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Levetiracetam in the Preventive Treatment of Transformed Migraine: A Prospective, Open-Label, Pilot Study

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ABSTRACT

Background: Most preventive agents used for transformed migraine (TM) have not been studied specifically for the treatment of this syndrome. Open-label trials have demonstrated the effectiveness of levetiracetam in the treatment of refractory headaches.

Objective: The aim of this study was to assess the effectiveness and tolerability of levetiracetam in the preventive treatment of refractory TM.

Methods: This prospective, open-label, pilot study was conducted at The New England Center for Headache, Stamford, Connecticut. We included patients aged ≥18 years with refractory TM according to the criteria proposed by Silberstein et al. All participants had failed on at least 1 but not more than 3 preventive drugs. Other preventive drugs were allowed if they had been received at a stable dose for >30 days. The dosage of the levetiracetam tablets ranged from 1000 to 3000 mg/d in 2 divided doses. The treatment phase lasted 3 months. The primary end point was headache frequency (expressed as the number of headache days per month), and the secondary end point was the frequency of moderate or severe headache (d/mo). Other end points were headache score, Migraine Disability Assessment (MIDAS) Questionnaire score, and Headache Impact Test (HIT-6) score. Statistical analyses were performed in the intent-to-treat (ITT) population (patients who received at least 1 dose of study medication) using data subjected to the last-observation-carried-forward algorithm. We also conducted per-protocol (PP) analyses in patients who completed the study.

Results: The ITT population consisted of 36 patients (26 women, 10 men; mean [SD] age, 46.5 [17.4] years). The mean headache frequency at baseline was 24.9 d/mo, and a significant reduction in headache frequency was obtained at 1, 2, and 3 months of treatment (19.4, 18.4, and 16.2 d/mo, respectively; all, $P < 0.001$

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vs baseline). At baseline, the mean number of moderate or severe headache days was 16.8 d/mo compared with 13.2, 11.9, and 9.7 d/mo at 1, 2, and 3 months, respectively (P = NS, <0.01, and <0.01, respectively). The mean MIDAS score was significantly reduced at 3 months compared with baseline (40.8 vs 62.8 d/mo; $P = 0.01$). The mean HIT-6 score was 59.4 at 3 months versus 63.4 at baseline ($P < 0.01$). In the PP population, the mean (SD) headache frequency was reduced from 26.1 (4.1) d/mo at baseline to 14.3 (4.8) d/mo at the end of the study ($P < 0.001$). The mean (SD) headache score was reduced from 51.3 (17.1) at baseline to 34.0 (22.0) at 3 months ($P < 0.016$).

Conclusion: The results of this study in patients with TM support the role of levetiracetam in the preventive treatment of refractory TM. (*Curr Ther Res Clin Exp.* 2005;66:212–221)

Key words: levetiracetam, transformed migraine, chronic daily headache, preventive treatment, prevention.

INTRODUCTION

Transformed migraine (TM) is the most frequent subtype of chronic daily headache (CDH) seen in headache clinics.[1–3] Most patients with TM have a history of episodic migraine, reporting a process of transformation characterized by an increase in headache frequency over months to years, with the associated symptoms becoming less severe. Patients then develop a pattern of daily or near-daily headache, the phenomenology of which may resemble that of chronic tension-type headache, with a few attacks of full-blown migraine superimposed.[4]

The pharmacologic treatment of TM poses a challenge to the physician. Most preventive agents used for TM have not been examined specifically for the treatment of this syndrome; they are used empirically based on their efficacy in the treatment of episodic migraine.[5]

Neuromodulators are frequently used in the preventive treatment of migraine[5,6] and TM.[6,7] Multiple threads of research over the past 15 years have led to the concept that migraine is generated from a hyperexcitable brain.[8,9] Although we do not know whether migraine is generated in the cortex or brainstem, one possible scenario includes a cascade of events beginning with either brainstem or cortical activation followed by the other, leading to activation of ascending and descending pathways, with initiation of perimeningeal vasodilatation and neurogenic inflammation, and, ultimately, central sensitization.[10,11] From a theoretical perspective, the efficacy of neuromodulators in the preventive treatment of migraine may correlate with their neuronal stabilization properties.

