# Palmitoylethanolamide Versus a Nonsteroidal Anti-Inflammatory Drug in the Treatment of Temporomandibular Joint Inflammatory Pain

**Ida Marini, MD, DDS**
Professor
Department of Oral Sciences
University of Bologna
Bologna, Italy

**Maria Lavinia Bartolucci, DDS**
Postgraduate Student
Department of Oral Sciences
University of Bologna
Bologna, Italy

**Francesco Bortolotti, DDS**
Postgraduate Student
Department of Oral Sciences
University of Bologna
Bologna, Italy

**Maria Rosaria Gatto, PhD**
Professor
Department of Oral Sciences
University of Bologna
Bologna, Italy

**Giulio Alessandri Bonetti, MD, DDS**
Professor
Department of Oral Sciences
University of Bologna
Bologna, Italy

**Correspondence to:**
Dr Ida Marini
Professor of Orthodontics and Gnathology
Department of Oral Sciences
University of Bologna
via san Vitale, 59–40125
Bologna, Italy
Fax: +390365375057
Email: idmarini@tin.it

***Aims:*** *To carry out a randomized clinical trial to compare the effect of palmitoylethanolamide (PEA) versus ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), for pain relief in temporomandibular joint (TMJ) osteoarthritis or arthralgia. PEA acts as an endogenous agent with an autacoid local inflammation antagonism and modulates mast cell behavior controlling both acute and chronic inflammation.* ***Methods:*** *A triple-blind randomized clinical trial was conducted on 24 patients (16 women and 8 men) aged 24 to 54 years and suffering from TMJ osteoarthritis or arthralgia. The patients were enrolled from a group of 120 consecutive patients referred to the University of Bologna's Department of Orthodontics. Patients were randomly divided into two groups: group A (12 subjects) received PEA 300 mg in the morning and 600 mg in the evening for 7 days and then 300 mg twice a day for 7 more days. Group B (12 subjects) received ibuprofen 600 mg three times a day for 2 weeks. Every patient recorded the intensity of spontaneous pain on a visual analog scale twice a day. Maximum mouth opening was recorded by a blind operator during the first visit and again after the 14th day of drug treatment. A* t *test was used for data comparisons.* ***Results:*** *Pain decrease after 2 weeks of treatment was significantly higher in group A than in group B (*P = *.0001); maximum mouth opening improved more in group A than in group B (*P = *.022).* ***Conclusion:*** *These data suggest that PEA is effective in treating TMJ inflammatory pain.*
J OROFAC PAIN 2012;26:99–104

**Key words:** NSAIDs, palmitoylethanolamide, TMJ arthralgia, TMJ osteoarthritis, TMJ pain

Osteoarthritis (OA) is the most common degenerative disease of joints, affecting at least 50% of people over 65 years of age and occurring in younger individuals following joint injury.[1,2] The temporomandibular joint (TMJ) is also commonly affected by OA. The disease is characterized initially by cartilage degradation, which precedes changes in the underlying bone. Patients present with pain (predominantly function-related), stiffness, joint sounds (crepitus), and reduced function resulting in a limited mandibular range of motion.[3] Currently, there are no available disease-modifying agents to treat OA; thus, TMJ management consists of pain-relief treatment, physiotherapy,[4] lasertherapy,[5] and ultimately surgical joint replacement. A major concern in the management of these patients is the risk of serious side effects with the use of chronic nonsteroidal anti-inflammatory drugs (NSAIDs), such as gastric ulceration and bleeding.[6] Recent evidence of an increasing

cardiovascular risk with the more selective COX-2 antagonists has also added alarm and restricted prescribing practices.[7,8] There is hence an overwhelming need for the development of new safer drugs to treat OA, which reflects chronic pain that may also have a neuropathic component.[9,18–20]

