

# Headache attributed to idiopathic intracranial hypertension and persistent post-idiopathic intracranial hypertension headache

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## REVIEW ARTICLE

# Headache attributed to idiopathic intracranial hypertension and persistent post-idiopathic intracranial hypertension headache: A narrative review

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## Abstract

**Objective:** Headache is a near-universal sequela of idiopathic intracranial hypertension (IIH). The aim of this paper is to report current knowledge of headache in IIH and to identify therapeutic options.

**Background:** Disability in IIH is predominantly driven by headache; thus, headache management is an urgent and unmet clinical need. At present, there is currently no scientific evidence for the directed use of abortive or preventative headache therapy.

**Methods:** A detailed search of the scientific literature and narrative review was performed.

**Results:** Headache in IIH is driven by raised intracranial pressure (ICP) and reduction of ICP has been reported in some studies to reduce headache. Despite resolution of papilledema and normalization of raised ICP, a majority suffer persistent post-IIH headache. The lack of evidence-based management approaches leaves many untreated. Where clinicians attempt to manage IIH headache, they use off-label therapies to target the prevailing headache phenotype. A recent prospective open-label study demonstrated the effective use of a calcitonin gene-related peptide monoclonal antibody therapy in IIH for persistent post-IIH headache.

**Conclusions:** There is overwhelming evidence of the headache burden in IIH. Studies are required to investigate the biological foundations of headache related to ICP and to develop treatments specifically directed to manage headache in IIH.

## KEYWORDS

headache, glucagon-like peptide-1, idiopathic intracranial hypertension, obesity, raised intracranial pressure

**Abbreviations:** 11 $\beta$ -HSD1, 11 $\beta$ -hydroxysteroid dehydrogenase type 1; CGRP, calcitonin gene-related peptide; CSF, cerebrospinal fluid; GLP-1R, glucagon-like peptide 1 receptor; HIT-6, headache impact test-6; ICP, intracranial pressure; ICHD-3, International Classification of Headache Disorders, 3rd edition; ICHD-2, International Classification of Headache Disorders, 2nd edition; IIH, idiopathic intracranial hypertension; LP, lumbar puncture; MOH, medication overuse headache; OSA, obstructive sleep apnea; ONSF, optic nerve sheath fenestration.

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## INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a disabling secondary headache disorder characterized by raised intracranial pressure (ICP) and papilledema with the potential risk of permanent visual loss.<sup>1,2</sup> There is an established association with obesity<sup>3,4</sup> and increasing prevalence<sup>5–7</sup> currently estimated at 68 per 100,000 females.<sup>6</sup> Although there has been progress in diagnostic algorithms,<sup>8–11</sup> there are little data to help guide treatment decisions for headache.<sup>9,12</sup>

IIH has a detrimental effect on all aspects of the patient's quality of life,<sup>13,14</sup> predominantly driven by headache.<sup>14</sup> Clinical trials report a substantial headache burden,<sup>15–17</sup> and there are no directed trials investigating headache therapies. The onset of headaches attributable to IIH is temporally related to increased ICP, which improve in response to reduction of ICP.<sup>18</sup> Following resolution of papilledema, those with persistent post-IIH headache frequently have migraine-like characteristics<sup>15–17</sup> contributing to long-term morbidity.<sup>19</sup> Patients and physicians have ranked headache as a high research priority.<sup>20</sup> The aim of this narrative review is to describe the progress in understanding of headache attributed to IIH and to generate momentum to identify effective therapies.

## METHOD

A detailed search of the scientific literature included all English language papers on PubMed, Cochrane, and Google Scholar between inception until January 1, 2021 combining free-text and controlled vocabulary terms for IIH. Keywords (MeSH Unique ID) included the following: ICP (D007427); headache (D006261); obesity (D009765); papilledema (D010211); pseudotumor cerebri (D011559); and weight loss (D015431).

## Classification of headache attributed to IIH

The International Classification of Headache Disorders, 3rd edition (ICHD-3), classifies headache attributed to IIH as a secondary headache disorder.<sup>18</sup> The descriptive diagnosis is based on clinical history of a new-onset headache or a significant worsening of a pre-existing headache caused by and accompanied by other symptoms and signs of IIH with a temporal relationship to raised ICP.<sup>18</sup> The second edition of the International Classification of Headache Disorders (ICHD-2) required headache improvement after ICP reduction as a criterion.<sup>21</sup> However, the updated ICHD-3 removed this criterion because more than one half of IIH patients report a persisting chronic headache in spite of the normalization of ICP reflecting mixed headache phenotypes such as low-pressure headache following lumbar puncture (LP) and medication overuse (Figure 1).<sup>22</sup> The ICHD-3 mentions that headache relief after removal of cerebrospinal fluid (CSF) is supportive of IIH but not diagnostic.<sup>18</sup> It has already been noted that relief of headache in migraine may follow LP.<sup>23</sup> The changes from the ICHD-2 to the ICHD-3 beta criteria resulted in improved sensitivity from 60% to 86%, and a decreased specificity from 86% to 53% in

distinguishing IIH.<sup>23</sup> The challenge posed for using headache as a diagnostic criterion is the relative rarity of the disease and the paucity of investigative data to determine and validate it.