Levetiracetam is an anticonvulsant medication with an incompletely understood mechanism of action.[12] Its use has been approved in the United States and Europe for the treatment of epilepsy. Case series have suggested the effectiveness of levetiracetam in the treatment of refractory headache.[13,14] However, levetiracetam has not been specifically studied in the treatment of TM. Therefore, the aim of this study was to prospectively assess the effec-

tiveness and tolerability of levetiracetam in the preventive treatment of refractory TM.

PATIENTS AND METHODS

This prospective, open-label, pilot study was conducted at The New England Center for Headache, Stamford, Connecticut. Inclusion and exclusion criteria were as follows: (1) age ≥18 years; (2) a diagnosis of TM with or without medication overuse, according to the criteria proposed by Silberstein et al[4]; (3) previous failure on at least 1 but no more than 3 preventive drugs; (4) previous failure with no more than 1 antiepileptic drug used in therapeutic migraine doses for an adequate time period; (5) a stable dose of preventive medication for at least 1 month (other preventive drugs were allowed if a stable dose had been used for >30 days); and (6) no use of other antiepileptic drugs within the previous 30 days.

There was a 1-month baseline observation period, and information was collected prospectively using headache calendars. After the baseline period, levetiracetam was started at 250 mg hs and increased by 250 mg every 5 days up to a dose of 1000 mg hs. After the dose adjustment (second month), the dose could be increased further over the next 2 weeks up to a total dosage of 3000 mg/d in 2 divided doses. The treatment phase lasted 3 months (1 month of adjustment and 2 months of stable dosing).

Headache information was collected using headache calendars. Disability was assessed using the Migraine Disability Assessment (MIDAS) Questionnaire[15] (scale: 0–5 = grade I [minimal or infrequent disability]; 6–10 = grade II [mild or infrequent disability]; 11–20 = grade III [moderate disability]; and ≥ 21 = grade IV [severe disability]) and the Headache Impact Test (HIT-6) version 1.1[16] (scale: 38–49 = little or no impact on patient's life; 50–55 = some impact; 56–59 = substantial impact; 60–78 = very severe impact).

The primary end point was headache frequency (ie, the number of headache days per month), and the secondary end point was the number of days with moderate or severe headache (d/mo). Other end points included headache score (frequency multiplied by severity assessed on a 4-point scale [0 = no pain to 3 = severe pain]), and MIDAS[15] and HIT-6[16] scores.

Patients were instructed to return for monthly follow-up. At all visits, patients were specifically asked whether they had experienced any unexpected symptoms or signs. *Adverse events* (AEs) were defined as any untoward medical occurrences during the study, regardless of causal relationship with the treatment. These included any occurrence that was new in onset or aggravated in severity or frequency from the baseline condition.

Statistical Analysis

Statistical analyses were performed in the intent-to-treat (ITT) population (patients who received at least 1 dose of study medication) using data subjected to the last-observation-carried-forward algorithm. We also conducted per-

protocol analyses in patients who completed the study. To compare data from several time points, we used 1-way analysis of variance after normality testing. Data were compared with the paired *t* test, assuming a 5% 2-tailed significance level. Our study was powered at 80% to detect a 30% difference using matching comparisons at the 5% level.

This study protocol received institutional review board approval prior to the initiation of the study. All participants signed an institutional review board–approved informed-consent form.

RESULTS

The ITT population consisted of 36 patients (26 women, 10 men; mean [SD] age, 46.5 [17.4] years) (**Table I**). Twenty patients (55.6%) completed the study; 8 (22.2%) withdrew because of AEs, 5 (13.9%) withdrew consent, and 3 (8.3%) were lost to follow-up (**Figure 1**).

Table I. Baseline demographic and clinical characteristics of the study population (N = 36).

Characteristic	Value
Age, mean (SD), y	46.5 (17.4)
Sex, no. (%)	
Female	26 (72.2)
Male	10 (27.8)
Race, no. (%)*	
White	25 (69.4)
Black	7 (19.4)
Other†	4 (11.2)
Preventive medication, no. (%)	
None	11 (30.6)
Propranolol	11 (30.6)
Amitriptyline	10 (27.8)
Nortriptyline	9 (25.0)
Verapamil	3 (8.3)
Candesartan	3 (8.3)
Nadolol	2 (5.6)
Other‡	5 (13.9)

*Percentages do not total 100 due to rounding.
†Includes Hispanic and not specified.
‡Includes magnesium, riboflavin, coenzyme Q10, flunarizine, and venlafaxine.

