Controlled Trial of Imipramine for Chronic Low Back Pain

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Chronic low back pain is a common problem that has been noted in several studies to exist as a component of masked depression. To determine the usefulness of imipramine in the treatment of chronic low back pain, either by a direct action or indirectly via resolution of a depressive equivalent, 50 consecutive patients were entered into a controlled trial that employed serum imipramine and desipramine levels and Beck depression questionnaires. Forty-one patients completed the study, and 48 were used in the statistical analysis. Imipramine had a statistically significant effect over placebo in most, but not all, of the clinical parameters that were measured. A linear relationship between serum drug levels and reported symptoms was not noted. Only 10 of the 50 patients entered into the study were judged clinically depressed and, of these, 7 were depressed according to standard criteria. There was no statistically significant difference noted in either the initial or the change in Beck depression scores between those on imipramine and those on placebo. However, among those on the active drug, the patients with a greater symptomatic response had a simultaneous change in the total Beck depression scores (toward less depression) that approached statistical significance when compared with those with a less symptomatic response. Although the results are not conclusive, imipramine may possibly be useful in the treatment of chronic low back pain, especially so when it exists as a component of masked depression.

Low back pain is a massive health problem in contemporary America. In 1955 Russek reported that low back pain accounted for 12.4 percent of all industrial injuries and 16 percent of all compensation made in the state of New York.[1] More recently, a study in California revealed that 72,645 patients were admitted to a hospital in 1974 with a diagnosis of back pain.[2] The total cost of almost $103 million, when extrapolated to a national scale, comes to $1.38 billion per year. This does not include outpatient care expense or loss of income.

It has been noted that low back pain can be seen

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as a depressive equivalent. In a study of the personality traits of patients with chronic low back pain, Sternbach and Wolf found their group had composite scores for depression, as measured by the Minnesota Multiphasic Personality Index, approximately two standard deviations above the mean of the normal population.[3] In addition, a multicenter double-blind trial of imipramine in patients with osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis demonstrated a highly significant effect of imipramine over placebo.[4] For these reasons, a prospective controlled trial was conducted to determine whether there was any effect of imipramine, a tricyclic antidepressant, on low back pain, either by a primary mechanism or by a secondary amelioration of a depressive equivalent.

Methods

The study was conducted between September 1, 1980, and March 1, 1981, at the Department of Family Practice, Naval Regional Medical Center (NRMC), Charleston, and the Department of Family Medicine, Medical University of South Carolina (MUSC), Charleston, South Carolina. Imipramine hydrochloride (Tofranil) and a placebo of identical size, color, and taste were used in a randomized fashion. Neither the medical personnel nor the patients initially knew who was receiving the active drug or the placebo. Only the chief of pharmacy at the two locations knew the treatment code.

The nature of the drug and the study design were carefully explained to all patients, and informed consent was obtained. All participants in the study underwent a complete physical examination, and a medical history was obtained by one of the participating physicians. A complete blood cell count with a differential, Westergren sedimentation rate, urinalysis, electrocardiogram, and lumbosacral spine x-ray series (anterior-posterior, lateral, and oblique) was obtained on all patients. To be included in the study, the patient had to be experiencing low back pain for at least six weeks if it were a first episode, or the patient had to have had two or more prior episodes lasting at least two weeks with a current episode of a minimum of two weeks' duration.

After being randomly assigned to either placebo or drug, each study participant was warned about alcohol intake during the course of the study and given a two-week supply of pills. Initially, one pill (75 mg of imipramine) was taken for the first three days. This was then increased to two pills a night. The duration of the study was eight weeks. A Beck depression questionnaire was completed by the patient at the initial and final visits. A blood pressure reading was obtained at each visit. At two, four, and eight weeks the patient completed a short back pain questionnaire, the number of pills in the bottle were counted, the physician-investigator evaluated the patient, and serum imipramine and desipramine (an active metabolite of imipramine) levels were drawn. The drug levels were not released to the investigators until the entire study was completed.

Patient Population

Sixty consecutive patients with chronic low back pain were referred by their family physician for possible participation in the study. Eight were excluded without further evaluation because their back pain did not meet the study criteria for chronicity. After the evaluation described above, only two other patients had conditions that were exclusions to participation: one had a persistent diastolic blood pressure reading of more than 90 mmHg, and the other had electrocardiogram changes consistent with an old myocardial infarction. Of the 50 patients entered into the study between September 15, 1980, and January 1, 1981, 41 completed the study. Two participants, both of whom were on active duty in the Navy and on the active drug, moved from the area at the fourth and sixth week of the study, respectively, whereas two others, both on placebo, decided to discontinue their participation in the study only after five and seven days, respectively. There were also five patients who dropped out because of reported intolerable side effects of imipramine (mainly dry mouth and constipation, but also lethargy and impaired sexual function) between two and four weeks, only in the sense that the medication was not continued. They completed all the questionnaires for the remainder of the study. There were no dropouts resulting from the development of any of the contraindications to the use of imipramine.

