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Obesity and Headache: Part II – Potential Mechanism and Treatment Considerations

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Abstract

Obesity and headache are both associated with a substantial personal and societal impact, and epidemiologic studies have consistently identified a positive association between obesity and headache in general, as well as obesity and migraine specifically (see part I). In the current manuscript, we will discuss the potential mechanisms for the migraine–obesity association, with a focus on the central and peripheral pathophysiological pathways which overlap between migraine and those modulating the drive to feed. We then discuss surgical, behavioral, and pharmacological

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treatment considerations for overweight and obese migraineurs as well as for those with idiopathic intracranial hypertension. We close by briefly discussing where future research may be headed in light of this data.

Keywords

headache; migraine; obesity; body mass index

Obesity is a risk factor for headache in general, as well as for episodic migraine (EM) and chronic migraine (CM) specifically.[1,2] Obesity is also associated with certain secondary headache conditions such as idiopathic intracranial hypertension (see Part I).[1] Although the direction of the headache/migraine–obesity association has not been determined, it has been hypothesized that shared overlapping pathophysiologic mechanisms and/or lifestyle and behavioral factors may contribute to this relationship. Further, given that obesity is a modifiable risk factor for migraine, the question as to the efficacy of weight loss programs (non-surgical or surgical) for migraine prevention is an important one.

In this manuscript, we first review the central and peripheral pathways regulating feeding and adipose tissue function, with a focus on the overlapping mechanisms implicated in migraine. Next, we review the surgical and behavioral treatment options (including diet and exercise therapies) for overweight and obese patients with migraine as well as those with idiopathic intracranial hypertension, a secondary headache condition with strong associations with obesity. We also discuss pharmacologic considerations when treating overweight or obese headache patients. We close by touching on the current data on surgical and lifestyle interventions for overweight and obese migraineurs, as well as where future research is headed.

Central Regulation of Feeding and Its Overlap With Migraine Pathophysiology

The regulation of feeding is controlled by the hypothalamus and its connections.[3] The arcuate nucleus (ARC) of the hypothalamus contains both orexigenic and anorexigenic neuropeptides.[4,5] Signals from the ARC neurons are then transmitted to other hypothalamic nuclei, including the paraventricular nucleus (which expresses adiponectin [ADP] and leptin receptors), the ventromedial nucleus, and the lateral hypothalamus (LH) nucleus.[3–6] The LH contains 2 groups of neurons:the orexin neurons (which stimulate feeding) and the melanin-concentrating hormone neurons (which inhibit food intake). These neurons subsequently project to the brainstem nuclei (eg, the nucleus tractus solitarius and the dorsomotor nucleus of the vagus) where the descending hypothalamic inputs are integrated with peripheral inputs from the gastrointestinal system.[3–5]

The hypothalamus has also been implicated in migraine. This was initially suggested based on the observations of hypothalamic premonitory and postdromal symptoms in migraineurs, such as food cravings as well as mood and sleep disturbances.[7] Additionally, functional imaging has demonstrated hypothalamic activation during acute migraine attacks.[8] Thus, one could hypothesize that a pathological modulation of the hypothalamus in migraineurs may result in hyperphagia and weight gain. Additionally, the existing data support that several hypothalamic peptides, proteins, and neurotransmitters involved in feeding contribute to migraine pathophysiology. Notably, these include serotonin, orexin, and adipokines (eg, ADP).[9] Therefore, it is also possible that modulation of the release of these hypothalamic peptides and proteins in association with the drive to feed or not feed and/or by states of obesity may trigger or contribute to the generation of migraine headaches. A full

review of the connection of these neurotransmitters and proteins with migraine and satiety has been previously published;[10] below, we summarize key points.

Serotonin

Serotonin is a neurotransmitter synthesized from the essential amino acid tryptophan. Interictal levels of plasma serotonin have been shown to be low in migraineurs.[11] In contrast, serotonin levels increase in migraineurs during acute attacks.[12]

In animal models, disruption of the 5-HT_{2C} receptor is associated with increased feeding and the development of obesity.[13] Thus, low serotonin states in migraineurs interictally may promote an increased drive for feeding, whereas high levels ictally may promote hypophagia.[14,15] Not surprisingly, several drugs that modulate serotonin and its receptors, including those receptors most directly implicated in satiety, the 5-HT_{1B} and 5-HT_{2C} receptors, are also used in the management of migraine.[11,16–18]

Orexin

As with serotonin, orexin has been linked to headache and satiety. Specifically, orexin A (OXA) and orexin B are peptides secreted by neuronal cell bodies primarily localized in the hypothalamus, with axonal projections to the cortex and brainstem, superficial lamina of the spinal cord, and the gastrointestinal tract.[19,20] Orexin acts on 2 G-protein-coupled receptors, OXR1 and OXR2, and have been shown to modulate the drive to feed.[19–22] Specifically, centrally administered orexin in rats has been shown to increase food intake.[23] Animal and human data also support a role for orexins in pain processing.[20] In rat pain models, intrathecally administered OXA has anti-hyperalgesic properties,[24–28] and the specificity of OXA's anti-hyperalgesic effect has been demonstrated by its inhibition when pretreated with the orexin receptor antagonist.[25,29] Additionally, in humans, OXA levels have been shown to be elevated in the cerebrospinal fluid of chronic daily headache sufferers.[30] The findings of OXA's anti-hyperalgesic properties in animal models and the elevated OXA levels in those with chronic daily headache may suggest orexin resistance or disruptions in orexin receptors in those with chronic headache (which explains the continued pain while having elevated OXA levels). The full role of the orexins and their receptors in migraine is still being determined. Further research evaluating ictal and interictal orexin levels in migraineurs as well as the integrity of orexin receptors is warranted.

Adipocytokines

In addition to peptides and neurotransmitters, adipocytokines participate in energy homeostasis as well as immunity and inflammation. ADP and leptin are 2 such adipocytokines.