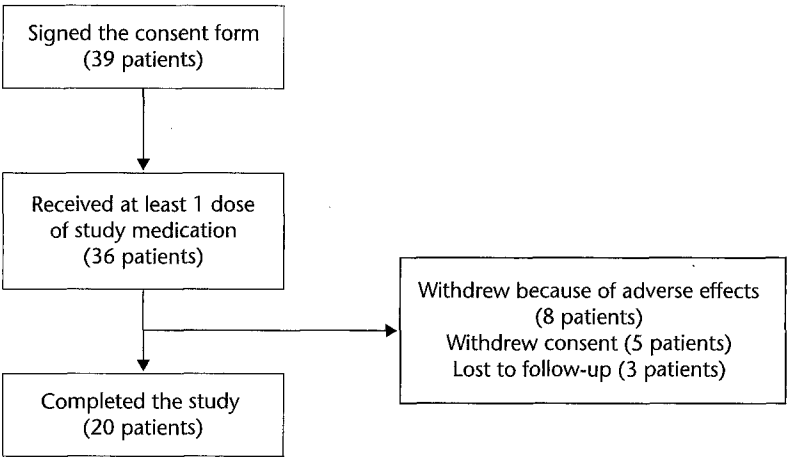

Figure 1. Study design.

Effectiveness

Intent-to-Treat Population

Eleven patients (30.6%) were not using other preventive drugs when enrolled, 10 (27.8%) were using 1 preventive drug, and 15 (41.7%) were using 2 or 3 preventive drugs.

Among those who completed the titration phase (33 patients [91.7%]), the median dose was 1250 mg (range, 750–2000 mg). The final doses were 750 mg in 1 patient (3.0%), 1000 mg in 11 (33.3%), 1250 mg in 12 (36.4%), 1500 mg in 7 (21.2%), and 1750 mg and 2000 mg in 1 patient each (3.0%).

At baseline, the mean headache frequency was 24.9 d/mo. A significant reduction in headache frequency was observed at 1 month (19.4 d/mo), 2 months (18.4 d/mo), and 3 months (16.2 d/mo) (all, $P < 0.001$ vs baseline) (**Figure 2**). The mean number of moderate or severe headache days at baseline (16.8 d/mo) was statistically similar compared with 1 month (13.2 d/mo). However, frequencies of moderate or severe headache were significantly lower at 2 and 3 months (11.9 and 9.7 d/mo, respectively; both, $P < 0.01$ vs baseline) (**Figure 3**).

The mean MIDAS[15] score was significantly reduced at 3 months compared with baseline (40.8 vs 62.8; $P = 0.01$). The mean HIT-6[16] score was 59.4 at 3 months compared with 63.4 at baseline ($P < 0.01$).

Per-Protocol Population

In regard to participants completing this study (20 patients [55.6%]), we correlated end points at baseline and completion (**Table II**). Mean (SD) headache frequency was reduced from 26.1 (4.1) d/mo at baseline to 14.3 (4.8) d/mo at the end of the study ($P < 0.001$). We also found significant differences in the number of moderate or severe headache days per month between baseline and study completion (18.0 [8.3] vs 9.7 [7.8] d/mo; $P < 0.006$), headache score (51.3 [17.1]

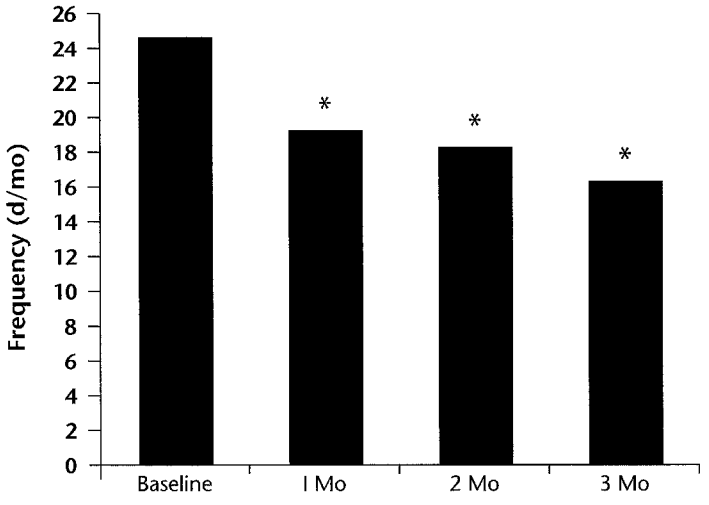

Figure 2. Frequency of headache before (baseline), during, and after 3 months of preventive treatment with levetiracetam in patients with transformed migraine (N = 36). *$P < 0.001$ versus baseline.

