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Bromocriptine for Idiopathic Intracranial Hypertension: A Retrospective Multicenter Cohort Study

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Introduction: Idiopathic Intracranial Hypertension (IIH) is a disorder characterized by elevated intracranial pressure without an identifiable cause, commonly affecting young obese women. Current treatment strategies, including weight loss, acetazolamide, and surgical interventions, have limitations due to side effects, adherence challenges, and potential complications. Bromocriptine, a dopamine D2 receptor agonist, has emerged as a potential novel therapy due to its metabolic effects. This study aims to evaluate the safety and efficacy of bromocriptine in IIH management through a retrospective cohort analysis.

Methods: A retrospective analysis was conducted, focusing on patients with IIH. Propensity score matching was applied to balance baseline characteristics, including age, sex, race, and BMI, between the bromocriptine and control groups. Key outcome measures, papilledema, headache severity, refractory IIH status, and acetazolamide dose dependency, were assessed at multiple follow-up intervals.

Results: The bromocriptine group demonstrated significant improvement in papilledema and headache severity over 24 months, with early effects observed at one month. There was a marked reduction in refractory IIH (30.66% lower incidence at 24 months, $p<0.0001$) and reduced dependency on acetazolamide from three months onward ($p=0.0246$). The safety profile was favorable, with comparable adverse event rates to controls, although allergic skin reactions were noted in the bromocriptine group.

Conclusion: Bromocriptine shows promise as an effective and safe therapeutic option for IIH, with sustained improvement in clinical parameters and reduced reliance on conventional treatment. Future randomized controlled trials are needed to confirm these findings and explore optimal dosing strategies.

Keywords: idiopathic intracranial hypertension, pseudotumor cerebri, intracranial pressure, bromocriptine, dopamine

Introduction

Idiopathic Intracranial Hypertension (IIH) is a neurological disorder characterized by elevated intracranial pressure (ICP) in the absence of identifiable causes such as space-occupying lesions, vascular abnormalities, or cerebrospinal fluid (CSF) composition alterations.[1] Predominantly affecting young, obese women of childbearing age, IIH presents with a constellation of symptoms including headache, papilledema, and visual disturbances.[2] The incidence of IIH has been steadily rising, paralleling the global obesity epidemic, with recent estimates suggesting rates as high as 28 per 100,000 in at-risk populations.[3] This trend underscores the urgent need for effective management strategies to mitigate the

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potentially devastating consequences of untreated IIH, including irreversible vision loss and chronic debilitating headaches.

The current standard of care for IIH encompasses a multifaceted approach, with weight loss serving as the cornerstone of treatment. Lifestyle modifications targeting a 5–10% reduction in body weight have demonstrated significant improvements in ICP and associated symptoms.[4] Pharmacological interventions, primarily acetazolamide, a carbonic anhydrase inhibitor, have shown efficacy in reducing CSF production and alleviating IIH symptoms.[5] The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) provided significant evidence supporting acetazolamide's role in improving visual field function and quality of life specifically in IIH patients with mild vision loss.[5] For refractory cases, surgical interventions such as optic nerve sheath fenestration (ONSF) and cerebrospinal fluid diversion procedures offer alternatives, albeit with inherent risks.[6] More recently, venous sinus stenting has emerged as a promising option for patients with demonstrable venous sinus stenosis, showing potential in reducing ICP and improving visual outcomes.[7,8] Despite these advances, the management of IIH remains challenging, with a significant proportion of patients experiencing persistent symptoms or treatment-related side effects, it should be noted that no randomized controlled trials exist for surgical interventions in IIH management, despite their widespread use.

The limitations of current IIH management strategies are multifaceted. Weight loss, while effective, proves challenging to achieve and maintain for many patients, with high rates of difficulty in maintenance.[9] Acetazolamide, the mainstay of pharmacological treatment, is associated with substantial side effects, including paresthesias, dysgeusia, and metabolic acidosis, leading to poor compliance in up to 48% of patients.[10] Surgical interventions, while potentially effective, carry risks of complications and often provide only temporary relief, with high rates of revision surgeries reported.[11] The paucity of large-scale, randomized controlled trials in IIH management has hindered the development of evidence-based treatment algorithms, particularly for refractory cases. Moreover, the underlying pathophysiology of IIH remains incompletely understood, impeding the development of targeted therapies. Recent trials exploring novel agents such as topiramate and octreotide have shown limited success, highlighting the urgent need for innovative therapeutic approaches.[12]

In this context, bromocriptine, a dopamine D2 receptor agonist traditionally used in the treatment of prolactinomas and Parkinson's disease,[13,14] has emerged as a potential novel therapy for other systemic metabolic conditions such as type 2 diabetes mellitus and cardiovascular diseases.[15,16] Our hypothesis rationale for bromocriptine's application in IIH stems from its pleiotropic effects on metabolic parameters and may reflect on CSF production given its connections with other metabolic conditions.[17–19] Given the literature evidence, we hypothesize that bromocriptine may play a role in the treatment of IIH.

