# Improvement in Cataplexy and Daytime Somnolence in Narcoleptic Patients with Venlafaxine XR Administration

Rafael J. Salin-Pascual, M.D., Ph.D.

Narcoleptic patients have been treated with stimulants for sleep attacks as well as daytime somnolence, without effects on cataplexy, while this symptoms has been treated with antidepressants, that do not improve daytime somnolence or sleep attacks. Venlafaxine inhibits the reuptake of norepinephrine, serotonin, and to lesser extent dopamine, and also suppressed REM sleep. Because some of the symptoms of narcolepsy may be related to REM sleep deregulation, venlafaxine was studied in this sleep disorder. Six narcoleptic patients were studied, they were drug-free and all of them had daytime somnolence and cataplexy attacks. They underwent the following sleep procedure: one acclimatization night, one baseline night, followed by multiple sleep latency test. After two days of the sleep protocol, patients received 150 mg of venlafaxine XR at 08:00 h. Two venlafaxine sleep nights recordings were performed. Patients were followed for two months with weekly visits for clinical evaluation. Sleep log and analog-visual scale for alertness and somnolence were performed on each visit. Venlafaxine XR was increase by the end of the first month to 300 mg/day. Sleep recordings showed that during venlafaxine XR two days acute administration the following findings: increase in wake time and sleep stage 1, while REM sleep time was reduced. No changes were observed in the rest of sleep architecture variables. Cataplexy attacks were reduced since the first week of venlafaxine administration. Daytime somnolence was reduced also, but until the 7th week and with 300 mg/day of venlafaxine XR administration. Side effects were mild and they were nausea, hiporexia and anxiety. Venlafaxine XR administration improved cataplexy with mild effect on somnolence, that could be explained because at low doses venlafaxine XR acts like selective serotonin reuptake inhibitor and only at high doses the effects on the norepinephrine reuptake is observed. Double blind protocols with venlafaxine are needed in order to determine the utility of venlafaxine XR in narcolepsy. **(Sleep and Hypnosis 2002;4(1):22-25)**

***Key words:*** *Narcolepsy, Venlafaxine XR, REM sleep, cataplexy*

## INTRODUCTION

Narcolepsy is a sleep disorder, which is characterized by excessive sleepiness, sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucinations (1). Narcolepsy has also been reported to occur in animals and has been most intensively studied in dogs. The cloning of the canine narcolepsy gene led to identify a mutation in the gene encoding the receptor to hypocretin-2 receptor, which believed to be cause of the canine narcolepsy (2). Also a knock-out mice for hypocretin/orexin peptides showed cataplexy as well as some sleep changes

From Departamento de Neurología y Psiquiatría, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán" and Departamento de Fisiología. Facultad de Medicina, Universidad Nacional Autónoma de México

Address reprint requests to: Rafael J. Salín-Pascual, M.D., Ph.D. Servicio de Psiquiatría., Departamento de Neurología y Psiquiatría INCMNSZ, Vasco de Quiroga 15, Tlalpan 14000, México City, México

Accepted March 17, 2002

similar to narcolepsy in humans and dogs (3). Hypocretin/orexin neuropeptides were found previously in lateral hypothalamus by two separate groups and a function in feeding regulation was first proposed (4,5). In humans, although familial cases of narcolepsy have been reported, most human occurrences are sporadic, and the disorder is generally believed to have multiple etiology. A malfunction of the hypocretin system has been observed in human narcolepsy (6).

The treatment of narcolepsy has been oriented in two areas: stimulation of the CNS (7,8), which increased vigil, like amphetamines or methylphenidate and antidepressants like clomipramine, imipramine or fluoxetine, which reduce cataplexy (9,10). REM sleep suppression effect seems to be the main mechanism of action of the above mentioned drugs, and in narcolepsy REM sleep abnormalities have been addressed as the main area of dysfunction. Venlafaxine is an antidepressant with a dual mechanism of action, that is inhibition of the reuptake of both serotonin and norepinephrine neurotransmitters. Unlike tricyclic antidepressants, venlafaxine does not displace muscarinic, alpha-1, dopamine or histamine from their receptors in the rat membranes (11).