An initial diagnosis was established for each patient by the physician-investigator. The diagnoses

included lumbosacral strain, osteoarthritis, herniated nucleus pulposus, hip disease, and depression. At each visit the patient completed a back pain questionnaire that consisted of the following seven questions: (1) On the average, how many pain pills or tablets (in addition to the study pills) have you taken per day in the past week? (2) How many days in the past week have you had to lie down for two hours or more? (3) How many days in the past week have been characterized by at least some restriction of normal daily activity? (4) How would you rate your back pain during the past seven days: severe (bed rest), moderate (modification of major activities), mild (discomfort), or none (without pain)? (5) How often does your back pain limit your work? (6) How often does your back pain limit your recreational activities? and (7) How often does your back pain make you miserable? The five possible answers to the last three questions were all the time, most of the time, some of the time, little of the time, and none of the time. Finally, the patient was asked to list all side effects. At each visit the physician-investigator obtained an interim history and performed an examination limited mainly to the back and lower extremities. He evaluated both the symptoms and physicial findings, reporting much worse, worse, no change, somewhat better, and much better.

Statistical analysis of the data on the 48 patients who completed at least two weeks of the study consisted of comparison t tests.

Table 1. Comparison of Patients Taking Imipramine with Those Taking Placebo

	Imipramine	Placebo
Number of patients	28	22
Average age (yr)	29.2	33.8
Sex		
Male	14	12
Female	14	10
Race		
White	22	18
Black	2	4
Hispanic	4	0
Clinical diagnosis		
Lumbosacral strain	18	15
Herniated nucleus pulposus	8	6
Hip disease	0	0
Osteoarthritis	2	1
Depression	6	4
Previous back surgery	4	3
Previous back injury	10	7
Number of episodes of back pain		
1 to 3	5	2
4 to 6	3	3
7 or more	20	17
Duration of back pain		
Less than 2 years	8	5
2 to 4 years	6	4
More than 4 years	14	13

Results

Demographic and various clinical characteristics of study patients on imipramine and those on placebo are noted in Table 1. Twenty-eight patients were randomly assigned to imipramine and 22 to placebo. No significant difference was noted between the two groups. Dry mouth was the most frequent side effect, occurring in 22 of 28 patients (78.6 percent) on imipramine, followed by tremor (7 patients), constipation (5 patients), and difficulty initiating urination (5 patients).

Of the 137 possible sets of imipramine and desipramine serum levels that could be used in analysis of the data of the 48 patients, only 125 (91.3 percent) were available. Three (all at the eight-week visit) could not be drawn during the course of the study, four were lost in transit, and five could not be done at the laboratory because of technical difficulties. There was no linear relationship between serum imipramine and desipramine levels and symptoms of low back pain during the course of the study in those patients on the active drug. Using the criteria of Beck et al[5] (scores of 18, 25, and 30 indicate mild, moderate, and severe depression, respectively) four of the patients (three on placebo and one on active drug) admitted to the study were mildly depressed on their initial Beck depression inventory scores, and three (one placebo and two active drug) were severely depressed. As noted in Table 1, the investigators

Table 2. Statistical Analysis of Clinical Parameters: Imipramine Versus Placebo (n = 48)

	P Value
1. Pain pills per day	.15
2. Number of days had to lie down for 2 hours or more	.002
3. Number of days with at least some restriction of normal activity	.004
4. Severity of back pain	.058
5. Limitation of work	.004
6. Limitation of recreational activities	.001
7. How often back pain makes patient miserable	.064
8. Initial Beck depression score	.759
9. Change in Beck depression score	.680
10. Overall evaluation of symptoms	.345
11. Overall evaluation of physical findings	.334

judged three other patients, all assigned to imipramine, as depressed also. Although the majority of the patients on imipramine had a negative value for their change in Beck depression scores, indicating a trend toward less depression, a linear relationship between serum imipramine and desipramine levels and the change in Beck depression scores was not noted.