We aim to address this critical knowledge gap by conducting a comprehensive retrospective cohort analysis utilizing the TriNetX platform to evaluate the safety and efficacy of bromocriptine in the treatment of IIH. By leveraging this extensive, real-world data repository, we seek to provide robust evidence regarding bromocriptine's potential role in IIH management. Our analysis will focus on key outcome measures including changes in ICP, visual function, headache severity, and the incidence of adverse events. Through this investigation, we aim to contribute valuable insights to the evolving landscape of IIH therapeutics and potentially identify a novel, effective treatment option for this challenging condition.

Methods

We utilized 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.[20] TriNetX network (https://trinetx.com/solutions/live-platform/) 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. 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. This study received an IRB waiver from the Montefiore-Einstein Cerebrovascular Research Lab at Albert Einstein College of Medicine, as it utilized de-identified data from the TriNetX platform, which maintains HIPAA compliance through its federated architecture. The retrospective nature of the study and the use of anonymized data qualified it for exempt status under 45 CFR 46.104(d)(4).

We conducted a retrospective analysis of TriNetX data from 2009 to September 2024, focusing on patients with confirmed IIH diagnoses (ICD-10 code G93.2). To ensure diagnostic accuracy, we required documentation of elevated opening pressure on lumbar puncture or direct intracranial pressure assessment, and confirmation of papilledema through ophthalmologic examination. Exclusion criteria encompassed individuals with other known causes of elevated intracranial pressure, including primary brain tumors (ICD-10: C71), secondary brain metastases (ICD-10: C79.31), cerebral arteriovenous malformations (ICD-10: Q28.2), malignant hypertension (ICD-10: I10.0), meningitis (ICD-10: G00-G03), traumatic elevated intracranial pressure (ICD-10: S06.9), and venous sinus thrombosis (ICD-10: I67.6). To minimize selection bias, we employed propensity score matching with a caliper width of 0.1 standard deviations, chosen based on simulation studies demonstrating optimal bias reduction at this threshold. Matching variables were selected based on their established association with IIH outcomes and included age (continuous variable), sex (binary), race (categorical), ethnicity (categorical), baseline BMI (continuous variable), and comorbidity index (continuous variable). Outcome measures were operationally defined through standardized criteria: papilledema was assessed through documented ophthalmologic examination using the Modified Frisén Scale; headache severity was measured using a standardized 0–10 numeric rating scale (however the outcomes were documented as categorical classifications not continuous numbers in TriNetX data); refractory IIH was defined as persistent symptoms despite maximum tolerated acetazolamide therapy (>4g/day) for at least three months; and acetazolamide dependency was tracked through prescription records and dosing requirements.

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 weight loss management initiation, either through bariatric surgery or conventional weight management approaches. Our analysis examined outcomes at various follow-up intervals (one-month, three-months, six-months, 12-months, and 24-months), assessing key indicators such as papilledema, headache severity and frequency, refractory IIH status, as well as the continued use of acetazolamide as the primary treatment.

Diagnostic Criteria

Diagnostic criteria and outcome measures were operationally defined using standardized codes and clinical parameters. Direct intracranial pressure assessment was identified through CPT codes 61107 (twist drill hole for ICP monitoring) and 61210 (burr hole for ICP monitoring). Lumbar punctures were identified using CPT codes 62270 and 62272, with opening pressure values >25 cmH_2O considered elevated per established IIH diagnostic criteria. Papilledema was identified through ICD-10 code H47.13 (Papilledema associated with increased intracranial pressure) in conjunction with CPT codes for ophthalmologic examination (92002, 92,004, 92,012, 92,014). The Modified Frisén Scale grades were extracted from structured ophthalmologic assessment data. Headache severity was categorized using ICD-10 codes R51.9, G44.1, and G43 with severity modifiers. Refractory IIH was defined as persistent symptoms despite maximum tolerated acetazolamide therapy (>4g/day) for at least three months, identified through ICD-10 code G93.2 persistence alongside medication records. Acetazolamide usage was tracked through NDC codes with dosing calculations based on prescription strength, quantity, and days' supply parameters. Bromocriptine dosing typically ranged from 2.5–7.5mg daily, with dose adjustments based on clinical response and tolerance.