## Clinical characteristics of headache in IIH

The preponderance of IIH is characterized by symptoms of raised ICP, which include headache, visual disturbances, pulsatile tinnitus, and papilledema.<sup>1,2</sup> The historical features of raised ICP, such as a waking nonspecific headache that occurs in the minority, underline the importance of fundoscopy in all-new-onset headache and those have an exacerbation of their headache history.<sup>24</sup> In adults, headache features often resemble those with primary headache disorders.<sup>15</sup> When phenotyping headache in IIH recurrent episodes of headache may vary considerably in terms of frequency, duration, and pain intensity.<sup>15,16,19</sup> In a large trial, IIH headache was described as pressure-like in 47% and throbbing in 42%.<sup>15</sup> Photophobia, phonophobia, nausea, vomiting, and worsening on physical activity were also reported.<sup>15</sup> Headache severity in IIH appears to be moderate to severe.<sup>19</sup> Typically patients describe a near daily background headache with superimposed exacerbation of pain (Figure 1).<sup>19</sup> In new-onset IIH, the phenotype near universally mimics primary headache disorders, such as episodic migraine and tension-type headache.<sup>15</sup> Where papilledema has resolved (termed ocular remission), persistent post-IIH headache can continue with the phenotype typically mimicking chronic migraine.<sup>19</sup>

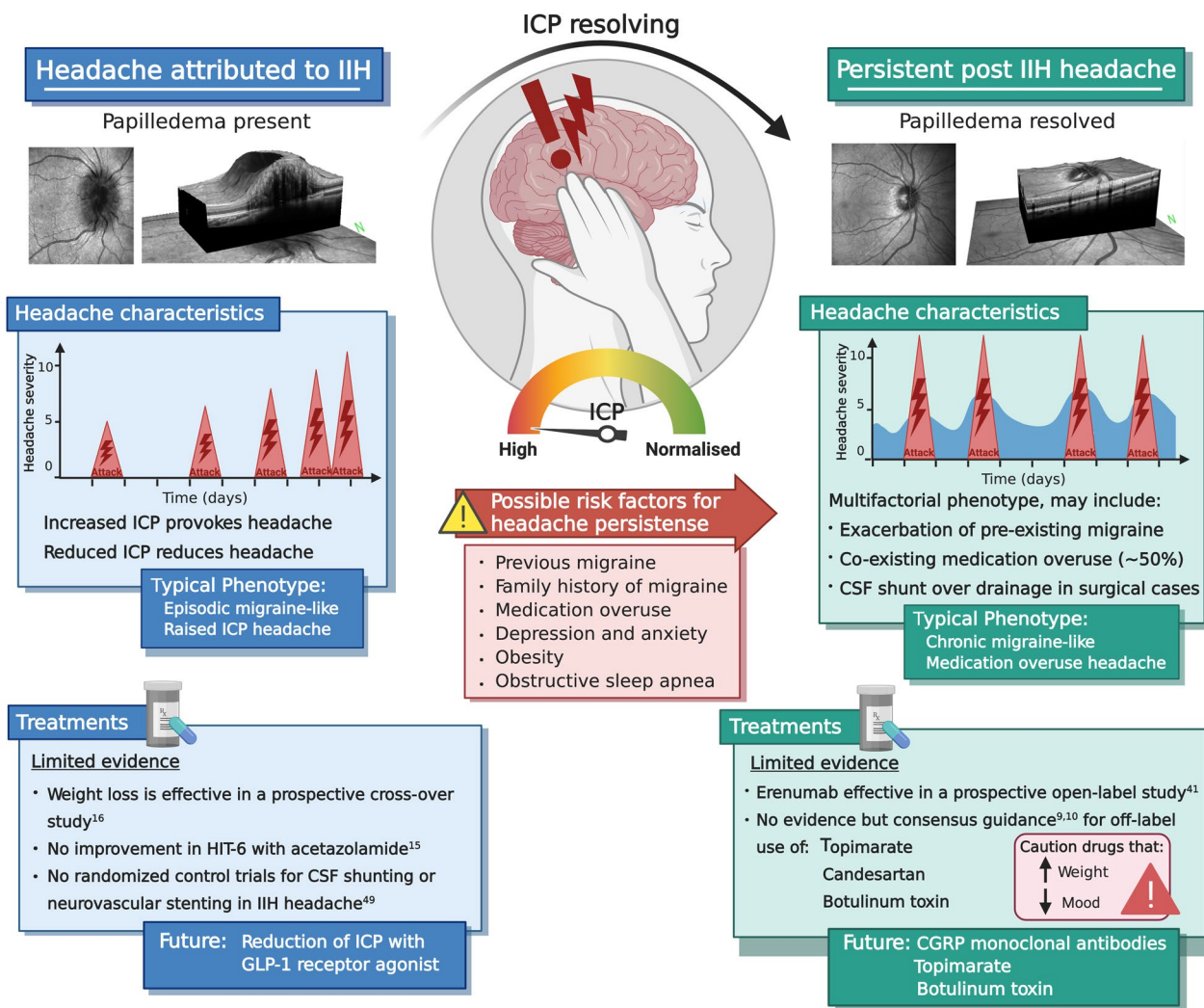
## Medication overuse in IIH

Because there are currently no licensed therapies for headache attributable to IIH, regular use of analgesic medications is recorded in up to half of IIH patients depending on the study (Table 1). Medication overuse in the general population is reported to be between 1% and 2%,<sup>21</sup> and in primary headache disorders such as migraine, it is reported to be between 25% and 50%.<sup>25</sup> It is notable that obesity and female sex pose important risk factors for medication overuse,<sup>26</sup> which are defining characteristics of IIH. Overuse of analgesic medications may contribute to the frequency and severity of headache and may have a role in progression from episodic headache to a chronic phenotype as postulated in the literature discussing other headache disorders.<sup>27</sup> It is recommended that patients with IIH headache who frequently take acute medication should be counseled about the risks of medication overuse and medication overuse headache (MOH).<sup>9</sup>

