



Effects of noradrenergic and serotonergic antidepressants on chronic low back pain intensity

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Abstract

To understand the relative efficacy of noradrenergic and serotonergic antidepressants as analgesics in chronic back pain without depression, we conducted a randomized, double-blind, placebo-control head-to-head comparison of maprotiline (a norepinephrine reuptake blocker) and paroxetine (a serotonin reuptake blocker) in 103 patients with chronic low back pain. Of these 74 completed the trial; of the 29 who did not complete, 19 were withdrawn because of adverse effects. The intervention consisted of an 8-week course of maprotiline (up to 150 mg daily) or paroxetine (up to 30 mg daily) or an active placebo, diphenhydramine hydrochloride (up to 37.5 mg daily). Patients were excluded for current major depression. Reduction in pain intensity (Descriptor Differential Scale scores) was significantly greater for study completers randomized to maprotiline compared to placebo ($P = 0.023$), and to paroxetine ($P = 0.013$), with a reduction of pain by 45% compared to 27% on placebo and 26% on paroxetine. These results suggest that at standard dosages noradrenergic agents may provide more effective analgesia in back pain than do selective serotonergic reuptake inhibitors. Published for the International Association for the Study of Pain by Elsevier Science B.V.

Keywords: Antidepressants; Analgesia; Back pain

1. Introduction

Antidepressants are widely prescribed as analgesics for chronic back pain (Broadhead et al., 1991), on the rationale that they block reuptake of neurotransmitters (e.g. norepinephrine and serotonin) important to pain modulation (Spiegel et al., 1983; Yaksh et al., 1988). Despite this practice several important questions remain. First, evidence for the efficacy of antidepressants as analgesics for chronic back

pain is based on just a handful of studies (Goodkin and Gullion, 1989; Onghena and Van Houdenhove, 1992), and this literature thought to have distinct limitations (Turner and Denny, 1993). For example, there is extensive evidence for efficacy from rigorously controlled trials in selected neuropathic pain states, such as painful diabetic neuropathy and postherpetic neuralgia (Watson et al., 1982, 1992; Max et al., 1987, 1991, 1992; Sindrup et al., 1990a,b). By contrast only five randomized placebo controlled studies have addressed the analgesic efficacy of antidepressants in back pain without depression (Jenkins et al., 1976; Alcock et al., 1982; Pheasant et al., 1983; Goodkin et al., 1990; Atkinson et al., 1998), and the results are mixed. Reviews (Turner and Denny, 1993) have been critical of the methodology of

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much of the earlier work, with regard to sampling from tertiary care pain clinic samples which may be negatively biased by selecting for treatment ‘failures,’ restricted range of dosages or duration of treatment, small sample size and high attrition, lack of assessment of orthopedic and psychiatric comorbidity, and reliance on non-standard outcome measures. Recent work designed to address some of these limitations has documented the efficacy of nortriptyline, a noradrenergic reuptake inhibitor (Richelson, 1994, 1996), as analgesic for back pain (Atkinson et al., 1998). Nevertheless, additional research with other noradrenergic agents is needed to substantiate these results.

Secondly, there is some evidence in neuropathic pain for differential efficacy according to antidepressant mechanism of action. Noradrenergic action is thought to be analgesic (Max et al., 1987, 1991, 1992, Watson et al., 1992), but selective serotonin reuptake inhibitors may be ineffective (Max et al., 1992) except at very high serum concentrations (Sindrup et al., 1991). In contrast the efficacy of selective serotonergic reuptake inhibitors remain untested for back pain. From a clinical viewpoint, comparative efficacy is relevant since early work guiding current practice (Jenkins et al., 1976; Alcock et al., 1982; Ward, 1986) used tricyclic antidepressants with mixed noradrenergic and serotonergic effects (e.g. amitriptyline, imipramine). Because tricyclic drugs also are associated with troublesome or hazardous side effects (e.g. dry mouth, sedation, cardiac conduction delay) (Janicak et al., 1993) it would be important if selective serotonin reuptake inhibitors were efficacious, since these are generally safer and more tolerable. From a research perspective it is important to determine if serotonergic activity is itself analgesic, or if it simply augments noradrenergic analgesia (Max, 1994), because the answer to this question would provide a rationale for further research involving combination therapy and augmentation strategies.