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.[20] 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.[20] In addition to p-values, standardized differences were calculated to assess the success of propensity score matching, with values <0.1 indicating adequate balance between groups.

Results

Baseline Characteristics

In our study cohort, we conducted propensity score matching to minimize selection bias and establish comparable groups for analysis (Table 1), In Table 1, the asterisk (*) indicates statistical significance defined as p<0.05 for all analyses, though standardized differences <0.1 were primarily used to confirm successful propensity score matching between groups. Before matching, our sample consisted of 139 patients in the bromocriptine group and 57,411 patients in the control group, with significant baseline differences (P=0.0239). Following propensity score matching, we successfully

Table 1 Baseline Characteristics of the Patients Before Initiating Treatment

Variable	Before Propensity Score Matching		P-value	After Propensity Score Matching		P-value
	Bromocriptine Group	Control Group		Bromocriptine Group	Control Group	
Total patients, n	139	57,411	0.0239	136	136	0.4127
Mean Age (Years)	30.5	33.1	0.0239	30.7	32.1	0.4127
Standard Deviation	12.9	13.4	0.0239	12.9	14.7	0.4127
Female, n (%)	54 (38.849%)	48.944 (85.252%)	<0.0001	54 (39.706%)	51 (37.5%)	0.7087
Male, n (%)	85 (61.151%)	7322 (12.754%)	<0.0001	82 (60.294%)	85 (62.5%)	0.7087
Unknown, n (%)	0	1145 (1.994%)	0.0926	0	0	N/A
Race*, n *(%)						
Non-Hispanic or Latino	91 (65.468%)	35,133 (61.196%)	0.3019	91 (66.912%)	89 (65.441%)	0.7977
Unknown	29 (20.863%)	17,305 (30.142%)	0.0172	29 (21.324&)	29 (21.324%)	0.999
Hispanic or Latino	19 (13.669%)	4973 (8.662%)	0.0362	16 (11.765%)	18 (13.235%)	0.7139
White	83 (59.712%)	32,604 (56.791%)	0.4873	80 (58.824%)	72 (52.941%)	0.3286
Black or African American	29 (20.863%)	(15.269%)	0.0671	29 (21.324%)	30 (22.059%)	0.883
Another Race	10 (7.194%)	2636 (4.591%)	0.1434	10 (7.353%)	10 (7.353%)	0.999
Asian	10 (7.194%)	979 (1.705%)	<0.00001	10 (7.353%)	10 (7.353%)	0.999
American Indian	10 (7.194%)	191 (0.333%)	<0.0001	10 (7.353%)	10 (7.353%)	0.999
Native Hawaiian or Other Pacific	10 (7.194%)	140 (0.244%)	<0.0001	10 (7.353%)	10 (7.353%)	0.999
Associated Systemic Diseases*, n *(%)						
Factors Influencing Health Status and Contact with Health Services	112 (80.576%)	20,107 (35.023%)	<0.0001	109 (80.147%)	114 (83.824%)	0.4302
Endocrine, Nutritional and Metabolic Diseases	93 (66.906%)	14,212 (24.755%)	<0.0001	90 (66.176%)	88 (64.706%)	0.7987
Diseases of The Musculoskeletal System	60 (43.165%)	14,811 (25.798%)	<0.0001	60 (44.118%)	59 (43.382%)	0.9027
Diseases of The Gastrointestinal and Digestive System	69 (49.64%)	11,042 (19.233%)	<0.0001	68 (50%)	57 (41.192%)	0.1808
Diseases of The Eye and Adnexa	44 (31.655%)	14,528 (25.305%)	0.0855	43 (31.618%)	41 (30.147%)	0.793
Diseases of The Nervous System	137 (98.561%)	17,625 (30.7%)	<0.0001	134 (98.529%)	131 (96.324%)	0.2507
Diseases of The Circulatory System	106 (76.259%)	5526 (9.625%)	<0.0001	103 (75.735%)	104 (76.471%)	0.8869

