

Outcomes measures in idiopathic intracranial hypertension

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DOI:

[10.1080/14737175.2021.1931127](https://doi.org/10.1080/14737175.2021.1931127)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Mollan, S & Sinclair, A 2021, 'Outcomes measures in idiopathic intracranial hypertension', *Expert Review of Neurotherapeutics*, vol. 21, no. 6, pp. 687-700. <https://doi.org/10.1080/14737175.2021.1931127>

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Outcomes measures in idiopathic intracranial hypertension.

Abstract

Introduction

Idiopathic Intracranial Hypertension is condition characterised by raised intracranial pressure, papilledema, and normal neuroimaging (aside from radiological signs of raised intracranial pressure). Symptoms of idiopathic intracranial hypertension include chronic headaches and for some, visual loss. New treatments are an unmet clinical need.

Areas covered

The aim of this review is to present the evidence base and considered opinion on outcome measures to determine successful management of idiopathic intracranial hypertension.

Expert opinion

Less invasive measures of disease activity such as optical coherence tomography will continue to grow in this field, both as a measure of papilledema, and potentially as a surrogate for intracranial pressure and visual function. As a highly disabling aspect of the disease is headache, treatment outcomes for headache morbidity need to be appropriately chosen and standardized to allow comparison between trials.

Keywords

Idiopathic intracranial hypertension; intracranial pressure; headache; obesity; optical coherence tomography; papilledema; pseudotumour cerebri; randomized control trial; vision and weight loss.

Abbreviations

CGRP, Calcitonin gene-related peptide

CSF, cerebrospinal fluid

HVF, Humphrey visual field

ICHD3b, International Classification of Headache Disorders 3b;

IIH, idiopathic intracranial hypertension;

ICP, intracranial pressure;

HADS, hospital anxiety and depression scale;

HIT-6, headache impact test-6;

LP, lumbar puncture

MD, mean deviation;

MHD, monthly headache days;

MmsHD, monthly moderate/severe headache days;

MOH, overuse headache;

NRS, Numeric Rating Scale;

OP, opening pressure;

OCT, Optical Coherence Tomography

PSD, pattern standard deviation;

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SF-36, Short Form-36 Health Survey.

Expert commentary

1. Introduction

Idiopathic intracranial hypertension (IIH) is characterized by raised intracranial pressure (ICP), papilledema with the potential risk of permanent visual loss.[1][2] IIH has an established association with obesity [3][4] and has a detrimental effect on important aspects of the patient's quality of life; the majority of which is determined by headache.[5] The incidence and prevalence are rising consistent with the global obesity epidemic. [6][7][8] Young obese women are most commonly affected, although rarely, it may occur in men or children and is not always associated with obesity.[1][6] The disease is more common in those who are socially disadvantaged.[6][9]

Important principles for the management of IIH have been agreed [1] where modifying the underlying pathophysiology, with weight management is key for all patients with typical disease and a raised body mass index.[4] In those with rapidly declining visual function, now between 7-9% of those with IIH[6], an emergency intervention is warranted to save sight. However headache management remains a high priority as it confers morbidity to the majority of patients.[5] The 2015 Cochrane review concluded that there is a lack of high class evidence to guide management of the condition.[10] There are few published randomised clinical trials (RCTs) and a small number of open label trials (Table 1).[11][12][13][14][15][16][17][18][19] The choice of a primary end point to determine successful outcome has varied in trials between intracranial pressure and visual function (Table 1). To date there has been no randomized control trial evaluating treatment for headache attributed to IIH, although a recent open label study used a primary end point of change in monthly moderate and severe headache days.[15] Given the multidisciplinary

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nature of the condition investigators rely on their specialist experience to define successful treatment outcomes. To address these differences and to consider patients and carers views the James Lind Alliance, a United Kingdom National Institute for Health Research-supported priority setting partnership initiative was established. This defined diagnostic and management outcomes that should be prioritized for research, determined by patients, carers and health care physicians.[20]

2. Aims and Methods

The aim of this commentary was to review previous clinical studies investigating an intervention in IIH and define the outcome measures which best reflect successful management in IIH. To support this a detailed search of the scientific literature included all English language papers on PubMed, Cochrane and Google Scholar between inception until April 22nd, 2021 combining free-text and controlled vocabulary terms for IIH. Key words included Idiopathic intracranial hypertension; intracranial pressure; headache; obesity; optical coherence tomography; papilledema; pseudotumour cerebri; randomized control trial; surgery; shunting; stenting; venous sinus stenosis; vision and weight loss. Primary and secondary outcomes used in IIH randomised control trials were selected for discussion as to the merits and disadvantages of the measurement. The clinical trials themselves were not assessed for publication or other bias, which was beyond the remit of this article.

3. Intracranial pressure, as an outcome measure for IIH

One of the key criteria for a diagnosis of IIH is measurement of intracranial pressure. [1] The most common method of ICP measurement in IIH remains lumbar puncture (LP), with several documented negative aspects such as complications and patient experience.

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[21][22][23] There are some factors that can influence the accuracy of the measurement including levels of anxiety, Valsalva manoeuvre and patient positioning.