This placebo-controlled study was a head-to-head comparison of the efficacy of maprotiline, a pure noradrenergic reuptake blocker, with paroxetine, a strong selective serotonin reuptake inhibitor (Richelson, 1994, 1996). We hypothesized that either or both maprotiline and paroxetine would be analgesic, based on recent evidence for noradrenergic analgesia in both back pain (Atkinson et al., 1998) and neuropathic pain (Max et al., 1991, 1992), along with known antinociceptive effects of serotonin at the level of midbrain and spinal cord (Yaksh et al., 1988).

Care was taken to address methodological limitations of prior studies (Turner and Denny, 1993). The study sample was recruited from primary care clinic populations and community volunteers, rather than from specialty pain clinic settings, to improve generalizability. Depressed patients were excluded, because the intent was to examine analgesia independent of an antidepressant effect. Standardized measures of pain, psychiatric and orthopedic status were used. Finally, an active placebo (diphenhydramine) was employed to enhance masking, since side effects

alone may be associated with reports of analgesia in chronic pain (Max et al., 1987; Turner et al., 1994).

2. Methods

2.1. Protocol

The research protocol was approved by the Committee on Investigations Involving Human Subjects of the University of California, San Diego (UCSD) School of Medicine and the Department of Veteran Affairs (VA) Healthcare System, San Diego, California, and written informed consent was obtained for entry to the study. Subjects were reimbursed for travel expenses, but there were no announced financial incentives to participate. Subjects were recruited by screening patients at the UCSD and San Diego VA primary care and orthopedic clinics, and in the local community by paid and public service advertisement in newspaper, flyers, and word of mouth. Subjects were told that they would be assigned to a placebo, or to one of two licensed medications used commonly in treating depression. It was explained these medications also might have analgesic effects because of their actions on nervous system neurotransmitters (serotonin and noradrenaline) known to be involved in pain. Inclusion criteria were: (1) ages 21–65; (2) low back pain (at T-6 or below) present on a daily basis for the preceding six months or longer and (3) able to understand the study measures (based on an 8th grade literacy level). Individuals were excluded for: (1) major coexisting medical illness (e.g. chronic obstructive pulmonary disease or cardiac disease); (2) coexisting orthopedic or pain disorder other than those related to the lumbar lesion; (3) current mood disorder (e.g. major depression, dysthymia, or bipolar mood disorder) and (4) history of a psychoactive substance use disorder within the preceding 12 months. Individuals were required to discontinue opioid analgesics (e.g. codeine) for the duration of the study, although ongoing use of non-opioids (e.g. aspirin, non-steroidal antiinflammatory drugs) was permitted. Back pain with a radicular component was defined as: (1) pain, burning, or tingling discomfort extending below the knee, and traveling within the anatomic distribution of a nerve root, with (2) either diminished knee or ankle reflexes, or decreased vibratory or pain sensation or motor strength. This met criteria for at least Classification 4 (or higher) on the Quebec Nomenclature for Activity-Related Spinal Disorders (Spitzer et al., 1987).

Each thirty-minute visit during the treatment phase of the study consisted, first, of monitoring of routine vital signs, then completion of laboratory or questionnaire measures by research personnel, and finally a brief medication visit with the study physician. Using manuals and scripts from established methods, the study treating physician was trained to focus on pharmacological treatment and to avoid providing social support above and beyond that needed to complete

the protocol requirements (Fawcett et al., 1987; Frank et al., 1990).

2.2. Intervention

Treatment with study drugs commenced within 24 h of baseline assessment. For each of the active agents the protocol specified rapid dose escalation to the range of what is used clinically as an antidepressant dosage, but this goal was not a condition for continuation on study. The target daily dose for maprotiline was 150 mg; the target daily dose for paroxetine was 30 mg, and for diphenhydramine 37.5 mg daily. The dose escalation schedule for maprotiline was to start treatment at 50 mg daily for three days, then to increase to 100 mg daily for three days, and then to increase to 150 mg daily thereafter, if tolerated. Otherwise, treatment was continued at maximum tolerable dose. The starting dose for paroxetine was 10 mg for three days; the dose was then increased by 10 mg increments every three days thereafter to a maximum of 30 mg daily. If this target daily dose were not achieved, treatment was continued at the maximum tolerable dose. The placebo, diphenhydramine, was increased every three days, as tolerated, starting at 12.5 mg daily, then to 25 mg daily, and then to 37.5 mg daily. Study drugs and placebo were packaged in identical gelatin capsules and the daily dose was administered at 2100 h. After a subject attained maximum dosage specified by the protocol (or maximum tolerable dose), the total daily dose was combined into a single capsule (again manufactured by the research pharmacy) which was taken once daily at 21:00 during the remainder of the study. This was done in an effort to maintain an equivalence across groups in number of pills ingested each day (i.e. one pill daily during the maintenance phase).