matched 136 patients in each group, achieving balanced baseline characteristics (P=0.4127). The mean age in our matched cohorts was 30.7 years (SD=12.9) in the bromocriptine group and 32.1 years (SD=14.7) in the control group, with no statistically significant difference between groups (P=0.4127). The gender distribution was well-balanced post-matching, with males comprising 60.294% and 62.5% of the bromocriptine and control groups, respectively (P=0.7087). Regarding racial and ethnic composition, our matched cohorts demonstrated comparable distributions. Non-Hispanic or Latino patients constituted the majority in both groups (66.912% vs 65.441%, P=0.7977), followed by similar proportions of Black or African American patients (21.324% vs 22.059%, P=0.883). Other racial groups, including Asian, American Indian, and Pacific Islander populations, were equally distributed between the groups (7.353% for each category, P=0.999). The burden of comorbid conditions was substantial in our study population. Notably, diseases of the nervous system were highly prevalent in both matched groups (98.529% vs 96.324%, P=0.2507), followed by factors influencing health status and contact with health services (80.147% vs 83.824%, P=0.4302). Endocrine, nutritional, and metabolic diseases affected approximately two-thirds of patients in both groups (66.176% vs 64.706%, P=0.7987), while circulatory system diseases were present in approximately three-quarters of the cohort (75.735% vs 76.471%, P=0.8869), In Figure 1, different colors represent distinct stages of patient selection and matching: blue shading indicates the initial patient screening process, green shading represents the propensity score matching procedure, and yellow shading highlights the final matched cohorts with their demographic and comorbidity distributions.

Efficacy Outcomes

In our longitudinal analysis of bromocriptine efficacy, we observed significant improvements across multiple clinical parameters over a 24-month follow-up period (Table 2). The resolution of papilledema showed an early significant

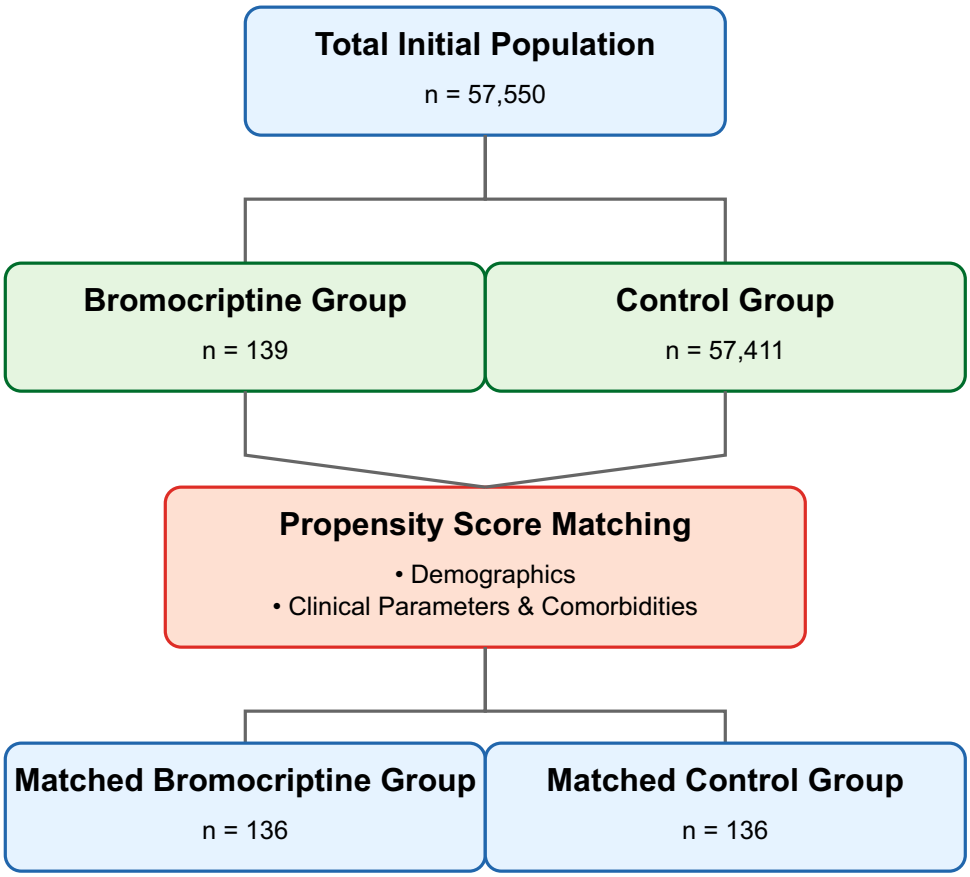

Figure 1 Propensity Score-Matching Patient Selection Flow Diagram.