Variability could be minimized by asking participants to relax their breathing and avoid Valsalva manoeuvre, in addition to allowing time to ensure a stable LP opening pressure (OP) reading is taken.[24] As ICP is the key driver for visual morbidity and headache measuring LP opening pressure (OP) change over time has been the primary outcome for a number of trials (Table 1).

There is a difference in opinion over what is a normal LP OP, whether all values outside the normal range should be considered pathological, and what factors may influence the normal limits. The International Headache Society (IHS) defines increased cerebrospinal fluid (CSF) OP as above 25 cm H₂O for the non-obese and above 28 for obese children, documented in the International Classification of Headache Disorders 2018 [25]. The limits of what is considered a normal CSF OP have been revised over the last two decades, and it was previously considered that 20 cm H₂O was the upper limit in the IHS Classification from 2004. [26]

Bø *et al.* evaluated 339 patients undergoing lumbar puncture from neurology outpatient clinics. The mean CSF OP was 17.5 cm H₂O, with the minimum value at 4.0 cmCSF and the maximum value at 30.0 cmCSF. The mean CSF OP for women was 16.9cmCSF, mean CSFOP for men was 18.5cmCSF ($p = 0.003$). They concluded that CSFOP levels above 20 cm H₂O and 25 cm H₂O are frequent and do not always indicate a pathological condition. CSF OP was significantly lower in women compared to men, becoming significantly lower as age increased and higher as BMI increased. [27] The IIH BODPOD Study the relationship

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between ICP, body mass index (BMI), percentage body fat and distribution of body fat in non-IIH patients was evaluated. They found that BMI, waist circumference, hip circumference and percentage body fat all positively correlated with LP OP. When broken down by gender, the correlation between LP OP and BMI, waist and hip circumference was stronger in females compared to males and the percentage body fat was more predictive in men.[28]

Determination of a clinically meaningful change of LP OP in IIH can be deduced from the existing literature (Table 1). The Birmingham weight loss prospective trial demonstrated that a very low-calorie diet (1777 kJ/day (425 kcal/day)) resulted in significant weight loss ($15.3 \pm 7.0\%$ of body weight), and significantly lowered ICP. The LP OP was shown to be significantly reduced by $8 \pm 4.2\text{cmCSF}$, $p < .001$. This led to clinical remission with improvement in papilloedema, vision and headache outcomes.[11] In the IIH treatment trial (IIH TT) LP OP was a secondary outcome. At baseline the average (SD) CSF OP, obtained using a standardized lumbar puncture protocol, was 343.5 (86.9) mm H₂O (range, 210–670 mm H₂O). Only 85 participants (47 [55%] in the acetazolamide group and 38 [48%] in the placebo group) agreed to a lumbar puncture at 6 months follow-up. The adjusted mean change in CSF pressure was -112.3 mm H₂O (from 357.2 mm H₂O at baseline to 244.9 mm H₂O at 6 months) in the acetazolamide group and -52.4 mm H₂O (from 357.2 mm H₂O at baseline to 304.8 mm H₂O at 6 months) in the placebo group (treatment effect, -59.9 mm H₂O; 95% CI, -96.4 to -23.4 mm H₂O; $P = .002$).[14] As both groups in the IIHTT improved over the course of the trial, the minimum clinically meaningful change in this study could be interpreted as a reduction of LP OP of 6.0cmCSF. It is worth noting that clinical remission may not reflect total normalization of ICP to below pre-diagnosis levels i.e. CSF OP below 25

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CmCSF, as seen in the Birmingham weight loss study where clinical remission as noted in vision, headache and patient reported outcomes where the LP OP at diet end was measured as a mean LP OP of 30.0 (4.9) cmCSF.[11] In the planning of the IIH:weight trial[18] the effect size required for change in ICP to be significant was based on the assumption that a reduction of LP OP of 8cmCSF would occur in the bariatric surgery arm and that a smaller reduction of 3cmCSF would occur in the diet arm (a value to reflect changes slightly greater than the baseline fluctuations seen in Sinclair *et al* [Sinclair]).[29] They planned to detect a mean difference of 5cmCSF between the two trial arms.[29] The IIH Weight Trial detected a greater difference between the two trial arms of a mean of -6.0 cm CSF at 12 months and -8.2 cm CSF at 24 months. [18]

Measurement of ICP by other means, such as telemetric ICP monitoring, are now being deployed in clinical trials.[19]. Early indications show that telemetric ICP monitoring is highly accurate and provides insight into CSF dynamics in IIH and facilitates management decisions. It is likely that in the future, these more direct methods may be used particularly for early phase trials to monitor response to interventions but due to their invasive nature, they are unlikely to be employed in large scale phase 3 trials.