## Treatment of IIH

### Weight management

Weight loss is an effective treatment for IIH.<sup>16,28</sup> Studies report that weight reduction in the order of 11%–15% leads to clinical



**FIGURE 1** Infographic of headache attributed to idiopathic intracranial hypertension (IIH) and persistent post-IIH headaches describing the stage of the disease. New onset with raised intracranial pressure (ICP), where there is papilledema (as seen by the optical coherence tomography [OCT] infrared images of the optic nerve head disk volume). Persistent post-IIH headaches in the setting of no papilledema (OCT images of resolved papilledema). The likely risk factors that may contribute to the conversion of the headache phenotype. The current treatments and potential future therapeutics

remission.<sup>16,29</sup> An extremely low-calorie diet prospective cross-over study resulted in significantly lowered ICP measured by LP and improvement in papilledema. Importantly, there was a 50% reduction in headache severity and frequency with a parallel reduction in analgesic use.<sup>16</sup> The most durable method of weight loss is currently being explored in a randomized control trial<sup>30</sup> comparing diet with bariatric surgery because of concern over recurrence secondary to weight gain.<sup>31</sup> The recent STEP-3 randomized control trial investigating semaglutide,<sup>32</sup> a glucagon-like peptide 1 receptor (GLP-1R) agonist, found semaglutide to be superior in weight loss when used as an adjunct to behavioral therapy and initial low-calorie diet compared with placebo. This noninvasive weight management therapy will likely be of direct clinical relevance to those with IIH; exendin-4, a GLP-1R agonist, has been found in an animal model to modulate CSF secretion at the choroid plexus and subsequently reduce ICP.<sup>33</sup>

The role of obesity in the pathogenesis of IIH is of interest because truncal weight loss has been shown in IIH to be correlated with ICP.<sup>34</sup> Truncal adiposity is also a known source of androgen synthesis. A unique profile of excess androgen has been identified in IIH, which is distinct from that observed in control groups with obesity and those with polycystic ovarian syndrome. Androgen excess in IIH has been shown to be implicated in dysregulation of CSF dynamics in vitro.<sup>35</sup>

### Carbonic anhydrase inhibition

A carbonic anhydrase inhibitor, acetazolamide, was given in escalating doses and compared with placebo in patients with mild to moderate visual loss in the IIH treatment trial. The treatment effect from baseline to 6 months was measured as the perimetric mean deviation, which is a global measure of the visual field. Acetazolamide used in

TABLE 1 Clinical studies in adults describing headache features in idiopathic intracranial hypertension (IIH)

Author, year in order of recent publication	Study characteristics	Demographics	Prior history of headache	Family history of migraine	Total number with/ without headache	Phenotype (as per ICHD-3 $\beta$ )	Medication overuse	Headache frequency	Headache severity mean ( $\pm$ standard deviation)	HIT-6 mean ( $\pm$ standard deviation)
Yiangou et al. 2020 <sup>19</sup>	Prospective, single-center open-label study in those with persistent post-IIH headache	55 women, mean (SD) age 35.3 (9) years		44%	100% with a mean duration of headaches 10.4 (8.4) years and 3.7 (0.9) preventative treatment failures	100% migraine-like	48%	Mean baseline monthly severe headache days was 16.1 (4.7)	6 ( $\pm$ 1.3)	67.2 ( $\pm$ 4.4)
	Birmingham, United Kingdom							Total mean monthly headache days was 29 (2.3)		
Raggi et al. 2018 <sup>64</sup>	Observational, cross-sectional single center in Milan, Italy	51 (45 females; 6 – males)	60 had a prior history of migraine in those who had headaches	–	40 (78.4%) had headache diagnosis	–	–	Mean frequency 35.7 (SD 35.2) per 3 months 20 (39.2%) chronic headache diagnosis (migraine or tension type on >15 days a month for 3 months)	5.6 ( $\pm$ 2.5)	–
Friedman et al. 2017 <sup>15</sup>	Randomized control trial of acute onset IIH Multicenter (38 sites) in North America	165 (161 females; 4 males)	60 had a prior history of migraine in those who had headaches	–	139 (84%) reported headache at baseline 5 had no headache throughout the study	52% migraine 22% tension-type headache 16% probable migraine 4% probable tension-type headache 7% unclassifiable	38 (23%) reported daily analgesic use 51 (37%) participants were overusing pain medications prior to enrolment	Mean frequency 12 days per month at baseline 38 chronic or daily headaches at baseline, as determined by analgesic use	6.3 ( $\pm$ 1.9)	59.7 ( $\pm$ 9.00)
Yri et al. 2014 <sup>22</sup>	Prospective, single-center	44 (98% females; 2% males)	11 (25%) prior history of migraine	–	100% had headache	68% migraine	3 (7%)	64% constant, 86% daily, 6% 2–4 days a week, and 2% <1 day per week	5.3 ( $\pm$ 2.6)	–