Sleep effects of venlafaxine were studied in rats in which REM sleep was suppressed (11). Also in normal volunteers, venlafaxine administration produced REM sleep complete suppression by the fourth night of its administration. Increase in wake time and periodic leg movement were observed in six out of eight volunteers (12). Since venlafaxine seems to have both REM sleep suppression effect plus a moderate CNS stimulation type of effect, six narcoleptic patients received this medication in the present study.

## METHOD

Six narcoleptic patients were studied, 3 males and 3 females, between 35 and 60 year of age (Mean±SD=46.16±9.4 years). All patients were clinically evaluated and after the full protocol was explained, the informed consent statement were signed. Patients were drug free, for at least two weeks before enter into the study. All patients must have cataplexy and daytime somnolence as inclusion criteria for to enter into the study. No other medical or psychiatric illnesses were present. Patients underwent the following sleep procedure: one acclimatization night; one all-night polysomnographic recording, followed by four naps of 20 minutes the day after Multiple Sleep Latency Test (MSLT). Naps interval was of 90 minutes, and they started at 10:00, 12:00, 14:00 and 16:00 hrs. Two days after that patients started with venlafaxine XR (slow release) 150 mg. Night sleep recordings were obtained the next two following nights. Sleep recordings were scored by a technician who was blind to the order in which the all-night register were done. Scoring was done according to standard criteria (13). After the sleep procedures ended, patients attended to one weekly visit during two months for clinical evaluation of cataplexy and daytime excessive somnolence, with sleep log and an Analog-Visual Scale (0=very alert to 10=very sleepy). Venlafaxine XR was increased up to 300 mg in all subjects by the end of the first month, and was always administered during breakfast time (around 08:00 to 10:00 hr).

## RESULTS

All narcoleptic patients had excessive daytime somnolence and cataplexy as part of the clinical picture and the inclusion criteria for this study. At MSLT all the patients showed at least two naps with REM sleep onset (REM sleep below 10 minutes). Table 1 shows the sleep architecture at baseline and after each one of the two nights of venlafaxine XR 150 mg. Waking time and sleep stage 1 were increased with venlafaxine (One-Way ANOVA: $F=26.8$, $df=2,15$, $p<0.0001$, for waking time and $F=15.38$, $df=2,15$, $p<0.0004$ for stage 1). No sleep changes were observed in sleep stages 2, 3 and 4. REM sleep were reduced dramatically

**Table 1. Sleep architecture in narcoleptic patients at baseline and during Venlafaxine XR (Mean±SD minutes).**

| | WAKE | STAGE 1 | STAGE 2 | STAGE 3 | STAGE 4 | REMS | REML |
|---|---|---|---|---|---|---|---|
| Baseline | 34.1 ± 14.8 | 30.3 ± 11.3 | 206.8 ± 21.8 | 15.6 ± 6.4 | 92.0 ± 19.2 | 100.8 ± 13.48 | 19.8 ± 12.02 |
| Venlafax 150 | 58.0 ± 18.2* | 77.16 ±13.7* | 221.0 ± 31.5 | 18.8 ± 7.8 | 84.5 ± 22.9 | 23.3 ± 9.07* | 147.2 ± 36.3* |
| Venlafax 150 | 93.3 ± 12.3* | 77.16 ± 13.7* | 208.1 ± 16.7 | 20.1 ± 8.7 | 70.5 ± 6.4 | 5.6 ± 3.7 | 281.6 ± 36.4* |
| ANOVA | p<0.0001 | P<0.0004 | n.s. | n.s. | n.s. | P<0.0001 | P<0.0001 |

