

## VENLAFAXINE IN CHRONIC DAILY HEADACHE

### Kronik günlük baş ağrısında venlafaksin

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#### Abstract

**Objective:** To determine efficacy of venlafaxine, a new anti-depressant in the treatment of chronic daily headache.

**Method:** This study was carried out on patients having chronic daily headache at PTT Teaching Hospital Neurology Department, Istanbul. Patients treated with venlafaxine for three months were followed up to determine their response to drug. The results were reported as improvement, no change, or increase in headache frequency.

**Results:** Nineteen of 42 patients reported improvement; 11, no change; 5, an increase in headache frequency and 7 patients gave up treatment because of side effects within fifteen days. The most common side effect was fatigue. Fifteen patients had no side effect.

**Conclusion:** Venlafaxine may be considered as an effective drug for chronic daily headache prophylaxy, especially in patients not taking any other medication. However, placebo controlled studies are needed to confirm these findings.

**Key Words:** Headache, Therapeutic

Headache is an important problem increasing in frequency and number in recent years. It results in the loss of 150 million daily-work hours and 1 million school days per year in the world (1). Its incidence in society is 80% (2,3) but few seek medical attention. The most common headache is tension type. Its incidence is estimated to be more than 40% in the society. (4,5) Unconscious drug usage is common and results in drug abuse, chronicity of headache and loss of time and money. (6) Chronic tension-type headache is a daily, or continuous, headache which may have some

#### Özet

**Amaç:** Kronik günlük baş ağrısının tedavisinde yeni bir antidepresan olan venlafaksin'in etkinliğini belirlemek.

**Gereç ve Yöntem:** İstanbul PTT Eğitim Hastanesi Nöroloji Kliniğinde, kronik günlük baş ağrısı tanısıyla takipte olan hastalarda yapılan bu çalışmada; hastaların üç aylık venlafaksin tedavisine cevabı araştırıldı. Sonuçlar baş ağrısı sıklığında artma, hiçbir değişiklik olmaması veya iyileşme şeklinde rapor edildi.

**Sonuçlar:** Kırkiki hastanın 19 (%54.2)'unda iyileşme, 11'inde hiçbir değişiklik olmaması, 5'inde ise baş ağrısı sıklığında artma gözlemlendi. 7 (%16.6) hasta ilk onbeş gün içinde yan etkileri nedeniyle tedaviyi bıraktı. En sık görülen yan etki halsizlikti. Onbeş hastada hiçbir yan etki görülmedi.

**Sonuç:** Venlafaksin özellikle herhangi bir tedavi almayan hastalarda kronik baş ağrısı profilaksisi için etkili bir ilaç olarak düşünülebilir. Ancak gene de bunu doğrulamak için plasebo kontrollü çalışmalara ihtiyaç vardır.

**Anahtar Kelimeler:** Baş ağrısı, Tedavi

variability in the intensity of pain during a 24-hour cycle. There may be some soreness, constricting band sensation, weight or pressure-like sensations, and often a sensation of a tight skull cap. Many of these patients complain of early or frequent awakening, a sign of underlying depression. Chronic daily headache seems to be a mixed type of tension and migraine. Migraneous type may subsequently develop chronic daily headache in following years. The first line of treatment is very important in prevention of chronicity. Chronic headache by definition, means a headache recurring more than 15 days a month (7). For years, anti-depressants have been used in the treatment of chronic daily headache. The analgesic effect is independent of their antidepressant action, although the mechanism is not exactly known. Antidepressant drugs have

analgesic action over and above their antidepressant effect. Several antidepressants have been investigated in headache treatment. Tricyclic antidepressants have shown better efficacy than selective serotonin reuptake inhibitors (SSRIs), possibly as a result of norepinephrine reuptake inhibition. Venlafaxine is a new agent affecting neurotransmitters. It is a norepinephrine and serotonin reuptake inhibitor, and also inhibits dopamine reuptake. It does not cause the side effects commonly associated with tricyclics because it lacks affinity for muscarinic and histaminergic receptors. This study was designed in consideration of previous favorable experience with tricyclics in chronic daily headache treatment.

