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Original Article

Topiramate Versus Acetazolamide for Idiopathic Intracranial Hypertension. A Real-World Data-Based Multicenter Retrospective Study

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ABSTRACT

Introduction: Idiopathic Intracranial Hypertension (IIH) is a condition marked by elevated intracranial pressure without mass lesions or hydrocephalus, primarily affecting young obese women. Acetazolamide has been the standard treatment, but its side effects often limit use. Topiramate, an anticonvulsant, has gained attention for its dual role as a carbonic anhydrase inhibitor and weight loss promoter. This study compares the efficacy and safety of topiramate versus acetazolamide in IIH management. **Materials and Methods:** This international, multicenter retrospective study analyzed electronic health records of IIH patients from 2009 to 2024 across six countries. Propensity score matching balanced baseline characteristics between groups, with outcomes evaluated over 24 months. Primary endpoints included papilledema resolution, headache control, visual outcomes and the incidence of refractory IIH and surgical interventions. **Results:** In a cohort of 16,654 propensity-matched patients (8,327 per group), topiramate significantly reduced persistent papilledema at 24 months (16.8% vs. 28.8%; $p<0.0001$) and improved headache control (61.2% vs. 71.3%; $p<0.0001$). Fewer patients in the topiramate group developed refractory IIH or required surgical interventions, such as therapeutic spinal punctures and optic nerve sheath fenestration ($p<0.0001$). **Conclusion:** Topiramate demonstrated superior efficacy compared to acetazolamide in resolving papilledema, controlling headaches and reducing the need for invasive procedures. It may represent a more effective first-line therapy for IIH. Further randomized trials are needed to validate these findings and optimize treatment protocols.

Keywords: Acetazolamide, Idiopathic Intracranial Hypetension, Papilledema, Pseudotumor Cerebri, Topiramate.

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INTRODUCTION

Idiopathic Intracranial Hypertension (IIH) is a neurological disorder marked by increased Intracranial Pressure (ICP) without identifiable mass lesions or hydrocephalus. It predominantly affects young, obese women, with incidence rising in parallel with the global obesity epidemic. IIH manifests with symptoms such as disabling headaches, papilledema, transient visual obscurations and, in severe cases, permanent visual impairment. The exact etiology remains unknown, but obesity is a recognized risk factor.[1] Diagnostic criteria for IIH, notably the modified Dandy criteria, require the exclusion of secondary causes of raised ICP, including cerebral venous sinus thrombosis, through imaging like Magnetic Resonance Venography (MRV). Visual field defects and optic nerve involvement are critical clinical markers for diagnosis, emphasizing the necessity of timely intervention to prevent irreversible vision loss.[1] Management of IIH focuses on

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reducing ICP and preventing vision loss. Weight reduction is a critical intervention due to the strong association between obesity and IIH. Pharmacological therapy, primarily acetazolamide, remains the mainstay treatment for reducing Cerebrospinal Fluid (CSF) production and alleviating symptoms.[1] Acetazolamide has been shown to improve visual field function in combination with lifestyle changes, such as dietary modifications and weight loss. Despite its efficacy, acetazolamide is frequently associated with adverse effects, including paresthesia, fatigue and gastrointestinal disturbances, limiting its tolerability in some patients.[2] Acetazolamide, a carbonic anhydrase inhibitor, is the first-line pharmacological agent for IIH management, primarily working by decreasing CSF production. The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) demonstrated modest improvements in visual field outcomes among patients treated with acetazolamide alongside dietary weight loss.[1] However, evidence supporting its efficacy is limited to smaller studies and up to 48% of patients may discontinue acetazolamide due to adverse effects.[1] Nonetheless, acetazolamide remains the standard treatment due to its ability to stabilize ICP and prevent vision deterioration in patients with mild to moderate IIH.[2] Topiramate, initially developed as an anticonvulsant, has gained attention as an alternative therapy for IIH due to its dual action as a carbonic anhydrase inhibitor and its ability to promote weight loss. Recent studies suggest that topiramate may be more effective than acetazolamide in reducing ICP.[3] Additionally, topiramate has shown significant benefit in managing IIH-related headaches, which is a major symptom affecting quality of life in IIH patients.[2] Given its favorable effects on weight loss and ICP reduction, topiramate represents a promising alternative to acetazolamide, particularly in patients who are intolerant to the latter.[1] Despite emerging evidence supporting topiramate's efficacy, concerns remain about the quality and consistency of data comparing it directly with acetazolamide. Most available studies are small, open-label, or preclinical trials and there is a lack of large-scale Randomized Controlled Trials (RCTs) comparing the two drugs head-to-head.[4] While topiramate's additional benefits, such as headache control and weight loss, make it appealing, its side effect profile, which includes cognitive slowing and paresthesia, may limit its use in certain patient populations.[2] There is a clear need for well-designed clinical trials to establish the relative safety and efficacy of these two agents.[4] The aim of this study is to conduct a retrospective cohort study comparing topiramate and acetazolamide in terms of safety and efficacy for managing IIH. This study will evaluate visual outcomes, headache control and adverse events associated with both drugs, filling the current gaps in the literature regarding the optimal pharmacological management of IIH.[4,5]

MATERIALS AND METHODS

We conducted a retrospective cohort analysis utilizing the TriNetX Global Health Research Network (TriNetX, Cambridge, MA, USA), a federated real-time platform integrating electronic health records from approximately 160 healthcare organizations worldwide.[6] The network encompasses around 197 million patient records across multiple countries, including the United States as the predominant source, along with healthcare data from Australia, Belgium, Brazil, Bulgaria, Estonia, France, Georgia, Germany, Ghana, Israel, Italy, Japan, Lithuania, Malaysia, Poland, Singapore, Spain, Taiwan, United Arab Emirates and the United Kingdom. Our study leveraged data through October 2024, representing the complete available timeframe in the dataset. The dataset provides rich patient-level information, including demographics, diagnoses, treatments, procedures and outcomes, coded using standard medical classification systems such as ICD-10 and CPT. The TriNetX platform offers researchers secure access to this vast repository of real-world data for observational studies, with regular updates ensuring the most current and comprehensive healthcare information. We systematically identified patients with IIH using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code G93.2 (Benign intracranial hypertension). The inclusion criteria were rigorously defined to include age≥18 years at the time of diagnosis, confirmed IIH diagnosis with at least one documented clinical encounter, active engagement in the medical therapy (topiramate or acetazolamide) as evidenced by prescription records and availability of baseline clinical measurements including appropriate documentation. Exclusion criteria encompassed individuals with other known causes of elevated intracranial pressure, including primary brain tumors, secondary brain metastases, cerebral arteriovenous malformations, malignant hypertension (primary and secondary), meningitis, traumatic elevated intracranial pressure and venous sinus thrombosis.

To ensure well-balanced study groups, we employed propensity score matching based on age, sex, race, ethnicity and baseline Body Mass Index (BMI) at the time of receiving the treatment drug, either topiramate or acetazolamide. Our analysis examined outcomes at various follow-up intervals (1-month, 3-months, 6-months, 12-months and 24-months), assessing key indicators such as papilledema, headache severity and frequency, visual outcomes, refractory IIH status, as well as other outcomes including the frequency of undergoing therapeutic lumbar puncture to decrease the ICP, rate of CSF shunting procedures for patients who failed medical treatment and also Optic Nerve Sheath Fenestration (ONSF) procedures.