Table 2 presents the results of the statistical analysis of the various clinical parameters between those patients on imipramine and those on placebo. As noted, except for the number of pain pills per day, there was either a statistically significant result or a result that approached statistical significance for imipramine over placebo for the seven questions that made up the back pain questionnaire. In addition, there was no statistically significant difference between those patients on imipramine and those on placebo with regard to the initial Beck depression score, the change in the Beck depression scores, and the overall evaluation of both symptoms and physical findings by the investigators.

The 21 patients on imipramine who completed the study were divided into 11 nonresponders and 10 responders on the basis of their sum scores on the back pain questionnaire. As noted in Table 3, there was no statistically significant difference in the initial Beck depression score and the number of positive findings on the initial physical examination. A result that approached statistical significance, however, was noted for the change in Beck depression scores between the two groups of patients. In addition, there was no statistically significant difference with regard to the serum imipramine and desipramine levels.

Discussion

Currently there are two major hypotheses regarding the mechanism whereby the tricyclic antidepressants relieve chronic pain. The first postulates a "direct" effect on pain mediating structures in the central nervous system, independent of any effect on depression. The other hypothesis invokes an "indirect" effect whereby the tricyclic antidepressant first relieves the depressive signs and symptoms that often accompany chronic pain, which in turn is followed by a presumed reduction in sensitivity to painful stimuli. There are studies in the literature to lend support to either hypothesis. With regard to chronic musculoskeletal pain, two studies have demonstrated a statistically significant therapeutic effect of imipramine over placebo.[6,7] These studies, however, did not at-

Table 3. Comparison of Nonresponders (n = 11) Versus Responders (n = 10) in Patients Taking Imipramine Completing the Study

Clinical Parameter	P Value
1. Initial Beck depression score	.36
2. Change in Beck depression scores	.057
3. Number of positive physical findings on the initial examination	.90
4. Imipramine levels	.85
5. Desipramine levels	.59

tempt to evaluate depression as a possible contributing factor. Jenkins et al did evaluate depression as a possible contributing factor in patients with low back pain in a double-blind placebo controlled trial.[8] There was no statistically significant result of imipramine over placebo with respect to low back pain, and psychologic testing showed no difference between drug and placebo. Nevertheless, several faults in methodology, including short duration (four weeks), subtherapeutic dosage (75 mg a day), and absence of plasma levels of imipramine and desipramine, raise doubts about the validity of these results.

It has been shown that imipramine, a tertiary amine, and desipramine, a secondary amine, have different central neuropharmacologic actions, with imipramine blocking the uptake of both serotonin and norepinephrine in central synapses, and desipramine primarily blocking the central uptake of norepinephrine, with little or no effect on the uptake of serotonin.[9] A review of the literature reveals that there exists a general consensus on the presence of a linear relationship between plasma levels of imipramine and desipramine and an antidepressant effect. For this reason, plasma levels of imipramine and desipramine were obtained during the course of this study. In those studies demonstrating a linear relationship between plasma levels of imipramine and desipramine and clinical efficacy, there was a homogenous patient population (ie, tricyclic responsive nondelusional endogenous depressed inpatients).[10,11] This study had a heterogenous outpatient population, with only 10 of 50 patients entering into the study judged clinically depressed by the investigators. This may account for the lack of a linear relationship between serum levels and therapeutic effect. In addition, age, smoking, and degree of protein binding have been reported to account for individual variation in plasma levels on the same dose[12] and may have been a possible contributing factor. Of interest is that the average plasma levels of imipramine and desipramine were approximately one half those noted in a study conducted by Oliver-Martin et al, in which the same dose (150 mg a day) was used in patients with endogenous depression whose improvement correlated significantly with plasma levels of imipramine and desipramine.[13]

The dropout rate of 10 percent (5 of 50 entered) that was due to side effects is consistent with that noted in previous studies, as is the incidence of various anticholinergic side effects.[14,15]

The number of patients entered into the study who were depressed by standard criteria[5] (7 of 50) is consistent with a study by Pilowsky et al, in which 10 percent of patients with chronic pain were diagnosed as depressed.[16] The low number of depressed patients in this study also probably accounts for the statistically insignificant difference in the change in Beck depression scores between those patients on the active drug and those on placebo.

Of interest is that, although most symptoms reported by patients were either statistically significant or approached statistical significance for the active drug over placebo, the evaluation of symptoms and physical findings by the investigators did not. The lack of a pure double-blind conduction

of this study may explain this discrepancy. For example, as part of the required informed consent, potential participants were told of all possible side effects, including the anticholinergic ones, that could result from tricyclic antidepressants. Thus, given the rather high incidence of such side effects, both patient and physician may have been aware of the use of the active drug with a possible subsequent alteration of the final results. The only way to correct for this would have been to use a placebo with similar anticholinergic side effects instead of the inert one employed.