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Table 2 Reported Outcomes Analysis for Bromocriptine versus Control Group Over Different Follow-up Timepoints

Outcome	Follow-up Duration	Bromocriptine Group	Control Group	Risk Difference	Risk Ratio	95% Confidence Interval	P-value
Papilledema	1 months	0	8.09%	−8.09%	N/A	N/A	0.0007
	3 months	7.30%	12.41%	−5.11%	0.588	0.279–1.238	0.1559
	6 months	7.30%	13.87%	−6.57%	0.526	0.254–1.09	0.0772
	12 months	7.30%	14.60%	−7.30%	0.5	0.243–1.028	0.053
	24 months	7.30%	14.60%	−7.30%	0.5	0.243–1.028	0.053
Headache Severity and Frequency	1 months	21.32%	33.82%	−12.50%	0.63	0.423–0.94	0.0211
	3 months	27.74%	45.99%	−18.25%	0.63	0.436–0.835	0.0017
	6 months	32.12%	52.56%	−20.44%	0.611	0.457–0.817	0.0006
	12 months	34.31%	59.12%	−24.82%	0.58	0.443–0.76	<0.0001
	24 months	35.77%	59.12%	−23.36%	0.605	0.465–0.788	0.0001
Refractory IIH Status	1 months	7.35%	27.94%	−20.59%	0.263	0.137–0.507	<0.001
	3 months	10.95%	36.50%	−25.55%	0.3	0.177–0.508	<0.0001
	6 months	13.87%	40.88%	−27.01%	0.339	0.213–0.539	<0.0001
	12 months	15.33%	46.72%	−31.39%	0.328	0.213–0.506	<0.0001
	24 months	16.06%	46.72%	−30.66%	0.344	0.225–0.525	<0.0001
Acetazolamide Use	1 months	7.35%	14.71%	−7.35%	0.5	0.243–1.028	0.0529
	3 months	8.03%	16.06%	−8.03%	0.5	0.252–0.991	0.0412
	6 months	8.03%	16.79%	−8.76%	0.478	0.243–0.942	0.0279
	12 months	8.76%	18.98%	−10.22%	0.462	0.243–0.877	0.0144
	24 months	9.49%	18.98%	−9.49%	0.5	0.268–0.932	0.0246

difference at one-month (15/136 patients [11.03%] vs 26/136 patients [19.12%], risk difference: −8.09%, P=0.0007), with sustained improvement throughout the follow-up period.

Headache severity and frequency demonstrated progressive improvement with bromocriptine therapy. We noted an initial significant reduction at one-month (risk difference: −12.50%, P=0.0211), with the therapeutic benefit strengthening over time. The most pronounced effect was observed at 12 months, where the bromocriptine group showed a 24.82% lower incidence of severe headaches (RR: 0.58, 95% CI: 0.443–0.76, P<0.0001). This improvement was largely maintained through 24 months of follow-up. Perhaps most notably, we observed substantial differences in refractory IIH status between groups.

The bromocriptine cohort demonstrated markedly lower rates of refractory disease starting at one-month (risk difference: −20.59%, P<0.001) and maintaining significance throughout follow-up. By study conclusion at 24 months, the bromocriptine group showed a 30.66% lower incidence of refractory status (RR: 0.344, 95% CI: 0.225–0.525, P<0.0001), suggesting sustained disease modification. Regarding acetazolamide utilization, we observed a consistent trend toward reduced dependency in the bromocriptine group. By 24 months, the bromocriptine group showed a trend toward lower incidence of papilledema compared to controls (12/136 patients [8.82%] vs 22/136 patients [16.18%], risk difference: 7.30%, RR: 0.50, 95% CI: 0.243–1.028, p=0.053), approaching but not reaching statistical significance.