ADP—ADP is a protein primarily secreted from adipocytes, with receptors expressed in the endothelium of blood vessels and the brain, including in the hypothalamus.[31,32] ADP's pro- or anti-inflammatory properties are primarily determined by the form of ADP involved. ADP undergoes oligomerization and is released in the blood as trimers (low molecular weight [LMW]), hexamers (middle molecular weight [MMW]), larger complexes (high molecular weight [HMW] multimers), and a globular fraction (globular ADP [gADP]). In humans, while HMW-ADP and MMW-ADP *activate* the NFkβ pathways and induce interleukin (IL)-6 secretion, LMW-ADP *decreases* IL-6 secretion.[33] Additionally gADP may have both pro and anti-inflammatory properties.[34] Animal and human macrophages pre-exposed to *low* doses of gADP for 24 hours showed marked secretion of pro-inflammatory cytokines with re-exposure to gADP; however, macrophages pre-exposed to *high* dose gADP for 24 hours inhibited subsequent cytokine secretion. Investigators

hypothesized that ADP-mediated induction of macrophages can form tolerance and cause an "anti-inflammatory" effect when there is high enough circulating levels.[34]

As with migraine, ADP exhibits a sexual dimorphism, with women having greater ADP levels compared with men.[34,35] The majority of studies also support that ADP levels are inversely associated with obesity, with obese individuals having lower fasting ADP levels.[36,37]

In the first trial evaluating interictal ADP levels in episodic and chronic migraineurs,[38] ADP and its multimers were measured in 37 participants (EM: 13; CM: 12; Control 12). Total (T)-ADP levels were increased in chronic migraineurs at baseline level of pain as compared with controls, but not in episodic migraineurs (when pain-free) as compared with controls. The authors reported that this elevation in total ADP in chronic migraineurs was largely due to the increase in HMW-ADP.[38]

In a more recent pilot study of 20 female episodic migraineurs, Peterlin et al evaluated ictal ADP levels in 20 EM participants before and after treatment with either sumatriptan/naproxen sodium or placebo. In all 20 participants, both the HMW : LMW ADP ratio and LMW-ADP multimer levels were associated with migraine severity.[9] Specifically, for every 1 point increase in the HMW : LMW ratio, pain severity increased by 0.22 (95% CI: 0.07, 0.37; $P = .004$). In contrast, for every 0.25 μg/mL increase in LMW-ADP, pain severity decreased by 0.20 (95% CI: −0.41, −0.002; $P = .047$). Further, following administration of the study treatment, T-ADP levels were reduced at 30 min (12.52 ± 3.4; $P = .03$), 60 min (12.32 ± 3.2; $P = .017$), and 120 min (12.65 ± 3.2; $P = .016$) as compared with prior to treatment onset(13.48 ± 3.8), in the 11 treatment responders. Responders also showed a decrease in the HMW : LMW ratio (ie, toward an anti-inflammatory direction) at 60 min (2.37 ± 1.1; $P = .002$) and 120 min (2.76 ± 1.4; $P = .02$) after treatment as compared with onset (3.70 ± 1.9). In contrast, non-responders showed an increase in the HMW : LMW ratio (ie, toward a pro-inflammatory direction) at 120 min (1.93 ± 1.69; $P = .025$) as compared with onset. These findings suggest that ADP has potential as an operational acute migraine biomarker and of treatment response in migraineurs. Larger studies evaluating ictal and interictal ADP and its oligomers in both women and men are warranted.

Leptin—Like ADP, leptin is primarily produced by adipocytes, but also by several other tissues including the brain.[39] Leptin is inhibited by testosterone and increased by ovarian sex steroids, with women exhibiting levels which are 2–3 times higher than men even when matched for age and body mass index (BMI).[10,40] Additionally, although leptin is associated with satiety, obese individuals generally exhibit high circulating concentration of leptin, suggesting leptin resistance in states of obesity.[36]

As with orexin and ADP, leptin has also been implicated in the modulation of inflammation and pain.[4,41] However, studies evaluating leptin levels in migraineurs have been inconclusive, with data suggesting both low and elevated levels in migraineurs. In a study of 61 episodic migraineurs and 64 controls, fasting leptin levels were reported to be decreased in migraineurs (40.1 ± 21.2 ng/mL) interictally as compared with controls (48.5 ± 24.5 ng/mL; $P < .05$).[42] A second study which evaluated serum leptin levels in migraineurs before and after preventive treatment (tx) with amitriptyline reported increased leptin levels after treatment (pre-tx: 7.15 ± 1.12; post-tx: 16.85 ± 2.38, $P < .01$).[43] However, one small case series of 6 migraine patients reported that leptin was decreased by 39.2 ± 6.5% from baseline following 20 weeks of treatment ($P = .013$).[44] Most recently Bernecker et al evaluated fasting leptin levels in 40 non-obese female migraineurs. Although crude leptin levels in EM participants (15.07 ± 9.63) were greater than controls (9.99 ± 5.62; $P < .01$), this association was no longer significant after adjustment for age and BMI.[45] Given the

available data, one could speculate that leptin levels may be low in migraineurs who have had the disease for longer durations since some data have suggested that chronic exposure to inflammation may be associated with decreased leptin levels.[46]

Peripheral Regulation of Adiposity and Its Overlap With Migraine Pathophysiology

Expansion of adipose tissue during weight gain leads to the recruitment of macrophages and T-cells, and directly results in the induction of adipocytokines and expression of several pro-inflammatory cytokines,[6,47] including IL-1, IL-6, and tumor necrosis factor (TNF)-α. Approximately one third of the IL-6 concentration in the circulation of obese individuals comes from adipocytes.[3,35] TNF-α has also been shown to induce insulin resistance and inhibit adipocyte differentiation, further contributing to this vicious cycle.[31]

Several alterations in cytokines have been reported in patients with migraine. Specifically, serum TNF-α and IL-6 have been shown to be increased ictally in episodic migraineurs, while cerebrospinal fluid TNF-α has been shown to be increased in chronic daily headache sufferers.[48,49] In addition, serum levels of the anti-inflammatory cytokine, IL-10, have also been suggested to be lower following treatment of acute episodic migraine attacks with sumatriptan, suggesting elevated levels of IL-10 during acute attacks, perhaps in response to acute inflammation.[50] ADP and leptin have been shown to have reciprocal relationships with several of these cytokines. Thus future studies evaluating the association between adipocytokines and cytokines in migraineurs may be of interest.

TREATMENT CONSIDERATIONS FOR OVERWEIGHT AND OBESE HEADACHE PATIENTS

Obesity has been demonstrated to be a risk factor for migraine and secondary headache conditions such as idiopathic intracranial hypertension (IIH). Obesity and headache share overlapping mechanisms as detailed previously. In light of these data, the potentially modifiable nature of obesity makes it an attractive target for headache treatment. Weight loss, by either surgical or conservative means, have been theorized to be possibly beneficial in overweight/ obese migraineurs. While one prospective study evaluating episodic and chronic migraineurs' response to prophylactic medication did not find a difference in the mean reduction of headache frequency based on their baseline weight (i.e. regardless of baseline weight, all participants were able to improve with medication), this study did not take into account the effect of weight loss at follow-up in their participants.[51] Conversely, multiple recent studies with a focus on surgical weight loss in obese migraineurs have suggested that weight loss may be beneficial for improving headache pain and frequency. In the following section, we will discuss the evidence and precautions associated with both surgical and non-surgical weight loss options and their potential efficacy for improving headache.

