Venlafaxine in the Treatment of Atypical Facial Pain: A Randomized Controlled Trial

Heli Forssell, DDS, DMedSci
Associate Professor
Department of Oral Diseases/Pain Clinic
Turku University Central Hospital
Turku, Finland

Tiina Tasmuth, MD, DMedSci
Research Fellow
Pain Clinic
Department of Anaesthesia and Intensive Care Medicine
Helsinki University Central Hospital
Helsinki, Finland

Olli Tenovuo, MD, DMedSci
Consultant
Department of Neurology/Pain Clinic
Turku University Central Hospital
Turku, Finland

Göran Hampf, MD, DDS, DMedSci
Associate Professor
Facial Pain Clinic
University of Helsinki
Helsinki, Finland

Eija Kalso, MD, DMedSci
Professor
Pain Clinic
Department of Anaesthesia and Intensive Care Medicine
Helsinki University Central Hospital
Helsinki, Finland

Correspondence to:
Dr Heli Forssell
Turku University Central Hospital
Department of Oral Diseases/Pain Clinic
Lemminkäisenkatu 2
Fin-20520 Turku
Finland
Fax: +358 2 3338248
Email: heli.forssell@tyks.fi

Aims: *To study in a randomized placebo-controlled design the efficacy of the antidepressant venlafaxine, a serotonin and a weak noradrenaline reuptake inhibitor, in the treatment of atypical facial pain (AFP).* ***Methods:*** *The study was a randomized, double-blind, crossover comparison of venlafaxine and a placebo. It consisted of 2 treatment periods, each of 4 weeks' duration, separated by a 2-week washout period. Thirty patients suffering from chronic pain who had been diagnosed with AFP after a thorough clinical examination were recruited. Pain intensity and pain relief were registered at 6 visits. Anxiety, depression, and adverse effects were recorded. Venous blood samples were collected at the end of each treatment period for the determination of serum levels of venlafaxine and its metabolites.* ***Results:*** *Twenty patients completed the trial. Eight patients discontinued because of adverse effects and 2 patients were excluded because of noncompliance. Two patients completed the trial but were excluded from the analysis because they experienced no pain at the baseline visit. There was no significant difference in pain intensity reduction between the maximum tolerated dose of venlafaxine (75 mg in most cases) and the placebo. Pain relief was significantly greater with venlafaxine than with the placebo treatment. Significantly more escape medication was consumed during the placebo period compared with the venlafaxine period. No significant correlation was found between the serum concentration of the drug and the response to treatment. Anxiety and depression scores did not differ between venlafaxine and placebo treatment. Adverse effects were equally common during both treatments.* ***Conclusion:*** *Venlafaxine was only modestly effective in the treatment of AFP.*
J OROFAC PAIN 2004;18:131–137

Key words: antidepressants, atypical facial pain, chronic pain, neuropathic pain, venlafaxine

Atypical facial pain (AFP) has remained the most enigmatic chronic facial pain problem, presenting both diagnostic and therapeutic challenges. The term AFP is used to cover cases of chronic facial pain with unknown etiology or without a clear organic pathology.[1,2] A diagnosis of AFP is made only after local orofacial, neurological, and related systemic diseases have been ruled out.[3] An overwhelming majority of AFP patients are older women.[4,5] The pain is often persistent, but its intensity can vary from mild to severe. It is described as diffuse, drawing, burning, or stabbing pain felt in the bone or deep tissues of the orofacial region.[5] Although both the etiology and the pathophysiology of AFP are uncertain, deafferentation mechanisms associated with peripheral nerve injury and subsequent central sensitization have been suggested.[6] Recent electrophysiological studies have shown signs of trigeminal dysfunction in the majority of AFP patients.[7]

Most of the findings indicate subclinical neuropathy. The importance of the underlying psychopathology in AFP has also been stressed.[8,9]

Antidepressants are the most commonly recommended treatment for AFP,[1,3,4] but only limited data are available to demonstrate their effectiveness. In an early controlled trial, Lascelles[10] demonstrated the efficacy of phenelzine, a monoamine oxidase (MAO)-inhibitor antidepressant, in the treatment of AFP. The effectiveness of dothiepin, another antidepressant, in the treatment of AFP was tested in a controlled study by Feinmann et al,[8] but it is difficult to assess because patients with both AFP and facial arthromyalgia were included.