After 40 years of research in pharmacology, new compounds displaying anti-inflammatory and analgesic properties, and effective for neuropathic pain, have been characterized. Among these, palmitoylethanolamide (PEA), a fatty acid amide that belongs to the N-acylethanolamine (NAE) family,[10] a chemical analog of the endocannabinoid anandamide (AEA)[11] but without central psychotropic effect, is an interesting molecule taken into account in the present study. The anti-inflammatory and analgesic effects of PEA are due to different actions. It has been reported that PEA acts by down-regulating mast cell degranulation via an "autacoid local inflammation antagonism" (ALIA) effect[12]; however, an "entourage effect" of PEA, ie, an effect due to an enhancement of the anti-inflammatory and antinociceptive effects exerted by AEA, has also been postulated.[13] A "receptor mechanism" has also been proposed, based on the capability of PEA to stimulate directly either an as-yet uncharacterized cannabinoid CB2 receptor-like target, or the nuclear peroxisome proliferator-activated receptor-a (PPAR-a), which clearly mediates many of the anti-inflammatory effects of this compound, or the orphan receptor G-protein coupling, GPR55.[14]

Until now, no study has evaluated the PEA effect on inflammation and pain associated with the TMJ. The aim of this study was to carry out a randomized clinical trial to compare the effect of PEA versus ibuprofen, an NSAID, for pain relief in TMJ OA or arthralgia.

## Materials and Methods

### Subjects

A triple-blind, randomized, parallel arms clinical trial was conducted on 24 patients (16 women and 8 men) aged 24 to 54 years, recruited from a group of 120 consecutive patients with a complaint of orofacial pain and referred to the Department of Orthodontics, University of Bologna, Italy. The study was approved by the local ethics committee, and informed consent was obtained in accordance with guidelines of the Helsinki Declaration.

A temporomandibular disorder (TMD) diagnosis was made using Axis I group III of the Research Diagnostic Criteria for TMD (RDC/TMD).[15] Inclusion criteria were the presence of arthralgia or OA. The OA diagnosis consisted of joint pain at rest and during function, evoked pain on TMJ palpation, and crepitus. The arthralgia diagnosis was based on TMJ pain at rest, during function, and on palpation. Exclusion criteria for the study were the presence of myogenic pain, musculoskeletal pain based on Axis I of the RDC/TMD, depressive disorders according to Axis II of the RDC/TMD, odontogenic pain, pregnancy, malignancy, and other systemic rheumatologic diseases such as rheumatoid arthritis. An anamnestic questionnaire was administered to all patients to determine the participant's eligibility for the study, and a dental examination was performed to exclude odontogenic pain. Patients were screened by an experienced and RDC/TMD calibrated orofacial pain specialist (MI) who was blind to the drug administered. T1- and T2-weighted magnetic resonance imaging (MRI) was performed on each patient by the same radiologist using the same device to detect anatomical changes of both hard and soft tissues, such as flattening and erosion of the articular surfaces and possible intra-articular effusions or soft tissue involvement, in order to investigate the cause of the acute pain reported by the patients and to confirm the clinical diagnosis.

Twenty patients were found to be affected by OA and four by arthralgia. Two groups were created by using a balanced block randomization; each block was made of two subjects who were assigned to the treatments. The patients with arthralgia were randomly assigned to the groups, two in each of them. The therapeutic pattern provided 2 weeks of treatment. Group A (12 patients) received PEA 300 mg (Normast 300 Epitech) in the morning and 600 mg in the evening for 7 days and then 300 mg twice a day for another week. Group B (12 patients) received ibuprofen 600 mg three times a day after meals for 2 weeks. A supervisor assigned the subjects to the treatment; the operator who administered the treatments and the patients were blinded.

### Pain Assessment

All patients were given a 14-day diary including for each day two visual analog scales (VAS), 100-mm long, in which 0 represented "no pain" and 100 represented "the worst pain imaginable," and were instructed to report current pain level every morning and evening by putting a mark at the level that best represented their pain at the time of assessment, as described by Huskisson.[16] The differences between VAS values obtained at baseline, measured on day 1 before starting the treatments, and those measured on the last day of treatment were used for statistical analysis.