Surgical Weight Loss

Surgical Weight Loss in Obese Migraine Patients—Bond et al conducted the first prospective clinic-based study to evaluate changes in headache frequency and severity after bariatric surgery in 24 episodic migraineurs with severe obesity (BMI ≥ 35 kg/m^2).[52] Participants (88% women, mean age 39.3) completed the Migraine Disability Assessment (MIDAS) questionnaire as a measure of headache frequency, intensity, and disability preoperatively and 6 months postoperatively. With an average reduction of BMI from 46.6 to 34.6 postoperatively, monthly headache frequency decreased on average from 3.7 headache days per month pre-operatively to 2.2 headache days per month postoperatively (*P*

= .01). Additionally, participants who achieved greater weight loss had greater odds of experiencing a ≥50% reduction in headache frequency. Finally, findings showed significant postoperative reductions in headache severity as well as a reduction in the percentage of participants with moderate-to-severe disability (50–12.5%, $P = .008$).[52]

Subsequently, Novak et al conducted a second prospective clinic-based study that examined changes in headache characteristics after bariatric surgery in 29 women (mean age 33.2) with severe obesity (mean BMI 43.0) and episodic migraine.[53] The investigators echoed the findings of Bond et al,[52] demonstrating improvements in headache frequency and disability 3 months (mean BMI 37) and 6 months (mean BMI 34) postoperatively. The median monthly headache frequency decreased from 4 headache days to 2 headache days per month 3 months postoperatively, and to 1 headache day per month 6 months postoperatively. In addition, the authors reported improved headache-related disability (both the MIDAS and headache impact score [HIT]-6), decreased headache duration, and improved headache-associated symptoms following surgery.[53]

Most recently, Gunay et al conducted a retrospective study that included data from 81 morbidly obese patients (mean age 40, 90% women, mean BMI 48) with preoperative diagnosis of migraine who underwent Roux-en-Y gastric bypass (RYGB). Findings showed that migraine symptoms were improved in 89% of patients within approximately 6 months (range 1–36; $P < .01$, chi-square test) of undergoing RYGB.[54]

The above studies provide encouraging data to suggest that bariatric surgery may potentially have a role in the treatment of episodic migraineurs with severe obesity. However, further research is warranted in the area. One limitation of the above surgical weight loss studies include the retrospective documentation of changes in headache frequency and related parameters vs a prospective headache diary. Thus, larger controlled studies that include assessment of potential mediators and prospective measures of monthly headache frequency are needed to substantiate these findings. Moreover, although the above studies suggest that weight loss could be a principal mechanism underlying the potential benefits of bariatric surgery, it is also possible that several downstream mechanisms may also be at play, such as favorable changes in inflammatory cytokines and adipokines, improved psychological symptoms (eg, depression), or behavioral activity (eg, dietary changes including decreased exposure to migraine food triggers as a result of postoperative dietary restrictions, increased engagement in physical activity due to weight loss, and improved physical function, etc). Additionally, given that many obese and overweight migraineurs may not choose or may be ineligible for bariatric surgery, it is important to evaluate whether weight loss achieved via non-surgical approaches (ie, lifestyle interventions such as diet and exercise) produce similar improvements in headache frequency and severity in controlled trials before formal recommendations are able to be made.

Finally, it is not yet known whether weight loss-related improvements in migraine can be sustained over time as the above studies assessed changes in migraine during the initial active weight loss period. This question carries significant clinical implications given that maintaining a significant weight loss is a challenging task for many overweight and obese patients. However, recent observational and experimental research suggests that long-term weight loss maintenance is possible. In a recent study from the National Weight Control Registry, an estimated 87% of nearly 3000 participants who had an average weight loss of 31.3 kg at baseline were able to maintain a ≥10% weight loss at 5- and 10-year follow-up periods.[55] Additionally, findings from the Look AHEAD trial, which randomly assigned more than 5000 overweight or obese patients with type 2 diabetes to intensive lifestyle intervention or diabetes support and education, showed that intensive lifestyle intervention participants who achieved an average 8.6% loss of initial body weight at year 1 maintained

an average 6.0% weight loss at year 10.[56] Further, sustained weight loss of 20% at 6 years after bariatric surgery, and up to 16% at 10 years have been reported in a majority of post-surgical patients.[57,58]

Surgical Weight Loss in IIH Patients—As with migraine, there is some evidence supporting surgical weight loss for treatment of IIH.[59,60] When 19 severely obese women (mean BMI = 47) with IIH underwent bariatric surgery and were followed for 1 year, the mean BMI decreased to 30, and only 1 patient had persistent headache.[60] A more recent small clinical trial also showed promising results. When 4 female patients (mean BMI = 46.1) underwent laparoscopic adjustable gastric banding, with subsequent weight loss of 64.1% at follow-up, all 4 patients reported either total resolution or significant improvement in pain score.[59] However, larger randomized studies are not available at this time.

Behavioral Interventions

Behavioral Interventions in Migraine Patients—Physical exercise and diet are key weight loss strategies and are often recommended to migraine patients. Lack of exercise has been demonstrated to be associated with a 21% increased risk of headache attacks in adult migraineurs (hazard ratio 1.209; $P < .01$)[61] and a 50% increased risk of migraine in adolescents (odds ratio 1.5; 95% CI: 1.0–2.2).[62] However, activity has also been reported by migraineurs to be a headache trigger,[63] raising concern among some migraineurs that exercise may exacerbate their migraine. This concern has been addressed by multiple studies that ultimately support moderate exercise in migraineurs (Table 1).[64–70] In the following section, we will discuss the effect of various behavioral interventions on migraine relief.