4. Headache as an outcome measure for IIH

Headache is the predominate presenting feature in IIH.[30][31] Patient morbidity is high because of disabling headaches which are the key driver for poor quality of life. [5][32] Research into headache treatments were endorsed as clinically relevant by a priority setting partnership which included patients', carers' and physicians' opinions.[20] Initially the headaches develop in a temporal relationship to raised ICP [25], but for many are not typical

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of a well known “textbook’ raised ICP headache waking the patient, and more often resemble a primary headache disorder such as migraine.[30][31] In patients with IIH in whom the pressure has normalized (IIH in ocular remission), persistent post-IIH headaches can remain, contributing to long term morbidity.[31] Both headache attributed to IIH and persistent post-IIH headaches can be exacerbated by co-existing medication overuse.[30][31] There have been no randomised control trials evaluating treatment options for IIH headache, but given the striking similarities to migraine, it should be anticipated that both abortive and preventative therapies should be evaluated in IIH. Care should be taken to design trials with treatment-free control groups, to mitigate against the placebo phenomenon which is commonly reported in headache trials.[34] Furthermore headache outcomes utilized in migraine therapy trials may well be suited to deployment in IIH headache trials.

A 28-day diagnostic headache diary is used in headache clinical trials to prospectively collect information on headache duration, characteristics, associated symptoms, and use of acute analgesic medications. These are filled daily by the patient, to prevent recall bias. Headache outcomes are clinically relevant to IIH, due to the burden of headache reported by patients.[35] The International Headache Society have recommended core outcome measures for both abortive [34] and preventative migraine therapies[36]. The American Headache Society recommends a number of headache outcomes to identifying patients who are benefiting from headache therapy such as: monthly moderate to severe headache days (MmsHD); headache responder rate ($\geq 50\%$ reduction in monthly headache days [MHD]); and headache responder rate ($\geq 50\%$ reduction in MmsHD). [37] It seems reasonable, given

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the phenotype of IHH headache for these types of outcomes to be utilized in IHH trials (Table 2).

Number of Monthly Headache Days (MHD) should include all headache days, defined as those with an onset, continuation or recurrence, any severity or phenotype of headache and lasting at least 30 minutes or which require acute headache analgesia. A moderate/severe headache day should be defined as a day with moderate or severe head pain that lasts at least 4 hours or that requires acute headache analgesic medications. Change in monthly headache days (MHD), incorporate all headache days in a month, whereas change in MmsHD document those days with the most morbidity. MmsHD was recently reported as the primary endpoint in a prospective open label study provides evaluating the effectiveness of erenumab, a calcitonin gene-related peptide (CGRP) monoclonal antibody, to treat headaches in IHH patients.[15] IHH patients had severely disabling headaches at baseline, and MmsHD was a helpful indicator to differentiate improvements in the treatment, particularly as the headache burden in IHH, here was chronic.[15]

Headache responder rate ($\geq 50\%$ reduction in MHD) is defined as the proportion of patients achieving at least 50% reduction in the mean number of MHD of any intensity from baseline to the defined study end point. This criterion is likely to be clinically relevant for IHH, as it is used as an empirical review for continuing or discontinuing preventive therapy in headache preventative therapy.[36] Headache responder rate ($\geq 50\%$ reduction in MmsHD) is defined as the proportion of patients achieving at least 50% reduction in the mean number of MmsHD baseline to the defined study end point. It is recognized that 50% responder rates may not fully capture the benefits of preventive treatment [38]. For example, a patient may improve from a disabling 20 severe headache days per month to 11 moderate headache

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days per month. Despite a considerable clinical benefit, such a patient would not be considered a responder because headache days were not reduced by 50%, and might lose access to beneficial treatment. [39] This is why a documented change in MmsHD is important. Responder rates of both $\geq 50\%$ reduction and $\geq 30\%$ reduction can also easily compare studies in meta-analysis of placebo controlled randomised controlled trials.

Collecting data about headache intensity and before any rescue medication use is critical for the analysis of the pain-free efficacy outcome measure. Recording a decrease in intensity is an indicator of reduced disability, a clinically meaningful headache outcome. Measuring consumption of acute rescue medication reflects a judgement of the inefficacy of the test treatment is a helpful secondary outcome. In Sinclair *et al.* reduction in analgesic days was significant, correlating with clinical remission of IIH.[11] Additionally a high portion of IIH, up to 48% [15] reported medication overuse and medication overuse headache, and measuring a reduction in analgesic days mitigates these two serious confusions in the treatment of chronic headache.

5. Visual function as an outcome

With papilledema being a key sign of IIH and it's ability to impact on visual function, it is not surprising that tests of vision and visual function have been central to studies of IIH.[1][2]

Visual acuity is a predominant component of visual function in people. In IIH, visual acuity is mildly affected by a hypermetropic shift secondary to raised ICP [40] and only in severe disease is the visual acuity more markedly affected. Investigators have found no association

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between the visual acuity and measures of papilledema in those patients with mild visual loss as determined by Humphrey visual fields.[41]

Automated perimetry is an objective measure of the visual field, widely used in clinical practice.[42] Importantly, there are a number of factors that make visual fields unreliable to interpret in IIH. The visual field type, either static or kinetic, and the program settings significantly affect the pick-up of defects depending on the visual field strategy [43], with a preference for automated perimetry for a more sensitive pick up rate. [44] The visual field test is dependent on technician and patient performance and is prone to variability and inaccuracy. [45][46] Initially patients can perform poorly on automated perimetry [45], and many trials sanction multiple attempts for familiarization and learning. [46] [47] In the IIHTT, up to 21% of patients had a performance failure at one data point. [45]. For IIH there is a further complicating factor in the interpretation of visual fields with the high prevalence of functional vision loss presenting as non-organic visual fields in this disease. [47] [48]