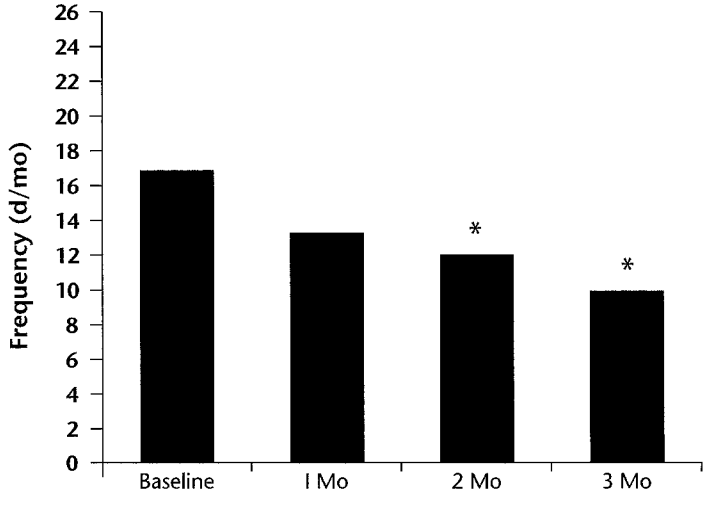

Figure 3. Frequency of moderate or severe headache before (baseline), during, and after 3 months of preventive treatment with levetiracetam in patients with transformed migraine (N = 36). *$P < 0.01$ versus baseline.

Table II. End points as assessed in the per-protocol analysis (n = 20). Data are expressed as mean (SD).

End Point	Baseline	3 Months	*P*
Frequency of headache, d/mo	26.1 (4.1)	14.3 (4.8)	<0.001
Frequency of moderate or severe headache, d/mo	18.0 (8.3)	9.7 (7.8)	<0.006
Headache score*	51.3 (17.1)	34.0 (22.0)	<0.016
MIDAS Questionnaire[15] score†	76.7 (32.1)	29.3 (23.0)	0.01
HIT-6[16] score‡	64.8 (5.9)	57.7 (7.9)	<0.006

MIDAS = Migraine Disability Assessment; HIT-6 = Headache Impact Test.
*Calculated as frequency multiplied by severity as assessed on a 4-point scale (0 = no pain to 3 = severe).
†Scale: 0–5 = grade I (minimal or infrequent disability); 6–10 = grade II (mild or infrequent disability); 11–20 = grade III (moderate disability); and ≥21 = grade IV (severe disability).
‡Scale: 38–49 = little or no impact on patient's life; 50–55 = some impact; 56–59 = substantial impact; 60–78 = very severe impact.

vs 34.0 [22.0]; $P < 0.016$), MIDAS[15] score (76.7 [32.1] vs 29.3 [23.0]; $P = 0.01$), and HIT-6[16] score (64.8 [5.9] vs 57.7 [7.9]; $P < 0.006$).

Tolerability

AEs were reported by 18 patients (50.0%); 8 patients (22.2%) withdrew from the study because of poor tolerability (somnolence, 2 patients [5.6%]; lack of concentration, 2 [5.6%]; and chest tightness, constipation, anorgasmia, and ankle edema, 1 [2.8%] each). The most common AEs were somnolence and asthenia (10 patients [27.8%] each) and anxiety (5 patients [13.9%]). Weight gain (4 patients [11.1%]) and depression and emotional instability (2 patients [5.6%] each) also occurred. The following AEs were also reported by 1 patient (2.8%) each: anorgasmia, ankle edema, constipation, and chest tightness.