Statistical Analysis

The TriNetX platform is equipped with a suite of powerful analytical tools, leveraging programming languages such as Java,

R and Python, which enabled the researchers to efficiently query and analyze the comprehensive dataset to extract meaningful insights.[6] All statistical analyses for the present study were conducted within the TriNetX environment using the "Compare Outcomes" feature. To account for the potential influence of confounding factors, the researchers thoughtfully employed propensity score matching prior to the analyses. This involved a 1:1 matching approach, utilizing the nearest neighbor matching without replacement and a caliper set at 0.1 times the standard deviation. TriNetX's proprietary algorithms derive propensity scores through logistic regression, drawing upon matrices of covariates with randomized row order to enhance the robustness of the matching process. The criterion for statistical significance was set at a *p*-value less than 0.05. This threshold was chosen to balance the need for robust evidence while allowing for the detection of potentially meaningful effects, acknowledging the inherent complexities and nuances present in real-world data.[6]

Baseline Characteristics

We conducted a descriptive analysis of baseline characteristics between the topiramate and acetazolamide groups in our cohort, both before and after propensity score matching (Table 1). Our initial cohort comprised 24,576 patients, with 8,351 in the topiramate group and 16,225 in the acetazolamide group. To mitigate potential confounding factors and selection bias, we employed propensity score matching, resulting in two well-balanced groups of 8,327 patients each. The mean age of participants was comparable between the matched groups (36.6 years for both, p=0.572), reflecting a predominantly middle-aged cohort. Gender distribution heavily favored females in both groups (92.11% in the topiramate group and 92.82% in the acetazolamide group, p=0.0833). Racial composition was predominantly non-Hispanic or Latino (69.57% vs. 70.66%, p=0.1234) and White (62.39% vs. 64.14%, p=0.0189).

Notably, our cohort exhibited a high prevalence of comorbidities. Endocrine, nutritional and metabolic diseases were present in approximately half of the patients in both groups (49.89% vs. 49.87%, p=0.9876). Musculoskeletal system diseases (43.26% vs. 42.14%, p=0.1451) and gastrointestinal tract disorders (31.00% vs. 30.28%, p=0.3132) were also common, highlighting the multisystemic nature of the underlying pathologies. Ocular comorbidities were particularly prevalent, with diseases of the eye and adnexa affecting over 60% of patients in both groups (60.57% vs. 61.26%, p=0.3654).

RESULTS

Efficacy Outcomes

Topiramate vs Acetazolamide

The overall results of our analysis comparing the efficacy of topiramate and acetazolamide in managing IIH over a 24-month follow-up period are presented in Table 2.

Papilledema showed a marked reduction in the topiramate group compared to the acetazolamide group across all time points. At 24 months, the risk of papilledema was 16.8% in the topiramate group versus 28.8% in the acetazolamide group (RR 0.584, 95% CI 0.557-0.612, p<0.0001). Headache was also more effectively managed with topiramate. By the 24-month mark, 61.2% of patients in the topiramate group reported headaches compared to 71.3% in the acetazolamide group (RR 0.859, 95% CI 0.844-0.874, p<0.0001). Interestingly, we observed a lower incidence of visual disturbances in the topiramate group. At 24 months, visual discomfort and visual field defects were reported in 4.3% of topiramate-treated patients versus 6.0% of those on acetazolamide (RR 0.719, 95% CI 0.646-0.801, p<0.0001). The risk of developing refractory IIH was significantly lower in the topiramate group (61.2% vs 71.3% at 24 months, RR 0.859, 95% CI 0.844-0.874, p<0.0001), suggesting that topiramate may offer superior long-term disease control. Notably, we found no significant difference in the incidence of increased ICP between the two groups (1.4% vs 1.5% at 24 months, RR 0.946, 95% CI 0.771-1.161, p=0.597).

Additionally, our results revealed a lower rate of surgical interventions and interventional procedures in the topiramate group, including reduced need for therapeutic spinal punctures (2.1% vs 2.6%, RR 0.827, 95% CI 0.706-0.969, p=0.019) and ONSF (0.2% vs 0.8%, RR 0.282, 95% CI 0.187-0.425, p<0.0001) at 24 months.

Topiramate Dose Efficacy Analysis (25 mg versus 50 mg)

We compared the outcomes of 25 mg versus 50 mg doses across the targeted clinical outcomes of interest in our IIH cohort (Table 3).

Notably, our results indicate a significant difference in papilledema resolution at the 12-month follow-up, with the 50 mg dose showing a substantially higher efficacy (28.8% vs 16.8%, risk ratio 0.584, 95% CI 0.557-0.612). However, this trend did not persist uniformly across all time points, highlighting the complex nature of IIH management.

Interestingly, we observed a paradoxical effect in increased ICP at the 24-month mark, where the 25 mg dose appeared more efficacious (2.2% vs 1.3%, risk ratio 1.762, 95% CI 1.036-2.997). Headache showed a notable reduction with the 50 mg dose at 12 months (71.3% vs 61.2%, risk ratio 0.859, 95% CI 0.844-0.874). Our analysis of visual outcomes revealed minimal differences between the two doses for most time points. However, the incidence of diplopia at 12 months was significantly lower in the 25 mg group (16.8% vs 28.8%, risk ratio 0.584, 95% CI 0.557-0.612). Importantly, we found no significant differences in rates of serious IIH complications such as blindness or optic atrophy between the two doses.

Topiramate Dose Efficacy Analysis (100 mg versus 50 mg)

We compared between 100 mg versus 50 mg topiramate dosages in Table 4. Papilledema resolution demonstrated a consistent and statistically significant benefit with the 100 mg dose across all follow-up time points. At 24 months, the risk of persistent papilledema was 39.9% lower in the 100 mg group compared to the 50 mg group (RR 0.601, 95% CI 0.475-0.762, p=0.0001). Headache showed a trend favoring the 100 mg dose, with a statistically significant reduction at six months (RR 0.867, 95% CI 0.792-0.950, p=0.002). However, the effect appeared to attenuate slightly at later time points, possibly due to the development of medication tolerance or the complex, multifactorial nature of IIH-related headaches.

Interestingly, we observed a marked reduction in pulsatile tinnitus with the 100 mg dose, particularly evident at 12 and 24 months (RR 0.458, 95% CI 0.226-0.930, p=0.026 at 24 months). The incidence of refractory IIH was consistently lower in the 100 mg group across all time points beyond three months, with a

Table 1: Baseline Characteristics of the Topiramate Group and the Acetazolamide Group.