TABLE 1 –Continued

Author, year in order of recent publication	Study characteristics	Demographics	Prior history of headache	Family history of migraine	Total number with/without headache	Phenotype (as per ICHD-3 $\beta$ )	Medication overuse	Headache frequency	Headache severity mean ( $\pm$ standard deviation)	HIT-6 mean ( $\pm$ standard deviation)
Yri and Jensen 2015 <sup>23</sup>	Danish Headache Centre, Denmark		15 (34%) prior history of tension-type headache			82% migraine attacks <4 hr included 25% tension type 9% mixed migraine and tension 5% unclassifiable				

conjunction with a low-sodium weight-reduction diet resulted in the improvement in visual field function compared with diet alone.<sup>36</sup> In both trial arms, the headache impact test-6 (HIT-6) score improved, but at 6 months, there was no significant difference between those taking acetazolamide or those on placebo.<sup>15</sup> Acetazolamide use in this population is limited because of the reported side effects such as nausea, fatigue, tingling of the hands and feet and altered taste, all of which have resulted in poor patient compliance.<sup>37</sup>

The efficacy of topiramate in influencing visual function in IIH has been evaluated.<sup>37</sup> This open labels study demonstrated noninferiority of topiramate to acetazolamide. In terms of headache, there were no details at baseline of the characteristics of the headaches experienced. Twenty cases were assigned to each study group. Relief of headache was reported after a mean treatment period of 3.8 months in the topiramate group and 3.3 months in the acetazolamide group.<sup>38</sup> Case reports have also detailed the benefit of the use of topiramate in relief of headache in IIH.<sup>39</sup> Preclinical evidence supports the use of topiramate in a healthy rodent model. ICP was reduced significantly by topiramate compared with other medications that have been used in IIH, namely acetazolamide, furosemide, and octreotide.<sup>40</sup>

### 11 $\beta$ -hydroxysteroid dehydrogenase type 1 inhibition

11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) has previously been implicated in regulating CSF secretion.<sup>41</sup> A UK multicenter phase II randomized, double-blind, placebo-controlled trial used a reversible competitive 11 $\beta$ -HSD1 inhibitor, AZD4017, for 12 weeks to evaluate safety and tolerability in a cohort of patients with active IIH.<sup>17</sup> Ninety-seven percent of participants reported headache, with a mean baseline HIT-6 score of 63.6 (standard deviation 8.0). AZD4017 was safe and well tolerated and inhibited 11 $\beta$ -HSD1 activity in vivo. The secondary outcomes which related to headache were not statistically significantly different between AZD4017 and placebo at either 12 weeks or at the last follow-up in the study at 16 weeks. No significance difference was found between the study arms in terms of ICP.<sup>17</sup> There were significant metabolic improvements in those who received AZD4017.<sup>42</sup> These included lipid profiles with decreased cholesterol resulting in increased high-density lipoprotein and decreased cholesterol/HDL ratio. Hepatic function improved with decreased alkaline phosphatase and gamma-glutamyl transferase with increased lean muscle mass. There were no changes in the body mass index, fat mass, and markers of glucose metabolism or inflammation. The changes in the total lean muscle mass were positively correlated with increased levels of circulating androgens.<sup>42</sup>

### Medical management of headache attributed to IIH

Commonly in IIH, existing migraine preventative drugs are used off-label without evidence of efficacy in this population.<sup>9,10</sup> Preventative migraine drugs are often not tolerated, and some are contraindicated in IIH patients due to the risk of exacerbating obesity (a central driver



for IIH) and mental health disorders, such as depression. Physicians often consider prescribing topiramate for headache in IIH. This choice is driven by a number of factors, namely the headache phenotype mimics migraine; topiramate has been shown to reduce ICP<sup>40</sup>; it has the potential side effect of loss of appetite, and in some weight loss.<sup>9,10</sup> To date, there are no randomized control trials specifically investigating the management of headache in IIH for any medication.<sup>43</sup>

### Calcitonin gene-related peptide monoclonal antibody therapy

A recent prospective open-label study of 55 patients with IIH in ocular remission (resolved papilledema) and persistent post-IIH headaches investigated the use of erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody. Monthly headache diaries, IIH symptoms, HIT-6 score, as well as other quality-of-life outcome measures were recorded. The duration of the chronic headache symptoms after papilledema resolution was a mean of 1.7 years. MOH occurred in 48%, and family history of migraine was documented in 44%. The majority of patients required an increased dose of erenumab to 140 mg monthly (87% at 3 months, 89% at 6 months, 90% at 9 months, and 94% by 12 months). Erenumab was well tolerated with no withdrawals related to adverse effects, and only six discontinued due to lack of effect by 12 months. Erenumab reduced the frequency of monthly moderate/severe headache days by 71% and all headache days by 45% from baseline to 12 months. Erenumab significantly increased crystal clear days, reduced analgesic days, reduced severity, and reduced absenteeism and presenteeism.<sup>19</sup>

It is important to note that in this setting when the headache symptoms were so successfully treated, seven patients who regained weight had a recurrence of their raised ICP, as evidenced by papilledema. However, their headache did not recur. This suggests that IIH patients should be counseled regarding weight gain, particularly when their headaches are controlled and they need to be routinely monitored by ophthalmology for signs of papilledema recurrence.<sup>44</sup> These cases also suggest that CGRP could be involved in the underlying pathophysiology of headache in patients with active IIH.