Table 1 Pain Intensity in Patients at Baseline and After Treatment with Ibuprofen or PEA

| Treatment | Baseline VAS (mm) | Final VAS (mm) | %* |
|---|---|---|---|
| Ibuprofen (n = 12) | 68.42 ± 0.15 | 37.42 ± 0.36 | 54.09 ± 0.14 |
| PEA (n = 12) | 69.96 ± 0.22 | 7.69 ± 0.19 | 11.00 ± 0.09 |

*Represents % of baseline values.

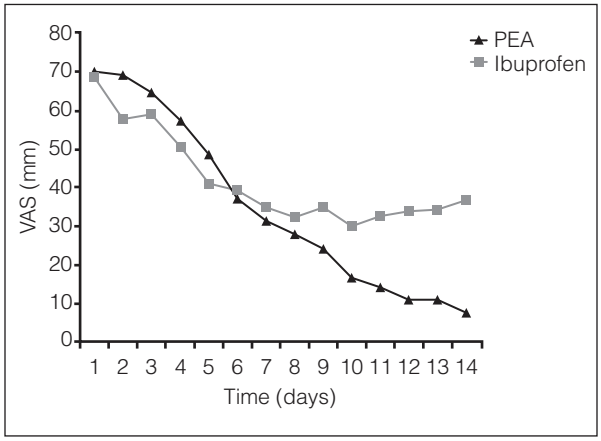


**Fig 1** VAS daily pain intensity ratings during ibuprofen or PEA treatment. The baseline VAS value was registered before starting the treatment. Values are expressed as mean ± SE; n =12 for each group; $P$ = .0001 for PEA versus ibuprofen.

### Maximum Active Mouth Opening Evaluation

Maximum active mouth opening was registered by a blinded operator before and at the end of the treatment, and a mean of three mouth-opening trials was computed each time. The vertical distance between maxillary and mandibular incisors was measured by a ruler and recorded in millimeters. The improvements of the maximum mouth opening in the ibuprofen- and PEA-treated groups were evaluated by considering the differences (expressed in millimeters) between the values obtained at the end of treatments minus baseline values. It was not possible to evaluate the improvement in the range of lateral excursion as the measurement in the acute pain phase was not reproducible.

### Adverse Effect Registration

Every patient was requested to report any adverse effect during treatment by means of a questionnaire.

### Statistical Analysis

For sample size determination, it was *a priori* assumed that data are normally distributed and variances in the groups are similar, and that group sizes are the same, and so the VAS difference measured at baseline and at the end of the treatments was computed between the two groups. The standard deviation (SD) could not be determined at the time of planning, and was given the value of 1, estimated by using the ratio between the largest VAS difference between the first day of the first week and the last day of the second week. Hypothesizing that the expected SD within each group was equal to 0.95 (a large effect size) and applying Cohen's f formula (f = 0.0475), with a power of 0.80 and $\alpha = 0.05$, 12 subjects for each group is needed.[17] Pain intensity as well as the improvement of the maximum mouth opening were obtained using mean ± SE, and VAS data were analyzed together since no significant differences were found between morning and evening in both groups by using $t$ test for paired samples. The Shapiro-Wilk test was used to examine the Gaussian distribution of the outcome variables; being that the distribution was not Gaussian, the course of pain during the two treatments was compared using $t$ test for independent samples; $\alpha$ level was *a priori* set at 0.05. The biostatistician who analyzed the data was also blinded.

