale), (3) quality of life (assessed using the Short-Form 36 quality-of-life instrument[23]), and (4) the nature and intensity (category rating) of adverse effects.

Table 1. Demographic Data and Baseline Characteristics among Enrolled Subjects

	Diabetic Neuropathy (n = 23)	Postherpetic Neuralgia (n = 22)
Age [yr; median (range)]	55 (40–64)	69 (36–78)
Sex [%]		
Men	52	55
Women	48	45
Race [%]		
White	100	95
African-American	0	5
Other	0	0
Duration of pain [yr; median (range)]	4.5 (1.3–24)	3.8 (0.3–13)
Duration of diabetes [yr; median (range)]	8 (1.5–24)	—
Hb A_{1c} [% range)]	8 (5.3–12.8)	—
Affected site [%]		
Trigeminal	—	9
Cervical	—	0
Thoracic	—	59
Lumbar	—	14
Sacral	—	18
Pain intensity [20-point Gracely score; mean (SD)]		
Burning	11.4 (5.1)	12.0 (5.0)
Aching	11.6 (5.3)	7.6 (8.1)
Tingling	10.5 (5.3)	6.4 (6.7)
Sharp	13.7 (5.1)	12.2 (6.6)
Allodynia	4.0 (5.3)	11.9 (6.5)
Concomitant medications [%]		
None	26	22
TCA	41	32
SSRI	5	5
Gabapentin	4	9
Nonsteroidals	5	13
Opioids	23	27

Hb A_{1c} = glycosylated hemoglobin; TCA = tricyclic antidepressants; SSRI = selective serotonin reuptake inhibitors.

Adequacy of Blinding

After each treatment period, patients and study nurses were asked to guess which medication they were taking. During the efficacy study, they were asked whether they thought that period's treatment was an experimental medication (dextromethorphan or memantine) or placebo. During the dose–response study, they were asked to guess which of the four dose levels had been given: 100, 50, or 25% of the experimental medication, or placebo.

Statistical Analysis

We aimed for a sample of 18 patients in each diagnostic group completing the efficacy study. This sample size was determined by selecting a type I error of 0.05, type II error of 0.2, a targeted therapeutic difference of approximately 3 points on the 20-point Gracely scale (where 3.7 points is the difference between "moderate" and "mild" pain intensity and assuming a SD of 4.1 units based on a previous study in diabetic neuropathy).[24] Between-treatment comparisons for all primary endpoints were accomplished by paired t tests. Where the rating scale was ordinal, we used the Wilcoxon signed-rank test. Each domain of the Short-Form 36 quality-of-life questionnaire was analyzed separately using analysis of covariance. Dose–response was analyzed using regression analyses. All P values reported are two-tailed.

Results

Efficacy Trial

Demographic and Baseline Characteristics. Nineteen subjects (83%) with DN took at least 3 weeks of each of the three treatments and were considered study completers. Median daily doses among these patients during the maintenance period were 400 mg/day for dextromethorphan, 55 mg/day for memantine, and 1.8 mg for lorazepam. Four patients withdrew from the study before providing interpretable comparative data: one patient withdrew after the first treatment (dextromethorphan) to pursue nonstudy therapies, one patient withdrew after reporting sedation with the first dose of each of the first two treatments (lorazepam and memantine), one patient had spontaneous remission of pain after completing one treatment, and one patient was lost to contact with the research team during the second treatment and provided no pain reports.