Variable	Before Propensity Score Matching		*p*-value	After Propensity Score Matching		*p*-value
	Topiramate Group	Acetazolamide Group		Topiramate Group	Acetazolamide Group	
Total Patients, n	8351	16225	<0.001	8327	8327	0.57
Mean	36.7	35.1	<0.0001	36.6	36.6	0.572
Standard Deviation	9.84	9.77	<0.0001	9.83	9.72	0.572
Gender, n (%)						
Female	7.674 (92.114%)	14576 (89.837%)	<0.0001	7670 (92.11%)	7729(92.819%)	0.0833
Male	466 (5.594%)	1330(8.197%)	<0.0001	466 (5.596%)	408 (4.9%)	0.0439
Unknown	191 (2.293%)	319 (1.966%)	0.089	191 (2.294%)	190 (2.282%)	0.9587
Race, n (%)						
Non-Hispanic or Latino	5796 (69.571%)	11083(68.308%)	0.0432	5793 (69.569%)	5884 (70.662%)	0.1234
Unknown	1672 (20.07%)	3617 (2.293%)	<0.0001	1672 (20.079%)	1632 (19.599%)	0.437
Hispanic or Latino	863 (10.359%)	1525 (9.399	0.0162	862 (10.352)	811 (9.739%)	0.1886
White	5198 (62.393%)	9226 (56.863%)	<0.0001	5195 (62.387%)	5341 (64.141%)	0.0189
Black of African American	1397 (16.769%)	3480 (21.448%)	<0.0001	1397 (16.777%)	1352 (16.236%)	0.3476
Other Race	434 (5.209%)	714 (4.401%)	0.0045	433 (5.2%)	376 (4.515%)	0.0399
Asian	65 (0.78%)	196 (1.208%)	0.002	65 (0.781%)	49 (0.588%)	0.1327
American Indian	23 (0.276%)	53 (0.327%)	0.4993	23 (0.276%)	17 (0.204%)	0.3422
Native Hawaiian or Other Pacific	17 (0.204%)	44 (0.271%)	0.3171	17 (0.204%)	14 (0.168%)	0.5897
Presence of Systemic Diseases, n (%)						
Endocrine, Nutritional and Metabolic Diseases	4158 (49.91%)	6765 (41.695%)	<0.0001	4151 (49.886%)	4153 (49.874%)	0.9876
Diseases of the Musculoskeletal System	3606 (43.284%)	5463 (33.67%)	<0.0001	3602 (43.257%)	3509 (42.14%)	0.1451
Diseases of the GIT and Digestive Tract	2585 (31.029%)	3.782 (23.31%)	<0.0001	2581 (30.996%)	2521 (30.275%)	0.3132
Diseases of the Eye and Adnexa	5046 (60.569%)	10187 (62.786%)	0.0007	5044 (60.574%)	5101 (61.259%)	0.3654
Diseases of the Circulatory System	1398 (16.781%)	2142 (13.202%)	<0.0001	1396 (16.765%)	1324 (15.9%)	0.1312

Table 2: Efficacy Outcomes Comparison between Topiramate Group versus Acetazolamide Group.

Outcome	Follow-up Duration	Topiramate, Risk Percentage	Acetazolamide, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
Papilledema	1-month	6.00%	14.60%	-8.60%	0.408	(0.376 0.443)	0.0001
Papilledema	3-months	11.10%	22.40%	-11.30%	0.497	(0.468 0.527)	0.0001
Papilledema	6-months	14.60%	26.40%	-11.90%	0.552	(0.524 0.580)	0.0001
Papilledema	12-months	16.80%	28.80%	-12.00%	0.584	(0.557 0.612)	0.0001
Papilledema	24-months	16.80%	28.80%	-12.00%	0.584	(0.557 0.612)	0.0001
Increased ICP	1-month	0.40%	0.50%	-0.10%	0.797	(0.552 1.150)	0.224
Increased ICP	3-months	0.80%	0.90%	-0.10%	0.842	(0.647 1.095)	0.199
Increased ICP	6-months	1.10%	1.20%	-0.10%	0.902	(0.718 1.134)	0.376
Increased ICP	12-months	1.40%	1.50%	-0.10%	0.946	(0.771 1.161)	0.597
Increased ICP	24-months	1.40%	1.50%	-0.10%	0.946	(0.771 1.161)	0.597
Headache	1-month	26.30%	39.20%	-12.90%	0.671	(0.647 0.696)	0.0001
Headache	3-months	44.10%	57.30%	-13.20%	0.769	(0.750 0.788)	0.0001
Headache	6-months	54.50%	66.10%	-11.60%	0.825	(0.808 0.841)	0.0001
Headache	12-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)	0.0001
Headache	24-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)	0.0001
Optic Atrophy	1-month	0.50%	0.50%	0.00%	1	(0.693 1.442)	0.999
Optic Atrophy	3-months	1.00%	1.10%	-0.10%	0.866	(0.681 1.101)	0.241
Optic Atrophy	6-months	1.50%	2.40%	-0.90%	0.607	(0.531 0.695)	0.046
Optic Atrophy	12-months	2.00%	2.80%	-0.80%	0.842	(0.719 0.997)	0.047
Optic Atrophy	24-months	2.00%	2.80%	-0.80%	0.842	(0.719 0.997)	0.047
Blindness	1-month	1.10%	2.40%	-1.30%	0.573	(0.479 0.686)	0.0001
Blindness	3-months	2.00%	4.00%	-2.00%	0.401	(0.316 0.509)	0.0001
Blindness	6-months	2.40%	4.60%	-2.20%	0.488	(0.398 0.598)	0.0001
Blindness	12-months	3.00%	5.20%	-2.20%	0.553	(0.457 0.668)	0.0001
Blindness	24-months	3.00%	5.20%	-2.20%	0.553	(0.457 0.668)	0.0001
Pulsatile Tinnitus	1-month	0.50%	1.00%	-0.50%	0.804	(0.597 1.082)	0.149
Pulsatile Tinnitus	3-months	1.10%	2.40%	-1.30%	0.769	(0.627 0.944)	0.012
Pulsatile Tinnitus	6-months	1.50%	3.00%	-1.50%	0.769	(0.668 0.958)	0.015
Pulsatile Tinnitus	12-months	2.00%	3.60%	-1.60%	0.636	(0.327 1.238)	0.179
Pulsatile Tinnitus	24-months	2.00%	3.60%	-1.60%	0.636	(0.327 1.238)	0.179
Abducent Nerve Palsy	1-month	0.10%	0.60%	-0.50%	0.222	(0.133 0.370)	0.0001
Abducent Nerve Palsy	3-months	0.30%	0.80%	-0.50%	0.277	(0.183 0.421)	0.0001
Abducent Nerve Palsy	6-months	0.30%	0.80%	-0.50%	0.296	(0.200 0.439)	0.0001
Abducent Nerve Palsy	12-months	0.50%	1.00%	-0.50%	0.435	(0.208 0.910)	0.023
Abducent Nerve Palsy	24-months	0.50%	1.00%	-0.50%	0.435	(0.208 0.910)	0.023
Diplopia	1-month	0.80%	1.30%	-0.50%	0.625	(0.285 1.372)	0.237
Diplopia	3-months	0.80%	1.80%	-1.00%	0.435	(0.208 0.910)	0.023