## Surgical procedures for headache in IIH

### Lumbar puncture

Therapeutic LP has a limited application for managing IIH headache in the long term. In a prospective cohort study, headache severity improved in 71%, following a standardized LP, but this improvement was small (1 point on the numerical rating score 0–10). There was a 64% chance of a significant headache exacerbation in the week following the LP, with one third of these experiencing a severe exacerbation of greater than or equal to 4 points on the numerical rating

scale. There was also noted to be no relationship between headache change and either the individual opening or closing LP pressure, where a uniform amount of CSF was removed.<sup>45</sup> In a large survey of 502 patients with IIH, more than one third recalled severe pain scores during an LP. This negative emotional experience is evidenced by nearly half having extreme anxiety regarding the thoughts of the requirement of undergoing a further LP.<sup>46</sup>

### Cerebrospinal diversion surgery (shunting)

The effect on headache symptoms following CSF diversion surgery is documented in several case series. In one retrospective case series of 53 IIH patients who underwent CSF shunting, headache was documented in 68% at 6 months. This increased to 77% at 12 months and to 79% at 2 years postoperatively.<sup>47</sup> This recurrence of headache in the long term was also seen in another series where 95% of patients had improvement in headache symptoms at 1 month following shunt placement. Headaches recurred in 19% by 1 year and in 48% by 3 years postprocedure.<sup>48</sup> In a further retrospective review of 163 patients, 42% were reported to have headache (over a mean duration of nearly 3 years).<sup>49</sup> CSF diversion is associated with significant morbidity and a high revision rate; with up to one third of patients requiring additional interventions after either a lumbo-peritoneal or ventriculoperitoneal CSF shunt.<sup>50</sup> Hence, many have recommended that headache symptoms alone should not be an indication for CSF diversion.<sup>9,10</sup>

### Cerebral venous sinus stenting

The safety and efficacy of dural venous sinus stenting as a treatment for IIH is currently based on retrospective studies and two open-label prospective studies.<sup>51</sup> About one third of patients undergoing cerebral venous stenting report a transient postprocedure headache. This typically lasts days and is ipsilateral to the side of stenting; this is thought to be secondary to dural stretch.<sup>52</sup> Overall case series suggest that nearly two thirds have improvement of their headaches,<sup>53</sup> which has been confirmed in a meta-analysis.<sup>54</sup> There remains a small but concerning risk of a serious adverse event secondary to the procedure and the longer-term complications of anticoagulation. The complications and lack of consistent reporting of headache outcomes currently preclude stenting from being routinely recommended in some countries as a treatment for IIH.<sup>10,51</sup>

### Optic nerve sheath fenestration

Optic nerve sheath fenestration (ONSF) is an orbital surgery that creates an opening in the dural sheath that surrounds the optic nerve to prevent sight loss from raised ICP in IIH.<sup>54,55</sup> It is typically carried out for loss of vision and carries the risk of severe

complications such as loss of vision, diplopia, and other complications such as pupillary dysfunction. Procedural failure may require repeat surgery or neurosurgical shunting and is reported in 10%.<sup>54</sup> Interestingly, headache is ameliorated in just under half of the patients in clinical studies. It is noteworthy that many of these studies do not report more details of the presence or absence of headache.<sup>54</sup> The overall effectiveness of ONSF over other surgical procedures is unknown as evidence is limited to uncontrolled case series. A randomized clinical trial of acetazolamide plus ONSF compared with acetazolamide alone had to be terminated early because of low enrolment. In the United States, neurosurgical shunting is used 10-fold more than ONSF. This may reflect the underlying concerns about lack of trial data or limitations in access to orbital surgical expertise.<sup>56</sup>

## Coexisting conditions in IIH that may influence headache

### Obesity

Migraine and obesity are both prevalent disorders.<sup>57</sup> Obesity is known to be related to chronic daily headache<sup>58</sup> and an increased frequency and severity of migraine.<sup>59,60</sup> The underlying mechanisms as to the association are likely to be multifactorial, from pathophysiological to behavioral.<sup>61</sup> In a pediatric cohort, weight loss was beneficial in terms of reduction of headaches over time.<sup>62</sup> The underlying mechanisms of the interplay between headache in IIH and headache reported in obesity are unknown and evaluation of which are the key drivers for headache and which are contributing are likely to be complicated.

### Depression and anxiety

Depression and anxiety are known to be prevalent among those with IIH.<sup>15,63,64</sup> The relationship between depression and migraine has been demonstrated to be bidirectional: when either disorder exists, there is an increased risk of new onset of the other disorder.<sup>65</sup> Anxiety disorders have also been demonstrated to have a relationship with migraine.<sup>65</sup> The combination of both anxiety and depression in people with migraine has also shown to be strongly associated with migraine.<sup>66,67</sup>

### Obstructive sleep apnea

The prevalence of the coexistence of obstructive sleep apnea (OSA) and IIH is unknown, yet a small retrospective case series suggested an association between OSA and IIH, with obesity as a postulated common causative factor.<sup>68-70</sup> As OSA is known to impact chronic headache,<sup>71</sup> and weight loss improves OSA,<sup>72</sup> evidence is now needed to understand these relationships in IIH and

whether treatment of OSA in IIH will impact headache symptoms meaningfully.