Serum concentrations of antidepressants were analyzed retrospectively. The mean daily dose at exit of maprotiline was 138 mg (range 50–150 mg); mean daily dose of paroxetine was 25 mg (range 10–30 mg); mean daily dose of diphenhydramine was 36 mg (range 25–37.5 mg). Plasma samples were obtained at weeks three and eight in all subjects. In study completers assigned maprotiline ($n = 20$), mean exit plasma concentration obtained 12 h after the last dose was 121 ± 106 ng/ml (median 86 ng/ml); for paroxetine these values were 57 ± 44 ng/ml (median 53 ng/ml). Concentrations obtained at week three on study did not differ statistically from those obtained at exit (week eight).

Treatment emergent side effects were determined weekly by the blinded study physician, using a checklist interview (Rabkin et al., 1992). In this procedure the subject was asked to endorse any symptoms experienced from among those identified on an extensive checklist. The physician reviewed the list, interviewed the subject to confirm the nature of the side effect, and rated how much the side effects interfered with everyday function (no interference, mild, moderate, or marked interference). At

conclusion of the interview the study physician completed this form specifying whether the dosage of 'study drug' could be increased (if the participant were in the escalation phase of the protocol), decreased, or maintained. This form was sealed and delivered by other personnel to the research pharmacist, who used this information to guide dosing in the dose escalation and maintenance phases of the protocol, as described below.

To maintain the blind from the treating physician and assessment personnel, a research pharmacist not connected with other aspects of the study escalated the dose of study drugs at each visit according to protocol guidelines, until either the target daily dose specified by the protocol was achieved, or until the subject reached maximum tolerable dose. This dose escalation was guided by review of the study physician's side effects checklist. During the dose escalation phase a study drug's dosage was not increased if side effects on the checklist were rated as 'moderately' or 'markedly' interfering with daily function.

2.3. Measures

Measures of pain and mood were obtained by blinded research personnel in a testing session separate from the treating study physician visit at baseline. At exit the measures were obtained similarly before the final visit with the study physician. The primary outcome measure was report of pain intensity on the Descriptor Differential Scale (DDS) (Gracely and Kwilosz, 1988). A secondary outcome was DDS pain unpleasantness. Several steps were taken to guard against confounding analgesic effects with mood-elevating or antidepressive action. Before entry and at exit a clinician interviewed each subject for a lifetime and current (one month) history of major depression, dysthymia, or bipolar mood disorder using the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al., 1990). Severity of mood symptoms were assessed by self-report and observer ratings, using the Beck Depression Inventory (Beck, 1967), Hamilton Rating Scale for Depression (Hamilton, 1960), Spielberger State Anxiety Inventory (Spielberger et al., 1969), and Hamilton Rating Scale for Anxiety (Hamilton, 1959). Pain and mood measures were obtained at entry and study exit.

The Descriptor Differential Scale (DDS) (Gracely and Kwilosz, 1988) contains 26 words that describe the intensity and unpleasantness of pain. Subjects rate their clinical pain relative to these descriptors. To reduce recall bias, the specific reporting period is current pain intensity at the time of assessment. Ratings are aggregated to provide a 0 to 20 point rating for pain magnitude. The DDS demonstrates good internal consistency, reliability, objective correlation with experimentally induced pain, and sensitivity to detect analgesic intervention in clinical pain (Gracely and Kwilosz, 1988; Doctor et al., 1995). DDS verbal descriptors of pain intensity correspond to pain magnitude ratings over

a wide range (e.g. DDS intensity 6–7 = very weak pain; 8 = mild pain; 9 = moderate pain; 10–11 = slightly intense pain; 12–13 = strong pain; ≥ 14 = intense to extreme pain) (Doctor et al., 1995).

The Beck Depression Inventory, a 21 item questionnaire measuring the cognitive and somatic aspects of depressed mood, is reliable and internally consistent (Beck et al., 1988). The Hamilton Rating Scale for Depression (HRSD), is an observer-rated semi-structured interview of depressive symptoms; the first 17 items on the original version were scored (Hamilton, 1960). The measure has acceptable reliability and validity (Hamilton, 1974). The Spielberger State Anxiety Inventory is a well-validated 20-item questionnaire addressing the emotional and cognitive aspects of anxiety, targeted to the individuals feelings at the present moment. The Hamilton Rating Scale for Anxiety (HRSA) is a 14-item interviewer rated measure of psychological and somatic symptoms of anxiety (Hamilton, 1959). To enhance inter-rater reliability we employed the Structured Interview Guide for the Hamilton Rating Scales (Williams, 1988). These ratings were done without knowledge of the scores or ratings on the independent measures of pain obtained by other evaluators.