## Results

At baseline, pain intensity was not significantly different between the two groups (Table 1). A progressive decrease of pain intensity was observed in ibuprofen- and PEA-treated groups during the first week of treatment; thereafter, the decrease of pain was higher in the PEA-treated group as compared to the ibuprofen-treated group (Fig 1). At the end of the treatment, pain intensity decreased to 37.42 ± 0.36 mm and 7.69 ± 0.19 mm in the ibuprofen- and PEA-treated

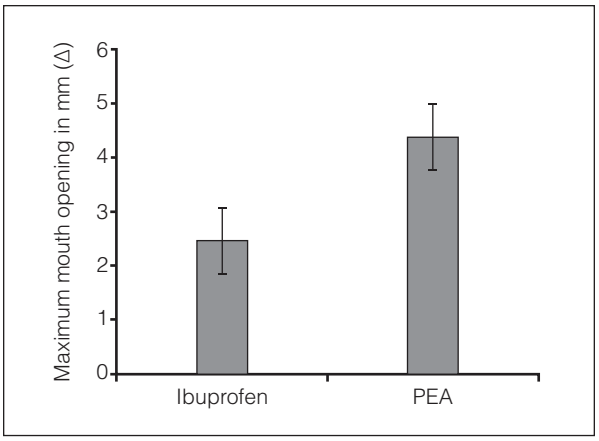


**Fig 2** Increase in maximum mouth opening in patients treated with ibuprofen or PEA reflected as the difference in maximum mouth opening between values obtained at the end of treatment minus baseline values in the two groups. Values are expressed as mean ± SE; n =12 for each group; $P$ = .022 for PEA versus ibuprofen.

groups, respectively; the difference in mean VAS values between baseline and those obtained at the end of treatment between the two groups was statistically significant ($P$ = .0001) (Fig 1).

The increase of mandibular opening in the two groups is reported in Fig 2. The maximum mouth opening mean values at baseline were 38.83 ± 0.97 mm and 38.00 ± 0.62 mm in the ibuprofen- and PEA-treated groups, respectively; mean values increased at the end of treatment, reaching the mean values 40.96 ± 0.55 mm and 42.38 ± 0.62 mm in the ibuprofen- and PEA-treated groups, respectively. The difference between the mean values obtained at the end of treatment and baseline was significantly higher in the PEA-treated group as compared to the ibuprofen-treated group ($P$ = .022).

As far as adverse effects, only three ibuprofen-treated patients reported stomachache during the second week of treatment; PEA-treated patients reported no adverse effects.

## Discussion

Degenerative joint disease with characteristic destruction of cartilage and alteration in bone is a very common cause of chronic pain, particularly in the elderly. The degree of pain does not always correlate with the extent of joint damage or the presence of active inflammation, raising the possibility that there may be a neuropathic and/or central component of the pain.[18–20] In agreement with such a view, recent studies have shown that long-term use of the standard NSAID treatment fails to reduce mean OA pain beyond minimal clinically important levels.[21,22] The results reported here corroborate this finding: the TMD patients treated with ibuprofen (at a daily dosage of 1,800 mg for 2 weeks) showed a rapid decrease in pain intensity during the first week of treatment, but there was a stabilization of VAS values starting from around day 9 to the end of treatment. A better control of pain intensity in the patients was obtained with PEA: the VAS decrease in the PEA-treated group was linear and continuous and at the end of treatment had reached a mean value < 1.0. PEA-induced pain relief was also associated with a higher improvement in maximum mouth opening at the end of the treatment as compared to ibuprofen.

PEA has been reported to exert anti-inflammatory and analgesic effects in different experimental models of acute as well as chronic pain.[23–28] The clinical use of PEA, in agreement with the Commission Directive 1999/21/EC of 25 March 1999, is allowed in Italy and other European countries as "dietary foods for special medical purposes."[29] PEA is commonly used for the treatment of chronic pain sustained by neuroimmune dysfunctions.[30,31] In previous reports, the PEA-induced pain relief has been attributed to its ability to downregulate mast cell degranulation through the ALIA effect. The pain relief induced by PEA in the TMD patients in the present study may thus be due to a control of mast cell activities. Mast cells are a normal constituent of the synovium and increase strikingly in a range of joint diseases to regulate the immune response.[32] Persistent activation and degranulation of mast cells can lead to the development of synovitis with consequent tissue damage and arthralgia and/or OA.[33] However, an involvement of peripheral and central glial cells activation in TMD pain cannot be excluded[9,34–36]; these findings raise the possibility that PEA may also downregulate the activity of glial cells as observed in cases of neuropathic pain in animal studies.[37,38]