## CONCLUSIONS

Headaches in IIH occur in the setting of raised ICP, with acute reduction of ICP improving headaches.<sup>18</sup> The headache phenotype in established IIH is typically migraine-like. In many people with IIH, headaches are multifactorial and suboptimally treated, which likely contributes to headaches being refractory to treatment. In patients with IIH in whom the ICP has normalized (IIH in ocular remission), persistent post-IIH headaches can remain and can contribute to long-term morbidity. Both headaches attributed to IIH and persistent post-IIH headaches are likely to be exacerbated by coexisting medication overuse. For the treatment of headache in IIH, the therapeutic reduction of ICP with acetazolamide has not yet been shown to be effective for headache resolution.<sup>15</sup> Evidence has been reported for the successful use of CGRP monoclonal antibodies to treat those with persistent post-IIH headaches.<sup>19</sup> The potential of novel therapies, such as GLP-1 agonists, to reduce ICP and to treat headache requires formal evaluation. The headache phenotype and trial outcomes relating to headache need to be routinely collected and reported in clinical studies. This should allow clear interpretation and enable comparison between studies to represent the benefit of interventions on headache. Overall, there is substantial evidence of the headache burden in IIH, and treatments specifically aimed at managing headache in IIH should be developed.

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## CONFLICT OF INTERESTS

Mollan has received honoraria from Novartis for speaking on funduscopy, but within a national headache network meeting (November 2019), and has been involved in consultancy work for Invex Therapeutics (2020). Grech has received consultancy fees from Invex Therapeutics (2020). Sinclair has received speaker fees and honoraria from Novartis (erenumab) and Allergan (BOTOX), besides being the company director with salary and stock options in Invex Therapeutics (2019, 2020). The authors declare no other financial relationships with any organizations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

## AUTHOR CONTRIBUTIONS

*Study concept and design:* Susan P. Mollan, Olivia Grech, Alexandra J. Sinclair. *Acquisition of data:* Susan P. Mollan. *Analysis and interpretation of data:* Susan P. Mollan, Alexandra J. Sinclair. *Drafting of the manuscript:* Susan P. Mollan. *Revising it for intellectual content:* Olivia Grech, Alexandra J. Sinclair. *Final approval of the completed manuscript:* Susan P. Mollan, Olivia Grech, Alexandra J. Sinclair.



