Original Article

The Effects of Pre-Emptive Treatment of Postherpetic Neuralgia with Amitriptyline: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract
Seventy-two patients older than 60 years of age who received a diagnosis of herpes zoster (HZ) were entered into a randomized, double-blind, placebo-controlled trial of daily amitriptyline 25 mg. Treatment with either amitriptyline or placebo continued for 90 days after diagnosis. Pain prevalence at 6 months was the primary outcome. Results showed that early treatment with low-dose amitriptyline reduced pain prevalence by more than one-half (p < 0.05; odds ratio, 2.9:1) This finding makes a strong case for the pre-emptive administration of amitriptyline, in combination with an antiviral drug, to elderly patients with acute herpes zoster. J Pain Symptom Manage 1997;13:327-331.© U.S. Cancer Pain Relief Committee, 1997.

Key Words
Herpes zoster, amitriptyline, pre-emptive treatment, postherpetic neuralgia, shingles, acyclovir

Introduction
A previous survey of patients randomly accepted by referral from primary care for treatment of postherpetic neuralgia (PHN) at least 3 months post-rash suggested that early treatment with amitriptyline might be a useful pre-emptive therapy, reducing the prevalence of longstanding PHN. Specifically, an analysis of age-matched patients demonstrated that the likelihood of pain relief was significantly greater in patients with shorter intervals between onset of acute herpes zoster (HZ) and beginning of treatment with amitriptyline. Indeed, more than 75% of patients beginning amitriptyline between 3 and 6 months post-rash were relieved of their pain, compared to only 25% of those beginning amitriptyline 24 or more months post-rash.1,2 This finding led to the hypothesis that very early treatment with an appropriate antidepressant, beginning in the acute phase of HZ, might lead to an even greater shortening of the time during which pain was experienced. A controlled trial of early treatment with amitriptyline was performed to test this hypothesis.

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Accepted for publication: September 20, 1996.
### Methods

Numbered bottles containing 90 tablets consisting of either amitriptyline 25 mg or identical-looking placebo were supplied to the pharmacy at Walton Hospital. The key identifying which bottles contained amitriptyline and which placebo was in a sealed envelope, also kept in the hospital pharmacy. This envelope was opened when all trials had been completed and all follow-up data had been collected.

Eighty patients (39% male) older than 60 years of age with acute HZ ("shingles") were recruited by 39 general practitioners (GPs), each of whom had been randomly given some numbered bottles (four in the first instance). Provided the diagnosis was made within 48 hr of rash onset, the patient was given one of the numbered bottles and instructed to take one tablet every night until they were finished, that is, 90 days. The test was double-blind: neither the distributor (the author), the receivers (GPs), nor the patients knew what the bottles contained. The GPs were at liberty to treat the acute shingles however they thought best. It transpired that some GPs treated all cases of acute shingles in this age group with an antiviral (acyclovir), provided they were seen within 48 hr of rash onset, whereas others never used the drug, treating acute shingles only with conventional mild analgesics.

Participating GPs filled in a form on which was written the patient's name and address, date of birth, dates of onset and diagnosis of shingles, site of shingles, number of bottle issued, and manner in which the acute shingles was treated. Patients were told that this preparation was being used in order to try and minimize the after-effects of shingles (particularly PHN), and were asked to note (a) any side effects (they were warned about the possibility of dry mouth), and (b) how long their pain lasted. Between 6 and 8 months later, the patients were followed up by the author (usually by telephone; sometimes by letter) and specifically asked (a) whether they took all the tablets; (b) whether they had experienced any side effects other than dry mouth; (c) how long their "shingles pain" had lasted; and (d) what the pain felt like.

Results were compared using Chi square and Fisher's exact test, and odds ratio, all using Arcus software.

### Results

Data presented in this paper refer only to patients who averred that they had taken all tablets. Six patients (average age, 67.8 years) who had not, by their own admission, taken all the tablets thereby failed to complete the trial. Three of these patients had been given amitriptyline and three had been given placebo (Table 1). Two further patients were lost to follow-up, and are not included in this study, as it proved impossible to obtain further information about them from their GPs.

As stated above, some of the participating GPs prescribed acyclovir for all their elderly patients with shingles and others did not. In total, 26 patients received acyclovir, and 52 did not receive any antiviral treatment. There was no difference in any of the measured parameters between those receiving acyclovir and...
Table 2