A general physical examination, routine laboratory determinations, electrocardiogram, standardized orthopedic assessment of spine disorders, and a rating of severity of back disease (Waddell and Main, 1984) was obtained as part of a qualification assessment at entry. This was repeated at exit by personnel blinded to group assignment. The orthopedic examination was conducted by a specially trained orthopedic research nurse, in consultation with the study orthopedic surgeon. Orthopedic diagnoses were rendered by the orthopedic surgeon according to the Quebec Nomenclature on Activity-Related Spinal Disorders (Spitzer et al., 1987). Diagnoses were made on all available clinical information, including history, physical examination, and laboratory assessment, which generally included imaging studies (e.g. X-ray, computed tomography, or magnetic resonance imaging) and in some cases nerve conduction velocities. At each weekly visit a standardized questionnaire (Atkinson et al., 1991) was used to survey for non-protocol medical or behavioral treatments for back pain during the study period. Use of psychoactive agents (anxiolytics, antidepressants, muscle relaxants) and opioid analgesics was prohibited during the study.

Plasma concentration of maprotiline and paroxetine were determined using high pressure liquid chromatography (Bio-Rad Inc., Hercules, CA). Patients on maprotiline, paroxetine and placebo underwent phlebotomy on the same schedule. To monitor adherence to the protocol and guard against confounding of outcomes by prescribed or illicit drug use, qualitative urine toxicology screens were obtained at baseline, four, and eight weeks visits. These screens assessed for presence of amphetamines, barbiturates, benzodiazepines, cocaine and benzoylcgonine, and opioids (e.g. codeine, morphine, methadone).

2.4. Statistical analysis

Analyses of variance (ANOVA) were conducted on background and baseline variables to determine whether randomization produced comparable groups. Next, the primary hypothesis of an analgesic effect was evaluated in the sample consisting of subjects who completed eight weeks on treatment ($n = 74$). An analysis of completers was considered the primary analysis since the main aim of the research was to examine comparative effects on pain intensity of noradrenergic and serotonergic agents 'if taken'. An intent-to-treat analysis was conducted thereafter to assess for generalizability of results and overall effectiveness. To address the primary hypothesis we conducted a priori ANOVA contrasts comparing differences between the active treatment groups and placebo in terms of change scores calculated from baseline to exit on the Descriptor Differential Scale pain intensity. ANOVA contrasts were also conducted to compare group differences in pain intensity change scores between patients with radicular pain. Student's *t*-tests compared differences in pain intensity change scores between radicular and non-radicular subgroup within treatment arms. A supplemental intent-to-treat analysis (ANOVA) likewise was conducted on change scores of pain intensity; this analysis included all randomized subjects and used the last available score. Categorical background variables (e.g. proportion married, proportion with prior back surgery) were compared between groups using chi-square tests. All *P*-values were 2-tailed, unless otherwise stated. Based on our study of patients with chronic back pain treated with tricyclic antidepressants (Atkinson et al., 1998) an effect size of 0.5 SD on DDS pain intensity was considered clinically relevant analgesia. Power analyses indicate that a sample size of 20 individuals per group would yield an 80% chance (at $\alpha = 0.05$) of detecting a difference between groups with an effect size of at least 0.4 SD in the population. Statistics were performed by using commercially available software (Norusis, 1992).

2.5. Assignment

Upon completion of baseline assessment individual participants were randomly assigned to maprotiline, paroxetine or placebo using a random number table held by a research pharmacist not involved in other aspects of the trial. To assure equivalence across groups on presence of a radicular component of back pain, the allocation scheme stratified subjects on absence or presence of radicular pain.

2.6. Masking

Maprotiline, paroxetine, and diphenhydramine were administered in identical capsules to be taken in a single dose at 21:00 daily. The code for subject assignment was held by the research pharmacy until completion of data analysis. The similar rates of side effects across study