Tricyclic antidepressants (TCAs) are generally considered the "gold standard" for the relief of various kinds of neuropathic pain.[11,12] Their ability to inhibit the reuptake of both serotonin and noradrenaline is thought to be responsible for their analgesic effect.[13] TCAs have also antihistaminergic and anticholinergic effects, which decrease patient compliance. Venlafaxine, an antidepressant, is a serotonin and a weak noradrenaline reuptake inhibitor, but does not significantly affect other receptors.[14] Due to these properties, venlafaxine has a better adverse effect profile and thus has been associated with a higher rate of compliance than TCAs and may have a promising future in the treatment of chronic pain.[15,16] So far, however, only 2 controlled studies on its efficacy in pain treatment have been published.[17,18] In the study by Tasmuth et al,[17] venlafaxine was shown to be modestly effective in treating neuropathic pain caused by breast cancer treatment. Sindrup et al[18] reported that venlafaxine and the TCA imipramine have comparable efficacy in the treatment of painful polyneuropathy.

Therefore, the aim of the present study was to examine, in a randomized placebo-controlled design, the efficacy of venlafaxine in the treatment of AFP. The primary effect variable was the change in mean pain intensity from baseline to the end of the treatment period on the maximum tolerated drug dose.

Materials and Methods

Patients

The patients considered for this study presented with chronic facial pain at the Departments of Oral Diseases or Neurology at the Turku University Hospital or at the Pain Clinic of the Helsinki University Hospital between 1998 to 2000. They underwent a thorough clinical examination, complemented by imaging studies and neurophysiological studies when indicated. The diagnostic workup of the study group included magnetic resonance imaging of the brain in 14 cases, computed tomography scans of the maxillary sinus in 7 cases, blink reflex (BR) testing in 14 cases, and thermal quantitative sensory tests (QSTs) of the symptomatic trigeminal region in 2 cases. Because no clear pathology or somatic findings explaining the facial pain were found, the patients were diagnosed with AFP. To be eligible for the study, AFP patients had to estimate the intensity of their facial pain to be at least 3 on a numeric rating scale of 0 to 10. The patients had to be free from clinically overt cardiac, hepatic, or renal disease. Concomitant medication with MAO inhibitors, drugs that are significantly metabolized by the P4502D6 isoenzyme, or drugs that inhibit this enzyme, was also a contraindication for the participation in the study. Thirty patients met the inclusion criteria.

The study was approved by the Institutional Ethics Committees of the Turku and Helsinki University Hospitals and the National Agency for Medicines. All participants gave their written informed consent.

Study Design

The study was a randomized, double-blind, crossover comparison of venlafaxine and placebo (Table 1). Wyeth-Lederle, a pharmaceutical company, provided the 37.5 mg venlafaxine (Efexor) and identical placebo capsules and performed the randomization using computer-generated numbers. Patients were allocated consecutively. The study consisted of 2 treatment periods (each of 4 weeks' duration), separated by a 2-week washout period. During the first 2 weeks, the patients took 1 capsule of venlafaxine or placebo in the evening. During the second 2 weeks, the patients took 2 capsules, 1 in the morning and 1 in the evening. Patients were permitted to reduce the dose to the previous level if they experienced unacceptable adverse effects. Compliance was monitored by counting the capsules at the end of each treatment period and by measuring plasma concentrations of venlafaxine and its metabolites. Six visits were scheduled at 2-week intervals. The randomization code was not opened during the trial, and the data regarding the plasma concentrations of venlafaxine and the treatment codes were kept separate from the investigators carrying out assessments until the database was closed.