Physical Activity Component Only: Several randomized controlled trials and non-controlled clinical trials have consistently demonstrated reductions in migraine intensity and migraine-related disability after participation in an exercise program.[65–69] Multiple studies have also demonstrated a decrease in migraine frequency after participation in an exercise program (see Table 1).[65,66,69] The most recent prospective randomized controlled study by Darabaneanu et al, which included 16 episodic migraineurs (8 age/gender matched controls) found that the mean number of headache days per month decreased from 3.8 ± 1.3 to 2.3 ± 1.7 in the exercise group compared with 3.3 ± 1.3 to 3.6 ± 1.4 in the control group, after 10 weeks of exercise, $P = .048$.[69] This study also demonstrated significant decreases in the duration and intensity of the migraine attacks in those episodic migraineurs in the exercise group compared with the controls (see Table 1).[69] However, none of these studies were able to determine if it was the exercise itself or the weight reduction as a result of exercise that accounted for the improved migraine symptoms. Future studies are needed to further define these possibilities.

Dietary Component Only: Diet is an integral aspect of a successful and healthy weight loss plan. Further, dietary triggers of certain foods have long been described in migraineurs.[71] While for weight loss in general, there is evidence suggesting that adherence to a diet is more important than any particular diet type,[72] for migraine in particular, a variety of specific diets have been tried for headache prevention given the previously discussed overlaps in migraine and obesity pathophysiology. Some have suggested a low fat or a low protein diet,[73,74] while others have suggested a high fat or a low carbohydrate diet as possible migraine preventative therapy.[75,76] However, all such studies have been either negative or methodologically flawed preventing conclusions. Thus, we remain without definitive scientific evidence substantiating the efficacy of any particular diet as a part of migraine therapy. Encouragingly, several research teams (including the authors D.S.B. and B.L.P.) are currently conducting prospective, randomized studies that involve testing the

efficacy of specific diets for treating migraine (eg, D.S.B.: low-fat diet in conjunction with physical activity; and B.L.P.: low-fat vs low-carbohydrate diet).

Physical Activity and Dietary Components: At least 2 studies have evaluated the efficacy of multidisciplinary interventions (with both dietary and physical activity components) on migraine (see Table 1). One of the first randomized controlled clinical trials evaluating the effect of a multidisciplinary program on migraine was by Lemstra et al in 2002.[64] Eighty participants (including 36 controls) were assigned to group exercise sessions 3 times/week for 6 weeks, along with stress management, relaxation, dietary lectures, as well as massage therapies. Investigators found significant differences in improvement of pain frequency, severity, duration, and quality of life measures between migraine and control groups after participation in the multidisciplinary program for 6 weeks. Though again, this study did not specify participants' initial weight or changes in weight after the program. Most recently, Verrotti et al assigned 135 adolescent (ages 14–18) migraineurs to a program consisting of physical exercise, dietary, and behavioral training. This study showed that lowering BMI (baseline BMI 32.9 ± 4.6, BMI at 12 months 29.9 ± 6.0, $P < .01$) was significantly associated with better migraine outcomes 12 months after the interdisciplinary intervention program for weight loss (see Table 1).[77] Larger randomized control studies are underway to further evaluate the efficacy of a standardized weight loss intervention for reducing migraine frequency in the adult population.[78]

Behavioral Interventions in IIH Patients—Weight loss has often been suggested for IIH patients as a treatment strategy, and both retrospective reviews and prospective studies evaluating the efficacy of weight loss for IIH have yielded positive results.[79–84] A recent prospective cohort study involving 25 morbidly obese women with IIH (excluded those who had undergone surgery to treat IIH) demonstrated improvement of headache frequency, headache severity, vision, and intracranial pressure after an intensive 3-month diet.[79] With weight loss from baseline BMI 38.2 ± 5 to 32.8 ± 4.4, HIT-6 improved from 57.5 ± 9 to 46.9 ± 10.1 ($P = .004$), headache severity (10 point visual analog pain score) decreased from 3.8 ± 2.4 to 2.1 ± 2.8 ($P = .015$), and headache frequency decreased from 3.8 ± 2.9 days/week to 2.1 ± 2.8 days/week ($P = .011$).

Pharmacological Considerations

Medications used for migraine frequently modulate weight (see Table 2).[85,86] Additionally, weight gain is among one of the most common reasons for a patient to reject a migraine prophylactic medication.[87] Some of the most common migraine prophylactic medications that can induce weight gain include tricyclic antidepressants (amitriptyline) and anticonvulsant medications (valproic acid).[88,89] Alternatively, protriptyline, timolol, and topiramate are more likely to be weight neutral or associated with weight loss (see Table 2).[44,85,90] Given the migraine–obesity association, physicians of episodic and chronic migraine patients should consider the impact of migraine preventatives on weight when choosing pharmacological treatment options.

CONCLUSION

Obesity increases the risk of both episodic and chronic migraine, and this risk increases with increasing obesity status. While the causal relationship is not known, obesity and migraine share overlapping central and peripheral mechanisms that may contribute to their association. In addition, lifestyle and behavioral factors may, at least in part, contribute. Data on the effect of weight loss, either surgical or non-surgical, in overweight or obese migraineurs are limited. However, preliminary and pilot data suggest bariatric surgery has potential to be part of an effective migraine prevention treatment strategy for obese

migraineurs. Currently, there are no substantial data supporting a specific diet for overweight and obese migraineurs, although research in this area is underway. Similarly, for headache patients with idiopathic intracranial hypertension, there are encouraging but limited data on both surgical and non-surgical weight loss for disease modification. Overall, current recommendations for clinicians treating overweight and obese headache patients should be to take particular care in the choices of medications prescribed to their patients, given that many drugs can modulate weight both positively and negatively, as well as to promote healthy lifestyle choices in regards to both diet and exercise.