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## REFERENCES

- Mollan SP, Grech O, Alimajstorovic Z, Wakerley BR, Sinclair AJ. New horizons for idiopathic intracranial hypertension: advances and challenges. *Br Med Bull*. 2020;136:118-126.
- Virdee J, Larcombe S, Vijay V, et al. Reviewing the recent developments in idiopathic intracranial hypertension. *Ophthalmol Ther*. 2020;9:767-781.
- Daniels AB, Liu GT, Volpe NJ, et al. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). *Am J Ophthalmol*. 2007;143:635-641.
- Andrews LE, Liu GT, Ko MW. Idiopathic intracranial hypertension and obesity. *Horm Res Paediatr*. 2014;81:217-225.
- McCluskey G, Doherty-Allan R, McCarron P, et al. Meta-analysis and systematic review of population-based epidemiological studies in idiopathic intracranial hypertension. *Eur J Neurol*. 2018;25:1218-1227.
- Adderley NJ, Subramanian A, Nirantharakumar K, et al. Association between idiopathic intracranial hypertension and risk of cardiovascular diseases in women in the United Kingdom. *JAMA Neurol*. 2019;76:1088-1098.
- Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. *Eye*. 2019;33:478-485.
- Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. *Neurology*. 2013;81:1159-1165.
- Mollan SP, Davies B, Silver NC, et al. Idiopathic intracranial hypertension: consensus guidelines on management. *J Neurol Neurosurg Psychiatry*. 2018;89:1088-1100.
- Hoffmann J, Mollan SP, Paemeleire K, et al. European headache federation guideline on idiopathic intracranial hypertension. *J Headache Pain*. 2018;8:93.
- Mollan SP, Hornby C, Mitchell J, Sinclair AJ. Evaluation and management of adult idiopathic intracranial hypertension. *Pract Neurol*. 2018;18:485-488.
- Mollan SP, Hoffmann J, Sinclair AJ. Advances in the understanding of headache in idiopathic intracranial hypertension. *Curr Opin Neurol*. 2019;32:92-98. <https://doi.org/10.1097/WCO.0000000000000651>
- Kleinschmidt JJ, Digre KB, Hanover R. Idiopathic intracranial hypertension: relationship to depression, anxiety, and quality of life. *Neurology*. 2000;25:319-324.
- Mulla Y, Markey KA, Woolley RL, et al. Headache determines quality of life in idiopathic intracranial hypertension. *J Headache Pain*. 2015;16:521.
- Friedman DI, Quiros PA, Subramanian PS, et al. Headache in idiopathic intracranial hypertension: findings from the idiopathic intracranial hypertension treatment trial. *Headache*. 2017;57:1195-1205.
- 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;7:c2701.
- Markey K, Mitchell J, Botfield H, et al. 11 $\beta$ -Hydroxysteroid dehydrogenase type 1 inhibition in idiopathic intracranial hypertension: a double-blind randomized controlled trial. *Brain Commun*. 2020;2:fcz050.
- Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
- Yiangou A, Mitchell JL, Fisher C, et al. Erenumab for headaches in idiopathic intracranial hypertension: a prospective open-label evaluation. *Headache*. 2021;61(1):157-169. <https://doi.org/10.1111/head.14026>
- Mollan S, Hemmings K, Herd CP, et al. What are the research priorities for idiopathic intracranial hypertension? A priority setting partnership between patients and healthcare professionals. *BMJ Open*. 2019;9:e026573.
- Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24:9-160.
- Yri HM, Rönnbäck C, Wegener M, Hamann S, Jensen RH. The course of headache in idiopathic intracranial hypertension: a 12-month prospective follow-up study. *Eur J Neurol*. 2014;21:1458-1464.
- Yri HM, Jensen RH. Idiopathic intracranial hypertension: clinical nosography and field-testing of the ICHD diagnostic criteria. A case-control study. *Cephalalgia*. 2015;35:553-562.
- Mollan SP, Spitzer D, Nicholl DJ. Raised intracranial pressure in those presenting with headache. *BMJ*. 2018;363:1-5.
- Diener H-C, Dodick D, Evers S, et al. Pathophysiology, prevention, and treatment of medication overuse headache. *Lancet Neurol*. 2019;18:891-902.
- Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. *Nat Rev Neurol*. 2016;12:575-583.
- Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre—Clinical characteristics and treatment outcomes. *Cephalalgia*. 2004;24:483-490.
- Mollan SP, Tahrani AA, Sinclair AJ. The potentially modifiable risk factor in idiopathic intracranial hypertension: body weight. *Neurol Clin Pract*. 2021. <https://doi.org/10.1212/CPJ.0000000000001063>
- Ang JL, Teo KZ, Fraser CL. Weight loss in idiopathic intracranial hypertension: a retrospective review of outcomes in the clinical setting. *J Neuroophthalmol*. 2020. <https://doi.org/10.1097/WNO.0000000000001107>
- Ottridge R, Mollan SP, Botfield H, et al. Randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of idiopathic intracranial hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol. *BMJ Open*. 2017;27:e017426.
- Ko MW, Chang SC, Ridha MA, et al. Weight gain and recurrence in idiopathic intracranial hypertension: a case-control study. *Neurology*. 2011;76:1564-1567.
- Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA*. 2021;325(14):1403. <https://doi.org/10.1001/jama.2021.1831>
- Botfield HF, Uldall MS, Westgate CSJ, et al. A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. *Sci Transl Med*. 2017;9:eaan0972.
- Hornby C, Botfield H, O'Reilly MW, et al. Evaluating the fat distribution in idiopathic intracranial hypertension using dual-energy X-ray absorptiometry scanning. *Neuroophthalmology*. 2017;42:99-104.
- O'Reilly MW, Westgate CS, Hornby C. A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics. *JCI Insight*. 2019;4:e125348.
- Wall M, McDermott MP, Kiebertz KD, et al. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. *JAMA*. 2014;311:1641-1651.
- Ball AK, Howman A, Wheatley K, et al. A randomised controlled trial of treatment for idiopathic intracranial hypertension. *J Neurol*. 2011;258:874-881.