Cognitive deficits have also been reported in IIH [49] and have shown deficits in key areas such as memory, learning, visuospatial skills, concentration, language and executive function. [50][51][52][53][54] Deficits in reaction time and processing speed have also been demonstrated, which could impact on those with IIH to perform visual fields reliably. [50]

Cognitive deficits have been demonstrated to affect the performance of visual fields in other diseases. [55][56]

6. Measurement of papilledema as an outcome measure

Papilloedema is a reliable sign of raised intracranial pressure.[57] Change in papilloedema has been used by all randomised control trials in IIH to date to determine clinical

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improvement (Table 1). Change in papilloedema has either been graded by experts using the Frisén classification[58] and more recently reliably measured by optical coherence tomography (OCT) imaging. Waisbourd *et al* [59] reported on 91 eyes of 48 patients, and showed that the OCT peripapillary retinal nerve fibre layer (pRNFL)(Figure 1) could discriminate between different degrees of optic nerve head (ONH) swelling correlating with clinical appearance of the optic nerves on fundoscopy. Average pRNFL thickness was statistically different between the groups: normal optic disc/mild elevation group ($N = 20$) – 89 μm (95% CI, 80–98 μm), mild elevation group ($N = 51$) – 109 μm (95% CI, 101–117 μm), and papilledema group ($N = 20$) 124 μm (95% CI, 100–153 μm) ($P = 0.004$). Hence pRNFL may be a better measure of categorization of papilloedema over Frisén grading, as it is a continuous measure and not a categorical scale.[59]

OCT imaging is a rapid, reproducible, non-invasive, inexpensive and a highly adaptable technology. Both initial and longitudinal imaging have key roles in diagnosing and managing IIH (Figure 2 and Figure 3).[42][60] It is important to note that although reduction in a previously noted elevated optic nerve head may indicate improvement in the condition the reduction itself cannot readily be separated between resolution of oedema and damage to the axons caused by optic atrophy. Despite this issue the measures of the ONH are valuable clinical tools in IIH [60][61][62][63] Skau *et al*[63] demonstrated the utility of OCT in diagnosis of raised ICP by employing a multiple regression model using RNFL and total retinal thickness with the ICP as measured by a LP and were able to detect ICP > 25 cmCSF (~18.4 mmHg) in those with newly diagnosed IIH.

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3-Dimensional imaging of the ONH height and volume analysis have been shown to correlate with disease state, being diagnostic and a progression parameter in IIH with higher sensitivity to ICP changes measured by LP compared to pRNFL measures. [60][64] Kaufold *et al*[64] reported that the pRNFL thickness did not show differences between controls and IIH patients. Optic nerve head volume (ONHV) and optic nerve head height (ONHH) discriminated between controls, treated and untreated patients. In their analysis ONHV and ONHH measures were related to levels of intracranial pressure (ICP). [64]. Jivraj *et al* [65] showed in longitudinal studies that baseline and absolute changes in TRT and ONHV were significantly superior to pRNFL changes among patients with papilloedema.

OCT imaging ONH central thickness (CT) is one parameter of the Spectralis™ ONH volume scan (Figure 4). In Vijay *et al* [62] the maximum height of the optic nerve head at the highest point and the maximum height of the optic nerve head at the central slice (as defined by the point of vessel emerging at the OHN) with the central volume and thickness (CT) were all equally predictive of intracranial pressure. Pragmatically, CT was chosen to represent these measures later in the publication. While any measure of the optic nerve head volume could be used to predict disease activity, it is more likely that CT and central volume would be the parameters that may more accurately reflect current ICP. The treatment effect on ICP was predicted by bootstrap surrogacy analysis. They found a reduction in CT of 100 µm at 12 months was highly likely to be associated with a reduction in ICP at 12 months (mean decrease of 5.9 cmH₂O, 95%CI 1.9 – 9.1 cmH₂O). Similarly, observation of a reduction of CT of at least 50 µm at 24 months is highly likely to be associated with a reduction in ICP (mean decrease of 6.5 cmH₂O, 95%CI 2.3 – 9.9 cmH₂O).[62]

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Professional bodies and recent literature reviews recommend the directed use of OCT in diagnosis and longitudinal monitoring of papilloedema in routine clinical care. [1][42][66] It would seem unlikely that OCT imaging would be omitted from future clinical trials evaluating treatment effects in those patient with active IIH with papilledema.