References

1. Chai NC, Scher AI, Moghekar A, Bond DS, Peterlin BL. Obesity and headache: Part I – A systematic review of the epidemiology of obesity and headache. Headache. 2013 Submitted.
2. Evans RW, Williams MA, Rapoport AM, Peterlin BL. The association of obesity with episodic and chronic migraine. Headache. 2012; 52:663–671. [PubMed: 22404044]
3. Bray GA. Drug insight: Appetite suppressants. Nat Clin Pract Gastroenterol Hepatol. 2005; 2:89–95. [PubMed: 16265126]
4. Coppola A, Diano S. Hormonal regulation of the arcuate nucleus melanocortin system. Front Biosci. 2007; 12:3519–3530. [PubMed: 17485318]
5. Crowley VE, Yeo GS, O'Rahilly S. Obesity therapy: Altering the energy intake-and-expenditure balance sheet. Nat Rev Drug Discov. 2002; 1:276–286. [PubMed: 12120279]
6. Tilg H, Moschen AR. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006; 6:772–783. [PubMed: 16998510]
7. Blau JN. Migraine prodromes separated from the aura: Complete migraine. Br Medical J. 1980; 281:658–660.
8. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Hypothalamic activation in spontaneous migraine attacks. Headache. 2007; 47:1418–1426. [PubMed: 18052951]
9. Peterlin BL, Tietjen GE, Gower BA, et al. Ictal adiponectin levels in episodic migraineurs: A randomized pilot trial. Headache. 2013 Mar.53:474–490. [PubMed: 23489216]
10. Peterlin BL, Rosso AL, Rapoport AM, Scher AI. Obesity and migraine: The effect of age, gender and adipose tissue distribution. Headache. 2010; 50:52–62. [PubMed: 19496830]
11. Peterlin BL, Rapoport AM. Clinical pharmacology of the serotonin receptor agonist, zolmitriptan. Expert Opin Drug Metab Toxicol. 2007; 3:899–911. [PubMed: 18028032]
12. Hamele, SPR. 5-hydroxytryptamine involvement in migraines. In: Olesen, J.; Goadsby, PJ.; Ramadan, NM.; Tfelt-Hansen, P.; Welch, KMA., editors. The Headaches. 3. Philadelphia: Lippincott, Williams and Wilkins Publishers; 2006. p. 275-280.
13. Nonogaki K, Strack AM, Dallman MF, Tecott LH. Leptin-independent hyperphagia and type 2 diabetes in mice with a mutated serotonin 5-HT2C receptor gene. Nat Medical. 1998; 4:1152–1156.
14. Blundell JE. Serotonin and the biology of feeding. Am J Clin Nutr. 1992; 55(1 Suppl):155S–9S. [PubMed: 1728826]
15. Leibowitz SF, Alexander JT. Hypothalamic serotonin in control of eating behavior, meal size, and body weight. Biol Psychiatry. 1998; 44:851–864. [PubMed: 9807640]
16. Halford JC, Harrold JA, Boyland EJ, Lawton CL, Blundell JE. Serotonergic drugs: Effects on appetite expression and use for the treatment of obesity. Drugs. 2007; 67:27–55. [PubMed: 17209663]
17. Bhatt DK, Gupta S, Jansen-Olesen I, Andrews JS, Olesen J. NXN-188, a selective nNOS inhibitor and a 5-HT1B/1D receptor agonist, inhibits CGRP release in preclinical migraine models. Cephalalgia. 2013; 33:87–100. [PubMed: 23155193]
18. Dunlop J, Marquis KL, Lim HK, et al. Pharmacological profile of the 5-HT(2C) receptor agonist WAY-163909; therapeutic potential in multiple indications. CNS Drug Rev. 2006 Fall-Winter; 12:167–177. [PubMed: 17227285]

19. Tsujino N, Sakurai T. Role of orexin in modulating arousal, feeding, and motivation. Front Behav Neurosci. 2013; 7:28. [PubMed: 23616752]
20. Chiou LC, Lee HJ, Ho YC, et al. Orexins/ hypocretins: Pain regulation and cellular actions. Curr Pharm Des. 2010; 16:3089–3100. [PubMed: 20687883]
21. Bingham S, Davey PT, Babbs AJ, et al. Orexin-A, an hypothalamic peptide with analgesic properties. Pain. 2001; 92:81–90. [PubMed: 11323129]
22. Heinonen MV, Purhonen AK, Makela KA, Herzig KH. Functions of orexins in peripheral tissues. Acta Physiol (Oxf). 2008; 192:471–485. [PubMed: 18294339]
23. Sakurai T, Amemiya A, Ishii M, et al. Orexins and orexin receptors: A family of hypothalamic neuro-peptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998; 92:573–585. [PubMed: 9491897]
24. Mobarakeh JI, Takahashi K, Sakurada S, et al. Enhanced antinociception by intracerebroventricularly administered orexin A in histamine H1 or H2 receptor gene knockout mice. Pain. 2005; 118:254–262. [PubMed: 16202530]
25. Feng XM, Mi WL, Xia F, et al. Involvement of spinal orexin A in the electroacupuncture analgesia in a rat model of post-laparotomy pain. BMC Complement Altern Med. 2012; 12:225.10.1186/1472-6882-12-225 [PubMed: 23173601]
26. Suyama H, Kawamoto M, Shiraishi S, Gaus S, Kajiyama S, Yuge O. Analgesic effect of intrathecal administration of orexin on neuropathic pain in rats. In Vivo. 2004; 18:119–123. [PubMed: 15113038]
27. Holland PR, Akerman S, Goadsby PJ. Modulation of nociceptive dural input to the trigeminal nucleus caudalis via activation of the orexin 1 receptor in the rat. Eur J Neurosci. 2006; 24:2825–2833. [PubMed: 17156207]
28. Holland PR, Akerman S, Goadsby PJ. Orexin 1 receptor activation attenuates neurogenic dural vasodilation in an animal model of trigemino-vascular nociception. J Pharmacol Exp Ther. 2005; 315:1380–1385. [PubMed: 16160082]
29. Kajiyama S, Kawamoto M, Shiraishi S, et al. Spinal orexin-1 receptors mediate anti-hyperalgesic effects of intrathecally-administered orexins in diabetic neuropathic pain model rats. Brain Res. 2005; 1044:76–86. [PubMed: 15862792]
30. Sarchielli P, Rainero I, Coppola F, et al. Involvement of corticotrophin-releasing factor and orexin-A in chronic migraine and medication-overuse headache: Findings from cerebrospinal fluid. Cephalalgia. 2008; 28:714–722. [PubMed: 18479471]
31. Peterlin BL, Bigal ME, Tepper SJ, Urakaze M, Sheftell FD, Rapoport AM. Migraine and adiponectin: Is there a connection? Cephalalgia. 2007; 27:435–446. [PubMed: 17448181]
32. Kos K, Harte AL, da Silva NF, et al. Adiponectin and resistin in human cerebrospinal fluid and expression of adiponectin receptors in the human hypothalamus. J Clin Endocrinol Metab. 2007; 92:1129–1136. [PubMed: 17213280]
33. Haugen F, Drevon CA. Activation of nuclear factor-kappaB by high molecular weight and globular adiponectin. Endocrinology. 2007; 148:5478–5486. [PubMed: 17702846]
34. Tsatsanis C, Zacharioudaki V, Androulidaki A, et al. Adiponectin induces TNF-alpha and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. Biochem Biophys Res Commun. 2005; 335:1254–1263. [PubMed: 16115611]
35. Tsao TS, Tomas E, Murrey HE, et al. Role of disul-fide bonds in Acrp30/adiponectin structure and signaling specificity. different oligomers activate different signal transduction pathways. J Biol Chem. 2003; 278:50810–50817. [PubMed: 14522956]
36. Matsubara M, Maruoka S, Katayose S. Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. Eur J Endocrinol. 2002; 147:173–180. [PubMed: 12153737]
37. Bidulescu A, Liu J, Hickson DA, et al. Gender differences in the association of visceral and subcutaneous adiposity with adiponectin in african americans:The Jackson heart study. BMC Cardiovasc Disord. 2013; 13:2261-13-9.
38. Peterlin BL, Alexander G, Tabby D, Reichenberger E. Oligomerization state-dependent elevations of adiponectin in chronic daily headache. Neurology. 2008; 70:1905–1911. [PubMed: 18474846]

