

included drowsiness/tiredness (3), increased appetite/weight gain (2), mood swings (2) and worsening of headache (2). Flunarizine was discontinued in 17: due to adverse effects in 8 and poor response in 9. **Conclusions:** In the cohort studied, Flunarizine appears to be highly effective in hemiplegic migraine in comparison to other subgroups. In 14% of this group, adverse effects led to discontinuation of Flunarizine.

PO346

Zonisamide in prophylaxis therapy of the episodic and chronic cluster headache. An open study

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Objectives: To evaluate the efficacy and tolerability of zonisamide in prophylaxis therapy of ECH and CCH.

Background: The prophylactic therapy of the episodic (ECH) and chronic cluster headache (CCH) is based on verapamil and carbolothium. Besides several patients are not responders at this drugs. In these cases the use of antiepileptic drug has been proposed. Zonisamide, a new antiepileptic drug, has been reported efficacy in the migraine patients. The drug has mechanisms of action that suggest it may reduce the neuronal hyperexcitability. These mechanisms include facilitation of dopaminergic and serotonergic neurotransmission, reduction of glutamate-mediated synaptic excitation and increased gamma-aminobutyric acid (GABA) release. Zonisamide has a favourable pharmacokinetic profile which includes high oral bio-availability and a long half-life (63 hours), permitting a once or twice daily dosing regimen. Recent clinical experience indicates a place for zonisamide in the management of headache disorders.

Methods: 13 patients (pz), (4 F,7 M) mean age 42.8 years (SD 5.8), range 36–56 years, suffering from ECH (8pz) and CCH (5 pz) (ICDH '04 criteria) were studied. In all patients with ECH prophylaxis therapy with verapamil, carbolothium and valproic acid was failed in the past and patients with CCH continued therapy with carbolothium (2 pz) and verapamil (1 pz). During the three months evaluation period zonisamide was administered (starting dose 25 mg/die, target dose 100 mg/die). All patients filled a headache-diary card during the evaluation.

Results: In patients with ECH the basal frequency of attack/days and 1, 2, 3 months respectively was 4.2 (SD 1.9): 2.4 (SD 0.9), 1.6 (SD 0.9), 0.8 (SD 1.1) ($P < 0.0001$). In patients with chronic CH the basal frequency of attack/days and 1, 3, 6 months respectively was 2.8 (SD 1.3): 0.4 (SD 0.3), 0.2 (SD 0.2), 0.1 (SD 0.1) ($P < 0.005$) (*t*-test analysis). In all patients zonisamide was well tolerated (5 patients complained somnolence, lack of concentration, vertigo and nausea but not withdrew the study).

Conclusions: These data showed a good efficacy in reduction of frequency of attacks. Still, the drug is tolerable, in fact none patients withdrew the study. Our study suggests that zonisamide could be an alternative or complementary prophylaxis therapy for ECH and CCH. Controlled studies are warranted to determine the efficacy of zonisamide in prophylaxis therapy for ECH and CCH.

PO347

Repression of acute and chronic inflammatory changes in trigeminal ganglion neurons and glia in response to cocoa enriched diets

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Objectives: To determine the cellular effects of a cocoa-enriched diet on neurons and glia in the trigeminal ganglion under basal conditions, and in response to acute or chronic inflammation.

Background: Recent studies involving *Theobroma cacao* have shown promise in the treatment of a variety of disorders. However, most research involving the beneficial effects of cocoa has been limited to *in vitro* studies. The balance between inflammatory proteins such as the MAP kinases (MAPK), and anti-inflammatory proteins such as the MAP kinase phosphatases (MKP) play a critical role maintaining homeostasis in the trigeminal nociceptive system. It is thought that an imbalance between MAPK and MKP proteins may play a role in the pathophysiology of migraine.

Methods: Sprague Dawley rats were fed a control diet or isocaloric diets enriched in cocoa [1% (g/g) or 10% (g/g)] for 14 days prior to an injection of capsaicin or complete Freund's adjuvant (CFA). While capsaicin injection mediates an acute inflammatory response, CFA was used to cause a chronic inflammatory response. Levels of active ERK, active p38, iNOS, CGRP, MKP-1, MKP-3, and IL-10 were examined in trigeminal ganglion neurons and glia by immunohistochemistry. In addition, total RNA was isolated and then used in qPCR to determine the effect of cocoa enriched diets on CGRP mRNA levels.