The main limitations of this study were the lack of a placebo group (which would have assessed the real efficacy of PEA), the small sample size, and the short time of observation. Nevertheless, the high reduction of pain obtained with PEA in so short

a time is remarkable. An open question is maintenance of the PEA effects after the end of the treatment. It is necessary to obtain further insights in the reported PEA effects to validate the results in a larger study and to aquire more information concerning the maintenance of the effects. Nevertheless, these results are of particular interest since they confirm the total lack of side effects ascribed to the use of PEA, as demonstrated by clinical studies conducted on a great number of young as well as older adult subjects affected by respiratory diseases.[39–42]

In contrast, NSAIDs have been associated with an increased risk for gastrointestinal complications[43,44] and cardiovascular events including thrombosis, myocardial infarction, and stroke,[45] which can limit their chronic use in some patients, even though they offer important benefits in acute pain states. In the present study, three patients treated with ibuprofen reported stomachache during the second week of treatment.

Another possible limitation could be that a computed tomography (CT) scan, the gold standard to assess hard tissues remodelling, was not used. As the diagnosis of OA was made clinically by means of the RDC/TMD, MRI was performed to permit an evaluation of soft tissue damage and blood effusions since it has a fair sensitivity and an excellent specificity to detect OA[46] and to avoid exposing patients to radiation.

The endogenous nature of PEA and its capacity to act locally and to protect tissues against damage are the premises upon which its therapeutic applications are based: first, the lack of side effects allows the therapeutic use of PEA for long periods, and this is particularly important for patients manifesting pain associated with chronic diseases and who are already undergoing several debilitating pharmacological therapies. Secondly, the presence of a double therapeutic effect, anti-inflammatory and antinociceptive,[47] is particularly important for pathologies presenting chronic inflammatory processes such as TMJ or joint OA that continuously stimulate the somatosensory system and induce allodynia and hyperalgesia.

In conclusion, the results of the present study demonstrate that PEA is effective in reducing TMD-related OA and arthralgia pain, thus suggesting its therapeutic use as an alternative tool to ibuprofen.

## Acknowledgments

The present study was not sponsored. The authors thank very much Dr Francesco Della Valle for the scientific support.