Table 1 Study Design

	Week						
	0	2	4	Washout	6	8	10
Recordings							
Pain intensity							
VASpi	X	X	X		X	X	X
VRSpi	X	X	X		X	X	X
Pain relief							
VASpr		X	X			X	X
VRSpr		X	X			X	X
Anxiety (STAI)	X	X	X		X	X	X
Depression (BDI)	X	X	X		X	X	X
Adverse effects (VAS)		X	X			X	X
Analysis							
Serum venlafaxine, metabolites			X				X

VAS = visual analog scale; VRS = verbal rating scale; pi = pain intensity; pr = pain relief; STAI = State and Trait Anxiety Inventory; BDI = Beck Depression Inventory.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen) were allowed to be used as escape medication, and their use was recorded by the patients daily. One patient who had used levodopa (3.5 50-mg tablets per day) and clomipramine (10 mg per day) for a long time continued these treatments during the trial.

Outcome Measures

The patients rated their current pain intensity (pi) on a visual analog scale (VAS), a 100-mm horizontal line marked "no pain" at one end and "worst imaginable pain" at the other, and on an 8-point verbal rating scale (VRS) before the treatment started and at each follow-up visit. The predefined primary outcome measure was the change in mean VASpi from baseline to the end of the treatment period on the maximum tolerated drug dose. Pain relief (pr) was estimated on the VASpr, a 100-mm horizontal line with "not at all" at one end, and "complete" at the other, and on a 5-point VRS.

On each visit, the State and Trait Anxiety Inventory (STAI)[19] was used to measure the patient's anxiety. Possible scores range from 20 to 80; high state anxiety scores indicate high levels of anxiety at the time of measurement. Depression was assessed with the Beck Depression Inventory (BDI).[20] Possible scores range from 0 to 63, with higher scores indicating more severe depression.

Other Measurements

At each follow-up visit, the patients were asked about 10 adverse effects (difficulty urinating, fatigue, appetite, nausea, dry mouth, constipation, sweating, nightmares, headache, palpitations). The patients also evaluated the severity of adverse effects on a 100-mm VAS.

Analysis of Serum Concentrations of Venlafaxine

Venous blood samples were collected at the end of the 4-week treatment period, 12 to 16 hours after the last dose of venlafaxine or placebo was taken. Serum levels of venlafaxine and its metabolites, O-demethylvenlafaxine, N-demethylvenlafaxine, and N,O-didemethylvenlafaxine, were determined by high-performance liquid chromatography with fluorescence detection after extraction with solid-phase columns.[21] The sensitivity of the assay was 20 nmol/L for venlafaxine and O-demethylvenlafaxine and 10 nmol/L for N-demethylvenlafaxine and N,O-didemethylvenlafaxine. The measurements were performed at the Department of Pharmacology, University of Lund, Sweden.

Statistical Analysis

Statistical differences between paired data were calculated with the Wilcoxon signed rank test. For comparison of nonparametric data, the Mann-Whitney test was applied. For analyzing parametric data, the Student *t* test was used to compare the mean values of 2 independent groups. The differences in pain scores between treatments were analyzed by the Wilcoxon signed rank test. Carryover effect and period effect were examined with the Mann-Whitney test. The correlation between plasma levels of venlafaxine and treatment effect

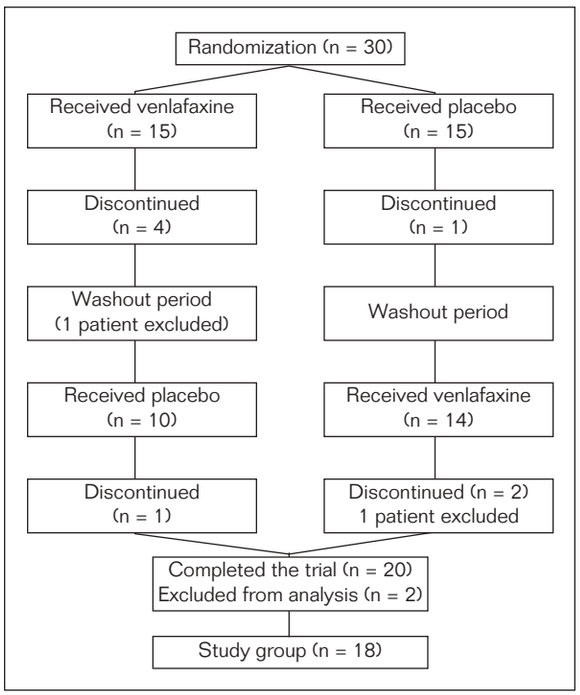

Fig 1 Study flow diagram.

was assessed with the Spearman rank correlation. Significance was set at $P < .05$.

