TOPIRAMATE VS AMITRIPTYLINE ON DIABETIC PERIPHERAL NEUROPATHIC PAIN

Based on a poster presented by López-Trigo J,* Serra J,† Ortiz P,* Sancho J†

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Neuropathic pain is a complex entity that encompasses diverse etiologies, pathophysiologies, and clinical symptoms. Although neuropathic pain is commonly encountered in neurology practice, it is often difficult to treat.

Tricyclic antidepressants are currently the best documented agents for the treatment of neuropathic pain, with efficacy against continuous burning or shooting pain and stimulus-induced allodynia. While the exact mechanism of action of these agents is not known, the agents are known to block the inactivation of norepinephrine and, to varying degrees, the inactivation of serotonin, primarily by blocking their reuptake into the nerve terminal. There is also evidence that tricyclic antidepressants may have a direct effect on the transport of these neurotransmitters.

Topiramate, a new antiepileptic drug that has been shown to be effective in the treatment of migraine, has in vitro activity against voltage-sensitive sodium and calcium currents, as well as GABAergic and antiglutamatergic properties. Some of these mechanisms have been implicated in the pathophysiology of neuropathic pain.

To ascertain whether topiramate is useful in the treatment of neuropathic pain, the investigators designed a study to assess the efficacy, safety, and tolerability of a tricyclic antidepressant, amitriptyline, and topiramate in patients with painful diabetic neuropathy.

Study Design and Patient Population

The open-label, 12-month cohort study involved 40 patients from 2 centers. Patients were treated with either topiramate 200-400 mg/day (n = 20) or amitriptyline 25-75 mg/day (n = 20). Concomitant use of nonopioid analgesics was allowed during the course of study.

Planned evaluations were scheduled at 1, 3, 6, 9, and 12 months. Pain was assessed by the 10-point Visual Analog Scale (VAS) for maximum intensity and daily average intensity, by the Interference With (IWS) scale, and by the Clinical Global Impression (CGI) scale. Safety and adverse events were monitored and classified as either mild (no need for dose adjustment or drug change), moderate (need for a drug change or an additional medication to control the adverse event), or severe (need to withdraw from the study).

All 40 patients had distal symmetric sensory diabetic polyneuropathy with or without autonomic involvement and chronic pain symptomatology, a history of neuropathic pain for at least 5 years prior to study entry, and no previous treatment with either amitriptyline or topiramate. VAS scores were measured for 2 weeks prior to study entry and were at least 7 at baseline. Demographic characteristics were similar in both groups.

Results

An improvement in all efficacy scales was noted in both groups, with maximal improvement reached...
during the third month of treatment. Median VAS scores of maximal pain intensity were similar in the 2 cohorts. Scores assessed at 3-month and 12-month visits were roughly equal in both groups, indicating that tolerance to the analgesic effects of amitriptyline and topiramate had not developed.

More improvement in the IW S scale scores was noted in the group receiving topiramate, who reflected better pain relief at night with this agent. More somnolence was noted in the patients receiving amitriptyline, who had less pain relief at night than those receiving topiramate.

Patient CGI scale scores were numerically superior in the topiramate group at 6 months, with 7 of 20 patients reporting much or moderate improvement as compared with 4 of 20 patients in the amitriptyline group. At 12 months, 10 of the 20 patients receiving topiramate reported much improvement, as compared with 7 of the 20 patients in the amitriptyline group. Patient CGI scale scores were similar to the clinician CGI scale scores, which reflected much or moderate improvement at the end of the study in 11 of the 20 patients receiving topiramate and in 7 of the 20 patients receiving amitriptyline.

Conclusion

In this study, both amitriptyline and topiramate were effective in controlling neuropathic pain, with beneficial effects sustained throughout the 12-month study period. Improved sleep was also noted in both groups, although greater improvement was seen in patients receiving topiramate.

Although somnolence was the most common adverse event reported in both groups, it was more frequent in those patients receiving amitriptyline. In general, adverse events were less severe in the group receiving topiramate.

While the results of this study are promising, further research is needed to clarify the potential role of topiramate as a treatment of neuropathic pain.