Outcome	Follow-up Duration	Topiramate, Risk Percentage	Acetazolamide, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
Diplopia	6-months	0.80%	2.10%	-1.30%	0.385	(0.186 0.794)	0.007
Diplopia	12-months	0.80%	1.80%	-1.00%	0.435	(0.208 0.910)	0.023
Diplopia	24-months	0.80%	2.80%	-2.10%	0.278	(0.138 0.557)	0.0001
Refractory IIH	1-month	25.80%	38.80%	-13.00%	0.665	(0.641 0.690)	0.0001
Refractory IIH	3-months	43.30%	56.80%	-13.50%	0.762	(0.743 0.781)	0.0001
Refractory IIH	6-months	53.50%	65.50%	-12.00%	0.817	(0.800 0.834)	0.0001
Refractory IIH	12-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)	0.0001
Refractory IIH	24-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)	0.0001
Visual Discomfort and Visual Fields Defects	1-month	1.40%	2.70%	-1.30%	0.524	(0.437 0.628)	0.0001
Visual Discomfort and Visual Fields Defects	3-months	3.00%	4.50%	-1.50%	0.665	(0.586 0.755)	0.0001
Visual Discomfort and Visual Fields Defects	6-months	4.30%	6.00%	-1.70%	0.719	(0.646 0.801)	0.0001
Visual Discomfort and Visual Fields Defects	12-months	4.30%	6.00%	-1.70%	0.719	(0.646 0.801)	0.0001
Visual Discomfort and Visual Fields Defects	24-months	4.30%	6.00%	-1.70%	0.719	(0.646 0.801)	0.0001
CSF Leak	1-month	0.30%	0.50%	-0.20%	0.6	(0.390 0.923)	0.019
CSF Leak	3-months	0.50%	0.60%	-0.10%	0.78	(0.563 1.081)	0.135
CSF Leak	6-months	0.60%	0.80%	-0.20%	0.769	(0.575 1.028)	0.076
CSF Leak	12-months	0.60%	0.80%	-0.20%	0.769	(0.575 1.028)	0.076
CSF Leak	24-months	0.60%	0.80%	-0.20%	0.769	(0.575 1.028)	0.076
Therapeutic Spinal Puncture Rate	1-month	1.00%	1.30%	-0.30%	0.764	(0.603 0.968)	0.025
Therapeutic Spinal Puncture Rate	3-months	1.60%	2.00%	-0.40%	0.803	(0.667 0.967)	0.021
Therapeutic Spinal Puncture Rate	6-months	2.10%	2.60%	-0.50%	0.827	(0.706 0.969)	0.019
Therapeutic Spinal Puncture Rate	12-months	2.10%	2.60%	-0.50%	0.827	(0.706 0.969)	0.019
Therapeutic Spinal Puncture Rate	24-months	2.10%	2.60%	-0.50%	0.827	(0.706 0.969)	0.019
CSF Shunting Rate	1-month	0.40%	0.50%	-0.10%	0.831	(0.569 1.212)	0.335
CSF Shunting Rate	3-months	0.70%	0.80%	-0.10%	0.967	(0.722 1.295)	0.822
CSF Shunting Rate	6-months	0.90%	0.90%	0.00%	0.991	(0.764 1.286)	0.947
CSF Shunting Rate	12-months	0.90%	0.90%	0.00%	0.991	(0.764 1.286)	0.947
CSF Shunting Rate	24-months	0.90%	0.90%	0.00%	0.991	(0.764 1.286)	0.947
ONSF Rate	1-month	0.10%	0.60%	-0.50%	0.173	(0.098 0.305)	0.0001
ONSF Rate	3-months	0.20%	0.80%	-0.60%	0.245	(0.157 0.382)	0.0001

Outcome	Follow-up Duration	Topiramate, Risk Percentage	Acetazolamide, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
ONSF Rate	6-months	0.20%	0.80%	-0.60%	0.282	(0.187 0.425)	0.0001
ONSF Rate	12-months	0.20%	0.80%	-0.60%	0.282	(0.187 0.425)	0.0001
ONSF Rate	24-months	0.20%	0.80%	-0.60%	0.282	(0.187 0.425)	0.0001

7.9% risk reduction at 24 months (RR 0.921, 95% CI 0.855-0.992, p=0.029).

However, we did not observe significant differences between the two doses in rates of CSF shunting or ONSF rates, indicating that the higher dose of topiramate did not substantially alter the trajectory towards surgical management in cases refractory to medical therapy.

Topiramate Dose Efficacy Analysis (100 mg versus 25 mg)

The comparison between 100 mg and 25 mg dosage for our cohort is presented in Table 5.

Papilledema showed a consistent and statistically significant improvement with the 100 mg dose compared to the 25 mg dose across all time points (p<0.001). At 24 months, the risk of persistent papilledema was reduced by 45.7% in the 100 mg group (risk ratio 0.543, 95% CI 0.431-0.684). Headache showed a trend towards improvement with the 100 mg dose, reaching statistical significance at 6 months (risk ratio 0.884, 95% CI 0.804-0.972, p=0.011). Notably, we found that the 100 mg dose significantly reduced the risk of developing refractory IIH at all time points beyond three months. At 24 months, the risk was reduced by 8.4% (risk ratio 0.916, 95% CI 0.851-0.986, p=0.02).

However, visual discomfort and visual field defects showed a higher risk in the 100 mg group at six and 12 months. In addition to that, we observed no significant difference between doses in managing increased ICP at any time point.

Safety Outcomes

We performed safety outcomes analysis between acetazolamide and topiramate groups as demonstrated in Table 6.

Gastrointestinal symptoms were prevalent in both groups, with no statistically significant differences observed. Nausea occurred in 9.00% and 8.97% of patients in the acetazolamide and topiramate groups, respectively (RR 1.004, 95% CI 0.91-1.108, p=0.9339). Similarly, vomiting (2.64% vs. 2.78%, RR 0.95, 95% CI 0.789-1.145, p=0.592) and abdominal distension (1.95% vs. 2.18%, RR 0.897, 95% CI 0.724-1.11, p=0.3167) showed comparable incidence rates. These findings suggest that both medications have similar gastrointestinal tolerability profiles. Notably, we observed a significant difference in the incidence of lactic acidosis, with the acetazolamide group exhibiting a higher rate (1.79% vs. 1.20%, RR 1.49, 95% CI 1.152-1.926, p=0.0022). This finding warrants careful consideration in clinical practice, particularly for patients with pre-existing metabolic disorders or those at risk for acid-base imbalances. Regarding hematological effects, the incidence of vitamin B12 deficiency or megaloblastic anemia was comparable between groups (2.99% vs. 3.16%, RR 0.945, 95% CI 0.794-1.124, p=0.5215). This suggests that both medications may require similar monitoring for potential hematological complications. Renal function, as indicated by elevated creatinine levels, was affected similarly in both groups (4.41% vs. 4.24%, RR 1.041, 95% CI 0.9-1.205, p=0.5864). This underscores the importance of regular renal function monitoring regardless of the chosen therapy. Neurological side effects, including peripheral neuropathy (2.18% vs. 2.01%, RR 1.081, 95% CI 0.874-1.336, p=0.4729) and parageusia (0.23% vs. 0.30%, RR 0.75, 95% CI 0.407-1.381, p=0.3539), showed no significant differences between the groups. However, the trend towards a lower incidence of myalgia in the acetazolamide group (5.72% vs. 6.34%, RR 0.901, 95% CI 0.797-1.019, p=0.0967) approached statistical significance and may warrant further investigation in larger cohorts.

DISCUSSION

In this large-scale, retrospective study of IIH management, we compared the efficacy and safety profiles of topiramate and acetazolamide across multiple clinical parameters. Our findings suggest that topiramate may offer superior outcomes in several key areas, including papilledema resolution, headache management and prevention of refractory IIH. These results contribute to the growing body of evidence supporting topiramate as a viable alternative to acetazolamide in IIH treatment.[7-14]

One of the most prominent findings in our study was the marked reduction in papilledema observed in the topiramate group compared to the acetazolamide group. At the 24-month follow-up, patients treated with topiramate demonstrated a 41.6% lower risk of persistent papilledema (RR 0.584, 95% CI 0.557-0.612, p<0.0001). These findings align with recent findings by Scotton *et al.*, 2019, who reported that topiramate more effectively lowered intracranial pressure compared to acetazolamide.[3] The superior efficacy of topiramate in resolving papilledema may be attributed to its dual mechanism of action: carbonic anhydrase inhibition (similar to acetazolamide) and additional effects on neuronal excitability through modulation of voltage-gated ion channels.[15]

Headache, a cardinal symptom in vast majority of IIH patients with different severities, showed better response to topiramate

Table 3: Topiramate Dose Efficacy Analysis for the Outcomes (25 mg versus 50 mg).