The division of the active drug group into "nonresponders" and "responders" was arbitrary. Although there was no statistically significant difference in the initial Beck depression scores between these two groups, the difference in the change in Beck depression scores was close to statistical significance. Thus, even though only a small number of patients on the active drug were depressed (1 of the "responders" and none of the "nonresponders" according to the criteria of Beck et al, and 3 of the "responders" and 2 of the "nonresponders" were judged clinically depressed), as a group those who responded to the medication symptomatically had a greater change toward less depression in their Beck depression scores. It should be noted that the number of patients in this statistical comparison was low (10 and 11 "responders" and "nonresponders," respectively) and, as just noted, a greater number of "responders" than "nonresponders" were initially depressed. Nevertheless, these results indicate possible support for the "indirect" hypothesis of the mechanism of action of tricyclic antidepressants in patients with chronic low back pain.

These findings are somewhat consistent with those of Forrest and Wolkind, who showed that patients with back pain who were "poor responders" to conventional treatment were characterized by an unrecognized depressive syndrome described principally in somatic terms.[17] In addition, it has been estimated that 80 percent of back pain syndromes are due to a benign reversible psychosomatic process within the neck and back musculature, which has been variously described as fibrositis, myofibrositis, and myofascial pain.[18] Although the existence of this entity has been questioned by some authorities, the results of this study lend some support to this theory. Contrary to previous studies,[3] it is interesting that the "responders" in this study had more positive physical findings on the initial physical examination in comparison with the "nonresponders."

Although the results are not conclusive, they do indicate a possible role for imipramine in the treatment of chronic low back pain, especially so in those patients in whom it exists as a component of depression. Obviously, further well-designed studies are needed to determine whether tricyclic antidepressants will play an important part in the treatment of this common and often disabling and expensive malady.

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References

1. Russek AS: Medical and economic factors relating to compensable back injury. Arch Phys Med 36:316, 1955
2. Pheasant HC: Backache—Its nature, incidence, and cost. West J Med 126:330, 1977
3. Sternbach LH, Wolf MB: Traits of pain patients: The low back pain. Psychosomatics 14:226, 1973
4. Gringas M: A clinical trial of Tofranil in rheumatic pain in general practice. J Int Med Res 4:41, 1976
5. Beck AT, Ward CH, Mendelsen M: An inventory for measuring depression. Arch Gen Psychiatry 4:561, 1961
6. Glick EN: A clinical trial of Tofranil in osteoarthritis. J Int Med Res 4:20, 1976
7. Gringas M: A clinical trial of Tofranil in rheumatic pain in general practice. J Int Med Res 4:41, 1976
8. Jenkins DG, Ebbutt AF, Evans CD: Tofranil in the treatment of low back pain. J Int Med Res 4:29, 1976
9. Mass JW: Biogenic amines and depression—Biochemical and pharmacologic separation of two types of depression. Arch Gen Psychiatry 32:1357, 1975
10. Risch SC, Huey LV, Janowsky DS: Plasma levels of tricyclic antidepressants and clinical efficacy: Review of the literature. J Clin Psychiatry 40:58, 1979
11. Gram LF, Reisby N, Ibsen I, et al: Plasma levels and antidepressive effect of imipramine. Clin Pharmacol Ther 19:320, 1976
12. Glassman AH, Perel JM: The clinical pharmacology of imipramine. Arch Gen Psychiatry 28:649, 1973
13. Oliver-Martin R, Marzin D, Buschenschultz E, et al: Concentrations plasmatiques de limipramine et la desmethylimipramine et effet antidepresseur an cours d'un traitment. Psychopharmacologia 41:187, 1975
14. Logue JN, Sachais BA, Feishner JP: Comparisons of maprotiline with imipramine in severe depression: A multicenter controlled trial. J Clin Pharmacol 19:64, 1979
15. Roger W, Rickels K, Norstad N, et al: Maprotiline and imipramine in depressed inpatients: A controlled study. J Int Med Res 3:413, 1975
16. Pilowsky I, Chapman CR, Banica JJ: Pain, depression, and illness behavior in a pain clinic population. Pain 4:183, 1977
17. Forrest AJ, Wolkind SN: Masked depression in men with low back pain. Rheumatol Rehabil 13:148, 1974
18. Sarno JE: Psychosomatic backache. J Fam Pract 5: 353, 1977