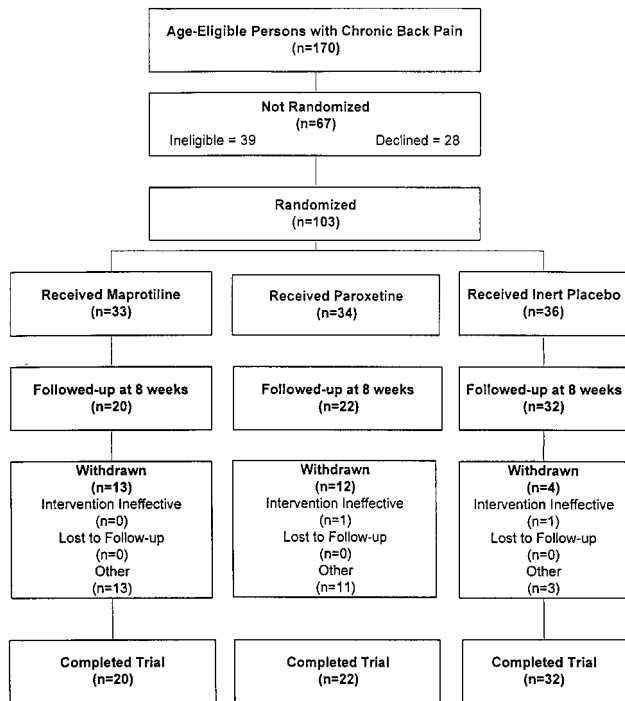


Fig. 1. Progress of participants through the trial. Reasons for ineligibility included meeting one or more exclusion criteria.

completers for the active and placebo groups (see Table 4) suggest that treatment masking was successful. Additionally subjects and blinded study physicians were asked to ‘guess’ treatment (active or placebo) at study exit (Moscucci et al., 1987). In the completers sample, data on subject’s guesses were obtained for 18 of 20 assigned maprotiline, 22 of 22 on paroxetine, and 31 of 32 given diphenhydramine. The vast majority of subjects completing on maprotiline, 16/18 (89%), guessed ‘active’ treatment, and the same was true for both paroxetine 21/22 (96%), and diphenhydramine, 22/31, (71%)(chi square, $P = 0.048$). The study physician guessed ‘active’ treatment for each group as follows: maprotiline (17/19, 90%), paroxetine (19/21, 91%), and diphenhydramine (17/30, 57%) (chi square $P = 0.006$).

Table 1
Demographic and clinical characteristics of low back pain patients ($N = 103$) in the clinical trial

Characteristic	
Age mean \pm SD, years	49.2 (9.4)
Gender, no. (%) men	65 (63.1)
Education mean \pm SD, years	14.9 (2.7)
Marital status, no. (%) married	70 (68)
Ethnicity, no. (%) White	87 (84.5)
Annual family income, \$, mean	450000
Pain duration, mean \pm SD, years	14.5 (11.1)
Orthopedic diagnosis, no. (%) DDD ^a	74 (71.8)
Previous back surgery, no. (%)	12 (11.8)
Radicular pain, no. (%)	14 (13.6)

^a Degenerative disk disease.

Although antidepressant treatment was more easily guessed than placebo, the high rates of an ‘active’ guess by subjects on placebo, as well as by the physician, suggest that masking was successful.

Unblinding was conducted in a face-to-face interview with another study physician not involved in data collection, randomization, or masking. This interview, usually occurring within 72 h after completing the last study visit, was performed at a site distant from the research clinic area.

3. Results

3.1. Participant flow and follow-up

Recruitment was conducted from July 1994 through December 1996. A total of 591 persons were screened by telephone for eligibility. Thereafter 170 possibly eligible individuals were screened in person. Of these eight (5%) were disqualified for concurrent medical illness; eight (5%) were excluded because their back pain was intermittent or of insufficient duration; 12 (7%) met a psychiatric exclusion (e.g. current major depression), eight (5%) had an alcohol or other substance use disorder; and three (2%) did not meet the literacy requirement. Twenty-eight possibly eligible individuals (16%) declined to participate after learning more about the study requirements (Fig. 1).

One hundred and three participants completed baseline evaluation and were randomly assigned to treatment (33 to maprotiline, 34 to paroxetine, and 36 to placebo) (demographic and clinical characteristics of these patients are given in Table 1). There were no statistically significant differences between these groups in background demographics, pain intensity, pain duration, orthopedic history, or mood (all P -values > 0.05).