39. Mantzoros CS, Magkos F, Brinkoetter M, et al. Leptin in human physiology and pathophysiology. Am J Physiol Endocrinol Metab. 2011; 301:E567–E584. [PubMed: 21791620]
40. Lin KC, Sagawa N, Yura S, Itoh H, Fujii S. Simultaneous increases of leptin and gonadotropin-releasing hormone following exogenous estrogen administration in women with normally menstrual cycle. Endocr J. 2005 Aug.52:449–454. [PubMed: 16127214]
41. Kutlu S, Canpolat S, Sandal S, Ozcan M, Sarsilmaz M, Kelestimur H. Effects of central and peripheral administration of leptin on pain threshold in rats and mice. Neuro Endocrinol Lett. 2003; 24:193–196. [PubMed: 14523356]
42. Guldiken B, Guldiken S, Demir M, Turgut N, Tugrul A. Low leptin levels in migraine: A case control study. Headache. 2008; 48:1103–1107. [PubMed: 18547265]
43. Berilgen MS, Bulut S, Gonen M, Tekatas A, Dag E, Mungen B. Comparison of the effects of amitripty-line and flunarizine on weight gain and serum leptin, C peptide and insulin levels when used as migraine preventive treatment. Cephalalgia. 2005; 25:1048–1053. [PubMed: 16232156]
44. Schutt M, Brinkhoff J, Drenckhan M, Lehnert H, Sommer C. Weight reducing and metabolic effects of topiramate in patients with migraine–an observational study. Exp Clin Endocrinol Diabetes. 2010; 118:449–452. [PubMed: 20200812]
45. Bernecker C, Pailer S, Kieslinger P, et al. GLP-2 and leptin are associated with hyperinsulinemia in non-obese female migraineurs. Cephalalgia. 2010; 30:1366–1374. [PubMed: 20959431]
46. Otero M, Lago R, Gomez R, et al. Towards a pro-inflammatory and immunomodulatory emerging role of leptin. Rheumatology (Oxford). 2006; 45:944–950. [PubMed: 16720637]
47. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003; 112:1796–1808. [PubMed: 14679176]
48. Sarchielli P, Alberti A, Baldi A, et al. Proinflammatory cytokines, adhesion molecules, and lymphocyte integrin expression in the internal jugular blood of migraine patients without aura assessed ictally. Headache. 2006; 46:200–207. [PubMed: 16492228]
49. Rozen T, Swidan SZ. Elevation of CSF tumor necrosis factor alpha levels in new daily persistent headache and treatment refractory chronic migraine. Headache. 2007; 47:1050–1055. [PubMed: 17635596]
50. Munno I, Marinaro M, Bassi A, Cassiano MA, Causarano V, Centonze V. Immunological aspects in migraine: Increase of IL-10 plasma levels during attack. Headache. 2001; 41:764–767. [PubMed: 11576199]
51. Bigal ME, Gironda M, Tepper SJ, et al. Headache prevention outcome and body mass index. Cephalalgia. 2006; 26:445–450. [PubMed: 16556246]
52. Bond DS, Vithiananthan S, Nash JM, Thomas JG, Wing RR. Improvement of migraine headaches in severely obese patients after bariatric surgery. Neurology. 2011; 76:1135–1138. [PubMed: 21444898]
53. Novack V, Fuchs L, Lantsberg L, et al. Changes in headache frequency in premenopausal obese women with migraine after bariatric surgery: A case series. Cephalalgia. 2011; 31:1336–1342. [PubMed: 21700645]
54. Gunay Y, Jamal M, Capper A, Eid A, Heitshusen D, Samuel I. Roux-en-Y gastric bypass achieves substantial resolution of migraine headache in the severely obese: 9-year experience in 81 patients. Surg Obes Relat Dis. 2013; 9:55–62. [PubMed: 22445649]
55. Thomas JG, Bond DS, Phelan S, Hill JO, Wing RR. 10-year weight loss maintenance in the national weight control registry (NWCR). Am J Prev Medical. 2013 in press.
56. Wing RR, Bolin P, et al. Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Medical. 2013; 369:145–154.
57. Adams TD, Davidson LE, Litwin SE, et al. Health benefits of gastric bypass surgery after 6 years. JAMA. 2012; 308:1122–1131. [PubMed: 22990271]
58. Health Quality Ontario. Bariatric surgery: An evidence-based analysis. Ont Health Technol Assess Ser. 2005; 5:1–148.
59. Egan RJ, Meredith HE, Coulston JE, Bennetto L, Morgan JD, Norton SA. The effects of laparoscopic adjustable gastric banding on idiopathic intracranial hypertension. Obes Surg. 2011; 21:161–166. [PubMed: 21088927]