Results: Rats that received injections of capsaicin or CFA were found to have increased levels of staining of the active forms of the MAPK's ERK and p38 in trigeminal ganglion neurons, while CFA injections also caused increased expression of the signaling protein iNOS, which plays an important role in mediating inflammatory responses. However, the stimulatory effects of capsaicin or CFA on these signaling proteins were repressed to basal levels in rats fed cocoa enriched diets. Expression of MKP-1 was increased in both neurons and glia while MKP-3 and the anti-inflammatory molecule IL-10 were increased only in neurons in rats on a cocoa enriched diet. Furthermore, rats on cocoa enriched diets exhibited decreased CGRP mRNA and protein expression in trigeminal ganglion neurons.

Conclusions: Cocoa enriched diets are able to repress the stimulated expression of proteins associated with the promotion and maintenance of inflammatory and nociceptive responses. The inhibitory effects of cocoa are likely to be mediated via increased basal expression of the anti-inflammatory proteins MKP-1, MKP-3, and IL-10. To our knowledge, this is first evidence for the use of cocoa as a dietary supplement to cause an upregulation of MKPs and IL-10 as well as repress expression of acute and chronic inflammatory responses within trigeminal ganglia. Importantly, our data also provide evidence that cocoa contains biologically active compounds that could be beneficial in the treatment of trigeminal-mediated diseases of the head and face.

PO348

Pilot study to assess the efficacy of combining valproic acid with a clenching reduction dental splint (NTI) as prophylactic treatment for primary headache disorders

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Objectives: To demonstrate that the combination of medical and dental prophylactic treatments for primary headache disorders will produce a greater benefit than either treatment alone.

Background: Preventive treatments for migraine and tension type headache are often limited by patient compliance and poor tolerability, as escalating adverse side effects are anticipated as dosages of preventive medications increase. Primary headache disorders have multiple mechanisms that lead to ongoing headaches and it is likely that more than one treatment might be needed in an individual patient to control the disorder. To date, there are few studies that assess combination treatments in primary headache disorders. In this pilot study we describe a comparative study of the efficacy of nociceptive trigeminal inhibition (NTI) and Valproic acid (VA) in the treatment of migraine and tension-type headaches.

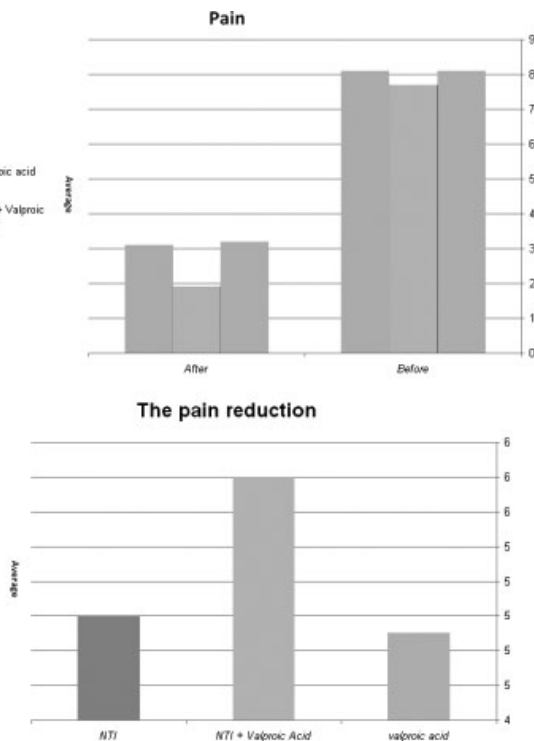


Figure 1

Methods: Sixty patients, 18 years of age and older, non-pregnant, who met International Headache Society criteria for migraine and tension-type headaches were randomly assigned to three treatment groups. 20 patients per treatment arm as follows: Valproic acid alone, NTI splint alone, and combination of NTI and Valproic Acid. Valproic Acid dose in the treatment arms was 200 mg bid. Clinical follow-up was performed for 8 weeks at weekly intervals. The patients reported headache on a visual analog scale before treatment and also after every week in their treatment period. Side effects were reported. Data were collected and compared between the groups using the Mann-Whitney and Wilcoxon test.

Results: VAS score changes were as follows:

Valproic acid users showed a 61% reduction in headache. NTI users showed a 62% reduction in headache. NTI and Valproic acid users showed a 76% reduction in headache. The P -value is <0.0001 for the combination treatment compared with either treatment alone. No side effects reported with the NTI splint. Side effects reported for Valproic Acid included: gastro-intestinal upset, alopecia and depression. No patients discontinued the study due to adverse events.

Conclusions: No statistical difference in treatment efficacy was noted between the Valproic acid and NTI treatment arms. However, there was a statically significantly superior improvement for the combination of Valproic Acid and NTI compared to either of the two individual treatments. There were no adverse side-effects with the NTI, while side effects were present for patients treated with Valproic Acid. Greater therapeutic gain, without an escalation of side effects, results from the combination of the two treatments.