DISCUSSION

TM is the most frequently seen headache syndrome at headache centers.[1,3,17,18] Previous studies show that the transformation process in patients with migraine is associated with increases in not only frequency but also associated disability.[19]

Based on a literature search (key terms: *refractory headache, treatment,* and *transformed migraine*; years, 1980–2005), most studies addressing the treatment of refractory headaches have focused on CDH overall,[14,20] while few studies have addressed the preventive treatment of TM as a distinctive subgroup of CDH. Most reports of TM are anecdotal.[21,22] An open-label trial assessing the possible benefits of sodium valproate in patients with CDH that was refractory to multiple standard treatments found that 50% of patients had some kind of response and 10% discontinued medication due to AEs.[20] Shuaib et al[23] treated 37 patients with refractory

migraine or CDH with topiramate in an open-label study. Thirty percent had an excellent result and 30% had a good result. Recent studies have assessed the prevention of CDH with botulinum toxin type A,[22] zonisamide,[24] tizanidine (in a double-blind study),[25] and quetiapine.[25] The reductions in headache frequency were 30% at 1 month in patients treated with tizanidine[25] and 37% at 3 months in patients treated with zonisamide.[24] A retrospective study found a reduction of 36.5% in headache frequency at 2 months in patients using daily naratriptan.[26]

We found that levetiracetam may be an effective drug in the prevention of TM. For the ITT population, headache frequency decreased 34.9%, the number of days with moderate or severe headache pain decreased by 42.2%, and disability scores decreased significantly (both, $P \leq 0.01$). In those who completed the study, headache frequency was reduced by 45.2%, and the number of moderate or severe headache days per month was reduced by 46.1%.

The treatment of refractory headache, including TM, is quite often unsuccessful.[1,2,5] Although we believe that ITT analyses provide a more balanced statistical approach, subanalyses of patients who completed the study can be of interest. For refractory headache, a drug that provides significant relief to even a small fraction of patients is useful. In a recent study, Saper et al[27] found that daily opioid therapy for refractory headache was useful in just 25% of patients in the long term. However, considering the degree of refractoriness of the sample, they concluded that this modality of treatment might provide relief to some selected patients with TM. We found that levetiracetam was effective overall, and subanalyses of the completers strongly reinforced the results of the ITT analysis.

We verified a high rate of AEs in our study population. AEs were reported by 50.0% of patients and led to a withdrawal rate of 22.2%. Most of those who withdrew from the study were using preventive medications in addition to levetiracetam, which may have increased their risk for AEs and/or drug–drug interactions. For most neuromodulators, polypharmacy is associated with a higher frequency of AEs.[28] Therefore, drug–drug interactions may at least partially explain our findings. Second, several trials have reported that the AE rates are higher in TM compared with migraine.[13,21,22] Double-blind trials investigating levetiracetam used as monotherapy are necessary to fully assess the tolerability of this drug.

Our results support previous findings. Drake et al[13] investigated levetiracetam use in the prevention of refractory headache, including CDH. Treatment with concomitant medications was continued. A clinical benefit was noted after 1 month of treatment. Ten patients (16.1%) discontinued the drug because of AEs. A second study investigated the use of levetiracetam in patients with CDH whose treatment had previously failed with 2 to 4 medications; 46.7% of the patients reported a reduction in headache frequency of at least 50%, and 26.7% discontinued treatment with the drug due to AEs.[14] While these studies investigated levetiracetam in the prevention of any type of refractory headache, we included only patients with TM in our study.

Caution should be used when analyzing our results for several reasons. First, although this pilot study was prospective, it was not placebo controlled.

Neither the patients nor the health care providers were blinded to treatment. Second, we included patients with TM with and without medication overuse; patients overusing medication had previously failed detoxification protocols. None of the patients discontinued medication overuse during our study. Because studies show that preventive medication is often ineffective in patients overusing acute care medication,[5,14,17,18,21] we may have underestimated the benefits of levetiracetam by including overusers. However, most of our patients (73.3%) were not overusing acute care medication. Additionally, some patients were using several different preventive medications. Finally, not all of the patients received the same dose of levetiracetam, which may have influenced some comparisons regarding efficacy and tolerability.

CONCLUSIONS

The results of this pilot study in patients with TM suggest that levetiracetam is a promising drug for the preventive treatment of TM, although it has neither been submitted to nor approved by the US Food and Drug Administration for this use. Because TM evolves from episodic migraine, our data suggest that levetiracetam may have a role in the preventive treatment of frequent episodic migraine. A necessary future step forward is to conduct a double-blind, placebo-controlled study of levetiracetam in the treatment of TM.

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