A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures

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Abstract

Objective

To study the efficacy and tolerability of amitriptyline and nortriptyline in a Brazilian population with fibromyalgia and to evaluate the instruments used to measure the efficacy of the treatment.

Methods

A total of 118 fibromyalgia patients were randomly assigned to 3 groups: amitriptyline (AM, n = 40), nortriptyline (NOR, n = 38) and placebo (PL, n = 40), and were blindly given 25 mg at bedtime of the assigned treatment for 8 weeks. Clinical evaluation before and at the end of the study included the number of tender points (NTP), FIQ score (FIQ), and global improvement as reported by the patients on a verbal scale (VSGI).

Results

The 3 groups were comparable at baseline for all the parameters studied. After 8 weeks, the 3 groups improved in all parameters: (36.5% AM, 26.7% NOR and 24% PL patients improved on FIQ; 13.9% AM, 19.5% NOR and 8.57% PL patients improved on NTP; 86.5% AM, 72.2% NOR and 57.6% PL patients improved on VSGI). Only the AM group differed from the PL group on VSGI. Side effects were noted among the groups, but none were serious (16 in the AM group, 31 in the NOR group, and 25 in the PL group).

Conclusion

All three groups improved after treatment. Only the patient’s subjective global assessment of improvement differed between the AM patients and the PL group (p < 0.03). In fibromyalgia, placebo groups are important in drug trials. Different measures of therapeutic effect are not better than the patient’s self assessment.

Key words

Fibromyalgia, clinical trials, pain measures, treatment outcome.
Introduction
Fibromyalgia is a chronic painful syndrome characterized by diffuse pain and tender points on physical examination. In approximately 80% of patients fatigue and sleep disturbances are also prominent features, and in more than 25% migraine, irritable bowel disease and changes in psychological status such as anxiety and depression are present (1-3).

Pain sensation is the hallmark of fibromyalgia and is a subjective feeling, depending not only on the organic abnormalities of disease, but also on social, cultural and economic variables (4); hence, different treatment regimens could achieve different degrees of success in different populations.

Pharmacologic treatment of fibromyalgia has been disappointing. Amitriptyline and cyclobenzaprine, the most extensively studied drugs, have shown good results in 30-40% of patients, all of whom were of Anglo-Saxon origin. Other medications have been even less successful (alprazolam, etc.), and none has been tested in a random and controlled fashion in Latin American populations (5-8).

Nortriptyline, a highly specific inhibitor of noradrenaline re-uptake, could in theory represent a good therapeutic option for the treatment of fibromyalgia, as it is an active metabolite of amitriptyline with fewer side effects (9, 10). However, so far there have been no studies suggesting its effectiveness.

It is also important to note that the instruments used to measure "treatment success", as for example the analog pain scores, tender point scores, etc., vary widely in the literature, with no clear evidence of their relevance and statistical significance (4).

The objective of this study was therefore to evaluate the efficacy and tolerability of amitriptyline and nortriptyline in the treatment of Brazilian patients with fibromyalgia and to evaluate the different outcome measures used in this clinical trial.

Material and methods
Sample size
The visual analog scale for pain measurement contained in the FIQ was used to establish the size of the sample. A one-tailed test was used; = 5% and = 20%. In this study, a mean reduction in pain equal or superior to "3" (approximately ± 30% compared with placebo) was considered clinically significant. For the sample size calculation we presupposed that amitriptyline and nortriptyline would be equally effective. Based on these parameters, 35 patients per group were considered necessary to establish significant differences among the treatment groups (5, 7, 11-15).

Selection of patients
Patients were recruited from the outpatient unit of the Rheumatology Division of E.P.M – U.N.I.F.E.S.P. (School of Medicine – Federal University of São Paulo) between March 1992 and August 1996.

The following inclusion criteria were used: the patients had to be female, ≥18 years of age, meet the classification criteria for fibromyalgia ACR 1990 (16); and have read and signed the written informed consent. They must not have participated in another study using these medications within the past 6 months, and had to withdraw from all medications such as anxiolytics, neuroleptics and/or antidepressives and analgesic narcotics at least 4 weeks prior to the initiation of the study. Use of acetaminophen was permitted. The patients must not have used amitriptyline or nortriptyline in the past; must not be suffering from heart arrhythmia, heart, renal or hepatic impairment, glaucoma, urinary retention, hyperthyroidism or chronic inflammatory diseases.