Results

Patient Characteristics

Thirty patients were enrolled in the study (Fig 1). Twenty patients completed the trial. Data regarding 2 patients who were pain-free at the time of the first visit were excluded from the analysis. The study group thus consisted of 18 patients, 6 men and 12 women, with a median age of 52 years (range 38 to 66 years). The mean duration of the pain was 4 to 5 years (range from 1 year to more than 10 years). The pain was reported to be constant or daily by 17 patients. All patients had received many types of treatments including dental treatments, antibiotics, maxillary sinus procedures, nerve blockades, and different types of physical treatments, all with little or no effect. Six patients had tried NSAIDs, and 13 patients had taken antidepressants (mainly amitriptyline). Seven patients had been prescribed carbamazepine, 4 had been prescribed gabapentine, and 1 had been prescribed levodopa. Two patients who were on amitriptyline were withdrawn from this medication by undergoing a washout period of 2 weeks before entering the study.

Seventeen patients could increase the dose of venlafaxine to 75 mg; 1 patient remained on 37.5 mg. During placebo treatment, all patients increased the dose to 2 capsules per day. There was no carryover effect or period effect.

Eight patients discontinued use of the medication because of adverse effects (6 while on venlafaxine, 2 on placebo). The reasons given for discontinuation of venlafaxine were nausea (5 patients) or fatigue (1 patient). Three of these patients discontinued use of medication soon after starting it, the other 3 during the third week on the medication. One of the patients discontinued using the placebo because of rash on the second day on the medication, the other because of dizziness during the third week. Two patients were dropped from the study because of noncompliance: 1 patient withdrew during the washout period because of poor response to venlafaxine, the other was excluded from the study because of noncompliance during the second part of the trial (Fig 1). There were no significant differences in the characteristics of these patients and their pain compared to those completing the study. Based on the capsule count, compliance was excellent among the patients who completed the trial.

Primary Outcome Measure

There was no significant difference between venlafaxine and the placebo ($P = .64$) in pain intensity reduction from baseline to the end of the treatment period on the maximum tolerated dose (Table 2). The mean pain intensity (± SD) at baseline, at 2 weeks, and at 4 weeks with either venlafaxine or the placebo is presented in Fig 2.

Secondary Outcome Measures

Table 2 summarizes the results concerning changes in pain intensity and experienced pain relief for the study population on the maximum tolerated dose. There was no significant difference between VRSpi scores during the venlafaxine treatment and VRSpi scores during the placebo treatment ($P = .65$). The difference in pain relief between venlafaxine and placebo did not reach statistical significance when estimated on VASpr ($P = .079$), but the difference in VRSpr scores between the groups was significant ($P = .010$). STAI and BDI scores did not differ significantly between the venlafaxine and placebo treatments (Table 2).

The amount of escape medication taken during the last week of each treatment period was significantly higher during the placebo period than during the venlafaxine period ($P = .014$).

Table 2 Summary of Results (Means with Ranges) Concerning Changes in Pain Intensity, Mood, and Experienced Pain Relief

	Venlafaxine treatment				Placebo treatment				
	Baseline		4 wk		Baseline		4 wk		
Test (range)	Mean	Range	Mean	Range	Mean	Range	Mean	Range	*P**
VASpi (0–100)	42	16–94	34	0–71	45	21–98	47	13–81	.64
VRSpi (0–7)	3.5	1–6	3.3	0–5	3.9	0–6	3.9	1–5	.65
VASpr (0–100)			25	0–80			12	0–66	.079
VRSpr (0–4)			0.9	0–3			0.3	0–1	.010
STAI (20–80)	42	20–66	40	26–64	42	28–60	43	27–62	.75
BDI (0–63)	12	1–24	9	1–32	11	1–29	11	0–25	.16

Data are presented for the 18 patients included in the study group.
*Venlafaxine versus placebo; $P < .05$ was considered significant.
VAS = visual analog scale; VRS = verbal rating scale; pi = pain intensity; pr = pain relief; STAI = State and Trait Anxiety Inventory; BDI = Beck Depression Inventory.