Seventeen subjects (85%) with PHN completed at least 1 week of each of the three treatments and were considered completers. Median daily doses among PHN sub-

Diabetic Neuropathy
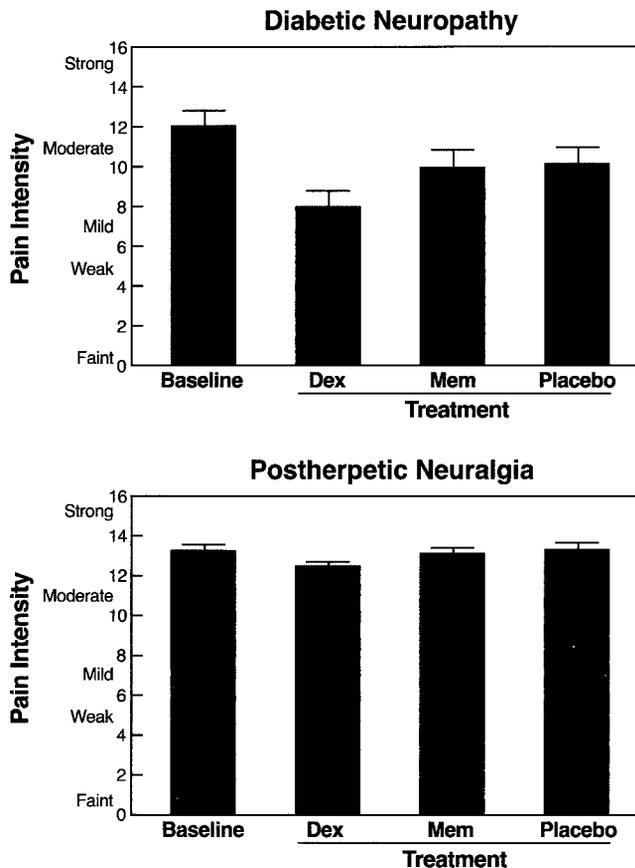

Postherpetic Neuralgia

Fig. 2. Efficacy trial. Mean pain intensity (0–20-point Gracely scale) during the baseline and the final week of treatment with dextromethorphan (Dex), memantine (Mem), and active placebo in patients with diabetic neuropathy (*top*; n = 19) and postherpetic neuralgia (*bottom*; n = 17). Neither drug reduced pain significantly more than placebo.

jects during the maintenance period were 400 mg/day for dextromethorphan, 35 mg/day for memantine, and 1.2 mg for lorazepam. Five patients withdrew: one patient developed a fever during the fourth week of the first treatment with dextromethorphan that recurred with rechallenge, one patient withdrew to pursue other treatment before providing data from the second treatment, one patient had a fatal heart attack during the second treatment (lorazepam), one patient had spontaneous remission of pain during the second treatment period and provided no data, and one patient withdrew during the second period because of a new diagnosis of cancer and provided no data. Table 1 summarizes the demographic and baseline information for both diagnostic subgroups.

Primary Endpoint (Efficacy).

Diabetic Neuropathy. During the final week of the maintenance period, mean pain intensities (± standard error of the mean) as determined by patient diaries were 8.2 ± 0.88 for dextromethorphan, 9.9 ± 1.1 for memantine, and 10.1 ± 1.2 for lorazepam among diabetic patients (fig. 2, top). Among DN patients, dextromethor-

phan reduced pain intensity by a mean of 33.4% from baseline, memantine reduced pain intensity by a mean of 17.4%, and lorazepam reduced pain intensity by a mean of 16.1%. Compared with lorazepam, neither dextromethorphan (mean difference, −1.9; 95% confidence interval, −4.7 to 0.9) nor memantine (−0.2; 95% confidence interval, −1.6 to 1.3) was significantly better overall.

Postherpetic Neuralgia. During the final week of the maintenance period, mean pain intensities (± standard error of the mean) as determined by patient diaries were 12.5 ± 5.8 for dextromethorphan, 13.1 ± 6.8 for memantine, and 13.3 ± 5.7 for lorazepam (fig. 2, bottom). Among PHN patients, dextromethorphan reduced pain intensity by a mean of 6.5%, memantine reduced pain intensity by a mean of 1.9%, and lorazepam had no detectable effect on baseline pain intensity. Compared with lorazepam, neither dextromethorphan (mean difference, −0.9; 95% confidence interval, −2.3 to 0.5) nor memantine (−0.3; 95% confidence interval, −1.3 to 0.7) was significantly better overall.