The exclusion criteria were: concomitant use of anxiolytics, neuroleptics and antidepressant medications; pregnancy; and the start of physical rehabilitation for therapeutic purposes (physiotherapy, water aerobics, etc.) concomitant to the study initiation.

A total of 120 patients were selected, of whom 118 were randomized (there was an accidental loss of 2 bottles of medication) into 3 treatment groups: one group received amitriptyline 25 mg Q.D. (n=40 patients); another received nortriptyline 25 mg Q.D. (n=38...
Amitriptyline, nortriptyline and placebo were all prepared by Sandoz Laboratory in standard packages for all groups, thus guaranteeing that the study remained blinded both for the investigator and the patients. The randomization tables were supplied by the same laboratory. The patients were assessed on 2 occasions: at the screening visit and after 8 weeks of treatment.

To control compliance with the dosing regimen, patients were instructed to return the medication bottle at the end of the study (last visit). The research protocol was approved by the Ethics in Research Committee of the EPM-UNIFESP.

Clinical evaluation
Clinical evaluation of the patients was always performed by the same investigator at baseline and at the end of treatment. Demographic, clinical and laboratory data were obtained at the first visit.

On both visits, the number of tender points (NTP) was determined. The count was performed by means of digital palpation of each of the 9 pairs of tender points established as parameters by the ACR (16). For a tender point to be considered positive, the patient had to report pain on palpation. On both visits the “Fibromyalgia Impact Questionnaire” (FIQ) was also administered (17) in order to analyze the impact of the disease on the patient’s quality of life, applied in the form of an interview without the investigator interfering in the patient’s answers. We analyzed the variation of each FIQ item independently, instead of using other analog scales for measurement of the impact of treatment on different symptoms of the disease. For the verbal scale of global evaluation by the patient concerning his/her well-being (VSGI), a scale from 1 to 5 was used (1 = great improvement, 2 = moderate improvement, 3 = slight improvement, 4 = no improvement and 5 = worsening). This scale was applied at the end of the study. Side effects were registered at any point during the study and at the end.

Statistical analysis
The following analyses were carried out: descriptive statistics for the demographic and clinical variables (mean and SE for the continuous variables and frequency for the categorical variables); two-way ANOVA (group effect: placebo, amitriptyline and nortriptyline; time effect: pre- and post-treatment) for the comparison of the therapeutic effect measured by FIQ and TP; Student’s t-test to compare the values of FIQ initial and NTP initial between the 2 groups, formed according to the values obtained in the VSGI; the 2 test to evaluate the difference between the three study groups in the improvement measured by VSGI; Spearman’s correlation test to evaluate the correlation between the scales; and the 2 to evaluate whether the number of drop-outs and the number of side effects in each group influenced the results. A significance level of 5% was considered for all tests.

Results

Table I shows the demographic characteristics and the baseline clinical measurements for the 118 subjects studied. Mean variance analysis (ANOVA) demonstrated no significant differences regarding age (p = 0.1413), FIQ scores (p = 0.5182) and the number of tender points (p = 0.9909), confirming the homogeneity of the three treatment groups.

Table II highlights data relating to the analysis of the FIQ values in each group pre- and post-treatment. An improvement of 36.5% in the amitriptyline group, 26.6% in the nortriptyline group, and 24% in the placebo group was noted. Although the amitriptyline and nortriptyline groups presented a decrease in the FIQ scores and in the number of tender points in relation to the placebo group, this difference was not statistically significant.

The number of tender points pre- and post-treatment in each of the study groups is shown in Table III. There was a decrease of 19.5% in the number of tender points in patients receiving nortriptyline, 13.9% in patients receiving amitriptyline, and 8.6% in the placebo group. These results were...
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Table III. Number of tender points (NTP), in each group, pre- and post-treatment. Data are expressed as the mean ± 2 SE (standard error).

