Topiramate for Phantom Limb Pain: A Time-Series Analysis

R. Norman Harden, MD, Tim T. Houle, PhD, Thomas A. Remble, MS, Wendy Lin, MD, Kenten Wang, DO, and Samuel Saltz, DO

Center for Pain Studies, Rehabilitation Institute of Chicago/Northwestern University Medical School, Chicago, Illinois, USA

ABSTRACT

There is growing evidence of topiramate’s efficacy in treating neuropathic pain. This article reports a detailed analysis of the response of four amputee subjects with phantom limb pain. Individual time-series analyses revealed that three out of four amputee participants receiving topiramate had statistically significant decreases in pain, with the peak effect noted at 800 mg daily. This analysis supports a hypothesis that topiramate may be effective in reducing phantom limb pain, and suggests a definitive study is indicated.

Key Words. Phantom Pain; Topiramate; Antiepileptics; Time-Series Analysis

Introduction

Phantom limb pain (PLP) has been reported to occur in up to 85% of amputees [1]. The exact physiological mechanisms that produce PLP are not well understood and consequently a strategy for medical management is difficult to develop. Pharmacological therapies studied in the past include antidepressants and/or anticonvulsants such as amitriptyline, nortriptyline, and carbamazepine [2]. Limitations of these pharmacological therapies for some patients include inconsistent pain relief, lack of improvement in daily function, and intolerable side-effects [3].

Topiramate is an anticonvulsant that has been reported to relieve neuropathic pain [3-5]. This medication is a gamma-aminobutyric acid (GABA) agonist, sodium channel blocker, and kainate antagonist [6,7]. Each of these mechanisms has been hypothesized to alleviate neuropathic pain [4,5], and thus may be helpful in reducing PLP.

The following case series describes a detailed analysis of four amputee subjects with PLP who received topiramate.

Four PLP subjects were treated during a larger prospective, double-blind, randomized, placebo-controlled, Institutional Review Board (IRB)-approved, pilot study conducted to test the efficacy of topiramate in managing various neuropathic pain conditions associated with rehabilitation (see [8] for spinal cord-injured subjects and detail of study design). Thus, the present case series is in effect a combination design: subjects and investigators were blinded to the drug condition (like a controlled study), yet subjects were analyzed individually (like a case study).

Methods

Subjects

No participants had hepatic or renal impairment, a history of kidney stones, present use of carbonic anhydrase inhibitors, or significant clinical depression. The following is a brief summary of the four participants:

Participant 124 was a 51-year-old African American male with a traumatic bilateral below knee amputation. At baseline he described the intensity of the pain as “mild.” He further...
described the quality of the pain as “heavy,” “sharp,” and “tender.” He reported a 6-year history of pain that began immediately after his amputation. Comorbidities were a history of ethyl alcohol (ETHOH) abuse with moderate elevation of liver function tests, and hypertension; there were no other Axis-I psychiatric comorbidities.

**Participant 131** was a 39-year-old white male with a vascular left below knee amputation. At baseline he described the intensity of the pain as “discomforting.” He further described the quality of the pain as “stabbing,” “sharp,” and “shooting.” His 5-year history of pain also reportedly began immediately after his amputation 5 years prior. Comorbidities were noninsulin-dependent diabetes, peripheral vascular disease, hypertension, and Hodgkin’s lymphoma; there were no Axis-I psychiatric comorbidities.

**Participant 123** was a 65-year-old African American male with a vascular left below knee amputation. At baseline he described the intensity of his PLP as “mild.” He further described the quality of the pain as “stabbing” or “sharp.” He reported a 4-year history of pain that began immediately after his amputation. Comorbidities were hypertension and insulin-dependent diabetes; there were no Axis-I psychiatric comorbidities.

**Participant 120** was a 43-year-old Hispanic male with a vascular bilateral left below knee amputation. At baseline he described the intensity of his PLP as “Horrible.” He further described the quality of the pain as “stabbing,” “sharp,” and “cramping.” He reported a 2-year history of pain that began immediately after his amputation. Comorbidities were insulin-dependent diabetes and hypercholesterolemia; there were no Axis-I psychiatric comorbidities.