There was no effect of age, pain duration, duration of diabetes, level of PHN, or characteristic of pain (burning, aching, standing–walking, sharp–shooting, cramping, cold, constricting pain, or presence of allodynia) on treatment effects (data not shown). Moreover, the subgroup of patients with allodynia (N = 16; DN, n = 6; PHN, n = 10) did not have overall significant benefit from either NMDA receptor antagonist compared with lorazepam (data not shown). We did not have the power to detect treatment differences between the subgroup of patients who responded to either dextromethorphan or memantine for any characteristic features that may differentiate them from the group of patients who did not respond to either active drug.

Secondary Endpoints.

Pain Relief. Analysis of the six-category pain relief responses (from pain worse to complete relief) during the last day of each treatment did not yield statistically significant results (DN, *P* = 0.12 for dextromethorphan and *P* = 0.66 for memantine; PHN, *P* = 0.19 for dextromethorphan and *P* = 0.84 for memantine; table 2). Among DN patients, 13 of 19 (68.4%) had moderate or better pain relief with dextromethorphan, 9 of 19 (47.4%) had moderate or better pain relief with memantine, and 7 of 19 (36.8%) had moderate or better pain relief with lorazepam. Among PHN patients, 5 of 17 (29.4%) had moderate or better pain relief with dextromethorphan, 2 of 17 (11.8%) had moderate or better pain relief with memantine, and 2 of 17 (11.8%) had moderate or better pain relief with lorazepam.

Reduction of Allodynia. We were unable to detect an effect of effect of dextromethorphan compared with lorazepam on the intensity of allodynia in the 16 DN and PHN subjects with allodynia (data not shown).

Table 2. Categorical Global Pain Relief Scores in the Efficacy and Dose–Response Trials

Efficacy Trial		Dextromethorphan	Memantine	Lorazepam
DN (n = 19)	Worse	0 (0)	0 (0)	1 (5)
	None	4 (21)	5 (26)	5 (26)
	Slight	2 (11)	5 (26)	6 (32)
	Moderate	7 (37)	7 (37)	4 (21)
	A lot	4 (21)	0 (0)	0 (0)
	Complete	2 (11)	2 (11)	3 (16)
PHN (n = 17)	Worse	1 (6)	2 (12)	3 (18)
	None	9 (53)	8 (47)	8 (47)
	Slight	2 (12)	5 (29)	4 (24)
	Moderate	4 (24)	1 (6)	2 (12)
	A lot	1 (6)	1 (6)	0 (0)
	Complete	0 (0)	0 (0)	0 (0)

| Dose–Response Trial | | Dextromethorphan | | | |
		0% MTD	25% MTD	50% MTD	100% MTD
DN (n = 10)	Worse	0 (0)	1 (10)	0 (0)	0 (0)
	None	3 (30)	4 (40)	1 (10)	0 (0)
	Slight	6 (60)	3 (30)	3 (30)	1 (10)
	Moderate	0 (0)	2 (20)	5 (50)	3 (30)
	A lot	1 (10)	0 (0)	1 (10)	6 (60)
	Complete	0 (0)	0 (0)	0 (0)	0 (0)

Values in parentheses are percentages.

DN = diabetic neuropathy; PHN = postherpetic neuralgia; MTD = maximally tolerated dose.

Quality of Life. Dextromethorphan significantly improved one of the eight dimensions (the emotional dimension) among DN patients. There was no significant effect of any of the treatments in PHN (table 3).

Blinding. If patients had guessed "active treatment" or "placebo" randomly with the assumption that two of three periods would be active treatment, five of every nine guesses (55%) would have been correct. In the study, patients made correct guesses in 72 of 108 (67%) of the treatment periods, not significantly different from chance (one-sided Fisher exact test, $P = 0.37$). The potential for inadequate blinding had little impact on the response rates, as the proportion of subjects with moderate or better pain relief was not significantly different between those who correctly guessed their treatment (dextromethorphan, 66%; memantine, 41%; lorazepam,

17%) and those not knowing their treatment (dextromethorphan, 57%; memantine, 29%; lorazepam, 38%).