<table>
<thead>
<tr>
<th></th>
<th>Amitriptyline N = 37</th>
<th>Nortriptyline N = 36</th>
<th>Placebo N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>16.4 ± 0.3</td>
<td>16.3 ± 0.4</td>
<td>16.0 ± 0.3</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>14.2 ± 0.7*</td>
<td>13.3 ± 0.9*</td>
<td>14.7 ± 0.6*</td>
</tr>
</tbody>
</table>

*p < 0.05 different from the correspondent pre-treatment; ANOVA: group effect [F (2, 103) = 0.352; p = 0.704], time effect [F (1, 103) = 35.395; p < 0.001], interaction group vs time effect [F (2, 103) = 1.781; p = 0.173].

Table IV. Frequency distribution of patients (absolute and relative (%)) to the correspondent study group, according to the levels of the VSGI (Verbal evaluation Scale for Global Improvement).

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Amitriptyline N = 37</th>
<th>Nortriptyline N = 36</th>
<th>Placebo N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Great</td>
<td>5 (17.5%)</td>
<td>6 (16.6%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>17 (45.9%)</td>
<td>18 (50.0%)</td>
<td>12 (36.4%)</td>
</tr>
<tr>
<td>Slight</td>
<td>15 (41.7%)</td>
<td>14 (38.9%)</td>
<td>11 (33.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>31 (86.5%)</td>
<td>26 (72.2%)</td>
<td>18 (54.5%)</td>
</tr>
</tbody>
</table>

No improvement or worsening

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Amitriptyline N = 37</th>
<th>Nortriptyline N = 36</th>
<th>Placebo N = 33</th>
</tr>
</thead>
<tbody>
<tr>
<td>No improvement</td>
<td>5 (13.5%)</td>
<td>8 (22.2%)</td>
<td>10 (30.3%)</td>
</tr>
<tr>
<td>Worsening</td>
<td>0 (0%)</td>
<td>2 (5.6%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (13.5%)</td>
<td>10 (27.8%)</td>
<td>13 (39.3%)</td>
</tr>
</tbody>
</table>

Table V. Comparison of F.I.Q. and N.T.P initials values between the 2 groups formed according to the values obtained in the VSGI. Data are expressed as mean ± 2*SE (standard error).

<table>
<thead>
<tr>
<th>Improvement</th>
<th>F.I.Q. initial</th>
<th>N.T.P initial</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=78)</td>
<td>66.01 ± 3.26</td>
<td>16.03 ± 0.52</td>
</tr>
<tr>
<td>Comparison among groups (t test)</td>
<td>0.477 (p = 0.634)</td>
<td>1.281 (p = 0.203)</td>
</tr>
</tbody>
</table>

Discussion

The symptom of “pain” is defined as a subjective manifestation of discomfort involving physical, psychological and cultural dimensions, causing incapacitation and loss of quality of life, and always having a negative effect on the patient. This is particularly true in cases of sharp pain, and even more so in cases of chronic pain. The painful symptom being basically a subjective experience, however, its improvement with or without treatment will depend on the interaction of different dimensions on the sick individual, this being difficult to quantify. Different individuals within the varied populations could react to pain and its treatment in completely different ways.

When pain is the symptom of a disease with established tissue damage or when laboratory alterations and imaging allow the doctor to establish improvement parameters, the therapeutic effects may be measured by universal
standards. However, when pain is both a symptom and the disease, the analysis of the efficacy of therapeutics in different populations becomes indispensable.

Fibromyalgia is an example of a syndrome without histologic lesions or laboratory alterations; symptoms such as pain, fatigue and others constitute the disease itself. For this reason it was considered necessary to conduct a therapeutic study with Brazilian fibromyalgia patients in order to establish the efficacy of different medications in our population and also to determine the parameters to be used in quantifying the therapeutic action of those proving to be effective. Therefore, this is the first randomized, controlled, double-blind study conducted in Brazil, designed to evaluate the efficacy of two drugs in the treatment of fibromyalgia and to assess the methods used in measuring their efficacy.