Adverse Effects

Adverse effects were equally common during the venlafaxine and placebo periods, but patients experienced more severe sweating and dryness of the mouth during venlafaxine use than during placebo use (Table 3).

Serum Concentration

The median serum concentrations (with ranges) were 56 nmol/L (0 to 380 nmol/L) for venlafaxine, 393 nmol/L (119 to 815 nmol/L) for O-demethylvenlafaxine, 0 nmol/L (0 to 214 nmol/L) for N-demethylvenlafaxine, and 92.5 nmol/L (23 to 274 nmol/L) for N,O-didemethylvenlafaxine. No significant correlation was found between the serum concentrations of venlafaxine and its main metabolite O-demethylvenlafaxine and the response to treatment. Two patients were slow hydroxylizers of venlafaxine and had venlafaxine: O-demethylvenlafaxine ratios of 1.1 and 1.7. The former patient responded well to venlafaxine treatment and experienced increased pain with placebo treatment. The latter had no relief on either treatment.

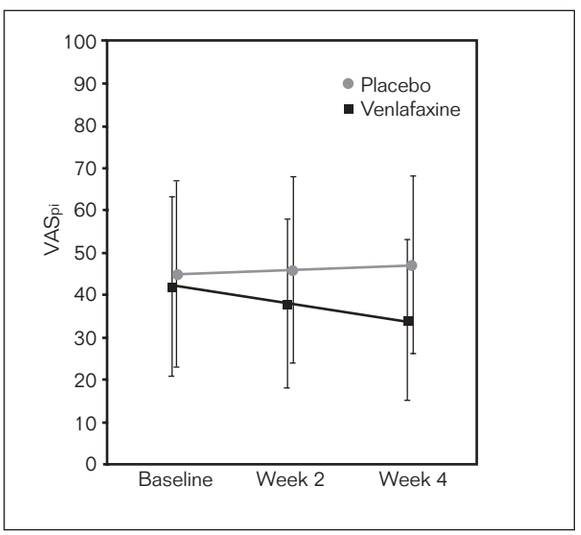

Fig 2 The mean (± SD) pain intensity during treatment with either venlafaxine or the placebo at baseline, 2 weeks, and 4 weeks.

Discussion

The present study failed to show any statistically significant difference between venlafaxine and placebo in the ability to relieve AFP when the change in mean pain intensity from baseline to the end of the treatment period was used as the primary effect variable. Most of the secondary outcome measures also did not differ significantly between the treatments. VRSpr scores as well as the use of escape medication indicated, however, statistically significant differences between the treatments in favor of venlafaxine. Scales measuring pain relief have been reported to be sensitive to small reductions in pain, and thus would seem to be more sensitive to treatment differences than pain intensity scales.[22]

The clinical ability of venlafaxine to alleviate AFP seemed only modest. Recently, it has been suggested that a reduction of approximately 30% of pain intensity or a category rating of "much improved" would imply a clinically meaningful improvement.[23] In the present study, only 3 patients had a 30% pain intensity reduction; 1 of these patients rated pain relief as much improved, but none had complete relief.

Table 3 No. of Patients Reporting Adverse Effects on the Maximum Dose and Their Severity on a VAS (0–100) Scale

	Venlafaxine		Placebo	
Symptom	n	Mean VAS	n	Mean VAS
Difficulty urinating	9	6	6	4
Fatigue	18	47	17	50
Loss of appetite	15	18	14	17
Nausea	12	13	11	11
Dry mouth	12	32*	12	21
Constipation	11	11	10	9
Sweating	18	50*	18	28
Nightmares	11	12	9	9
Headache	18	42	17	47
Palpitations	14	10	13	14

Data are presented for the 18 patients included in the study group.
*The difference between the mean VAS with venlafaxine and the mean VAS with placebo was statistically significant for dry mouth ($P = .033$) and for sweating ($P = .002$).