The study nurses guessed 58 of 104 (56%) of the treatment periods correctly (active drug *vs.* placebo), a proportion not significantly different from chance, reflecting their inability to distinguish between the two active drugs and the active placebo (lorazepam) despite having discussed side effects with the patients throughout the treatment.

Safety. Among all patients, 83% receiving dextromethorphan, 83% receiving memantine, and 58% receiving lorazepam experienced at least one adverse event of any intensity during the titration period. These included sedation (dextromethorphan, 71%; memantine, 63%; lorazepam, 38%), dry mouth (dextromethorphan, 30%; memantine, 21%; lorazepam, 25%), and gastrointestinal

Table 3. Quality of Life (SF-36) Scores during the Efficacy Trial

| | Diabetic Neuropathy (n = 19) | | | | Postherpetic Neuralgia (n = 17) | | | |
	Baseline	Dextromethorphan	Memantine	Lorazepam	Baseline	Dextromethorphan	Memantine	Lorazepam
Physical functioning	55.9 ± 5.2	60.6 ± 6.9	61.0 ± 6.8	59.7 ± 7.2	67.4 ± 4.8	76.7 ± 5.5	67.6 ± 5.6	71.3 ± 5.0
Role—physical	53.9 ± 5.1	61.8 ± 9.9	43.1 ± 10.6	67.1 ± 10.8	35.7 ± 9.4	56.7 ± 10.8	51.3 ± 8.4	28.1 ± 10.9
Role—emotional	67.0 ± 8.8	86.3 ± 8.1*	68.6 ± 9.5	64.9 ± 9.7	74.6 ± 9.2	77.8 ± 9.6	59.6 ± 10.4	60.4 ± 11.9
Vitality and energy	49.3 ± 4.7	53.4 ± 5.5	43.5 ± 4.1	47.9 ± 4.1	42.9 ± 3.6	47.7 ± 4.7	40.8 ± 5.2	37.8 ± 4.7
Mental health and emotional well-being	69.3 ± 4.1	76.5 ± 4.9	66.6 ± 4.0	69.7 ± 6.1	72.4 ± 4.1	76.5 ± 4.0	74.9 ± 4.7	73.4 ± 5.2
Social functioning	73.9 ± 5.2	75.7 ± 7.6	71.1 ± 7.5	76.3 ± 6.9	60.0 ± 5.5	73.8 ± 7.3	68.4 ± 7.4	57.0 ± 5.1
Bodily pain	39.4 ± 3.6	50.2 ± 7.6	47.3 ± 5.9	51.5 ± 6.5	33.1 ± 2.8	42.0 ± 3.4	41.4 ± 3.5	32.3 ± 4.0
General health	49.6 ± 4.7	62.1 ± 6.9	54.1 ± 6.3	56.7 ± 6.8	70.8 ± 3.5	71.3 ± 4.6	65.7 ± 4.4	67.3 ± 4.5

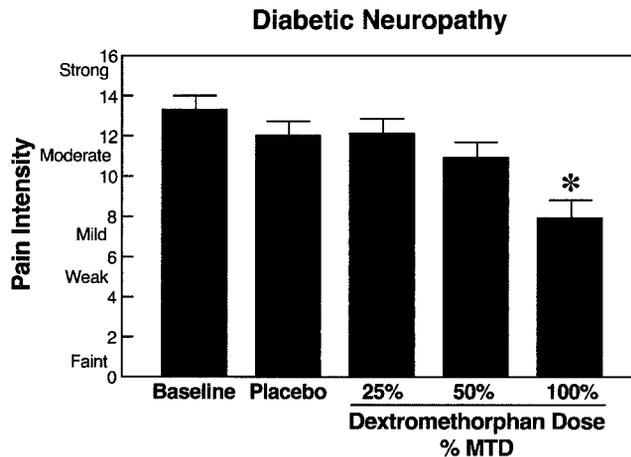* $P = 0.01$.