## **METHOD**

The patients having chronic daily headache were reported prospectively to determine their response to venlafaxine. Our aim was to study the response of daily headache to an outpatient treatment protocol. Our prospective study consisted of 35 females and 7 males, ages ranging between 20 and 53 years (mean: 37.8 years) (Table I). Two female patients had histories of trauma due to traffic accidents. The other case histories of our patients were daily life difficulties (37 in number) like fatigue, stress, unsuccessful marital relationships, habits, sexual problems; death of husband (1 in number); divorce (2 in number). Twenty patients suffering from chronic daily headache were taking analgesics daily, and 2 of them abused the drug.

The therapeutic protocol included: 1.Oral information to the patient about the role of analgesics and everyday life problems in the chronification of headache; 2.Administration of naproxene sodium as symptomatic medication, and 3.Prophylactic treatment with venlafaxine. Charts were prepared for response and side effects. The clinical response to the drug was classified according to following criteria;

- improved (decreased to two or fewer headaches per week),
- no change,

- increased in frequency.

Patients took 75 mg Venlafaxine BID for three months and were followed monthly.

The patients having diseases - organic and progressive disorders, epileptic disorders, endogenous depression, neurotic disorders, or hypertension and pregnant women - were not included in this study. Hamilton and Zung depression scales and clinical global review forms were used. The patients' sex, age, history of headache and diagnosis were noted. The diagnosis of daily headache was made according to International Headache Society Classification. Each of the patients had a history of headache for at least 2 years and were experiencing at least fifteen headaches a month. Two patients exclusively abused analgesics, 13 patients paracetamol and 5 patients other analgesics. In 12 patients various agents including analgesics and antidepressants, had been used for treatment of daily headache previously. In the remaining 30 patients, an antidepressant agent was used for the first time. During the previous six months patients used no other medication.

Pain and other symptoms were evaluated according to patients' self assessment. The objective of treatment and the method of follow-up were described at the first visit. Analgesics were allowed during the study but recommended when required (headache severity score 2). Naproxene sodium was advised in such cases. Patient's self assessment and monitoring allowed them to thoroughly evaluate their headache on a daily basis using the following criteria during a period of 3 months.

- a) Headache frequency.
- b) Headache intensity on graded scale:  
0 = No headache.  
1 = Mild headache not affecting work capacity.  
2 = Moderate headache affecting work capacity.  
3 = Relatively severe headache making patient bedridden.
- c) Analgesic consumption.

Although some patients had vascular or migrainous type headaches, their natural course did not

transform into chronic daily headache. The frequency of headache and the degree of headache on a graded scala has been noted (Table III), and determined for significance using paired t test.

## RESULTS

The results of the 42 patients after treatment with Venlafaxine 75mg BID were as follows ; 19 reported an improvement in the frequency of headache, 11 no change and 5 increased in frequency (Table II). Decline in the headache frequency (day/month) and the degree of headache were significant. The maximum intensity of the headache pain was reduced as well as the mean duration of the headache attacks which went from 12 hours to less than 5 hours at the end of the treatment period. Two patients abusing analgesics showed no improvement and carried on taking analgesics. Thirteen of the 19 improved patients showed an excellent improvement in frequency and intensity and completely gave up analgesics. Eight of the 19 patients were daily analgesic users.

Venlafaxine induced a prompt decrease in pain frequency and intensity in nineteen of 35 patients (%54.2). Thirteen (%56.1) of 23 patients who had

not used any medication previously reported decreased frequency. In younger ages ranging between 20-30, nine (%60) of 15 patients reported decrease in pain frequency.

Various side effects were reported. Fatigue and nervousness were the most common. The complaints are shown on Table IV. The side effects were transient but caused cessation of treatment in some patients: Seven patients gave up treatment because of tachycardia, 7 because of nervousness, 2 because of nightmares, and 1 because of diarrhea. Fifteen patients reported no side effects. In the following days of therapy, increased appetite (14 patients) and weight gain (10 patients) were reported. They were probably related to antidepressant effects (8 patients).