Patients Commencing Amitriptyline or Placebo at Onset of Herpes Zoster

<table>
<thead>
<tr>
<th>n</th>
<th>Regimen</th>
<th>Pain lost by 1 month</th>
<th>Pain lost between 2 and 3 months</th>
<th>Cumulative total pain free at 3 months</th>
<th>Pain lost between 4 and 6 months</th>
<th>Cumulative total pain free at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>All amitriptyline</td>
<td>18(47%)</td>
<td>10(26%)</td>
<td>28(73.7%)</td>
<td>4(10.5%)</td>
<td>32(84.2%)</td>
</tr>
<tr>
<td>9</td>
<td>Amitriptyline + acyclovir</td>
<td>5(55%)</td>
<td>2(22%)</td>
<td>7(77.8%)</td>
<td>1(11%)</td>
<td>8(89%)</td>
</tr>
<tr>
<td>29</td>
<td>Amitriptyline only</td>
<td>13(45%)</td>
<td>8(27.5%)</td>
<td>21(72.4%)</td>
<td>3(10.3%)</td>
<td>24(82.75%)</td>
</tr>
<tr>
<td>34</td>
<td>All placebo</td>
<td>13(38%)</td>
<td>8(23.5%)</td>
<td>21(61.75%)</td>
<td>1(3%)</td>
<td>22(64.7%)</td>
</tr>
<tr>
<td>17</td>
<td>Placebo + acyclovir</td>
<td>3(17.6%)</td>
<td>5(29.4%)</td>
<td>8(47%)</td>
<td>1(6%)</td>
<td>9(53%)</td>
</tr>
</tbody>
</table>

Odds ratios for all amitriptyline versus all placebo pain free at 6 months, 2.9:1.
Chi² and Fisher’s exact test for all amitriptyline versus all placebo pain free at 6 months, 0.05.

Discussion

The differences in the proportions of patients who were pain free at 6 months would not be altered by taking into consideration the six patients who failed to complete the course (Table 1), because they are equally divided between the acyclovir and no-acyclovir groups, and one from each group was still in pain at 6 months. The results strongly suggest that early treatment of older patients with acute HZ using low-dose amitriptyline reduces the long-term prevalence of PHN.

Four studies have shown that the prevalence of pain at more than 6 months is no different in acyclovir-treated and non-acyclovir-treated groups. In the present study, only 22% of the amitriptyline group and 50% of the placebo group were given acyclovir. There was no evidence in the GPs’ documentation that the patients who received amitriptyline had more severe HZ than those who did not, or differed from them in any other way, and there were no significant differences between the acyclovir and no acyclovir subgroups in terms of pain duration (Table 2). This latter finding was also noted in a previous survey. It would,
therefore, appear that acyclovir treatment did not influence the effect of early amitriptyline administration on pain presence or absence at 6 months. It should be pointed out, however, that patients who receive an antidepressant more than 6 months after acute HZ may be more likely to experience pain relief if the acute HZ had been treated with acyclovir. To this very important benefit may be added the observation that systemic acyclovir administered within the appropriate time window for the relief of acute HZ also limits the appearance of scars. This occurs in all patients, including those who go on to develop PHN—37.5% of whom, in the author’s total PHN patient population, are afflicted on the face or neck.

In the literature, estimates of the proportion of elderly HZ patients who had not received amitriptyline and were still in pain at 6 months or more vary widely—from a low of 5%\(^\text{10}\) to a high of more than 40%\(^\text{11}\) at 1 year. The figure derived from the placebo group in the present trial (35%) is at the higher end, nearly three times the figure (13.2%) reported by McKendrick et al., based on a survey of 317 patients. Even if the actual figure is lower than that observed in the present study, the need to identify a therapy that can effectively reduce the long-term prevalence of PHN is clear.

This controlled trial suggests that low-dose amitriptyline (25 mg) can reduce the prevalence of PHN at 6 months after acute shingles by more than one-half (15.8% versus 35.3% still in pain). The proportion of patients in this trial who received low-dose amitriptyline but were, nevertheless, still in pain at 6 months is not insubstantial. Because the analgesic action of amitriptyline may be dose dependent (although this is denied by some\(^\text{13}\)), higher doses should be evaluated. In the clinical setting, it might prove beneficial to recommend an increase in dose at an early stage for those still in pain after 6 weeks or so.

In conclusion, a case has been made for the immediate treatment of all cases of HZ in the elderly with acyclovir (or other effective antiviral agent) and low-dose (10 or 25 mg) amitriptyline. Further studies are needed to confirm this finding, evaluate other doses, clarify the benefits and risks associated with alternative drugs, and determine the optimal length of therapy.

Acknowledgment

The author is grateful to the doctors who collaborated in this double-blind prophylactic trial, particularly to Dr. J. Holden, who entered 14 patients; to Merck, Sharpe, and Dohm Ltd., who kindly provided and numbered the bottles containing 25-amitriptyline tablets or identical-looking placebo; to the pharmacy at Walton Hospital, Liverpool, who kept the code and issued the bottles; to colleagues and nursing staff in the Centre for Pain Relief at Walton Hospital, and particularly to Mrs. Brenda Hall who kept records and relocated case sheets for the composition of this article.

The Wellcome Foundation Ltd. kindly provided some financial support toward the project, but the bulk came from the Trustees of the Pain Relief Foundation.

References