Diabetic Neuropathy

Fig. 3. Dose–response trial. Mean pain intensity (0–20-point Gracely scale) during the baseline and the final week of treatment with active placebo and 25, 50, and 100% of the maximally tolerated dose (MTD) of dextromethorphan determined in the efficacy trial. The patients were the 10 diabetic patients who had reported a more favorable pain relief category score with dextromethorphan than with placebo in the first trial. The 35% reduction in pain intensity relative to placebo for the 100% dose was statistically significant (*$P = 0.03$; 95% confidence interval, 5–65%), as was the dose–response relation ($r^2 = 0.93$; $P = 0.04$).

distress (dextromethorphan, 17%; memantine and lorazepam, 0%). Side effects that were either severe or persisted for more than 1 day at a moderate level included anorexia (dextromethorphan, 1 patient; memantine, 1; lorazepam, 0), constipation (dextromethorphan, 1; memantine, 1; lorazepam, 0), and nausea or vomiting (dextromethorphan, 2; memantine, 3; lorazepam, 0). No new events occurred during the maintenance period.

Dose–Response Trial

Ten patients with DN and five with PHN enrolled and completed the dextromethorphan dose–response trial. Median doses in the 100% MTD group were 520 mg/day (range, 240–920 mg/day) among the 10 DN patients and 360 mg/day (range, 210–580 mg/day) among the 5 PHN patients. Two patients with PHN enrolled and completed the memantine dose–response trial (median dose, 27 mg/day). All subjects were able to reach their target doses for each treatment.

Primary Endpoint (Efficacy). The full-dose dextromethorphan treatment reduced pain significantly more than lorazepam (reduction in mean intensity, 34.8%; $P = 0.027$), but the lower-dose treatments did not (reduction in mean pain intensity: 50% MTD, 13.4%, $P = 0.091$; 25% MTD, 0.14%, $P = 0.98$). In the 10 DN patients who responded to dextromethorphan and enrolled in the dose–response trial, a dose–response effect was noted ($P = 0.035$; $r^2 = 0.93$; fig. 3.).

Among the five subjects with PHN who completed the dose–response study with dextromethorphan, the percent reduction in pain intensity over lorazepam was 9% for 100% MTD; among the two subjects with PHN who

received four doses of memantine, the percent reduction in pain intensity over lorazepam was 0% for 100% MTD.

Secondary Endpoints.

Pain Relief. Zero, one, six, and nine of 10 subjects with DN reported moderate or better pain relief with 0% MTD (lorazepam), 25% MTD, 50% MTD, and 100% MTD dextromethorphan doses, respectively. Results of the analyses of the 10 diabetics' categorical pain relief responses paralleled those of the pain intensity diaries (table 2). In contrast to the 25% MTD group, which was not significantly better than lorazepam, both the 50% MTD ($P = 0.0042$) and 100% MTD ($P = 0.0048$) dextromethorphan treatment groups resulted in pain relief scores significantly better than lorazepam. Among the five PHN patients receiving dextromethorphan, two receiving 100% MTD and two receiving lorazepam had moderate or better pain relief, whereas no subject receiving other doses of dextromethorphan achieved moderate pain relief. Among the two patients receiving memantine, one receiving 100% MTD and one receiving lorazepam reported moderate or better pain relief, whereas no subject receiving other doses of memantine achieved moderate pain relief.

Blinding. Patients and study nurses completed the blinding questionnaires for each treatment period. After each period, their guess was chosen from four possible treatments, so one would predict a success rate of approximately 25% from random guessing uninformed by specific drug effects. Patients guessed 27 of 68 (40%) of the treatment periods correctly ($P = 0.098$). The study personnel guessed 20 of 68 (29%) of each treatment period correctly ($P = 0.70$).