7. OCT measurements as a reflection of visual function

OCT measures have been demonstrated to be robust measures of neuronal loss in many neurological diseases, which correlate with visual loss. [67] Prior to OCT one study investigated the utility of confocal scanning laser ophthalmoscopy and compared the parameters with automated perimetry. The optic nerve head parameters such a volume above reference, volume above surface, effective mean height, and maximum height in contour were quantitatively correlated with visual field sensitivity losses. There results showed that improvement in the volumetric parameters were paralleled by recovery in perimetric sensitivity. The data here supported the use of volume measurements of the optic nerve head to determine perimetric loss of sensitivity. [68]

Rebolleda et al. [69] investigated visual field global indices of mean deviation [MD] and pattern SD [PSD] and changes in the OCT retinal nerve fibre layer (RNFL) overall thickness in IIH. They found that pRNFL thickness abnormalities assessed by OCT in patients with mild papilledema were quantitatively correlated with visual field sensitivity losses. This was both at diagnosis and follow-up. The mean average pRNFL was significantly correlated with the MD ($P = 0.002$) and PSD ($P = 0.013$) at diagnosis. The RNFL thickness decreased significantly ($P = 0.000$), whereas the mean MD and the mean PSD improved ($P = 0.000$ and $P = 0.005$,

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respectively) at each follow-up visit. Regression analysis showed that for every 10 μm of mean RNFL thickness increase at baseline, there was a 0.6-dB decrease in MD at the last follow-up.

Afonso *et al* [70] investigated the electrophysical responses of the retina by pattern electroretinogram [PERG]), visual loss measured by Humphrey visual fields and OCT measures in resolved papilloedema secondary to IIH and controls. They found that OCT was superior to the PERG in the ROC curve discriminating between eyes with papilloedema and controls and overall diagnostic ability of the two technologies similar in detecting visual loss from IIH.

Albrecht *et al.* [60] investigated 21 patients with OCT in IIH and compared them to 27 age- and sex-matched controls. With longitudinal monitoring they found the macular RNFL volume decreased by 5% in 3.5 months, and a stepwise multivariate regression analysis identified CSF pressure as the main influence on macular RNFL volume at diagnosis. Initial ONH volume was the only factor predicting macular RNFL volume loss with time. This implies that ONH volume can predict axonal loss and hence should be able to predict visual field loss over time. Indeed, Vijay *et al.*[62] found that OCT macular GCL measures were positively correlated with the Humphrey visual field MD at both baseline and 12 months. Where there was a worse MD value, the lower the GCL global volume value was found to be. Thus indicating that GCL can help to predict the functional disability caused by papilloedema.[62]

8. Patient reported outcome of the most bothersome symptom

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The use of the most bothersome symptom (MBS) as a trial endpoint has been successfully deployed in headache trials, but not previously in IHH trials.[34][36] The overarching aim is to align the clinical trial outcome with the symptom that is of primary importance to the individual patient. For IHH this may be a useful outcome as an alternative to requesting demonstration of a positive treatment effect on all the IHH associated symptoms. In general use of MBS requires larger sample sizes due to the need to consider the frequency of the symptoms experienced. The MBS endpoint should be selected just prior to study intervention and measured on a binary scale (present or absent). For example IHH subjects would be invited to select the MBS prior to randomization and use a time-locked recording device (e.g. an electronic diary) to record their MBS throughout the duration of the trial. [34][36]

9. Patient reported outcomes

IHH has been demonstrated through clinical studies to have a detrimental effect on aspects of the patient's quality of life; the majority of which is driven by headache. [5][32][71]

Patient reported outcomes in clinical trials are essential to permit health technology assessments, cost effectiveness analysis, and key outcomes for therapy effectiveness. [34].

There is currently no IHH disease specific quality of life outcome measures. Validated quality of life tools that are typically used in IHH clinical trials include: Short form (SF)-36 [72]; 25-Item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) [73]; 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25. [74]; EQ5D [75]; the Hospital anxiety and depression score [76]; and the six-item Headache Impact Test (HIT-6) [77]. It is important to note that no single quality of life tool was used in isolation. Whilst there are differences in

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the choice of the tools between the United Kingdom and the North American based trials, they all commonly use the SF-36 and the HIT-6.

IIH has confounding comorbid conditions that have been shown to affect quality of life measures such as obesity, depression, and anxiety.[71][78][79] In a matched case control study NEI-VFQ-25 and SF-36 subscale scores were found to be lower in IIH as compared with other neuro-ophthalmologic disorders and their evaluation of published normal people. Obesity and weight gain influence the relation between health related quality of life and IIH in the mental component score of the SF-36.[71] A retrospective cross-sectional analysis of patients with IIH demonstrated poor overall health-related QOL, measured by the SF-36, when compared with obese and normal weight controls. This study also noted IIH participants had increased depression and fatigue.[79]

Ball *et al* reported that there were only improvements in the SF-36 subscales of pain and change in health for all patients and there were no significant differences between the trial arms (acetazolamide versus placebo) at any visit.[13] In the IIH treatment trial (IIHTT) at baseline, the SF-36 Physical Component Summary (PCS) score was associated with self-reported cognitive dysfunction, dizziness/vertigo, nocturia, radicular pain, HIT-6 score, high-risk Berlin questionnaire score, nonpulsatile tinnitus, self-reported change in vision for worse in either eye, and transient visual obscurations. They also noted an association between the SF-36 Mental Component Summary (MCS) score and dizziness/vertigo, neck pain, photophobia, recent weight gain, years of education, HIT-6 score, high-risk Berlin questionnaire score, self-reported change in vision for worse in either eye, and transient visual obscurations.[32] The HIT-6 score was associated with every SF-36 subscale. However,