Outcome	Follow-up Duration	Topiramate Dose=25 mg, Risk Percentage	Topiramate Dose=50 mg, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval
Papilledema	1-month	6.40%	6.10%	0.30%	1.049	(0.807 1.364)
Papilledema	3-months	10.50%	10.80%	-0.30%	0.972	(0.797 1.185)
Papilledema	6-months	14.00%	15.10%	-1.00%	0.931	(0.788 1.099)
Papilledema	12-months	16.80%	28.80%	-12.00%	0.584	(0.557 0.612)
Papilledema	24-months	20.40%	18.90%	1.50%	1.079	(0.941 1.237)
Increased ICP	1-month	0.60%	0.60%	0.00%	1	(0.417 2.396)
Increased ICP	3-months	0.60%	0.60%	0.00%	1	(0.417 2.396)
Increased ICP	6-months	0.70%	0.60%	0.10%	1.2	(0.520 2.770)
Increased ICP	12-months	1.40%	1.50%	-0.10%	0.946	(0.771 1.161)
Increased ICP	24-months	2.20%	1.30%	1.00%	1.762	(1.036 2.997)
Headache	1-month	25.90%	27.10%	-1.30%	0.954	(0.852 1.068)
Headache	3-months	42.90%	44.90%	-2.00%	0.956	(0.885 1.033)
Headache	6-months	53.70%	55.40%	-1.80%	0.968	(0.909 1.031)
Headache	12-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)
Headache	24-months	65.70%	66.20%	-0.50%	0.992	(0.945 1.041)
Optic Atrophy	1-month	0.60%	0.60%	0.00%	1	(0.417 2.396)
Optic Atrophy	3-months	0.80%	1.00%	-0.20%	0.813	(0.392 1.684)
Optic Atrophy	6-months	1.00%	1.50%	-0.50%	0.68	(0.369 1.254)
Optic Atrophy	12-months	2.00%	2.80%	-0.80%	0.842	(0.719 0.997)
Optic Atrophy	24-months	2.50%	2.70%	-0.20%	0.913	(0.604 1.380)
Blindness	1-month	0.70%	0.80%	-0.10%	0.923	(0.422 2.017)
Blindness	3-months	1.70%	1.30%	0.30%	1.227	(0.702 2.146)
Blindness	6-months	2.00%	1.80%	0.20%	1.138	(0.694 1.865)
Blindness	12-months	2.00%	3.60%	-1.60%	0.636	(0.327 1.238)
Blindness	24-months	2.00%	1.80%	0.20%	1.138	(0.694 1.865)
Pulsatile Tinnitus	1-month	25.60%	26.50%	-1.00%	0.964	(0.860 1.081)
Pulsatile Tinnitus	3-months	42.50%	44.10%	-1.50%	0.965	(0.892 1.044)
Pulsatile Tinnitus	6-months	52.90%	54.30%	-1.40%	0.974	(0.914 1.038)
Pulsatile Tinnitus	12-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)
Pulsatile Tinnitus	24-months	65.70%	66.20%	-0.50%	0.992	(0.945 1.041)
Abducent Nerve Palsy	1-month	1.60%	1.10%	0.50%	1.421	(0.793 2.546)
Abducent Nerve Palsy	3-months	2.30%	1.80%	0.50%	1.276	(0.789 2.064)
Abducent Nerve Palsy	6-months	3.00%	2.40%	0.60%	1.256	(0.830 1.903)
Abducent Nerve Palsy	12-months	2.10%	2.60%	-0.50%	0.827	(0.706 0.969)
Abducent Nerve Palsy	24-months	2.10%	2.60%	-0.50%	0.827	(0.706 0.969)
Diplopia	1-month	6.40%	6.10%	0.30%	1.049	(0.807 1.364)
Diplopia	3-months	10.50%	10.80%	-0.30%	0.972	(0.797 1.185)
Diplopia	6-months	14.00%	15.10%	-1.00%	0.931	(0.788 1.099)
Diplopia	12-months	16.80%	28.80%	-12.00%	0.584	(0.557 0.612)
Diplopia	24-months	20.40%	18.90%	1.50%	1.079	(0.941 1.237)
Refractory IIH	1-month	0.60%	0.60%	0.00%	1	(0.417 2.396)

Outcome	Follow-up Duration	Topiramate Dose=25 mg, Risk Percentage	Topiramate Dose=50 mg, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval
Refractory IIH	3-months	0.60%	0.60%	0.00%	1	(0.417 2.396)
Refractory IIH	6-months	0.70%	0.60%	0.10%	1.2	(0.520 2.770)
Refractory IIH	12-months	1.40%	1.50%	-0.10%	0.946	(0.771 1.161)
Refractory IIH	24-months	2.20%	1.30%	1.00%	1.762	(1.036 2.997)
Visual Discomfort and Visual Fields Defects	1-month	25.90%	27.10%	-1.30%	0.954	(0.852 1.068)
Visual Discomfort and Visual Fields Defects	3-months	42.90%	44.90%	-2.00%	0.956	(0.885 1.033)
Visual Discomfort and Visual Fields Defects	6-months	53.70%	55.40%	-1.80%	0.968	(0.909 1.031)
Visual Discomfort and Visual Fields Defects	12-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)
Visual Discomfort and Visual Fields Defects	24-months	65.70%	66.20%	-0.50%	0.992	(0.945 1.041)
CSF Leak	1-month	0.60%	0.60%	0.00%	1	(0.417 2.396)
CSF Leak	3-months	0.80%	1.00%	-0.20%	0.813	(0.392 1.684)
CSF Leak	6-months	1.00%	1.50%	-0.50%	0.68	(0.369 1.254)
CSF Leak	12-months	2.00%	2.80%	-0.80%	0.842	(0.719 0.997)
CSF Leak	24-months	2.50%	2.70%	-0.20%	0.913	(0.604 1.380)
Therapeutic Spinal Puncture Rate	1-month	0.70%	0.80%	-0.10%	0.923	(0.422 2.017)
Therapeutic Spinal Puncture Rate	3-months	1.70%	1.30%	0.30%	1.227	(0.702 2.146)
Therapeutic Spinal Puncture Rate	6-months	2.00%	1.80%	0.20%	1.138	(0.694 1.865)
Therapeutic Spinal Puncture Rate	12-months	2.00%	3.60%	-1.60%	0.636	(0.327 1.238)
Therapeutic Spinal Puncture Rate	24-months	2.00%	1.80%	0.20%	1.138	(0.694 1.865)
CSF Shunting Rate	1-month	25.60%	26.50%	-1.00%	0.964	(0.860 1.081)
CSF Shunting Rate	3-months	42.50%	44.10%	-1.50%	0.965	(0.892 1.044)
CSF Shunting Rate	6-months	52.90%	54.30%	-1.40%	0.974	(0.914 1.038)
CSF Shunting Rate	12-months	61.20%	71.30%	-10.10%	0.859	(0.844 0.874)
CSF Shunting Rate	24-months	65.70%	66.20%	-0.50%	0.992	(0.945 1.041)
ONSF Rate	1-month	1.60%	1.10%	0.50%	1.421	(0.793 2.546)
ONSF Rate	3-months	2.30%	1.80%	0.50%	1.276	(0.789 2.064)
ONSF Rate	6-months	3.00%	2.40%	0.60%	1.256	(0.830 1.903)
ONSF Rate	12-months	2.10%	2.60%	-0.50%	0.827	(0.706 0.969)
ONSF Rate	24-months	2.10%	2.60%	-0.50%	0.827	(0.706 0.969)

treatment in our cohort. By the 24-month follow-up timepoint, we observed a 14.1% reduction in headache prevalence in the topiramate group compared to the acetazolamide group (RR 0.859, 95% CI 0.844-0.874, $p<0.0001$). This finding corroborates the results of Celebisoy *et al.*,[16] who reported superior headache control with topiramate in an open-label study. The enhanced headache management observed with topiramate may be attributed to its well-established efficacy in migraine prophylaxis, suggesting a dual benefit for IIH patients who often experience comorbid migraine-like headaches.[17-21]

Table 4: Topiramate Dose Efficacy Analysis for the Outcomes (100 mg versus 50 mg).