Open-label Experience with N-methyl-D-aspartate Glutamate Receptor Antagonists

Of the subjects who completed both studies, 9 of the 10 subjects with DN and 3 of the 5 with PHN chose to pursue open-label treatment with dextromethorphan. Six of nine (67%) with DN and one of three (33%) with PHN continued dextromethorphan treatment, including 4-week washout periods and clinic visits at 6-month intervals, for a maximum allowable 2-yr period, after which they were discharged to the care of their local physician. All patients continued to enjoy moderate to complete pain relief and consistently experienced increases in pain intensity within 2–3 days of discontinuing dextromethorphan at the beginning of the washout periods. Two patients with DN discontinued open-label treatment after 6 months, and one patient with PHN discontinued open-label treatment after 12 months, to pursue other treatment regimens. Another patient developed hypertension after 12 months of open-label treatment and discontinued therapy. One PHN patient stopped open-label dextromethorphan after 12 months because she experienced a spontaneous pain remission.

The two PHN patients who completed both studies

and chose to pursue open-label memantine therapy stopped this drug after 6 and 12 months, respectively, to pursue other treatments.

No serious adverse events related to either dextromethorphan or memantine were observed during open-label treatment, and drug-related side effects were well tolerated. No withdrawal symptoms were noted when patients abruptly discontinued either drug before a washout period.

Discussion

This study shows that many patients with painful DN derive pain relief from high-dose dextromethorphan. Although this trend favoring dextromethorphan over placebo was not statistically significant in the efficacy trial, in the follow-up dose–response trial the full dose reduced pain by 35% compared with placebo, with a statistically significant paired contrast and dose–response relationship. Exposing 19 diabetic patients to dextromethorphan identified six more responses of moderate or better pain relief to that drug than to the active placebo, for an "number needed to treat" of 3.2, comparable to that reported with the use of gabapentin, tricyclics, tramadol, and μ-opioid agonists in neuropathic pain.[25] The "number needed to treat" is the number of patients that would need to be given a treatment for one of them to achieve 50% pain relief, who would not have achieved it with a control.

This study introduces a novel two-stage design, aimed at maximizing the response in the first study with individual dose titration, and prospectively determining the individual dose–response curves in apparent responders entered into a second study. Although enrolling responders may potentially limit internal validity by unblinding the patients, because each subject had been previously exposed to the treatment being evaluated,[26] the demonstration of a dose–response effect in the second trial (despite using lorazepam as the placebo) suggests that the effect is real. Designs using individual dose titration alone tend to bias inferences about dose–response. The optimal dose is often overestimated in such designs, particularly if the therapeutic response is delayed.[27] In addition, the underlying dose–response relation is obscured by the tendency of patients who respond to low doses to stay at low doses and for completely nonresponsive patients to titrate to high doses.[27,28]

This design provided informative results. The higher mean dose of dextromethorphan may explain, in part, the greater effect that we saw among the diabetics responders. Reducing the dextromethorphan dose from the dose just causing side effects (100% MTD) to one half of that dose (mean 50% MTD, 263 mg/day) resulted in, on average, a reduction in pain improvement from 34.8% to 13.4%. McQuay et al.[29] were unable to show an effect of 81 mg/day,

on average, compared with placebo. It is possible that a mean dose of 263 mg/day of dextromethorphan, although not showing a statistically significant result in this sample size, might be a tolerable and useful ingredient in a combination drug therapy for neuropathy pain.

Maximally tolerated doses of memantine were ineffective compared with active placebo in the DN and PHN efficacy studies. Pellegrino et al.[30] claimed that a dose of memantine similar to the one we reached relieved pain more than placebo in patients with DN. Our patient preference data suggest that the modestly effective dextromethorphan was superior to memantine overall: among the 17 DN and PHN subjects who chose to continue with a study drug, 15 chose dextromethorphan, and only two chose memantine.