60. Sugerman HJ, Felton WL 3rd, Sismanis A, Kellum JM, DeMaria EJ, Sugerman EL. Gastric surgery for pseudotumor cerebri associated with severe obesity. Ann Surg. 1999; 229:634–640. discussion 640–2. [PubMed: 10235521]
61. Wober C, Brannath W, Schmidt K, et al. PAMINA Study Group. Prospective analysis of factors related to migraine attacks: The PAMINA study. Cephalalgia. 2007; 27:304–314. [PubMed: 17376107]
62. Robberstad L, Dyb G, Hagen K, Stovner LJ, Holmen TL, Zwart JA. An unfavorable lifestyle and recurrent headaches among adolescents:The HUNT study. Neurology. 2010; 75:712–717. [PubMed: 20720191]
63. Haque B, Rahman KM, Hoque A, et al. Precipitating and relieving factors of migraine versus tension type headache. BMC Neurol. 2012; 12:2377-12-82.
64. Lemstra M, Stewart B, Olszynski WP. Effectiveness of multidisciplinary intervention in the treatment of migraine: A randomized clinical trial. Headache. 2002; 42:845–854. [PubMed: 12390609]
65. Koseoglu E, Akboyraz A, Soyuer A, Ersoy AO. Aerobic exercise and plasma beta endorphin levels in patients with migrainous headache without aura. Cephalalgia. 2003; 23:972–976. [PubMed: 14984230]
66. Narin SO, Pinar L, Erbas D, Ozturk V, Idiman F. The effects of exercise and exercise-related changes in blood nitric oxide level on migraine headache. Clin Rehabil. 2003; 17:624–630. [PubMed: 12971707]
67. Dittrich SM, Gunther V, Franz G, Burtscher M, Holzner B, Kopp M. Aerobic exercise with relaxation: Influence on pain and psychological well-being in female migraine patients. Clin J Sport Medical. 2008; 18:363–365.
68. Varkey E, Cider A, Carlsson J, Linde M. A study to evaluate the feasibility of an aerobic exercise program in patients with migraine. Headache. 2009; 49:563–570. [PubMed: 18783448]
69. Darabaneanu S, Overath CH, Rubin D, et al. Aerobic exercise as a therapy option for migraine: A pilot study. Int J Sports Medical. 2011; 32:455–460.
70. Verrotti A, Agostinelli S, D'Egidio C, et al. Impact of a weight loss program on migraine in obese adolescents. Eur J Neurol. 2013; 20:394–397. [PubMed: 22642299]
71. Rockett FC, de Oliveira VR, Castro K, Chaves ML, da Perla AS, Perry ID. Dietary aspects of migraine trigger factors. Nutr Rev. 2012; 70:337–356. [PubMed: 22646127]
72. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: A randomized trial. JAMA. 2005; 293:43–53. [PubMed: 15632335]
73. Bic Z, Blix GG, Hopp HP, Leslie FM, Schell MJ. The influence of a low-fat diet on incidence and severity of migraine headaches. J Womens Health Gend Based Med. 1999; 8:623–630. [PubMed: 10839648]
74. Hasselmark L, Malmgren R, Hannerz J. Effect of a carbohydrate-rich diet, low in protein-tryptophan, in classic and common migraine. Cephalalgia. 1987; 7:87–92. [PubMed: 3607871]
75. Maggioni F, Margoni M, Zanchin G. Ketogenic diet in migraine treatment: A brief but ancient history. Cephalalgia. 2011; 31:1150–1151. [PubMed: 21727144]
76. Kossoff EH, Huffman J, Turner Z, Gladstein J. Use of the modified Atkins diet for adolescents with chronic daily headache. Cephalalgia. 2010; 30:1014–1016. [PubMed: 20656714]
77. Verrotti A, Agostinelli S, D'Egidio C, et al. Impact of a weight loss program on migraine in obese adolescents. Eur J Neurol. 2013; 20:394–397. [PubMed: 22642299]
78. Bond DS, O'Leary KC, Thomas JG, et al. Can weight loss improve migraine headaches in obese women? Rationale and design of the women's health and migraine (WHAM) randomized controlled trial. Contemp Clin Trials. 2013; 35:133–144. [PubMed: 23524340]
79. Sinclair AJ, Burdon MA, Nightingale PG, et al. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: Prospective cohort study. BMJ. 2010; 341:c2701. [PubMed: 20610512]
80. Newborg B. Pseudotumor cerebri treated by rice reduction diet. Arch Intern Medical. 1974; 133:802–807.

81. Kupersmith MJ, Gamell L, Turbin R, Peck V, Spiegel P, Wall M. Effects of weight loss on the course of idiopathic intracranial hypertension in women. Neurology. 1998; 50:1094–1098. [PubMed: 9566400]
82. Wong R, Madill SA, Pandey P, Riordan-Eva P. Idiopathic intracranial hypertension: The association between weight loss and the requirement for systemic treatment. BMC Ophthalmol. 2007; 7:15. [PubMed: 17888152]
83. Johnson LN, Krohel GB, Madsen RW, March GA Jr. The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). Ophthalmology. 1998; 105:2313–2317. [PubMed: 9855165]
84. Glueck CJ, Golnik KC, Aregawi D, Goldenberg N, Sieve L, Wang P. Changes in weight, papilledema, headache, visual field, and life status in response to diet and metformin in women with idiopathic intracranial hypertension with and without concurrent polycystic ovary syndrome or hyperinsulinemia. Transl Res. 2006; 148:215–222. [PubMed: 17145568]
85. Taylor FR. Weight change associated with the use of migraine-preventive medications. Clin Ther. 2008; 30:1069–1080. [PubMed: 18640463]
86. Peterlin BL, Calhoun AH, Siegel S, Mathew NT. Rational combination therapy in refractory migraine. Headache. 2008; 48:805–819. [PubMed: 18549358]
87. Kowacs PA, Piovesan EJ, Tepper SJ. Rejection and acceptance of possible side effects of migraine prophylactic drugs. Headache. 2009; 49:1022–1027. [PubMed: 19438733]
88. Maggioni F, Ruffatti S, Dainese F, Mainardi F, Zanchin G. Weight variations in the prophylactic therapy of primary headaches: 6-month follow-up. J Headache Pain. 2005; 6:322–324. [PubMed: 16362700]
89. Dodick DW, Freitag F, Banks J, et al. Topiramate versus amitriptyline in migraine prevention: A 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clin Ther. 2009; 31:542–559. [PubMed: 19393844]
90. Alberici A, Borroni B, Manelli F, et al. Topiramate weight loss in migraine patients. J Neurol Sci. 2009; 278:64–65. [PubMed: 19084843]