There are several possible explanations for the modest pain relief received with venlafaxine in the present study. The low total dose of venlafaxine used in the present trial may be the most important factor. At lower doses, venlafaxine acts primarily to inhibit serotonin reuptake; its noradrenergic effects appear at higher doses.[15,16,24] Venlafaxine could thus be more effective in pain relief at higher doses.[15] A recent randomized clinical trial (RCT)[18] on venlafaxine in painful polyneuropathy showed better results than the present study with a higher dose of venlafaxine. In that study daily doses of 225 mg probably provided high enough serum concentrations of venlafaxine and its metabolites for the inhibition of both serotonin and noradrenaline reuptake. The number needed to treat (NNT) for 1 patient to obtain at least moderate pain relief with venlafaxine was 5.2 whereas it was 2.7 for imipramine. The lowest (ie, the best) NNT value that has been achieved in previous studies in the treatment of neuropathic pain is 1.4, which was achieved with optimum doses of TCAs.[12] The high number of patients discontinuing the trial because of adverse effects might have rendered the use of any higher doses difficult in the present study. Nausea, a typical adverse effect of drugs that increase serotonin levels,[25] was the most frequent adverse effect leading to discontinuation.

To ensure adequate sensitivity of the present study, we tried to include only patients reporting at least moderate pain intensity (VASpi ≥ 3 on a scale of 1 to 10). However, on the first visit, the baseline VASpi for patients completing the trial ranged from 0 to 9, with a mean value of 3.8. In addition to the 2 patients who were pain-free at baseline and were excluded from further analysis, 8 patients had a baseline VASpi < 3. This, together with the small sample size, might have decreased the sensitivity of the present trial.[26]

The possible heterogeneity of the AFP diagnosis may also be a problem. Being aware of this, a careful diagnostic workup, including imaging and neurophysiological studies in many cases, was performed before patients were diagnosed in the present study with AFP. However, heterogenous patients with varying pathophysiological mechanisms may be diagnosed with AFP.[3] There are no unified, clearly defined diagnostic criteria for AFP.[5] The working criteria used in the present study followed those presented by Pfaffenrath et al[1] and Woda and Pionchon,[2] with the exception that some patients showed signs of subclinical neuropathy, as indicated by subtle changes in clinical sensory tests (2 cases), abnormal BR test results (2 patients with an abnormal afferent pattern of the BR and 2 with abnormal habituation), or signs of small-fiber dysfunction in QSTs (2 patients). Brain imaging studies showed normal findings in all these cases. This is in accord with a recent electrophysiological study of AFP patients.[7] In that study the BR test was found to be more sensitive than conventional brain imaging studies in revealing the subtle pathology of the trigeminal nerve. The BR test provided evidence of the role of neural mechanisms in AFP. In the present study, both patients with an abnormal BR, and thus presumably with clear neuropathy, had good pain relief.

Patients with AFP are generally considered difficult to treat.[1,3] All earlier treatment efforts had failed to produce essential symptom alleviation for the present patients. There were only 2 patients who had no earlier trials with drugs used to treat neuropathic pain.

Median serum concentrations of venlafaxine and its metabolites were similar to those in an earlier controlled trial in which 75 mg of venlafaxine was used for pain relief.[17] In that study, poor responders were found to have low venlafaxine concentrations whereas in the present study there was no correlation between venlafaxine serum concentrations and response to treatment. This lack of correlation may reflect the diagnostic problems and the possible heterogeneity of AFP.

Exaggerated responses to drugs and noncompliance with prescribed treatment have been associated with AFP patients.[3] These were also problems in the present study; about one fourth of the patients withdrew from the study because of adverse effects, but one fourth of the withdrawals occurred during the placebo period. The number of adverse effects reported by the patients completing

the study was very high, but interestingly, adverse effects were equally common during the treatments. It is difficult to estimate the actual tolerability of venlafaxine in pain treatment based on the present findings.

In conclusion, the effect of venlafaxine on AFP was only modest in terms of both statistical and clinical significance, and adverse effects were frequent. However, the result was achieved in a relatively small study with limited statistical power and with small doses of venlafaxine. This may signify that AFP patients, especially those who can tolerate higher doses of venlafaxine, may experience clinically meaningful pain relief. In the future, modern diagnostic methods may help to clarify the pain mechanisms in individual patients and lead to more carefully targeted treatment options for AFP.

Acknowledgments

This study was financially supported by the Helsinki University Central Hospital Research Fund. We are grateful to Wyeth-Lederle for providing the study medication.