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when controlled for HIT-6 score in a multiple regression model three other factors including headache accounted for decreases in QOL including visual acuity, perimetric mean deviation, double vision, and transient visual obscurations.[32] A high risk score on the Berlin Sleep Apnoea Questionnaire was associated with lower scores on the SF-36 PCS and MCS, and the general health subscale on the SF-36 indicating obstructive sleep apnoea can contribute to reduced quality of life as measured by the SF-36.[32] Of note, the quality of life measures in the IIHTT were performed following a lumbar puncture (LP) which could influence results as LP can be uncomfortable and for some traumatic.[21]

Following randomisation at 6 month follow-up in the IIHTT, improvements were noted in the acetazolamide arm as compared to the placebo arm in the SF-36 PCS score (3.0 points; $p = 0.03$), and the SF-36 MCS score (3.5 points; $p = 0.03$).[14] In depth analysis of the IIHTT by Bruce *et al.* evaluating the quality of life tools against symptoms of IIH found improvement in the SF-36 PCS was associated with resolution of transient visual obscurations (6.9 points; 95% CI 1.6–12.2, $p = 0.01$). However, no change in symptoms or signs were associated with changes in the SF-36 MCS. No association could be found between the SF-36 components and Frisén scale, body mass index, back pain, neck pain, radicular pain, photophobia, tinnitus (pulsatile or nonpulsatile), binocular diplopia, visual acuity and cerebrospinal fluid opening pressure (intracranial pressure).[80]

The HIT-6 is appealing as an outcome measure as it is widely deployed in headache trials and clinical practice.[77] The HIT-6 typically takes less time to complete as compared to other tools, such as the SF-36. In the Birmingham weight loss study baseline HIT-6 was 57.5 (± 9.0) which significantly improved after weight loss to 46.9 (± 10.1) ($P=0.004$). [11] The

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IIHTT HIT-6 mean baseline was a similar level at 59.7 (± 9.0).[] This reduced in both trial arms by over 9 points at 6 months, with no significant difference found between those taking acetazolamide or placebo.[81] In an open label extension of the IIH TT, 96 participants were sorted into remaining on acetazolamide (n = 34); switch placebo to acetazolamide (n = 35); switch acetazolamide to no treatment (n = 16); and switch placebo to no treatment (n = 11). At month 12 those who switched from placebo to acetazolamide had significant improvement HIT-6 with - 3.70 point reduction ($p=0.01$).[82] It is however well known that headache outcomes are prone to placebo effects and hence why where possible blinding to treatment allocation is advised. Despite this experience of drug related side effects (such as use of acetazolamide and experiencing paraesthesia), may unintentionally cause unmasking of the treatment allocation.

10. Expert opinion

There are a number of different outcome measures that could be chosen to determine successful management of IIH (Table 2). There is no hierarchical order of these outcomes, as the outcome may be determined by the disease state (new onset or chronic); disease severity; and the intervention (surgical or a medicinal product) being assessed. Indeed specific outcomes are likely to be different depending on the phase of the trial also.

Therefore this article has summarised an overarching approach by discussing trial outcomes that have previously been used (Table 1), and that have been shown to be important to patients [20]. There are several limitations of this article which should be considered.

Namely that there was no systematic assessment of the quality of the clinical studies and trials that have been referenced, and no assessment of publication bias has been made. An in depth discussion of confounding factors would be of future interest as any observed

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differences in outcome between the treatment groups can occur if a baseline characteristic of the participant or other potentially influential variable are not controlled, for example use of acetazolamide, presence of obstructive sleep apnoea, prior history of migraine or medication overuse.

Targeting the underlying pathophysiology, as well as the symptoms and signs is of clear importance for those with IIH for long-term remission of the disease. There is evidence that IIH is a disease that has specific metabolic underpinnings[83][84][85], and that preclinical work is essential to test hypotheses prior to early phase clinical trials.[86] The first phase 2 trial for IIH evaluating a novel symptomatic treatment to lower CSF secretion and ICP, was an example of translational work in this area.[16] Key outcomes in early phase work is determining dosing, and safety and tolerability.

Later phase trials have then the ability to direct the focus on things that are important in the clinical management of the patient, or a particular spectrum of the disease. The majority of patients with IIH have medical treatment or lifestyle advice, it is therefore more likely that trials investigating medical interventions will be easier to recruit to, and more popular. Trials investigating medicinal products will also be interested in the important outcomes of adverse events, rate of compliance, mean drug dosing and discontinuation rates. In patients who develop rapidly progressive visual loss emergency surgical intervention is required in order to save sight, and this appears to occur in around 7% of patients [6]. Clinicians agree that protecting the vision from fulminant papilloedema is essential, however there are currently no clinical trials to guide the surgical approach.[1] Options utilised include cerebrospinal fluid (CSF) shunting, optic nerve sheath fenestration and dural venous sinus