Following medical treatment, no changes in hematologic parameters or clinical examination findings were detected.

Chronic daily headache defining (location and characteristics as in acute tension headache, but occurs more frequently than 15 days a month ; no vomiting ; not more than one of the following criteria : nausea, photophobia, intolerance of noise)

**Table I.** Some demographical findings of the patients

Sex ( Female / Male )	35 / 7	
Current age ( years )	37.80 ± 8.75	Range(20-53)
Age at the onset of headache ( years )	28.135 ± 6.2	Range(17-42 )

**Table II.** Improvement in headache frequency with venlafaxine 75 mg BID for three months

Response	Female ( n: 30 )	Male ( n: 5 )	Total (n:35)	Percentage
Decreased frequency	17	2	19	% 54.2
No change	9	2	11	% 31.4
Increased frequency	4	1	5	% 14.3

\* 7 patients ( 5 female and 2 male ) gave up treatment because of side effects

**Table III.** Frequency and severity of headache related to venlafaxine treatment

	Before treatment, n=35	After treatment, n=35	t	p
Frequency of headache (day a month)	24.9 7.2	9.2 3.4	11.203	<0.0001
Duration of headache (hour)	12.3 5.4	5.1 2.5	9.419	<0.0001
Severity of headache (0-3 grading)	2.1 0.5	1.3 0.8	5.865	<0.0001

\*Paired-t test ; results were statistically significant. (  $p < 0.001$  )

**Table IV.** Side effects of venlafaxine treatment

SIDE EFFECTS	The number of patients ( n )
Fatigue	17
Nervousness	13
Nausea	11
Tachycardia	8
Insomnia	5
Night mares	3
Diarrhea	3
Cognitive difficulties	2
Sexual dysfunction	2

physical or radiological examination will rule out these conditions.

Pharmacological therapy must be prescribed cautiously. Because of the chronic addiction anxiolytic and analgesics should be avoided in treatment. Prophylactic treatment with antidepressants is important. Tricyclic drugs are the agents of choice (9-11). In literature studies, SSRI's had the same effect as tricyclic drugs and less side effects compared to tricyclic drugs (12,13). The tricyclics showed a better efficacy than SSRI's, possibly as a result of the norepinephrine reuptake inhibition; hence we designed a study with venlafaxine which is a serotonin and norepinephrine reuptake inhibitor, like tricyclics.

## DISCUSSION AND CONCLUSION

Tension headache is a manifestation of the body's reaction to a variety of emotional factors. It is a response characterized with dilatation of the external cranial vessels and contraction of the skeletal muscles of the head and neck. Tension type headache can be chronic which persists at least fifteen days per month for at least six months. The examining physician should review any family, work, school or marital conflicts. The interview may not be completed in several visits. Sometimes it is associated with depression. In our study, depression was excluded as it is an independent entity. The patient may relate the onset of the headache to a specific accident or psychological trauma, although

Our work confirms the epidemiological magnitude of chronic daily headache and shows that this is a treatable entity on an outpatient basis, combined with prophylactic treatment. In our study, the results indicate venlafaxine is an effective drug for treatment of daily headache. By the end of the third month of treatment, the frequency of headache, as well as the intensity and duration of headaches during the observation period, were reduced in patients treated with venlafaxine as compared with baseline. (Table III) When the frequency, duration and severity of post and pretreatment headache episodes were compared with paired t test ; statistically significant results were obtained ( $p < 0.001$ ). Particularly new patients who had not used any medication (23 in number) and younger

ones ages ranging between 20 and 30 years (15 in number) showed better improvement. There is a need for double-blind , placebo controlled studies of this agent because of limited knowledge in the treatment of headache with venlafaxine in the literature. In summary venlafaxine appears to be a good selection in the treatment of chronic daily headache.

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