PO349

Sustained efficacy of botulinum toxin type-A (BTXA) on migraine-related disability over 3 treatment cycles in a community-based setting

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Objectives: To retrospectively assess the effect of botulinum toxin type-A (BTXA) on migraine disability over 3 consecutive treatment cycles scheduled at 3-month intervals in a community-based headache subspecialty practice.

Background: Prior studies using BTXA have shown a decrease in migraine-related disability, headache days and acute medication usage. These findings have the potential to result in a substantial reduction in disease burden for patients, employers, insurers and society if this is maintained over serial treatment cycles.

Methods: Forty consecutive patients treated for either chronic migraine (15 or more headache days per month) or high frequency migraine (8–14 days per month) who underwent 3 consecutive courses of BTXA treatment at 3-month intervals were retrospectively reviewed. The primary endpoint was a reduction in Migraine Disability Assessment Scores (MIDAS). Secondary endpoints included a decrease in headache days and as well as a decrease in acute medication use.

Results: Average MIDAS scores decreased from a baseline of 62.8 to 29.2 (treatment 1), 31.1 (treatment 2) and 24.8 (treatment 3) over 3 consecutive cycles. Headache days decreased from a baseline of average of 20.7 days per month to 11.6 (treatment 1), 9.8 (treatment 2) and 9.5 (treatment 3) days per month respectively. Monthly acute medication doses decreased from a baseline average of 51.5 to 27.85 (treatment 1), 24.25 (treatment 2) and 21.4 (treatment 3) for the 3 cycles of treatment.

Conclusions: In our retrospective analysis of 40 consecutive patients there was a sustained reduction in migraine-related disability, headache days and acute medication use.

PO350

Levetiracetam as migraine prophylaxis in topiramate-failures

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Objectives: To report a series of topiramate-failures (TFs) who demonstrate success with levetiracetam (LVT) for migraine prophylaxis, and to illustrate key characteristics that may be associated with success in this subgroup.

Background: Failure of standard prophylactic treatments for migraine poses an important dilemma for headache specialists. Previous studies suggest that LVT might be equal to topiramate (TPM) but with better tolerability. LVT has a unique mechanism of action.

Methods: We present a case series of TFs whose headaches improved dramatically with LVT. Patients were included with a diagnosis of migraine meeting the new IHS classification criteria, ≥ 4 days per month of migraine for ≥ 3 months, and previous treatment with TPM for ≥ 3 months. Patients were excluded if they had ≥ 20 days per month of migraine for ≥ 3 months, chronic use of opiate medication, or an uncontrolled medical condition, including concurrent severe depression.

Results: Seven patients with migraine are presented; 2 cases with aura, and 5 without aura. The mean age was 54, with 6 females and 1 male. The mean number of years with migraine was 20 (range of 5–40). Each patient had failed various standard prophylactic treatments including propranolol, amitriptyline, verapamil, valproic acid, and in all patients, TPM, with doses up to 400 mg per day. With respect to TPM, 3 patients discontinued treatment due to intolerable side effects including hair loss, excessive drowsiness, and cognitive slowing, 3 continued treatment and 1 discontinued treatment due to lack of therapeutic

COMBINATION THERAPY: DEPAKOTE with an NTI Clenching Reduction Dental Splint for Prophylactic Treatment of Primary Headache: A Pilot Study for Efficacy Assessment

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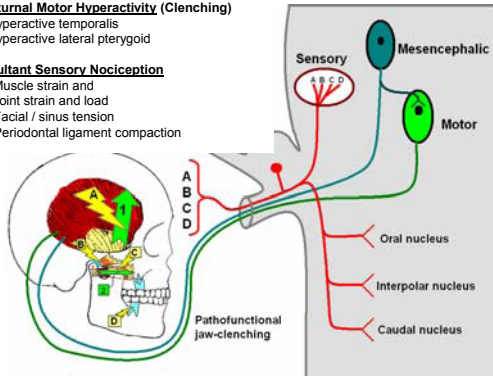
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Background – The NTI (Nociceptive Trigeminal Inhibition) intraoral device reduces maximum nocturnal trigeminal motor hyperactivity (jaw clenching), and is hypothesized to therefore reduce resultant noxious afferent activity. The NTI has been FDA approved for the prophylactic treatment of medically diagnosed migraine pain.