## References

1. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010;26:355–369.
2. Wieland HA, Michaelis M, Kirschbaum BJ, Rudoplhi KA. Osteoarthritis—An untreatable disease? Nat Rev Drug Discov 2005;4:331–344.
3. Stegenga B. Temporomandibular joint degenerative diseases: Clinical diagnosis. In: Stegenga B, de Bont LGM (eds). Management of Temporomandibular Joint Degenerative Diseases: Biologic Basis and Treatment Outcome. Basel: Birkhauser, 1996:13–25.
4. Stegenga B, Dijkstra PU, de Bont LGM, Boering G. Temporomandibular joint osteoarthrosis and internal derangement. Part II: Additional treatment options. Int Dent J 1990;40:347–353.
5. Marini I, Gatto MR, Alessandri Bonetti G. Effects of superpulsed low-level laser therapy on temporomandibular joint pain. Clin J Pain 2010;26:611–616.
6. Hinz B, Brune K. Pain and osteoarthritis: New drugs and mechanisms. Curr Opin Rheumatol 2004;16:628–633.
7. Boers M. NSAID and selective COX-2 inhibitors: Competition between gastroprotection and cardioprotection. Lancet 2001;357:1222–1223.
8. Farkouh ME, Greenberg BP. An evidence-based review of the cardiovascular risks of nonsteroideal anti-inflammatory drugs. Am J Cardiol 2009;103:1227–1237.
9. Hochman JR, French MR, Bermingham SL, Hawker GA. The nerve of osteoarthritis pain. Arthritis Care Res 2010;62:1019–1023.
10. Lambert DM, Vandenvoorde S, Jonsson KO, Fowler CJ. The palmitoylethanolamide family: A new class of anti-inflammatory agents? Curr Med Chem 2002;9:663–674.
11. Devane WA, Hanus L, Breuer A, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258:1946-1949.
12. Aloe L, Leon A, Levi-Montalcini R. A proposed autacoid mechanism controlling mastocyte behavior. Agents Actions 1993;39:145–147.
13. Ben-Shabat S, Fride E, Sheskin T, Tamiri T, Rhee MH, Vogel Z. An entourage effect: Inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. Eur J Pharmacol 1998;353:23–31.
14. Petrosino S, Iuvone T, Di Marzo V. N-palmitoyl-ethanolamine: Biochemistry and new therapeutic opportunities. Biochimie 2010;92:724–727.
15. Dworkin SF, Le Resche L. Research diagnostic criteria for temporomandibular disorders: Review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.
16. Huskisson EC. Measurement of pain. Lancet 1974;304: 1127–1131.
17. Cohen J. Chi-square tests for goodness of fit and contingency tables. In: Cohen J (ed). Statistical Power Analysis for the Behavioral Sciences, ed 2. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988:215–272.
18. Kosek E, Ordeberg G. Abnormalities of somatosensory perception in patients with painful osteoarthritis normalize following successful treatments. Eur J Pain 2000;4:229–238.
19. Kidd BL, Langford RM, Wodehouse T. Arthritis and pain: Current approaches in the treatment of arthritic pain. Arthritis Res Ther 2007;9:214.
20. Park JW, Clark GT, Kim YK, Chung JW. Analysis of thermal pain sensitivity and psychological profiles in different subgroups of TMD patients. Int J Oral Maxillofac Surg 2010;39:968–974.