Our results also suggest a difference in responsiveness to NMDA channel blockade between DN and PHN. Because of the modest sample size, the 95% confidence interval for dextromethorphan in the PHN efficacy study cannot exclude as much as a 17% reduction in pain. Even this is a small effect, and previous studies also showed a relative resistance of PHN to dextromethorphan[12] and memantine[30] relative to the drug's effect in DN. The apparent relative responsiveness of DN is unlikely to be an age effect on analgesic response or drug tolerability, as the relief in this study does not correlate with age, and mean doses were only slightly lower in the PHN than in the DN cohort. We speculate that the difference in response reflects the different temporal courses of the two diseases. Dyck et al.[31] reported that the presence of acute axonal necrosis in nerve biopsy specimens is strongly correlated with the presence of pain, perhaps because axonal injury triggers trains of action potentials.[32] In diabetic neuropathy, some axons are always degenerating, and dextromethorphan treatment may block effects of the resulting injury currents such as sensitization of central sensory neurons or excitotoxic damage to spinal cord interneurons that normally inhibit pain responses. In herpes zoster, axonal degeneration is largely limited to the few months after the acute episode, which may make NMDA receptor blockade later in the disorder less effective.

There is a striking contrast between the consistent efficacy of NMDA receptor antagonists in neuropathic pain in rats and the modest responses in patients. Because of the ubiquity of NMDA receptors in brain systems devoted to cognition, mood, and movement, the higher doses of low-affinity NMDA receptor antagonists required to block a sufficient number of channels[33] are likely to result in cognitive side effects. Steinberg et al.[34] administered oral dextromethorphan, 1,440 mg/day, three to four times our maximal doses, to preoperative neurosurgical patients and found drug concentrations in brain tissue to be at the low end of the tissue concentration–response curve for ischemic neuroprotection they had determined in rabbits.

Selecting a different target site in the NMDA receptor complex or altering the route of administration may improve the therapeutic ratio of NMDA receptor antagonists. Because NMDA receptors in the spinal dorsal horn are important in pain-induced sensory sensitization, local spinal administration is plausible. Unfortunately, preliminary results from dog studies with intrathecal ketamine, memantine, AP5, and MK801 have produced unacceptable neuropathologic changes at doses slightly above the therapeutic level (Tony L. Yaksh, Ph.D., Department of Anesthesiology, University of California, San Diego, CA, written communication, June 2001), and a recent case report[35] described a vacuolar myelopathy in a patient after long-term treatment with intrathecal ketamine. Systemically administered antagonists of NMDA receptor subtypes, such as the NR2B subtype,[36,37] may prove to have better therapeutic ratios than nonspecific channel blockers such as dextromethorphan. Alternatively, antagonists whose structure limits them to the periphery, where there are abundant NMDA receptors,[38] may lack the sedative and psychotomimetic effects of currently available drugs.

In contrast to opioids and tricyclic antidepressants, dextromethorphan is virtually devoid of potential for fatal overdose or organ toxicity.[39] Dextromethorphan is primarily metabolized by the cytochrome P450 2D6 isoenzyme, whose multiple genetic variants cause great variability in dose requirements.[40] Approximately 6% of whites are slow metabolizers at this locus and may require longer dosing intervals to avoid severe sedation or dissociative reactions. Similar adjustments are also indicated in any patient who has recently taken potent 2D6 enzyme antagonists such as quinidine, paroxetine, or fluoxetine; this interaction may occur up to 2 weeks after stopping fluoxetine because of the slowly eliminated metabolite norfluoxetine.[41-43] Because dextromethorphan increases serotonin levels at central synapses, combinations with antidepressants that block serotonin reuptake or monoamine oxidase inhibitors may cause a life-threatening serotonin syndrome.[44] Case reports have suggested that dextromethorphan may trigger mania in patients with bipolar disorder.[45] Physicians who prescribe high doses may need to seek out custom-compounding pharmacies because the additives in most commercial antitussive dextromethorphan preparations limit the dose.

Our results confirm efficacy of chronic administration of high-dose dextromethorphan in some patients with DN. Our dose–response data provide a rationale for initial selection of doses for future studies evaluating dextromethorphan alone or in combination with drugs that relieve pain by other mechanisms, including sodium channel antagonists, NMDA receptor antagonists with affinity at other sites, gabapentinoids, and opioids.

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