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stenting. Whilst preference for the option may be determined by local experience, CSF shunting is the most commonly performed procedure, followed by optic nerve sheath fenestration then neurovascular stenting in the United States.[87] Neurovascular stenting has been popularised and the safety and efficacy of dural venous sinus stenting as a treatment for IIH is currently based on retrospective studies and two uncontrolled and open label prospective studies.[17][88] Due to the varied outcomes reported, direct comparison of these studies chosen outcomes remains unclear and future work will help provide the necessary evidence for this intervention in IIH routine clinical care. Surgical and neuro-interventional trials may require specific designs to deal with eligibility, feasibility and outcomes. While surgical trials in general can choose to favor outcomes such as numbers of complications, time to failure or time to rescue treatment, patients have remarked that symptoms, symptom resolution and disease remission are among their more preferable outcomes for IIH research trials.[IIH UK November 2019, round table discussion with surgical patients and carer input on health technology assessment (NIHR131211)].

All experts acknowledge that weight loss has a key role in management of IIH in those with body mass index over 30kg/m². [1][42][89] There is an increasing recognition of obesity stigma and how both clinicians and patients should approach this.[4] Weight loss through very low calorie diet or weight loss surgery is known to treat IIH. [11][18] However these weight loss methods have pitfalls, particularly in terms of recurrence with weight gain with low calorie diets and indeed bariatric surgery is not suitable for everyone. The recent medical therapies that have a broad appeal for IIH are the glucagon-like peptide 1 receptor (GLP-1R) agonists. The GLP-1R agonist, exendin-4, has previously been found in an animal model to be able to modulate CSF secretion at the choroid plexus and subsequently reduce

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ICP.[90] In the STEP-3 randomized control trial investigating semaglutide (a GLP-1R agonist) and placebo found semaglutide to be superior for long term sustained weight loss.[91]

Therefore investigation of the utility of GLP-1R agonists in IIH would be appealing as a “dual treatment” for IIH by non-invasively reducing weight and ICP.

Whilst the incidence and prevalence of the disease is rising, recruitment to clinical trials will remain challenging particularly if the trial design requires many recruits to achieve statistical power and if it does not meet with the patient’s approval or need. Open label studies in IIH should be discouraged, due to the predominate placebo effect on headache outcomes and natural disease regression over time. As headache is a near universal sequela of IIH, those trials assessing headache therapy may be more feasible than those trials assessing interventions for sight loss, which is now much less common. Looking to the future the challenge will be to promote and validate less invasive trial outcomes and to evaluate therapies that address both symptoms and the underlying disease process.

Article highlights

- 1 Headache is the predominant symptom of IIH, is typically migraine like, and is prioritized highly by patients and physicians.
- 2 Headache influences quality of life in IIH rather than measures of vision.
- 3 Headache therapy is an unmet clinical need in this patient population, and trials investigating headache therapy are desperately needed.
- 4 Optical coherence tomography provides an accurate objective assessment of changes in optic nerve head height in papilloedema, as compared to more categorical groups used in clinical assessment of papilledema.

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- 5 Measurement of the optic nerve head with optical coherence tomography imaging have been shown to have the potential to be used to predict changes in intracranial pressure.
- 6 Measurement of the optic nerve head with optical coherence tomography imaging have been shown to be used to predict changes in the visual field.
- 7 Until a disease specific quality of life tool for IIH is developed and validated, it is likely investigators will continue to use multiple tools to measure changes in quality of life following interventions. Change in quality of life measurements may also be useful in clinical practice to allow for a holistic approach to managing IIH.
- 8 Outcome selection for emergency surgical treatment to mitigate visual loss is challenging but vital to assess in the setting of randomized controlled trials.

Figure 1

Optical coherence tomography imaging of the peripapillary Retinal Nerve Fibre Layer (pRNFL) of a right normal eye.

- A) This is an infrared image of the right optic nerve with a green circle around the optic nerve (peripapillary);
- B) This is the cross section through the retina at this green circle from A);
- C) This is the pRNFL thickness as measured in microns. [T=temporal; TS=temporal superior; NS= nasal superior; N=nasal; N/T is the ratio of nasal thickness to temporal thickness; NI=nasal inferior; TI=temporal inferior; T=temporal; PMB=papillomacular bundle and G=global thickness);

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- D) This is the cross section through the retina at this green circle showing the height as compared to a reference database of those with European descent (2009).

Figure 2

Optical coherence tomography imaging of the peripapillary Retinal Nerve Fibre Layer (pRNFL) of a right swollen optic nerve head secondary to papilledema.

- A) This is an infrared image of the right optic nerve with a green circle around the optic nerve (peripapillary);
- B) This is the cross section through the retina at this green circle in (A). Note the difference in the image as compared to Figure 1(B)
- C) This is the pRNFL thickness as measured in microns. Note the difference in the global pRNFL here (357 μm) as compared to Figure 1(C).
- D) This is the cross section through the retina at this green circle showing the height as compared to a reference database of those with European descent (2009), which is expectantly higher than Figure 1 (D).

Figure 3

Optical coherence tomography imaging of the peripapillary Retinal Nerve Fibre Layer (pRNFL) longitudinal progression analysis of the Global pRNFL in a left eye of a person with IIH.