REMS=REM sleep; REML=REM sleep latency

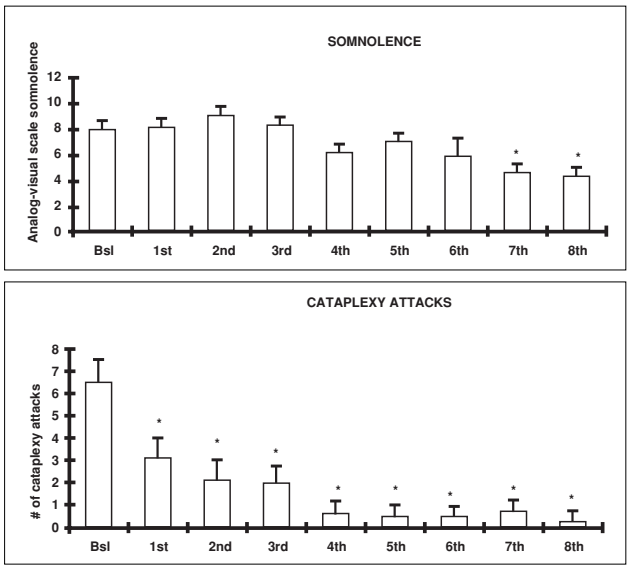


**Figure 1. Clinical changes in narcoleptics with venlafaxine: The upper panel shows the excessive daytime somnolence scored weekly. A reduction was observed since the 4th week of venlafaxine XR administration, but was only significant up to the 7th week (*p<0.05 vs. Baseline=Bsl; Wilcoxon Matched-pairs Signed-Rank test). The lower panel shows changes in weekly cataplexy attacks in six narcoleptic patients. A significant reduction was observed since the first week of venlafaxine XR administration. *p<0.05 vs. Baseline=Bsl; Wilcoxon Matched-pairs Signed rank test.**

during the first two days of venlafaxine administration (F=165.7, df=2,15, p<0.0001), while REM sleep latency was prolonged (F=110.46, df=2,15, p<0.0001). Periodic leg movements or restless legs were not observed in any of these patients.

Excessive daytime somnolence was also reduced, but it was only statistically significant after the seventh week of venlafaxine administration (see Figure 1) (Friedman Two-Way ANOVA: Chi-Square=39.71, df=8, p<0.00001). Cataplexy attacks were reduced since the first week of venlafaxine administration (see Figure1) (Friedman Two-Way ANOVA: Chi-Square=36.26, df=8, p<0.0001). Side effects reported in four out of the six patients were nausea, anorexia and anxiety, in all of them side effects were mild, and disappeared after one or two weeks of treatment.

## DISCUSSION

A clinical improvement of the cataplexy was observed in the present study. Somnolence improvement was moderated and was observed only after the seventh week of venlafaxine treatment. Side-effects were mild and all the patients ended the study with good tolerance.

Sleep effects of venlafaxine XR were the same as reported previously with the venlafaxine immediate release formulation (12), those are reduction in REM sleep and increase in both wake time and sleep stage 1. In a previous report Smith et al. (14), found that four narcoleptic patients that received venlafaxine had good effects in both excessive daytime sleepiness and cataplexy, with an average daytime dose of 206 mg (150 to 375 mg/day), but they received the acute release venlafaxine. Because venlafaxine inhibits the re-uptake of both serotonin and norepinephrine, the explanation of the therapeutic effect of venlafaxine in some narcoleptic patients should be explained in this direction. Amphetamine and methylphenidate, increases norepinephrine and dopamine availability in synapses. These type of stimulants have been used in narcolepsy (7,8). On the other hand, clorimipramine and fluoxetine that inhibit serotonin reuptake seems to have some beneficial effect on cataplexy in narcoleptic dogs (9). The delay effect on daytime sleepiness may be related that a low doses venlafaxine acts more

like a selective serotonin reuptake inhibitor (SSRI), while as soon as the dose was increased, the dual reuptake mechanism started to work through both serotonin and norepinephrine reuptake (15,16). Venlafaxine XR, needs to be studied in double blind conditions in order to test if it has good possibilities as a selective treatment to the narcolepsy patients with cataplexy.

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