Subjects were typically white, middle class, high school-educated men and women in their late 40s or early 50s, with persisting back pain usually diagnosed as degenerative disease, who rarely ($n = 12$; 12%) had prior back surgery. The median duration of back pain was 10 years. The principal orthopedic diagnoses were degenerative disc or degenerative joint disease ($n = 82$; 80%); musculoskeletal strain ($n = 8$; 8%); post-laminectomy persisting pain ($n = 6$; 6%); herniated nucleus pulposus ($n = 3$; 3%); spinal stenosis ($n = 3$; 3%); and other spine disorder ($n = 1$; 1%). Using nomenclature of the Quebec Task Force (Spitzer et al., 1987), back pain was categorized as pain without radiation ($n = 58$; 56%); pain with proximal radiation ($n = 17$; 17%); pain with distal radiation ($n = 16$; 16%); and pain with radiation and neurologic signs ($n = 12$; 12%). Mean (SD) DDS pain intensities in each diagnostic group did not differ meaningfully: pain without radiation 10.78 (3.57); pain with proximal radiation 10.64 (4.86); pain with distal radiation 11.14 (4.15); pain with radiation and neurological signs 10.88 (5.02) ($F_{3,99} = 0.05$, $P = 0.987$).

Seventy-four subjects completed the eight week trial.

Table 2
Primary reason for participant withdrawal from protocol

Primary reason for withdrawal	Maprotiline	Paroxetine	Placebo
Dizzy/lightheaded	1	1	0
Drowsiness	1	0	1
Dry mouth	2	0	0
Lethargy	0	2	0
Nausea/vomiting	0	1	0
Restless/nervous	1	0	0
Sexual dysfunction	1	0	0
Chest pain	0	1	0
Headache	0	1	0
Rash	2	0	0
Pain not improving	0	1	1
Time burden of study	0	1	2
Protocol violation	2	2	0
Unspecified	1	0	0
Dysarthria	1	0	0
Dissociated	1	0	0
Other reason	0	2	0
Total withdrawals	13	12	4

Twenty-nine patients (13 on maprotiline, 12 on paroxetine, and 4 on placebo) voluntarily withdrew or were dropped from the study. The distribution of the primary reason for withdrawal (Table 2) was similar in each group, and generally was related to adverse side effects. Two individuals withdrew after randomization because of deciding against taking medication for pain; one person in each of the active treatment arms was withdrawn because urine toxicology was positive for drugs of abuse, and one in each active arm was withdrawn because of developing or discovering an intercurrent medical or psychiatric exclusion. Drop rates were similar for maprotiline (13/33; 39%) and paroxetine (12/34; 35%), but these were significantly higher than the rate for placebo (4/36; 11%) (chi square = 8.09, d.f. = 2, $P = 0.018$). At baseline the demographic, clinical, and primary and secondary outcome characteristics of participants who completed the study in the maprotiline ($n = 20$), paroxetine ($n = 22$), and placebo ($n = 32$) conditions did not differ significantly from those in the entire randomized sample (all P -values non-significant).

Although no participants had been treated previously

Table 3
Completer sample ($N = 74$) DDS pain intensity scores at baseline, at exit, and change scores^a

Treatment	Number	Baseline	Exit	Decrease
Maprotiline	20	12.21 (4.52)	6.80 (4.72)	5.41 (4.99)
Paroxetine	22	10.54 (3.71)	8.20 (4.00)	2.34 (3.52)
Diphenhydramine	32	10.53 (3.74)	7.70 (4.63)	2.83 (3.31)

^a All values are given as mean (SD). DDS indicates Descriptor Differential Scale. A priori contrasts: Maprotiline > Placebo $t(71) = 2.32$, $P = 0.023$; Maprotiline > Paroxetine $t(71) = 2.55$, $P = 0.013$; Paroxetine = Placebo $t(71) = 0.46$, $P = 0.648$.

with the study antidepressants, 4 of 36 (11%) participants assigned to placebo had been treated with an antidepressant for a previous mood disorder, as had 2 of 33 (6%) subjects assigned to maprotiline and 6 of 34 (18%) randomized to paroxetine ($P = 0.333$). There were no significant differences at entry between treatment arms with regard to use of adjunct treatments: 13 of 33 (39%) persons on maprotiline, 12 of 34 (35%) persons on paroxetine, and 13 of 36 (36%) on placebo were taking salicylates or non-steroidal anti-inflammatory agents. Also, 32 on maprotiline, 31 on paroxetine, and 33 on placebo employed some form of a 'behavioral' (e.g. self-hypnosis, self-taught relaxation exercises) or physical therapy technique (e.g. back exercises, chiropractor) (all P -values non-significant). In study completers ($n = 74$), seven of 20 (35%) persons on maprotiline, nine of 22 (41%) on paroxetine, and 13 of 32 (41%) assigned placebo took salicylates or over-the-counter non-steroidal anti-inflammatory drugs on study. Ten completers (50%) on maprotiline, five (23%) on paroxetine, and 13 (41%) on placebo used a behavioral or physical therapy during the study (chi square = 3.50, df = 2, $P > 0.05$).