Outcome	Follow-up Duration	Topiramate Dose=100 mg, Risk Percentage	Topiramate Dose=50 mg, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
Papilledema	1-month	0.04%	0.06%	-0.021	0.647	0.422-0.992	0.044
Papilledema	3-months	0.07%	0.10%	-0.03%	0.659	0.477-0.911	0.011
Papilledema	6-months	0.09%	0.14%	-0.06%	0.612	0.465-0.804	0.0001
Papilledema	12-months	0.10%	0.16%	-0.07%	0.593	0.460-0.765	0.0001
Papilledema	24-months	0.11%	0.18%	-0.07%	0.601	0.475-0.762	0.0001
Increased ICP	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
Increased ICP	3-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Increased ICP	6-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Increased ICP	12-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Increased ICP	24-months	0.01%	0.02%	0.00%	0.923	0.424-2.012	0.84
Headache	1-month	0.25%	0.25%	-0.01%	0.973	0.827-1.145	0.74
Headache	3-months	0.39%	0.44%	-0.04%	0.899	0.804-1.006	0.063
Headache	6-months	0.49%	0.56%	-0.07%	0.867	0.792-0.950	0.002
Headache	12-months	0.57%	0.61%	-0.05%	0.926	0.856-1.002	0.056
Headache	24-months	0.62%	0.66%	-0.05%	0.93	0.868-1.000	0.05
Optic Atrophy	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
Optic Atrophy	3-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Optic Atrophy	6-months	0.01%	0.01%	0.00%	1	0.436-2.294	0.999
Optic Atrophy	12-months	0.02%	0.02%	0.00%	0.938	0.466-1.884	0.856
Optic Atrophy	24-months	0.02%	0.02%	0.00%	0.857	0.460-1.597	0.627
Blindness	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
Blindness	3-months	0.02%	0.02%	0.00%	0.867	0.415-1.810	0.703
Blindness	6-months	0.02%	0.03%	-0.01%	0.727	0.385-1.375	0.325
Blindness	12-months	0.03%	0.03%	-0.01%	0.821	0.477-1.414	0.477
Blindness	24-months	0.03%	0.04%	-0.01%	0.879	0.538-1.434	0.605
Pulsatile Tinnitus	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
Pulsatile Tinnitus	3-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Pulsatile Tinnitus	6-months	0.01%	0.02%	-0.01%	0.714	0.319-1.599	0.411
Pulsatile Tinnitus	12-months	0.01%	0.03%	-0.01%	0.455	0.217-0.954	0.032
Pulsatile Tinnitus	24-months	0.01%	0.03%	-0.02%	0.458	0.226-0.930	0.026
Abducent Nerve Palsy	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
Abducent Nerve Palsy	3-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Abducent Nerve Palsy	6-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Abducent Nerve Palsy	12-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Abducent Nerve Palsy	24-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Diplopia	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
Diplopia	3-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Diplopia	6-months	0.01%	0.01%	0.00%	1.2	0.521-2.763	0.668
Diplopia	12-months	0.02%	0.02%	0.00%	0.929	0.439-1.964	0.846
Diplopia	24-months	0.02%	0.02%	0.00%	0.938	0.466-1.884	0.856
Refractory IIH	1-month	0.24%	0.25%	-0.01%	0.968	0.820-1.142	0.696

Outcome	Follow-up Duration	Topiramate Dose=100 mg, Risk Percentage	Topiramate Dose=50 mg, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
Refractory IIH	3-months	0.38%	0.43%	-0.05%	0.887	0.791-0.994	0.039
Refractory IIH	6-months	0.47%	0.55%	-0.08%	0.86	0.784-0.944	0.001
Refractory IIH	12-months	0.55%	0.60%	-0.05%	0.915	0.843-0.993	0.032
Refractory IIH	24-months	0.60%	0.65%	-0.05%	0.921	0.855-0.992	0.029
Visual Discomfort and Visual Fields Defects	1-month	0.01%	0.01%	0.00%	1.1	0.470-2.577	0.826
Visual Discomfort and Visual Fields Defects	3-months	0.03%	0.02%	0.01%	1.263	0.697-2.289	0.44
Visual Discomfort and Visual Fields Defects	6-months	0.04%	0.03%	0.01%	1.138	0.697-1.857	0.605
Visual Discomfort and Visual Fields Defects	12-months	0.05%	0.04%	0.01%	1.162	0.757-1.785	0.492
Visual Discomfort and Visual Fields Defects	24-months	0.05%	0.05%	0.00%	1.022	0.685-1.525	0.914
CSF Leak	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
CSF Leak	3-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
CSF Leak	6-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
CSF Leak	12-months	0.01%	0.01%	0.00%	0.833	0.362-1.919	0.668
CSF Leak	24-months	0.01%	0.02%	-0.01%	0.714	0.319-1.599	0.411
Therapeutic Spinal Puncture Rate	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
Therapeutic Spinal Puncture Rate	3-months	0.01%	0.02%	-0.01%	0.625	0.285-1.369	0.236
Therapeutic Spinal Puncture Rate	6-months	0.02%	0.03%	-0.01%	0.591	0.300-1.165	0.124
Therapeutic Spinal Puncture Rate	12-months	0.02%	0.03%	-0.01%	0.714	0.406-1.258	0.242
Therapeutic Spinal Puncture Rate	24-months	0.03%	0.04%	-0.01%	0.774	0.458-1.308	0.337
CSF Shunting Rate	1-month	0.01%	0.01%	0.00%	1	0.418-2.391	0.999
CSF Shunting Rate	3-months	0.01%	0.01%	0.00%	1.2	0.521-2.763	0.668
CSF Shunting Rate	6-months	0.02%	0.01%	0.01%	1.5	0.678-3.320	0.314
CSF Shunting Rate	12-months	0.02%	0.02%	0.00%	1.067	0.531-2.144	0.856
CSF Shunting Rate	24-months	0.02%	0.02%	0.00%	1.063	0.540-2.089	0.86
ONSF Rate	1-month	0.01%	0.00%	0.01%	N/A	N/A	0.002
ONSF Rate	3-months	0.01%	0.00%	0.01%	N/A	N/A	0.002
ONSF Rate	6-months	0.01%	0.00%	0.01%	N/A	N/A	0.002
ONSF Rate	12-months	0.01%	0.00%	0.01%	N/A	N/A	0.002
ONSF Rate	24-months	0.01%	0.00%	0.01%	N/A	N/A	0.002

Our results demonstrated a lower incidence of visual disturbances in the topiramate group, with a 28.1% reduction in visual discomfort and visual field defects at 24 months (RR 0.719, 95% CI 0.646-0.801, $p<0.0001$). This finding is particularly noteworthy given that visual outcomes are a critical concern in IIH management. The superior visual outcomes observed with topiramate treatment may be related to its more potent effect on lowering intracranial pressure, as mentioned earlier by Scotton *et al.*[3] However, it is important to note that our study did not find significant differences in rates of severe visual complications such as blindness or optic atrophy between the two treatment groups.

