

Outcomes measures in idiopathic intracranial hypertension

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Table 1: Summary of published clinical studies evaluating therapies of IIH.

Trial	Design, location	Interventions	Primary outcome	Disease duration	Participant demographics	Results
IIH Weight Mollan <i>et al.</i> 2021 ¹⁸	Randomised control trial. Multicentre (5 sites) in United Kingdom	Bariatric surgery <i>versus</i> a community weight management intervention (CWI) [Weight Watchers™]	Intracranial pressure measured by lumbar puncture opening pressure	All that meet criteria for a diagnosis of IIH.	N=66 100% Women Mean age, 32 years	ICP was significantly lower in the bariatric surgery arm at 12 months (adjusted mean difference -6.00cmCSF [95% CI, -9.5 to -2.4]; p= .001) and at 24 months (adjusted mean difference -8.2cmCSF [95% CI, -12.2 to -4.2]; p< .001).
IIH Pressure Mitchell <i>et al.</i> 2020 ¹⁹	Randomised control trial. Single centre in United Kingdom	Exenatide, a Glucagon like peptide-1 receptor agonist, (10mcg twice daily sub-cutaneous) <i>versus</i> placebo	Intracranial pressure as measured by telemetric, intraparenchymal intracranial pressure monitor (Raumedic™)	All that meet criteria for a diagnosis of IIH.	N=16 100% Women Mean age [Mean BMI 38.1±6.2 kg/m ² , Mean ICP 30.6±5.1 cmCSF]	ICP, the primary endpoint, fell significantly (2.5 hours) -5.7 cmCSF (p=0.048), 24 hours -6.3 cmCSF (p=0.030) and 12 weeks -5.6cmCSF (p=0.058). Monthly headache days fell in the Exenatide treated cohort (-7.7 (9.2) p=0.069) and vision improved (logMar acuity -0.1 (0.04) p=0.004).
Yiangou <i>et al.</i> 2020 ¹⁵	Prospective, single centre open label study in those with persistent post IIH headache. Birmingham, United Kingdom	Erenumab, a calcitonin gene-related peptide monoclonal antibody	Change in monthly moderate/severe headache days from baseline (30-day pre-treatment period) compared to 12 months.	>1 year; IIH in ocular remission and those with post-IIH persistent headache	N=55; 100% women; Mean (SD) age 35.3(9) years.	Substantial reduction in monthly moderate/severe headache days and total monthly headache days (both P<0.001). Headache impact test-6 score and quality of life Short Form-36 Health Survey significantly improved at 12 months.

IIH Drug trial Markey <i>et al.</i> 2020 ¹⁶	Randomised control trial. Multicentre (3 sites) in United Kingdom	11 β -Hydroxysteroid dehydrogenase type 1 inhibitor, AZD4017	Intracranial pressure as measured by lumbar puncture opening pressure	All that meet criteria for a diagnosis of IIH.	N=31 100% Women Mean age 31.2 (SD = 6.9) years	ICP reduction by 13.5%. AZD4017 was safe, with no withdrawals related to adverse effects.
SIGHT surgical trial ClinicalTrials.gov Identifier: NCT03501966	Randomised control trial. Multicentre in North America	Ventriculoperitoneal Shunt <i>versus</i> Acetazolamide <i>versus</i> Optic nerve sheath fenestration	Humphrey visual field Perimetric mean deviation (PMD)	..	N=180	Closed due to enrolment targets not achieved.
Wall M <i>et al.</i> 2014 ¹⁴	Randomized control trial. Multicentre (38 sites) in North America	Acetazolamide plus low-sodium weight-reduction diet <i>versus</i> Placebo plus low-sodium weight-reduction diet	Humphrey visual field PMD	Acute, no more than 2 weeks of treatment for IIH, and within 1 week if treated with acetazolamide	N = 165 Women =161 Men =4 Average age was 29 years (range, 18-52 years).	The mean improvement in PMD was greater with acetazolamide (1.43 dB, from -3.53 dB at baseline to -2.10 dB at month 6; n = 86) than with placebo (0.71 dB, from -3.53 dB to -2.82 dB; n = 79); the difference was 0.71 dB (95% CI, 0 to 1.43 dB; <i>P</i> = .050).
Ball A <i>et al.</i> 2011 ¹³	Open-label, parallel-group randomized control trial. Multicentre (6 sites) in United Kingdom	Acetazolamide <i>versus</i> placebo	Disease remission as determined by physician	All that meet criteria for a diagnosis of IIH.	N=50 Women n=46 Men n=4 Median age 29 years in acetazolamide group and 33 years in the	44% judged to have IIH in remission at the end of the trial. Difficulties with recruitment were highlighted as well as poor compliance with acetazolamide therapy (12 patients). Based on the study data, a sample size of 320 would be required to demonstrate a 20% treatment effect in a substantive trial.