3.2. Analysis

Baseline scores and difference between groups in change scores for pain are described in Table 3 for the primary 'completers' analysis, designed to examine the comparative effect on pain intensity of noradrenergic and serotonergic agents.

The mean decrease in pain intensity was significantly ($P = 0.023$) greater for maprotiline (5.41 ± 4.99) compared to placebo (2.83 ± 3.31). Reduction of pain intensity also was significantly ($P = 0.013$) greater for maprotiline compared to paroxetine. This on average represented a 45% decrease in pain intensity on maprotiline, compared to a 27% decrease on placebo, and a 26% decrease on paroxetine. The mean reduction in pain intensity on paroxetine compared to placebo was not significant ($P = 0.648$). Among completers diagnosed with a painful lumbar radiculopathy (four each on maprotiline, paroxetine, and placebo) pain intensity change (maprotiline 5.24 ± 2.71 ; paroxetine 2.36 ± 3.65 , and placebo -0.09 ± 3.83) was statistically similar (all P -values non-significant) across all treatment arms, although there was a trend for maprotiline to outperform placebo ($t = 1.89$, $P = 0.09$). Pain intensity reduction was similar between participants with radicular ($n = 12$) and non-radicular pain ($n = 62$) within and between treatment arms (all P -values non-significant). In addition effect on pain unpleasantness also was analyzed. Decrease in pain unpleasantness was significantly greater for maprotiline compared to placebo (difference in mean change 3.19, $P = 0.009$; 47% reduction vs. 20% decrease in pain unpleasantness). Nevertheless decrease in pain unpleasantness did not differ between maprotiline and paroxetine, or paroxetine and placebo (all P -values non-significant).

An intent-to-treat analysis was conducted on all rando-

Table 4

Side effects (no., %) at any time on study attributed to maprotiline, paroxetine, or placebo for participants completing the clinical trial

	Maprotiline (<i>n</i> = 20)	Paroxetine (<i>n</i> = 22)	Placebo (<i>n</i> = 32)	<i>P</i> ^a
Any side effect	18 (90.0)	20 (90.9)	31 (96.9)	550
Dry mouth	17 (85.0)	9 (40.9)	19 (59.4)	014
Insomnia	14 (70.0)	14 (63.6)	17 (53.1)	455
Sedation	16 (80.0)	12 (54.4)	21 (65.6)	218
Orthostatic symptoms	10 (50.0)	5 (22.7)	13 (40.6)	174
Constipation	10 (50.0)	7 (31.8)	6 (18.8)	060
Increased sweating	1 (5.0)	7 (31.8)	3 (9.4)	026
Palpitations	2 (10.0)	0	5 (15.6)	155

^a Chi square.

mized subjects, using the last available score for subjects who did not complete eight weeks on treatment (i.e. last observation carried forward, LOCF). Reduction in pain intensity was significantly greater with maprotiline compared to paroxetine ($t = 2.26$, $P = 0.028$), and pain reduction on paroxetine was equivalent to placebo ($t = 1.48$, $P = 0.147$). Maprotiline decreased pain more than did placebo but this difference was not different statistically ($t = 1.10$, $P = 0.275$). Reduction in pain unpleasantness was not significantly different across groups ($P > 0.05$). Other analyses relevant to the primary findings were conducted. The correlation between decrease in pain intensity and plasma concentration of maprotiline at exit was not significant ($r = 0.04$, $P = 0.849$), and this was the case also for paroxetine ($r = -0.20$, $P = 0.363$). By design none of the patients met criteria for major depression. The low mean scores for self-report and observer-rated depression and anxiety symptoms confirmed this. At entry both mean self-report Beck Depression scores (6.1 + 5.3) and observer-rated Hamilton Depression scores (5.8 + 3.7) were within the normal range, as were Spielberger State Anxiety (33.5 + 11.2) and Hamilton Anxiety (5.9 + 3.2) scores (all P -values > 0.05). There were no significant differences in mean change scores for self-report or observer-rated mood, and no significant correlation between change in mood symptoms and pain intensity.

3.3. Adverse drug effects

Most patients experienced side effects of at least mild severity during the eight week trial (see Table 4). The most frequently reported side effects were dry mouth, insomnia, and sedation. In general the frequency of side effects was comparable across treatment arms, except for anticipated differences in some drug-specific areas (e.g. dry mouth on maprotiline, sweating on paroxetine).