21. Bjordal JM, Klovnig A, Ljunggren AE, Slordal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritis knee pain: A meta-analysis of randomised placebo-controlled trials. Eur J Pain 2007;11:125–138.
22. Neame R, Zhang W, Doherty M. A historic issue of the Annals: Three papers examine paracetamol in osteoarthritis. Ann Rheum Dis 2004;63:897–900.
23. Mazzari S, Canella R, Petrelli L, Marcolongo G, Leon A. N-(2-hydroxyethyl)hexadecanamide is orally active in reducing edema formation and inflammatory hyperalgesia by down-modulating mast cell activation. Eur J Pharmacol 1996;300:227–236.
24. Calignano A, La Rana G, Giuffrida A, Piomelli D. Control of pain initiation by endogenous cannabinoids. Nature 1998;394:277–281.
25. Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 ewceptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. Pain 1998;76:189–199.
26. Conti S, Costa B, Colleoni M, Parolaro D, Giagnoni G. Antiinflammatory action of endocannabinoid palmitoylethanolamide and the synthetic cannabinoid nabilone in a model of acute inflammation in the rat. Br J Pharmacol 2002;135:181–187.
27. Costa B, Conti S, Giagnoni G, Colleoni M. Therapeutic effect of the endogenous fatty acid amide, palmitoylethanolamide, in rat acute inflammation: Inhibition of nitric oxide and cyclo-oxygenase systems. Br J Pharmacol 2002;137:413–420.
28. D'Agostino G, La Rana G, Russo R, et al. Central administration of palmitoylethanolamide reduces hyperalgesia in mice via inhibition of NF-kappaB nuclear signalling in dorsal root ganglia. Eur J Pharmacol 2009;613:54–59.
29. Italian Department of Health website. http://www.salute.gov.it/imgs/C_17_pagineAree_1270_listaFile_itemName_3_file.pdf. Accessed 30 March 2012.
30. Calabró RS, Gervasi G, Marino S, Mondo PN, Bramanti P. Misdiagnosed chronic pelvic pain: Pudendal neuralgia responding to a novel use of palmitoylethanolamide. Pain Med 2010;11:781–784.
31. Indraccolo U, Barbieri F. Effect of palmitoylethanolamide-polydatin combination on chronic pelvic pain associated with endometriosis: Preliminary observations. Eur J Obstet Gynecol Reprod Biol 2010;150:76–79.
32. Nigrovic PA, Lee DM. Synovial mast cells: Role in acute and chronic arthritis. Immunol Rev 2007;217:19–37.
33. De Filippis D, D'Amico A, Iuvone T. Cannobinomimetic control of mast cell mediatore release: New perspective in chronic inflammation. J Neuroendocrinol 2008;20 (suppl 1):20–25.
34. Guo W, Wang H, Zou S, Wei F, Dubner R, Ren K. Long lasting pain hypersensitivity following ligation of the tendon of the masseter muscle in rats: A model of myogenic orofacial pain. Mol Pain 2010;6:40–52.
35. Garrett FG, Durham PL. Differential expression of connexins in trigeminal ganglion neurons and satellite glial cells in response to chronic or acute joint inflammation. Neuron Glia Biol 2008;4:295–306.
36. Chiang CY, Dostrovsky JO, Iwata K, Sessle BJ. Role of glia in orofacial pain. Neuroscientist 2011;17:303–320.
37. Loría F, Petrosino S, Mestre L, et al. Study of the regulation of the endocannabinoid system in a virus model of multiple sclerosis reveals a therapeutic effect of palmitoylethanolamide. Eur J Neurosci 2008;28:633–641.
38. Costa B, Comelli F, Bettoni I, Colleoni M, Giagnoni G. The endogenous fatty acid amide, palmitoylethanolamide, has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: Involvement of CB(1), TRPV1 and PPARgamma receptors and neurotrophic factors. Pain 2008;139:541–550.
39. Masek K, Perlík F, Klíma J, Kahlich R. Prophylactic efficacy of N-2-hydroxyethyl palmitamide (impulsin) in acute respiratory tract infections. Eur J Clin Pharmacol 1974;7: 415–419.
40. Plesník V, Havrlantová M, Jancová J, Januska J, Macková O. Impulsin in the prevention of acute respiratory diseases in school children. Cesk Pediatr 1977;32: 365–369.
41. Kahlich R, Klíma J, Cihla F, et al. Studies on prophylactic efficacy of N-2-hydroxyethyl palmitamide (Impulsin) in acute respiratory infections. Serologically controlled field trials. J Hyg Epidemiol Microbiol Immunol 1979;23:11–24.
42. Wiedermannová D, Lokaj J, Wiedermann D. Prophylactic administration of impulsin to clinically healthy children. The effect on T and B lymphocytes in peripheral blood [in Czech]. Cas Lek Cesk 1979;118:1249–1251.
43. Scheiman JM. The impact of nonsteroidal anti-inflammatory drug-induced gastropathy. Am J Manag Care 2001;7 (suppl 1):S10–S14.
44. Singh G, Ramey DR, Morfeld D, et al. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. Arch Intern Med 1996;156:1530–1536.
45. Warner TD, Mitchell JA. COX-2 selectivity alone does not define the cardiovascular risks associated with nonsteroidal anti-inflammatory drugs. Lancet 2008;371:270–273.
46. Ahmad M, Hollender L, Anderson Q, et al. Research diagnostic criteria for temporomandibular disorders (RDC/TMD): Development of image analyses criteria and examiner reliability for image analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:844–860.
47. Re G, Barbero R, Miolo A, Di Marzo V. Palmitoylethanolamide, endocannabinoids and related cannabimimetic compounds in protection against tissue inflammation and pain: Potential use in companione animals. Vet J 2007;173:23–32.