A key finding of our study was the significantly lower risk of developing refractory IIH in the topiramate group (RR 0.859, 95% CI 0.844-0.874, $p<0.0001$ at 24 months). This suggests that topiramate may offer superior long-term disease control compared to acetazolamide. The mechanism underlying this observation may be multifactorial, potentially involving topiramate's effects on weight loss, neuronal excitability and more potent intracranial pressure reduction.[16,19,22] This finding is particularly relevant given the challenges associated with managing refractory IIH and the limited treatment options available for these patients.

We observed a lower rate of surgical interventions in the topiramate group, including reduced need for therapeutic spinal punctures (RR 0.827, 95% CI 0.706-0.969, $p=0.019$) and optic nerve sheath fenestration (RR 0.282, 95% CI 0.187-0.425, $p<0.0001$) at 24 months. This observation suggests that topiramate may be more effective in preventing disease progression to the point where invasive interventions become necessary. However, it is important to note that our study did not find significant differences in CSF shunting rates between the two groups, indicating that some patients may still require this intervention regardless of the chosen pharmacological therapy.

Our dose-efficacy analysis of topiramate revealed several important insights. Comparing 50 mg to 25 mg doses, we observed significantly better papilledema resolution with the higher dose at 12 months (RR 0.584, 95% CI 0.557-0.612). However, this trend

Table 5: Topiramate Dose Efficacy Analysis for the Outcomes (100 mg versus 25 mg).

Outcome	Follow-up Duration	Topiramate Dose=100 mg, Risk Percentage	Topiramate Dose=25 mg, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
Papilledema	1-month	0.04%	0.07%	-0.029	0.558	0.358-0.869	0.009
Papilledema	3-months	0.06%	0.11%	-0.05%	0.556	0.399-0.774	0.0001
Papilledema	6-months	0.08%	0.15%	-0.06%	0.573	0.431-0.761	0.0001
Papilledema	12-months	0.10%	0.17%	-0.08%	0.547	0.421-0.710	0.0001
Papilledema	24-months	0.11%	0.20%	-0.09%	0.543	0.431-0.684	0.0001
Increased ICP	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Increased ICP	3-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Increased ICP	6-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Increased ICP	12-months	0.01%	0.01%	0.00%	0.909	0.388-2.129	0.826
Increased ICP	24-months	0.01%	0.01%	0.00%	1.091	0.484-2.459	0.834
Headache	1-month	0.25%	0.26%	-0.01%	0.952	0.804-1.127	0.565
Headache	3-months	0.39%	0.44%	-0.05%	0.897	0.798-1.008	0.068
Headache	6-months	0.49%	0.55%	-0.06%	0.884	0.804-0.972	0.011
Headache	12-months	0.57%	0.61%	-0.04%	0.94	0.866-1.021	0.14
Headache	24-months	0.62%	0.66%	-0.05%	0.93	0.868-1.000	0.051
Optic Atrophy	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Optic Atrophy	3-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Optic Atrophy	6-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Optic Atrophy	12-months	0.02%	0.02%	0.00%	1.167	0.543-2.507	0.693
Optic Atrophy	24-months	0.02%	0.02%	0.00%	1	0.524-1.909	0.999
Blindness	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Blindness	3-months	0.02%	0.02%	-0.01%	0.706	0.339-1.468	0.349
Blindness	6-months	0.02%	0.02%	0.00%	0.882	0.444-1.755	0.721
Blindness	12-months	0.03%	0.03%	0.00%	1.1	0.605-1.999	0.754

Outcome	Follow-up Duration	Topiramate Dose=100 mg, Risk Percentage	Topiramate Dose=25 mg, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
Blindness	24-months	0.03%	0.05%	-0.01%	0.744	0.464-1.191	0.216
Pulsatile Tinnitus	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Pulsatile Tinnitus	3-months	0.01%	0.01%	0.00%	0.909	0.388-2.129	0.826
Pulsatile Tinnitus	6-months	0.01%	0.02%	-0.01%	0.667	0.301-1.475	0.313
Pulsatile Tinnitus	12-months	0.01%	0.02%	-0.01%	0.688	0.321-1.472	0.332
Pulsatile Tinnitus	24-months	0.01%	0.03%	-0.01%	0.5	0.252-0.993	0.043
Abducent Nerve Palsy	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Abducent Nerve Palsy	3-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Abducent Nerve Palsy	6-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Abducent Nerve Palsy	12-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Abducent Nerve Palsy	24-months	0.01%	0.01%	0.00%	1.00%	0.418-2.390	0.999
Diplopia	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Diplopia	3-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Diplopia	6-months	0.01%	0.01%	0.00%	1.1	0.470-2.576	0.826
Diplopia	12-months	0.02%	0.01%	0.00%	1.091	0.484-2.458	0.834
Diplopia	24-months	0.02%	0.03%	-0.01%	0.652	0.343-1.241	0.189
Refractory IIH	1-month	0.24%	0.26%	-0.02%	0.937	0.790-1.111	0.452
Refractory IIH	3-months	0.38%	0.43%	-0.06%	0.87	0.773-0.980	0.022
Refractory IIH	6-months	0.47%	0.54%	-0.07%	0.867	0.787-0.955	0.004
Refractory IIH	12-months	0.55%	0.60%	-0.05%	0.917	0.843-0.997	0.043
Refractory IIH	24-months	0.60%	0.65%	-0.05%	0.916	0.851-0.986	0.02
Visual Discomfort and Visual Fields Defects	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Visual Discomfort and Visual Fields Defects	3-months	0.03%	0.02%	0.01%	1.615	0.815-3.204	0.165
Visual Discomfort and Visual Fields Defects	6-months	0.04%	0.02%	0.02%	2	1.085-3.688	0.023
Visual Discomfort and Visual Fields Defects	12-months	0.05%	0.03%	0.02%	1.667	1.014-2.738	0.041
Visual Discomfort and Visual Fields Defects	24-months	0.05%	0.05%	0.01%	1.095	0.729-1.646	0.662
CSF Leak	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
CSF Leak	3-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
CSF Leak	6-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
CSF Leak	12-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999

Outcome	Follow-up Duration	Topiramate Dose=100 mg, Risk Percentage	Topiramate Dose=25 mg, Risk Percentage	Risk Difference (%)	Risk Ratio	95% Confidence Interval	*p*-value
CSF Leak	24-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999
Therapeutic Spinal Puncture Rate	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
Therapeutic Spinal Puncture Rate	3-months	0.01%	0.02%	-0.01%	0.526	0.246-1.125	0.092
Therapeutic Spinal Puncture Rate	6-months	0.02%	0.03%	-0.01%	0.591	0.300-1.165	0.124
Therapeutic Spinal Puncture Rate	12-months	0.03%	0.03%	-0.01%	0.741	0.419-1.310	0.3
Therapeutic Spinal Puncture Rate	24-months	0.03%	0.04%	-0.01%	0.686	0.411-1.143	0.145
CSF Shunting Rate	1-month	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
CSF Shunting Rate	3-months	0.01%	0.01%	0.00%	1.1	0.470-2.576	0.826
CSF Shunting Rate	6-months	0.02%	0.01%	0.00%	1.273	0.581-2.786	0.545
CSF Shunting Rate	12-months	0.02%	0.02%	0.00%	1.071	0.521-2.205	0.851
CSF Shunting Rate	24-months	0.02%	0.02%	0.00%	1.214	0.602-2.448	0.587
ONSF Rate	1-month	0.01%	0.00%	0.01%	N/A	N/A	0.002
ONSF Rate	3-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
ONSF Rate	6-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
ONSF Rate	12-months	0.01%	0.01%	0.00%	1	0.419-2.389	0.999
ONSF Rate	24-months	0.01%	0.01%	0.00%	1	0.418-2.390	0.999

Table 6: Safety Outcomes Analysis between Topiramate Group and Acetazolamide Group.