4. Discussion

This randomized clinical trial suggests that maprotiline, a noradrenergic antidepressant, reduces pain intensity in non-depressed individuals with chronic low back pain, whereas

paroxetine, a serotonergic reuptake inhibitor, does not. Using established verbal descriptors of pain magnitude from the Descriptor Differential Scale (Gracely and Kwilosz, 1988; Doctor et al., 1995) maprotiline could be said on average to reduce pain intensity from 'strong' to 'mild'. Because scores on mood inventories were within the normal range, and patients with major depression were excluded, analgesia was not mediated by an antidepressant effect. Reduction of pain unpleasantness was less marked, which may be consistent with the argument that the primary mechanism was not related to modulation of affective state.

One recent influential review concluded that methodological limitations of previous research made it impossible to confirm or refute the efficacy of antidepressants as analgesics for back pain (Turner and Denny, 1993). The strength of the present study rests upon its attempt to address these limitations. We employed methodological criteria thought to be essential for establishing the validity and generalizability of outcome research for conservative treatments for low back pain (Deyo, 1983; Deyo and Diehl, 1983), including careful examination of orthopedic and psychiatric status, randomized design, tracking of co-interventions, use of an 'active' placebo, and confirmation of study blinding (Turner et al., 1994). Furthermore this sample is arguably more representative of the 'usual' back pain patient than those seen in specialty pain clinic settings, where depression is common, multiple surgeries and opioid use are prevalent, and litigation and impairment of function is extreme (Krishnan et al., 1985; France and Krishnan, 1988).

Nevertheless, this study has several limitations. Attrition was high in the antidepressant treatment groups, albeit in the range for clinical trials in other chronic back pain studies (e.g. Jenkins et al., 1976). The study design specified rapid dose escalation to maximum tolerable dose, which probably heightened attrition, since the vast majority (70%) of drop-outs occurred the first 14 days on protocol. This early attrition may have contributed to failure of the intent-to-treat analysis to fully support results from the completer's analysis. Another limitation of our dose escalation strategy is that full analgesic effects may not have been observed due to failure to test high enough or low enough doses by utilizing a strategy which 'optimized' each patient's treatment indi-

vidually. Next, this report uses sensitive self-report measurement of analgesia, analyzed as a continuous variable. Given the limited sample size, we cannot accurately estimate the proportion of patients who might achieve a specific 'target' magnitude of pain relief (e.g. proportion with reduction in pain intensity by 50%). Similarly, the small sample size of patients with radicular pain left us unable to gauge the relative responsiveness of radicular and non-radicular back pain. Studies with larger sample sizes will be needed to gauge differential responsiveness and overall treatment efficacy in terms of restoring function or enhancing life quality. Finally, the longer-term durability of analgesia, an important clinical concern in patients with chronic pain, cannot be assessed by an eight-week study.

These results may have implications for back pain practice and research. Regarding clinical practice, treatment selection might start with a strongly noradrenergic agent rather than a serotonergic drug. A strategy designed to enhance tolerability to maprotiline would be to start at low doses (e.g. 25 mg), escalate cautiously (e.g. by 25 mg increments every three days) to 150 mg daily, and consider giving the medication in two or three equally divided doses if side effects are bothersome. As with other first generation antidepressants (e.g. desipramine, imipramine), anticholinergic side effects may be especially evident in the elderly or those with coexisting systemic medical illness. In terms of research most antidepressant agents which relieve chronic pain block reuptake of norepinephrine: this includes nortriptyline for back pain (Atkinson et al., 1998), and amitriptyline (Watson et al., 1982, 1992; Max et al., 1987, 1988), desipramine (Kishore-Kumar et al., 1990; Max et al., 1991), and imipramine (Kvinesdal et al., 1984; Sindrup et al., 1990a,b) for chronic neuropathic pain. The role of selective serotonergic antidepressants is less certain. Although there is evidence for analgesic effects at very high serum concentrations (Sindrup et al., 1990a, 1991), fixed doses of a serotonergic antidepressant were ineffective in the present study, and in prior work in both chronic back pain (Goodkin et al., 1990) and chronic neuropathic pain (Watson et al., 1982; Max et al., 1991). Agents with combined noradrenergic and serotonergic effects may be superior to those blocking reuptake of only one neurotransmitter (Max, 1994). This has led to the hypothesis that serotonin reuptake is itself only weakly analgesic but augments noradrenergic analgesia (Max, 1994). Given the present results, the obvious next steps would be to conduct prospective concentration-response studies of maprotiline or other noradrenergic antidepressants in back pain, or studies using combinations of noradrenergic and serotonergic agents.

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