38. Celebisoy N, Gokcay F, Sirin H, Akyurekli O. Treatment of idiopathic intracranial hypertension: topiramate vs. acetazolamide, an open label study. *Acta Neurol Scand*. 2007;116:322-327.
39. Pagan FL, Restrepo L, Balish M, et al. A new drug for an old condition. *Headache*. 2002;42:695-696.
40. Scotton WJ, Botfield HF, Westgate CSJ, et al. Topiramate is more effective than acetazolamide at lowering intracranial pressure. *Cephalalgia*. 2019;39:209-218.
41. Hornby C, Mollan SP, Botfield H, O'Reilly MW, Sinclair AJ. Metabolic concepts in idiopathic intracranial hypertension and their potential for therapeutic intervention. *J Neuroophthalmol*. 2018;38:522-530.
42. Hardy RS, Botfield H, Markey K, et al. 11 $\beta$ HSD1 inhibition with AZD4017 improves lipid profiles and lean muscle mass in idiopathic intracranial hypertension. *J Clin Endocrinol Metab*. 2021;106:174-187.
43. Friedman DI. Headaches in idiopathic intracranial hypertension. *J Neuroophthalmol*. 2019;39:82-93.
44. Yiangou A, Mitchell JL, Vijay V, et al. Calcitonin gene related peptide monoclonal antibody treats headache in patients with active idiopathic intracranial hypertension. *J Headache Pain*. 2020;21:116.
45. Yiangou A, Mitchell J, Markey KA, et al. Therapeutic lumbar puncture for headache in idiopathic intracranial hypertension: minimal gain, is it worth the pain? *Cephalalgia*. 2019;39:245-253.
46. Scotton WJ, Mollan SP, Walters T, et al. Characterising the patient experience of diagnostic lumbar puncture in idiopathic intracranial hypertension: a cross-sectional online survey. *BMJ Open*. 2018;8:e020445.
47. Sinclair AJ, Kuruvath S, Sen D, et al. Is cerebrospinal fluid shunting in idiopathic intracranial hypertension worthwhile? A 10-year review. *Cephalalgia*. 2011;31:1627-1633.
48. McGirt MJ, Woodworth G, Thomas G, Miller N, Williams M, Rigamonti D. Cerebrospinal fluid shunt placement for pseudotumor cerebri-associated intractable headache: predictors of treatment response and an analysis of long-term outcomes. *J Neurosurg*. 2004;101:627-632.
49. Daou BJ, Sweid A, Weinberg JH, et al. Effect of shunting on visual outcomes and headache in patients with idiopathic intracranial hypertension. *World Neurosurg*. 2020;142:e73-e80.
50. Azad TD, Zhang Y, Varshneya K, Veeravagu A, Ratliff JK, Li G. Lumboperitoneal and ventriculoperitoneal shunting for idiopathic intracranial hypertension demonstrate comparable failure and complication rates. *Neurosurgery*. 2020;86:272-280.
51. Gurney SP, Ramalingam S, Thomas A, Sinclair AJ, Mollan SP. Exploring the current management idiopathic intracranial hypertension, and understanding the role of dural venous sinus stenting. *Eye Brain*. 2020;12:1-13.
52. Dinkin MJ, Patsalides A. Venous sinus stenting for idiopathic intracranial hypertension: where are we now? *Neurol Clin*. 2017;35:59-81.
53. Al-Mufti F, Dodson V, Amuluru K, et al. Neuroendovascular cerebral sinus stenting in idiopathic intracranial hypertension. *Interv Neurol*. 2020;8:164-171.
54. Satti SR, Leishangthem L, Chaudry MI. Meta-analysis of CSF diversion procedures and dural venous sinus stenting in the setting of medically refractory idiopathic intracranial hypertension. *Am J Neuroradiol*. 2015;36:1899-1904.
55. Jefferis JM, Littlewood RA, Pepper IM, Hickman SJ, Salvi SM. Optic nerve sheath fenestration via a supero-medial eyelid skin crease approach for the treatment of idiopathic intracranial hypertension in a UK population. *Eye*. 2021;135(5):1418-1426. <https://doi.org/10.1038/s41433-020-1024-8>
56. Hamedani AG, Thibault DP, Revere KE, et al. Trends in the surgical treatment of pseudotumor cerebri syndrome in the United States. *JAMA Netw Open*. 2020;3:e2029669.
57. Gelaye B, Sacco S, Brown WJ, Nitchie HL, Ornello R, Peterlin BL. Body composition status and the risk of migraine: a meta-analysis. *Neurology*. 2017;88:1795-1804.
58. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain*. 2003;106:81-89.
59. Bigal ME, Tsang A, Loder E, Serrano D, Reed ML, Lipton RB. Body mass index and episodic headaches: a population-based study. *Arch Intern Med*. 2007;167:1964-1970.
60. Bigal ME, Liberman JN, Lipton RB. Obesity and migraine: a population study. *Neurology*. 2006;66:545-550.
61. Bigal ME, Lipton RB, Holland PR, Goadsby PJ. Obesity, migraine, and chronic migraine: possible mechanisms of interaction. *Neurology*. 2007;68:1851-1861.
62. Hershey AD, Powers SW, Nelson TD, et al. Obesity in the pediatric headache population: a multicenter study. *Headache*. 2009;49:170-177.
63. Thaller M, Tsermoulas G, Sun R, Mollan SP, Sinclair AJ. Negative impact of COVID-19 lockdown on papilloedema and idiopathic intracranial hypertension. *J Neurol Neurosurg Psychiatry*. 2020:jnnp-2020-325519.
64. Raggi A, Marzoli SB, Chiapparini L, et al. Headache frequency and symptoms of depression as predictors of disability in patients with idiopathic intracranial hypertension. *Neurol Sci*. 2018;39(Suppl. 1):139-140.
65. Hamelsky SW, Lipton RB. Psychiatric comorbidity of migraine. *Headache*. 2006;46:1327-1333.
66. Merikangas KR, Angst J, Isler H. Migraine and psychopathology. Results of the Zurich cohort study of young adults. *Arch Gen Psychiatry*. 1990;47:849-853.
67. Tietjen GE, Peterlin BL, Brandes JL, et al. Depression and anxiety: effect on the migraine-obesity relationship. *Headache*. 2007;47:866-875.
68. Wong B, Fraser CL. Obstructive sleep apnea in neuro-ophthalmology. *J Neuroophthalmol*. 2019;39:370-379.
69. Purvin VA, Kawasaki A, Yee RD. Papilledema and obstructive sleep apnea syndrome. *Arch Ophthalmol*. 2000;118:1626-1630. <https://doi.org/10.1001/archophth.118.12.1626>
70. Thurtell MJ, Trotti LM, Bixler EO, et al. Obstructive sleep apnea in idiopathic intracranial hypertension: comparison with matched population data. *J Neurol*. 2013;260:1748-1751.
71. Mitsikostas DD, Vekelis M, Viskos A. Refractory chronic headache associated with obstructive sleep apnoea syndrome. *Cephalalgia*. 2008;28:139-143.
72. Edwards BA, Bristow C, O'Driscoll DM, et al. Assessing the impact of diet, exercise and the combination of the two as a treatment for OSA: a systematic review and meta-analysis. *Respirology*. 2019;24:740-751.

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