References

1. Pfaffenrath V, Rath M, Pöllmann W, Keeser W. Atypical facial pain—application of the IHS criteria in a clinical sample. Cephalalgia 1993;13:84–88.
2. Woda A, Pionchon P. A unified concept of idiopathic orofacial pain: Clinical features. J Orofacial Pain 1999;13: 172–184.
3. Tenenbaum HC, Mock D, Gordon AS, et al. Sensory and affective components of orofacial pain: Is it all in your brain? Crit Rev Oral Biol Med 2001;12:455–468.
4. Sharav Y. Orofacial pain. In: Wall PD, Melzack R (eds). Textbook of Pain (ed 4). London: Churchill Livingstone, 1999: 711–737.
5. Zakrzewska JM, Hamlyn PJ. Facial pain. In: Crombie IK (ed). Epidemiology of Pain. Seattle: IASP Press, 1999: 171–202.
6. Sessle BJ. The neurobiology of facial and dental pain: Present knowledge, future directions. J Dent Res 1987;66: 926–981.
7. Jääskeläinen SK, Forssell H, Tenovuo O. Electrophysiological testing of the trigeminofacial system: Aid in the diagnosis of atypical facial pain. Pain 1999;80:191–200.
8. Feinmann C, Harris M, Cawley R. Psychogenic facial pain: Presentation and treatment. Brit Med J 1984; 288:436–438.
9. Remick RA, Blasberg B. Psychiatric aspects of atypical facial pain. J Can Dent Assoc 1985;12:913–916.
10. Lascelles RG. Atypical face pain and depression. Br J Psychiatry 1966;112:651–659.
11. McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. Pain 1996;68:217–227.
12. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to mechanism of drug action. Pain 1999;83:389–400.
13. Onghena P, Van Houdenhove B. Antidepressant–induced analgesia in chronic non–malignant pain: A meta-analysis of 39 placebo-controlled studies. Pain 1992;49:205–219.
14. Holliday SM, Benfield P. Venlafaxine. A review of its pharmacology and therapeutic potential in depression. Drugs 1995;49:280–294.
15. Ansari A. The efficacy of newer antidepressants in the treatment of chronic pain: A review of current literature. Harvard Rev Psychiatry 2000;7:257–277.
16. Mattia C, Paoletti F, Coluzzi F, Boanelli A. New antidepressants in the treatment of neuropathic pain. A review. Minerva Anestesiol 2002;68:105–114.
17. Tasmuth T, Härtel B, Kalso E. Venlafaxine in neuropathic pain following treatment of breast cancer. Eur J Pain 2002;6:17–24.
18. Sindrup SH, Bach FW, Madsen C, Gram LF, Jensen TS. Venlafaxine versus imipramine in painful polyneuropathy. A randomized, controlled trial. Neurology 2003;60: 1284–1289.
19. Spielberger CD. The measurement of state and trait anxiety; conceptual and methodological issues. In: Levi L (ed). Emotions: Their Parameters and Measurement. New York: Raven, 1975:713–725.
20. Steer RA, Beck AT. Beck Depression Inventory (BDI). In: Sederer LI, Dickey B (eds). Outcomes Assessment in Clinical Practice. Baltimore: Williams & Wilkins, 1996: 100–103.
21. Reis M, Lundmark J, Bjork H, Bengtsson F. Therapeutic drug monitoring of racemic venlafaxine and its main metabolites in an everyday clinical setting. Ther Drug Monit 2002;24:545–553.
22. Littman GS, Walker BR, Scheider BE. Reassessment of verbal and visual analog ratings in analgesic studies. Clin Pharmacol Ther 1985;38:16–23.
23. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149–158.
24. Smith D, Dempster C, Glanville J, Freemantle N, Anderson I. Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: A meta-analysis. Br J Psychiatry 2002; 180:396–404.
25. Richelson E. The pharmacology of antidepressants at the synapse: Focus on newer compounds. J Clin Psychiatry 1994;55:34–39.
26. Kalso E. Better standardisation will improve the quality of analgesic studies. Acta Anaesthesiol Scand 1996;40: 399–407.