Double-Blind Randomized Trial of Bupropion Sustained Release for the Treatment of Neuropathic Pain

Based on a poster presented by Semenchuk MR,* Sherman S,* Davis B†
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Two case reports concluding that immediate-release bupropion was effective in nondepressed patients with chronic low back pain of undetermined origin1 and a small open-label trial suggesting that sustained-release bupropion was effective and well tolerated in patients with neuropathic pain2 prompted the investigators to undertake a trial comparing sustained-release bupropion with placebo in nondepressed patients with neuropathic pain.

Patient Population

Adults with daily neuropathic pain persisting for at least 3 months were recruited from the outpatient departments of both the Neurology Clinic and the Pain Clinic at the University of Arizona. Clinical diagnosis of neuropathic pain was documented by the patient's signs and symptoms—ie, pain, paresthesia, dysesthesia, numbness—and by electromyographic and nerve-conduction velocity testing when appropriate. Patients with a diagnosis of depression (Hamilton Depression Rating Scale scores above 11), seizure disorders, bulimia, or anorexia nervosa were excluded.

The 41 patients enrolled in the study presented with a variety of neuropathic pain syndromes, including peripheral neuropathy, axonal degenerative neuropathy, diabetic neuropathy, and neuropathy secondary to gammopathy. The median age of the 19 men and 22 women was 60 years (range, 23-88 years). The median duration of neuropathic pain was 4 years, suggesting that spontaneous resolution of pain during the 3 months of the study was unlikely.

Study Design and Assessments

The 12-week study consisted of 2 treatment periods of 6 weeks each, in which patients received identical tablets of sustained-release bupropion 150 mg or placebo in random order without an intervening
washout period. Placebo was followed by active treatment in 22 patients, while active treatment was followed by placebo in 19 patients.

Therapy was initiated with 150 mg once daily for 1 week and then escalated to 150 mg twice a day for 5 weeks. Patients who could not tolerate dose escalation or who became pain-free on 150 mg once a day were maintained on that dose. The use of additional analgesic agents was permitted if the patient was already taking such medication and if the dose regimen remained constant throughout the study.

Pain assessment instruments included the Wisconsin Brief Pain Inventory (WBPI) and the patient global assessment at baseline and at week 6 of each treatment period. Also included was a daily pain diary in which patients rated their pain on a daily basis using the zero-to-10 Visual Analog Scale in which zero indicates no pain and 10 indicates pain as bad as you can imagine.

The 10-point WBPI scale, with zero indicating no pain and 10 indicating pain as bad as you can imagine, was used to assess pain intensity at its worst, least, on average, and at the time of assessment (“right now”). It was also used, with zero indicating “not at all” and 10 indicating “extreme,” to assess the effect of the patient’s pain on various quality-of-life measures, such as general activity, mood, walking or moving around, ability to work, relations with people, sleep, and enjoyment of life.

Using the patient global assessment, patients made global ratings of their pain relief according to a 5-step categorical scale: pain worsened, pain unchanged, pain improved, pain much improved, pain-free.

Statistical Analysis

Mean average pain scores were determined each week, with the comparison of the mean scores for weeks 1 to 6 in the treatment and placebo groups being the primary outcome measure. These scores were compared with baseline using a paired, 2-tailed t test. Baseline scores were obtained by having patients rate their pain on average for the week before starting the study drug or placebo. Analysis of variance methods were used to examine period effect and treatment times period interaction scores for week 6.

Reductions in pain scores were calculated by subtracting the mean average pain score for each of the weeks in question from the mean average pain score at baseline. A paired, 2-tailed t test was used to compare WBPI scores for week 6 by each period, and a chi-square test was used for patient global ratings of pain relief categories. All analyses were done using the last observation carried forward.

Results

For the primary outcome measure of this study (mean pain intensity scores in week 6), a within-patient comparison showed that sustained-release bupropion was superior to placebo ($P < 0.001$). A within-patient comparison of the treatments for all 41 patients also demonstrated an analgesic effect of sustained-release bupropion for weeks 2 ($P < 0.05$) through 6 ($P < 0.001$), with no significant difference noted in the between-patient comparison.