					placebo group.	
Sinclair <i>et al</i> 2010 ¹¹	Prospective, multi-centre cross over cohort study. Birmingham, United Kingdom	Very low energy diet (425 kcal/day)	Intracranial pressure as measured by lumbar puncture opening pressure	All that meet criteria for a diagnosis of IIH.	N=25 100% women. Mean (SD) age was 34.4 (9.2) years.	Significant reductions in weight (mean 15.7 (SD 8.0) kg, P<0.001), intracranial pressure (mean 8.0 (SD 4.2) cm H(2)O, P<0.001), score on headache impact test (7.6 (SD 10.1), P=0.004), and papilloedema (optic disc elevation (mean 0.15 (SD 0.23) mm, P=0.002), diameter of the nerve sheath (mean 0.7 (SD 0.8) mm, P=0.004), and thickness of the peripapillary retina (mean 25.7 (SD 36.1) micro, P=0.001))
Celebisoy <i>et al.</i> 2007 ¹²	Prospective, single centre open label study. Turkey.	Topiramate <i>versus</i> acetazolamide	Bespoke visual field grade	All that meet criteria for a diagnosis of IIH.	N=40 Women n=35; Men n=5. Median age of onset in the acetazolamide group was 35 years, and 32 years in the topiramate group.	Visual field grade improved at. all time points of 3, 6 and 12 months as compared to baseline in both groups (p<0.0167). No statistically significant difference between the two groups in visual field grade was present. Prominent weight loss was recorded in the topiramate group.

Table 2: Outcome measure toolbox for treatments in IIH

Target		Outcome Measure
Underlying pathophysiology	Intracranial pressure	Lumbar puncture opening pressure (cm or mm CSF)
		Intracranial pressure by telemetric device (mmHg)
	Weight measures	Body Mass Index
		% weight change
Symptoms	Headache	Monthly headache days
		Moderate to severe monthly headache days
		Headache responder rate ($\geq 50\%$ reduction)
		Headache responder rate ($\geq 30\%$ reduction)
		Monthly analgesic days
		Headache severity (numerical rating scale)
	Visual function	Visual acuity
		Perimetric mean deviation
Signs	Papilledema	OCT global pRNFL
		OCT optic nerve head volume measures
		OCT macular ganglion cell analysis
		Frisén classification grade
Patient reported outcomes	Most bothersome symptom	Most bothersome symptom
	Quality of life measurement tools	SF-36
		NEI-VFQ-25
		10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25
		EQ5D
		Hospital anxiety and depression score
		Headache impact test-6
Other targeted considerations		
Early phase trials		Safety profile
		Tolerability
		Pharmacokinetics: Maximum tolerated dose Recommended dose/dose regimen
Later phase trials for medicinal products		Adverse events (severity and number)

	Drug tolerability (compliance and rate of discontinuation)
	Rate of rescue therapy
Surgical and neuro-interventional trials	Adverse events (severity and number)
	Number of revisions
	Rate of rescue treatment