Amitriptyline was chosen because it is the most frequently studied drug for the treatment of this syndrome, with positive results varying between 25% – 45% (5, 6, 18). Nortriptyline has never been studied in patients with fibromyalgia, which is curious since this drug is the metabolic amitriptyline active compound after hepatic metabolism (10), this being the reason for its inclusion in the present work.

The three treatment groups were similar as regards age and sex, as well as the parameters of intensity of fibromyalgia symptoms measured by means of the FIQ and number of tender points; therefore, randomization proved effective and the groups were comparable.

The number of tender points was chosen as one of the outcome measures since it is a form of evaluation widely used in studies (5-7, 11-14, 18-20) even though the relationship of this parameter to improvement or worsening of the clinical condition has not yet been proven. When dolorimetry scores are used, however, the increase or decrease in the pain threshold, as reported by the patient, cannot be considered clinically relevant in most cases.

Despite the FIQ not being validated in Brazil, it was used because it represents a structured instrument that measures several aspects of the diagnosis and its impact on the patient.

The subjective evaluation of well-being by the patient was taken into consideration because of the subjectivity of the fibromyalgia symptoms, since the patient is the only person who can report whether he/she feels better or worse. For this same reason an evaluation by the physician was not included, since we believe that the latter can only rely on a compilation of subjective data that are difficult to quantify.

The analysis of the results obtained from this study indicates that the difference among the 3 groups was not significant with regard to the number of tender points, the total FIQ scores, or the sub-scores pre- and post-treatment. However, on analyzing the verbal scale of global evaluation of the patient, the amitriptyline group showed a statistically significant improvement (P = 0.038), when compared to the placebo group.

It is important to point out that improvement was observed in all three groups (Tables II, III and IV), this being most evident in the patients’ evaluation and the rates being superior to those reported in the literature (6, 18, 19).

The high rate of improvement observed in the placebo group is probably one of the reasons why the other parameters were not statistically significant. The increase observed in the effect of
placebo may perhaps be reduced after a longer treatment period. The possibility that the size of our sample may have been insufficient does not seem probable, considering that in a review study of 24 therapeutic analyses (21) the average sample size was 51 patients, with only one study showing a sample size larger than ours.

There was a strong inverse correlation between the verbal scale of global evaluation and the difference in FIQ values, and a moderate inverse correlation with the number of tender points. However, these two parameters did not differentiate the groups receiving active medication; this was probably related to variability in the individual results of these instruments in the 3 groups, which demonstrated less sensitivity than the verbal scale. Another possibility could be that the FIQ would need longer periods of time to reveal small differences in the patients’ quality of life.

Neither the initial FIQ values nor the number of tender points were effective in predicting the therapeutic results. These results confirm the lack of correlation between the symptom of pain and painful palpation; it is common to find positive tender points on a physical examination while the patient is asymptomatic.

There were 12 drop-outs (10.17%) in this study, 7 in the placebo group, 3 in the amitriptyline group and 2 in the nortriptyline group. The number of drop-outs was smaller than those mentioned in other therapeutical studies on fibromyalgia (6,7,13,22,23) and did not influence the final result of the study, probably due to the short treatment period. Most outstanding was the frequency of certain side effects among the three groups (abdominal pain and heartburn, drowsiness, dizziness and nausea) and the unexpectedly larger incidence of side effects in the nortriptyline group in relation to the amitriptyline group, which could be attributed to the symptoms of the diagnosis itself. It is important to mention that no side effect was sufficiently serious to warrant an interruption of the treatment.

As this is the first assessment study of the efficacy of amitriptyline and nortriptyline to be conducted in a Brazilian population with fibromyalgia, we cannot disregard the possibility that the parameters used to measure the therapeuthic response were not sensitive enough to detect differences among the groups. Therefore, other studies will be necessary to define the best parameters to be used.

Conclusion

The efficacy of amitriptyline and nortriptyline was not superior to that of placebo except when analyzed by means of the verbal scale of global improvement evaluation by the patient. The FIQ and the number of tender points were not sufficiently sensitive instruments to detect changes in patients with fibromyalgia in our study; neither the FIQ nor the number of tender points at baseline were predictive markers. Our study demonstrates the need always to include a placebo group in randomized studies of fibromyalgia, due to the high rate of spontaneous improvement in controls.

References