- A) This is an infrared image of the left optic nerve with a green circle around the optic nerve of the most recent visit which is now nearly normal.
- B) Longitudinal progression analysis of the Global pRNFL in a left eye of a person with IIH, where each dot is the global pRNFL thickness at the scan visit.

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- C) This is a thumbnail image of the most recent cross section through the retina at this green circle showing the height as compared to a reference database of those with European descent (2009).

Figure 4

Optical coherence tomography imaging of an optic nerve head volume scan with longitudinal change analysis in a right eye of a person with IIH, who had a neurosurgical shunt for visual loss. There are 10 days between C and D.

- A) This is an infrared image of the right optic nerve at the follow-up following a neurosurgical shunt for fulminant IIH.
- B) Thumbnail image which is a cross section at the level of the green line shown in A)
- C) This is the reference optic nerve head volume scan. The global volume [mm^3] is in the left top hand colour in red. [10.04mm^3]. Maximum height anywhere, is denoted by the square ikon that has been moved to the area with the highest value, and denoted as "Marker [$1366\mu\text{m}$]"; Maximum height central is the central Max black number [$1345\mu\text{m}$]; Central thickness (CT) is the central number in the circle/roundel [$1159\mu\text{m}$]; and central volume (CV) is the red number [0.91mm^3]
- D) This is the selected optic nerve head volume scan, 10 days following neurosurgical shunt. The global volume [mm^3] is in the left top hand colour in red [7.23mm^3]. Maximum height anywhere, is denoted by the square ikon that has been moved to the area with the highest value, and denoted as "Marker [$1084\mu\text{m}$]"; Maximum height central is the central Max black number [$1099\mu\text{m}$]; Central thickness (CT) is the central number in the circle/roundel [$848\mu\text{m}$]; and central volume (CV) is the red number [0.67mm^3]

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- E) This is the change between C) and D) in the optic nerve head volume scan, 10 days following neurosurgical shunt. The change in global volume [mm^3] is in the left top hand colour in red [-2.81 mm^3]. Maximum height anywhere, is denoted by the square ikon that has been moved to the area with the highest value, and denoted as “Marker [-282 μm]”; Maximum height central is the central Max black number [-82 μm]; Central thickness (CT) is the central number in the circle/roundel [-311 μm]; and central volume (CV) is the red number [-0.24 mm^3].

Additional information

Financial disclosures

SPM - Invex therapeutics advisory board (2019); Invex therapeutics consultancy work (2020, 2021) Heidelberg engineering speaker fees (2019, 2020, 2021).

ASJ - Invex therapeutics, company director with salary and stock options (2019, 2020, 2021).

Acknowledgements

AS is funded by a Sir Jules Thorn Award for Biomedical Science.

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Reference annotations

* of interest

** of considerable interest

- 1 Yiangou A, Mitchell JL, Fisher C, et al. Erenumab for headaches in idiopathic intracranial hypertension: A prospective open-label evaluation. *Headache*. 2020 Dec 14. doi: 10.1111/head.14026
 - * A prospective open label study of 55 patients with IIH in ocular remission (resolved papilloedema) and persistent post-IIH headaches investigated the use of Erenumab, a CGPR monoclonal antibody. Erenumab reduced the frequency of 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.

- 2 The NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee. Effect of Acetazolamide on Visual Function in Patients With Idiopathic Intracranial Hypertension and Mild Visual Loss: The Idiopathic Intracranial Hypertension Treatment Trial. *JAMA*. 2014;311:1641–51.
 - * The Idiopathic Intracranial Hypertension Treatment Trial showed that IIH is almost exclusively a disease of obese young women. Patients with IIH with mild visual loss have typical symptoms, may have mild acuity loss, and have visual field defects. The use of acetazolamide with a low sodium weight reduction diet compared with diet alone resulted in modest improvements in the perimetric mean deviation as measured from the Humphrey visual field.

- 3 Digre KB, Bruce BB, McDermott MP, et al. Quality of life in idiopathic intracranial hypertension at diagnosis: IIH Treatment Trial results. *Neurology*. 2015;84:2449-56.
 - * Quantifies impact of IIH on quality of life, as they reported marked effect on quality of life in untreated patients with mild visual loss from IIH at baseline in the IIH treatment trial.

- 4 Markey K, Mitchell J, Botfield H, et al. 11 β -Hydroxysteroid dehydrogenase type 1 inhibition in idiopathic intracranial hypertension: a double-blind randomized controlled trial. *Brain Commun*. 2020;2:fcz050.
 - * A United Kingdom multi-center phase II randomized, double-blind, placebo-controlled trial of 12-week treatment with a reversible competitive 11 β -HSD1 inhibitor, AZD4017, reported the results of safety and tolerability of AZD4017 in a cohort of active IIH. This is the first phase 2 trial for IIH evaluating a novel symptomatic treatment to lower cerebrospinal fluid secretion and intracranial pressure.

Outcomes in IIH

- 5 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.

** This priority setting partnership encouraged people with direct experience of IIH to collectively identify critical gaps in the existing evidence. The overarching research aspiration was to understand the aetiology and management of IIH, in particular they highlighted the importance of research into headache and novel therapies to treat IIH.