Nocturnal Motor Hyperactivity (Clenching)
1. Hyperactive temporalis
2. Hyperactive lateral pterygoid

Resultant Sensory Nociception
A) Muscle strain and
B) Joint strain and load
C) Facial / sinus tension
D) Periodontal ligament compaction



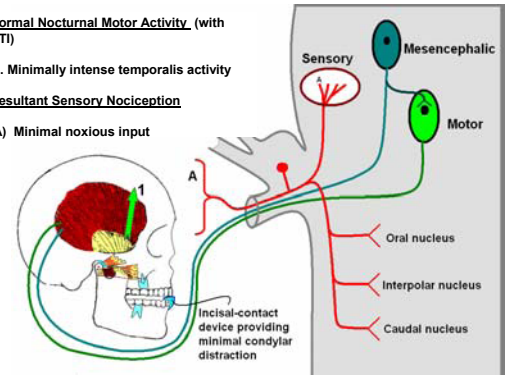
An NTI device is custom made by a dental professional, providing only for incisor-edge contact with minimal jaw-opening (to minimize TMJ strain)

Normal Nocturnal Motor Activity (with NTI)

1. Minimally intense temporalis activity

Resultant Sensory Nociception

A) Minimal noxious input



Providing for only incisor-edge contact with an NTI device minimizes trigeminal nociception.

Molar and canine tooth contact allows for pathologic intensity of trigeminal motor hyperactivity (nocturnal jaw clenching)

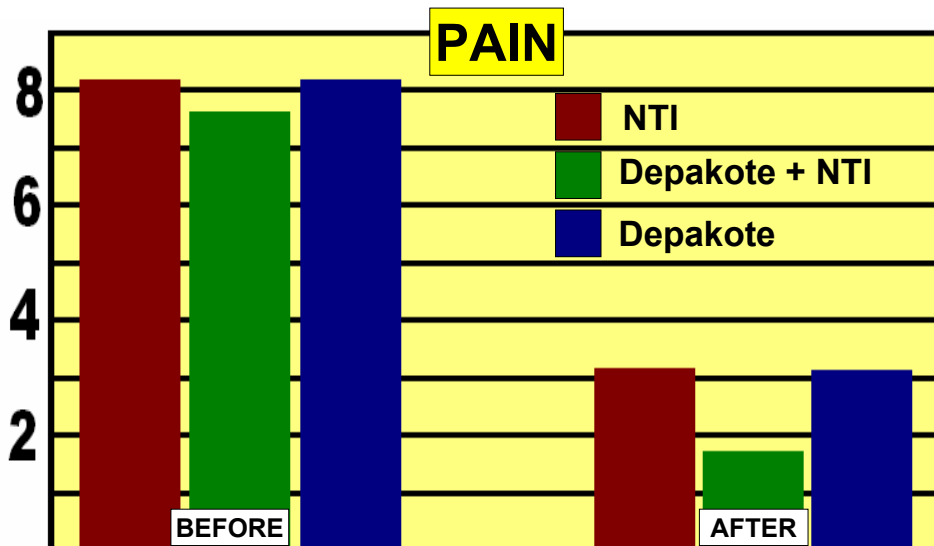
In a previous study (presented at the Headache and Migraine Trust International Congress 2008), 20 consecutive refractory CDH patients treated in a headache center, all scoring “severe and disabling” on their HIT-6 questionnaire despite maximal oral prophylactic medication, were properly fitted with an NTI device and wore nightly for 9 months.

Within two months of nightly NTI use, and then persisting for the nine months of observation, half of the subjects had a significant improvement, while 25% reported that chronic headache *no longer had any impact on their lives*.

DEPAKOTE (valproic acid) is FDA approved for prophylactic treatment of migraine.

The adverse events with Valproic acid treatment include: weight gain, fatigue, alopecia, hirsutism, tremor, and liver function abnormalities. Most of the side effects are dose related and worsen with higher doses.

Methods: 60 patients, 18 years of age and older, non-pregnant, met IHS criteria for migraine and tension-type headaches; randomly assigned to three treatment groups, 20 pts per arm: Valproic acid alone, NTI splint alone, and combination of NTI and Valproic Acid. Valproic Acid dosage in the treatment arms was 200 mg bid. Clinical follow-up was performed for 8 weeks at weekly intervals. The patients reported headache on a visual analog scale before treatment and also after every week in their treatment period. Side effects were reported. Data collected and compared between the groups using the Mann-Whitney and Wilcoxon test.



Results: There was a statically significantly superior improvement for the combination of Valproic Acid and NTI compared to either of the two individual treatments, with no statistical difference in treatment efficacy between the Valproic acid and NTI treatment arms. There were no systemic adverse side-effects with the NTI, while side effects were present for patients treated with Valproic Acid but did not worsen when combined with the NTI.

Conclusion: The known therapeutic gain of Valproic Acid can be increased *without risking the escalation of the known side effects of increasing dosage*, by combining Valproic Acid with the proper use of an NTI device.