**Statistical Analysis**

Statistical analyses were carried out using the SPSS for Windows statistical package (SPSS Inc., Chicago, IL). To identify the comparative effects of the drug over time, the VASs of the participant’s daily diary were modeled using a time-series regression analysis. After examination for outliers, daily pain scores were regressed on dosage levels. To better ensure the validity of the inferential statistics, potential autocorrelation was identified and where present, a first-order autoregressive error process was included to correct for the dependency in the residuals. Treatment changes from baseline were modeled using an abrupt, permanent intervention parameter (orthogonal dummy coding for levels of dose). This statistical technique allows each subject to be their own control,
with pain at various dosage levels being compared with pain at their baseline before medication was introduced. In this way, each subject's pain over time can be examined for dose-related changes.

**Results**

Violations in medication compliance and rescue medication use did not play a statistically significant role in any participant's pain reporting. The following is a summary of the four participants.

**Participant 124**

This participant reported statistically consistent decreases in VAS pain intensity, as compared with baseline, beginning immediately at the 25–50 mg dose levels and continuing to the final weeks at the 800 mg dose (see Figure 1). Although the greatest pain relief (97% reduction) occurred at the final week at 800 mg ($P < 0.05$ vs baseline), the difference between this dose and the previous doses was not statistically significant. This participant's low levels of reported pain at baseline (mean = 15) perhaps played a role in the low-dose response/effect of the medication.

**Participant 131**

This participant reported a profound decrease (80% reduction) in VAS pain intensity at the 25–50 mg dose levels only to report pain levels consistent with their baseline pain over the next few weeks (and corresponding increases in dose) (see Figure 1). Statistically consistent pain reduction, as compared with baseline, was reported at the 700–800 mg dose levels continuing to the end of treatment. Pain relief appeared to plateau during the final weeks of treatment at the 800 mg dose levels, averaging 36% pain reduction from baseline.

**Participant 123**

This participant did not report statistical changes in VAS pain intensity over any of the doses (see Figure 1). He complied with the drug regimen and used a consistent amount of rescue medication. At the end of treatment, subject 123's VAS scores were statistically equivalent to their baseline values (mean = 16.7 vs mean = 21.3).

**Participant 120**

This participant showed statistically significant decreases in pain intensity as compared with baseline at the 300–400 mg dose level (70% reduction). However, statistically consistent pain reduction, as compared with baseline, was not observed until the 700–800 mg dose levels and continued to the end treatment (see Figure 1).

**Discussion**

This case series analyzed by time-series methodology describes the use of topiramate in treating...
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PLP. Three of four subjects showed a significant decrease in pain at some dose level. However, consistent decreases in pain were not seen until the 800 mg dose level in two of the three responders, indicating a potential dose-related response. The three subjects who responded had experienced over 2 years of refractory PLP that was significantly reduced after treatment with topiramate.

All our subjects had relatively mild residual limb pain: severe residual limb pain might obfuscate results because subjects may tend to “average” the two types of pain and its response to treatment. This pain subset should be considered in any definitive trial because significant residual limb pain would be a treatment target, and perhaps a differentially responsive target. The mechanistic distinction, if any, between these two types of postamputation pain is still unclear.

Conclusions

These case series support the hypothesis that topiramate may be useful in the management of PLP, and identifies this compound as a bona fide candidate for definitive study. Specifically, longer duration, randomized, properly powered, placebo-controlled trials in PLP should be conducted to better assess the efficacy of the drug at different dose levels. It appears that the drug was safe and well tolerated in these subjects, even at high doses (800 mg). Although there have been published reports of topiramate induced acute myopia occurring within the first 4 weeks of treatment and uric acid stones [10], none of the participants in this 14-week study reported these side-effects. However, any definitive studies with topiramate should monitor carefully for this and any of the other known side-effects.

References