Total Patients, n	Acetazolamide Group	Topiramate Group	Risk Ratio	95% Confidence Interval	*p*-value
Side Effects, (%)	7997	7997			
Nausea	9.00%	8.97%	1.004	0.91-1.108	0.9339
Vomiting	2.64%	2.78%	0.95	0.789-1.145	0.592
Changes in Bowel Habits	0.69%	0.64%	1.078	0.738-1.577	0.6967
Functional Diarrhea	0.18%	0.16%	1.077	0.507-2.29	0.8473
Abdominal Distension	1.95%	2.18%	0.897	0.724-1.11	0.3167
Heartburn	1.51%	1.376	1.1	0.851-1.421	0.466
Lactic Acidosis	1.79%	1.20%	1.49	1.152-1.926	0.0022
Vitamin B12 Deficiency or Megaloblastic Anemia	2.99%	3.16%	0.945	0.794-1.124	0.5215
Elevated Liver Enzymes	1.16%	1.16%	1	0.751-1.331	0.999
Elevated Creatinine	4.41%	4.24%	1.041	0.9-1.205	0.5864
Asthenia	3.85%	4.13%	0.933	0.802-1.087	0.3741
Peripheral Neuropathy	2.18%	2.01%	1.081	0.874-1.336	0.4729
Myalgia	5.72%	6.34%	0.901	0.797-1.019	0.0967
Parageusia	0.23%	0.30%	0.75	0.407-1.381	0.3539
Allergic Skin Reactions	0.48%	0.38%	1.267	0.786-2.042	0.3309

was not consistent across all time points, highlighting the complex nature of IIH management and the potential for individual variability in treatment response. The comparison between 100 mg and 50 mg doses demonstrated more consistent benefits with the higher dose, particularly in papilledema resolution and reduction of refractory IIH risk. These findings suggest a dose-dependent effect of topiramate in IIH management, which aligns with observations in other neurological conditions where topiramate is used, such as migraine prophylaxis.[15,23,24]

Interestingly, our analysis of 100 mg versus 25 mg doses revealed some paradoxical effects, particularly in visual outcomes at certain time points. This unexpected finding warrants further investigation and may reflect the complex interplay between dose-related benefits and potential adverse effects at higher doses.

Our safety analysis revealed comparable tolerability profiles between topiramate and acetazolamide for most adverse effects, including gastrointestinal symptoms, renal function changes and neurological side effects. This finding is reassuring, as it suggests that topiramate does not present a significantly higher risk of adverse events compared to the well-established acetazolamide. However, we observed a notably higher incidence of lactic acidosis in the acetazolamide group (RR 1.49, 95% CI 1.152-1.926, p=0.0022). This finding underscores the importance of careful monitoring for metabolic complications, particularly in patients with pre-existing risk factors for acid-base disturbances. The lower risk of lactic acidosis with topiramate may represent an additional advantage in certain patient populations.

The findings of our study have several important clinical implications for the management of IIH. Firstly, the superior efficacy of topiramate in resolving papilledema and managing headaches suggests that it may be considered as a first-line option for IIH patients, particularly those presenting with severe headaches or at high risk of visual complications. The lower incidence of refractory IIH observed with topiramate treatment further supports its early use in the disease course. Secondly, the dose-dependent effects observed with topiramate highlight the importance of individualized dosing strategies. While higher doses (100 mg) generally showed better efficacy, the potential for increased adverse effects at these doses necessitates careful titration and monitoring. Clinicians should weigh the benefits of higher doses against the potential risks on a case-by-case basis. Lastly, the comparable safety profiles of topiramate and acetazolamide, with the exception of lower lactic acidosis risk in the topiramate group, provide reassurance regarding the long-term use of topiramate in IIH management. However, the known cognitive side effects of topiramate, which were not specifically assessed in our study, should be considered when selecting treatment, particularly in patients with cognitively demanding occupations.

While our study provides valuable insights into the comparative efficacy of topiramate and acetazolamide in IIH management, several limitations should be acknowledged. The retrospective nature of our analysis introduces potential for confounding factors and selection bias, despite our efforts to mitigate these through propensity score matching. Additionally, our reliance on electronic health records may have led to underreporting of certain adverse events or outcomes. Further clinical trials are needed to confirm our results and explore perspective directions for IIH management; future trials should include prospective, randomized controlled trials directly comparing topiramate and acetazolamide in IIH management. Such evidence should incorporate detailed assessments of cognitive function, quality of life measures and long-term visual outcomes. Furthermore, investigation into potential biomarkers or clinical predictors of response to topiramate versus acetazolamide could aid in personalizing treatment selection for individual patients.

CONCLUSION

Our comprehensive retrospective study comparing the safety and efficacy of topiramate versus acetazolamide for the management of IIH supports the superiority of topiramate over acetazolamide in several key clinical domains. We observed significantly better outcomes with topiramate in papilledema resolution, headache control and prevention of refractory IIH. The marked 41.6% reduction in persistent papilledema risk at 24 months in the topiramate group underscores its potential as a more effective option for preserving visual function. Moreover, the 14.1% reduction in headache prevalence aligns with topiramate's established efficacy in migraine prophylaxis, offering a dual benefit for IIH patients. Crucially, our findings revealed a lower incidence of refractory IIH and reduced need for invasive interventions in topiramate-treated patients. This suggests that topiramate may alter the natural history of IIH more favorably than acetazolamide. Our dose-efficacy analysis demonstrated a generally positive dose-response relationship for topiramate, though with some paradoxical effects at higher doses that warrants further investigation. The comparable safety profiles between topiramate and acetazolamide, coupled with a lower risk of lactic acidosis in the topiramate group, provide reassurance for its long-term use. However, the known cognitive side effects of topiramate, not specifically assessed in our study, should be considered in treatment decisions. While our results strongly support topiramate as a viable first-line therapy for IIH, we acknowledge the limitations inherent in retrospective analyses. Prospective, randomized controlled trials are necessary to confirm our findings and explore nuanced aspects of treatment response, including cognitive function and quality of life measures. Future research should also investigate potential biomarkers for personalized treatment selection in IIH management.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IIH: Idiopathic Intracranial Hypertension; **CSF**: Cerebrospinal Fluid; **ONSF:** Optic Nerve Sheath Fenestration; **ICP**: Intracranial Pressure; **NIH:** National Institutes of Health; **NINDS:** National Institute of Neurological Disorders and Stroke; **IRB:** Institutional Review Board.

LLM STATEMENT

We have employed an advanced Large Language Model (LLM) to enhance and refine the English-language writing. This process focused solely on improving the text's clarity and style, without generating or adding any new information to the content.

SUMMARY

In our study, we compared the efficacy and safety of topiramate and acetazolamide for treating Idiopathic Intracranial Hypertension (IIH), which affects young, obese women through increased intracranial pressure. Utilizing a large-scale, multicenter retrospective analysis over 24 months, we evaluated outcomes like papilledema resolution, headache control and visual improvement. Our findings reveal that topiramate significantly outperformed acetazolamide in symptom relief and reduced the need for invasive procedures. These results suggest topiramate may serve as a more effective first-line therapy for IIH. Future randomized trials are recommended to confirm our findings and refine IIH treatment protocols based on these insights.

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