Using the global descriptors of pain relief, 73% of the patients in the study reported their pain was improved or much improved after 6 weeks of therapy with sustained-release bupropion, a significant change from baseline ($P < 0.001$). A comparison of mean WBPI scores revealed significant improvements in quality-of-life measures at week 6 while patients were receiving bupropion compared with placebo.

Of the 41 patients in the study, 4 discontinued the study early—2 because of adverse effects (1 for nausea, 1 for dizziness) and 2 because of unrelated medical problems. The most frequently reported adverse effects while receiving bupropion included dry mouth (37%), insomnia (20%), headache (20%), gastrointestinal upset (17%), tremor (15%), constipation (15%), and dizziness (15%). These symptoms were rated as mild and tended to lessen with continuation of therapy.

Conclusion

The findings of this randomized, placebo-controlled trial provide additional evidence that 150 mg to 300 mg of sustained-release bupropion daily may be an effective treatment for neuropathic pain. Large-scale multicenter comparator studies are needed to extend the generalizability of these results.

REFERENCES

LEVETIRACETAM: NOVEL AGENT FOR REFRACTORY NEUROPATHIC PAIN

Based on a poster presented by Krusz JC*
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Levetiracetam, a new anticonvulsant with an unknown mechanism of action, has recently been shown to be effective in the treatment of refractory migraines and other headaches. Since the concepts of wind-up, kindling, and central sensitization are common to both headache disorders and neuropathic pain, the finding that levetiracetam was effective in refractory headache prompted an investigation into its effects in patients with chronic neuropathic pain, particularly those patients who had failed to respond to prior treatment with anticonvulsant agents.

PATIENT POPULATION AND DOSING REGIMENS

The 20 patients participating in this preliminary open-label study were selected from a chronic pain clinic. The majority of patients (n = 14) had failed to respond to therapy with 1 or more anticonvulsant agents, and 10 patients were on such therapy at the start of treatment with levetiracetam. The average duration of chronic painful symptoms was 6.2 years, and the average daily pain score on a zero-to-10 numeric rating scale was 7. The origins of neuropathic pain in this group of patients are listed in the Table.

Levetiracetam therapy was initiated at a dose of 250 mg in the evening for 5 days, with increases of 250 mg to about 2000 mg in 2 or 3 divided doses per day. Following a stable period on a titrated dose, additional titration was increased, ranging from 4000 mg/day to 5000 mg/day. Doses ranged from 1500 mg/day to 6000 mg/day, with the latter being the highest dose used in any patient in this study.

Results

After 3 months of therapy with levetiracetam (including 1 month of titration), 7 patients reported an average reduction in pain score of 76%, 3 patients reported an average reduction of 25% to 50%, and 2 patients reported an average reduction of less than 25%.

Two patients discontinued the drug because of adverse effects: 1 for nausea and 1 for extreme drowsiness. One patient was lost to follow-up and 7 are currently in the early titration phase.

Conclusion

In this small preliminary study, levetiracetam appears to be effective in reducing refractory chronic neuropathic pain in a difficult-to-treat population of patients with pain.

Although the drug's exact mechanism of action is not known at this time, it appears to be at least as effective as other older agents with known activity against neuropathic pain. In addition, levetiracetam appears to be safe over a wide dosing range. However, double-blind studies are needed to replicate and extend the observations in this study.

Table. Origins of Neuropathic Pain in the Study Population (n=20)

<table>
<thead>
<tr>
<th>Origin</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed neck or back surgery syndrome with ongoing radicular pain</td>
<td>8</td>
</tr>
<tr>
<td>Known structural disc disease with herniation or protrusion causing shooting, burning, or piercing pain</td>
<td>5</td>
</tr>
<tr>
<td>Features of complex regional pain syndrome, type 1</td>
<td>3</td>
</tr>
<tr>
<td>Post-herpetic neuralgia</td>
<td>1</td>
</tr>
<tr>
<td>Post-stroke pain</td>
<td>1</td>
</tr>
<tr>
<td>Failed carpal tunnel surgery with residual painful symptoms in the hand and arms</td>
<td>2</td>
</tr>
</tbody>
</table>