Table 1

Studies Evaluating Exercise for Migraine Prevention

Studies evaluating efficacy of exercise only for Migraine Prevention

Author (year)	Study Design	N (# con)	Sex	Mean Age (Range)	Mig Dx	Intervention	Program Duration (Ex Freq)	Primary Findings	Other Findings of Note
Koseoglu[65] (2003)	Non-R Non-Con, Clin trial	40 (0)	85% Women	32 (19–42)	ICHD	Aerobic exercise consisted of 10 min warm up, 20 min treadmill exercise at 60% maximal heart rate, 10 min cool down	6 weeks (3×/week)	The median number of headache days per month decreased from 2 (range: 1–3) HA/mo to 1 (0–3) HA/mo after 6 weeks, $P < .0001$	Pain intensity (based on 4 point scale) decreased from 3 (2–4) to 2 (0–4) after 6 weeks of treatment, $P < .0001$ Beta endorphin levels increased from baseline (32.3 ± 11.94) in all patients after 6 weeks (84.61 ± 38.30); $P < .0001$
Narin[66] (2003)	R-Controlled Clin Trial	40 (20)	100% Women	35.2 (20–50)	ICHD	Aerobic exercise consisted of 5 min warm-up, 10 min cycling, 10 min walking, 5 min stepper, 10 min upper extremities exercise, 10 reps neck and postural exercise, 10 reps rowing, 5 min cooling	8 weeks (3×/week)	The mean number of headache days per month decreased from 7.4 ± 2.9 to 3.6 ± 1.6 HA/mo in the exercise group, compared to 8.9 ± 3.3 to 7.0 ± 2.4 HA/mo in the control group after 8 weeks, $P < .05$.	Pain intensity improved from 8.8 ± 1.7 to 4.0 ± 1.4 in the exercise group compared to 8.5 ± 0.8 to 7.0 ± 0.9 in the control group. ($P < .05$)
Dittrich[67] (2008)	R-Controlled Clin trial	30 (15)	100% Women	NR	ICHD	Aerobic exercise consisted of 5 min warm up, 15–25 min aerobics, 10–20 min strength training, 5 min stretching	6 weeks (2×/week)	No significant difference in change in migraine attack frequency after 6 weeks between exercise group and control group.	After 6 weeks, pain intensity improved in the exercise group as compared to control group ($F = 5.722$, $P = .024$) Specifically, participants reporting

Studies evaluating efficacy of exercise only for Migraine Prevention

Author (year)	Study Design	N (# con)	Sex	Mean Age (Range)	Mig Dx	Intervention	Program Duration (Ex Freq)	Primary Findings	Other Findings of Note
									intense, very intense, and intolerable migraine decreased from 46.7% to 6.7% after 6 weeks of exercise, compared to 60% to 33.4% in control group.
Varkey[68] (2009)	Non-R Non-Con, Clin trial	20 (0)	85% Women	49 (36–63)	ICHD2	Aerobic exercise consisted of 15 min warm-up, 20 min exercise, 5 min cool-down	12 weeks (3×/week)	No significant change in migraine frequency pre (4.7 ± 2 HA/mo) and post (3.9 ± 1.6 HA/mo) exercise program.	Significant increase in quality of life s(based on MSQoL) after treatment (65 ± 25) compared with baseline (58 ± 37), $P < .01$. VO2max increased significantly as compared with baseline, 32.9 (10) mL/kg/minute vs 36.2 (8) mL/kg/minute ($P = .044$)
Darabaneanu[69] (2011)	R-Controlled Clin Trial	16 (8)	81.3% Women	(24–52)	ICHD	Aerobic exercise consisted of 10 minute warm-up, 30 min jogging within an aerobic heart rate range and a 10 minute cool-down phase	10 weeks (3×/week)	The mean number of headache days per month decreased from 3.8 ± 1.3 HA/mo to 2.3 ± 1.7 HA/mo in the exercise group, compared to 3.3 ± 1.3 HA/mo to 3.6 ± 1.4 HA/mo in the control group, $P = .048$	Significant decrease in intensity ($P = .028$) and duration ($P = .020$) of attacks compared to control

Studies evaluating efficacy of exercise ± diet, and other behavioral training for Migraine Prevention

Author (year)	Study Design	N (# con)	Sex	Mean Age (Range)	Mig Dx	Intervention	Program Duration (Ex Freq)	Primary Findings	Other Findings of Note
Lemstra[64] (2002)	R-Controlled Clin Trial	80 (36)	66.3% Women	35.6 (18+)	ICHD	The behavioral intervention included group exercise sessions consisting of aerobic exercise, stretching, & light weight training, dietary, relaxation, & stress management lectures	6 weeks (3×/week)	Pain frequency decreased in the intervention group by 33.64 ± 5.29 %, as compared to in the control group (−2.22 ± 2.22%) after 6 weeks, *P* = .000.	Pain intensity decreased in the intervention group by 19.55 ± 5.61% vs the control group −2.78 ± 1.98%; *P* = .001. Quality of life as measured by the self reported visual analogue scale improved in intervention group (by 35.34 ± 5.03% vs control group −1.94 ± 1.94%; *P* = .000
Verrotti[70] (2013)	Non-R Non-Con, Clin trial	135 (0)	58% Women	(14–18)	ICHD	The behavioral intervention included ≥60 min of moderate-intensity physical activity, dietary & behavioral training	12 months (most days of the week)	Headache frequency decreased from 5.3 ± 2.1 HA/mo to 2.2 ± 0.9 HA/mo; *P* < .01	Headache intensity (based on 10 point scale) decreased from 7.4 ± 1.7 to 3.9 ± 2.1, after 12 months, *P* < .01 BMI decreased from 32.9 ± 4.6 to 29.9 ± 6.0 after 12 months, *P* < . 01

Clin = clinical; Dx = diagnosis; Ex Freq = exercise frequency; HA = headache; Mig = migraine; mo = month; Non-Con = non-controlled; NR = not reported; R = randomized; vs = versus.

Table 2

Potential Migraine Preventative Medications and Weight Considerations

Drug Class/Drug	Weight Change
Antidepressants	
Amitriptyline	↑↑↑
Nortriptyline	↑↑
Protriptyline	↓
Venlafaxine	↔↓
Duloxetine	↔↓
Anticonvulsants	
Divalproex sodium	↑↑↑
Lamotrigine	↔
Gabapentin	↑
Topiramate	↓↓
β-Blockers	
Propranolol	↑
Timolol	↔
Metoprolol	↑
Angiotensin II receptor blocker	
Candesartan	↔↓
Telmisartan	↓
ACE-inhibitor	
Captopril	↔↓
Lisinopril	↔
Serotonin antagonists	
Methysergide	↑↑↑
Cyproheptadine	↑↑↑
Calcium channel blockers	
Flunarizine	↑↑↑
Verapamil	↔

Modified based on Peterlin et al 2008.[86]

ACE-inhibitor = angiotensin-converting-enzyme inhibitor.