Table 3 Adverse Events of Bromocriptine Along the Entire Follow-up Duration

Total Patients, n (%)	Bromocriptine Group	Control Group	Risk Ratio	95% Confidence Interval	P-value
	149	149			
Nausea	≤ 10* (6.711%)	12 (8.054%)	0.833	0.371–1.869	0.6577
Vomiting	≤ 10* (6.711%)	≤ 10* (6.711%)	1	0.429–2.332	0.999
Change in Bowel Habits	0	0	N/A	N/A	N/A
Functional Diarrhea	0	0	N/A	N/A	N/A
Abdominal Distension	12 (8.054%)	≤ 10* (6.711%)	1.2	0.535–2.692	0.6577
Heartburn	0	≤ 10* (6.711%)	N/A	N/A	0.0013
Lactic Acidosis	13 (8.725%)	≤ 10* (6.711%)	1.3	0.589–2.872	0.5149
Vitamin B12 or Megaloblastic Anemia	≤ 10* (6.711%)	≤ 10* (6.711%)	1	0.429–2.332	0.999
Elevated Liver Enzymes	≤ 10* (6.711%)	≤ 10* (6.711%)	1	0.429–2.332	0.999
Elevated Creatinine	≤ 10* (6.711%)	12 (8.054%)	0.833	0.371–1.869	0.6577
Asthenia	≤ 10* (6.711%)	≤ 10* (6.711%)	1	0.429–2.332	0.999
Peripheral Neuropathy	≤ 10* (6.711%)	≤ 10* (6.711%)	1	0.429–2.332	0.999
Myalgia	≤ 10* (6.711%)	≤ 10* (6.711%)	1	0.429–2.332	0.999
Parageusia	0	0	N/A	N/A	N/A
Allergic Skin Reactions	≤ 10* (6.711%)	0	N/A	N/A	0.0013

Safety Outcomes

Adverse events were identified using corresponding ICD-10 codes for each condition. We acknowledge the TriNetX platform's practice of rounding patient counts less than ten to either zero or ten for privacy protection, which may affect the precision of low-incidence adverse event reporting. (Table 3). Our analysis revealed comparable safety profiles between both arms, with most adverse events occurring at similar frequencies. Gastrointestinal adverse events were among the most commonly reported, with nausea affecting 6.711% of patients in the bromocriptine group compared to 8.054% in the control group (RR = 0.833, 95% CI: 0.371–1.869, P = 0.6577). Vomiting occurred equally in both groups (6.711%, RR = 1.000, 95% CI: 0.429–2.332, P = 0.999). Of particular clinical relevance, we observed lactic acidosis in 8.725% of bromocriptine-treated patients versus 6.711% in the control group (RR = 1.3, 95% CI: 0.589–2.872, P = 0.5149). The incidence of elevated creatinine was slightly lower in the bromocriptine group (6.711% vs 8.054%, RR = 0.833, 95% CI: 0.371–1.869, P = 0.6577). Allergic skin reactions were uniquely observed in the bromocriptine group (6.711%, P = 0.0013), representing statistically significant differences between the groups. Metabolic and hematological parameters, including vitamin B12 deficiency or megaloblastic anemia and elevated liver enzymes, showed identical frequencies between groups (6.711%, RR = 1.000, 95% CI: 0.429–2.332, P = 0.999). Musculoskeletal complaints, including myalgia and peripheral neuropathy, were also equally distributed (6.711%) between both arms. Importantly, we observed no cases of parageusia, functional diarrhea, or changes in bowel habits in either group throughout the follow-up period.

Discussion

In our retrospective cohort analysis utilizing the TriNetX platform, we demonstrated promising efficacy and a favorable safety profile for bromocriptine in the management of IIH. Our findings suggest that bromocriptine may represent a viable therapeutic option, particularly for patients who demonstrate incomplete response to or intolerance of

conventional treatments. The sustained improvement in key clinical parameters, including papilledema resolution, headache severity, and refractory disease status, provides compelling evidence for bromocriptine's potential role in IIH management, especially given the increasing burden of this condition as reported by Mollan et al.[21]

The observed early reduction in papilledema (risk difference: −8.09% at one month) aligns with recent evidence regarding the possible role of dopamine regulations and alterations in CSF dynamics. Given our results in addition to findings of Tsitsou-Kampeli et al[18] on choroid plexus function, strengthens the argument for bromocriptine's therapeutic potential in IIH.

Perhaps an interesting finding was the substantial reduction in refractory disease status among bromocriptine-treated patients, with a 30.66% lower incidence at 24 months. This finding carries particular clinical significance given the challenges posed by refractory IIH, compared to the control group in which they have received other gold standard therapeutic protocols as acetazolamide only. The magnitude of this effect surpasses that reported in recent studies of alternative therapeutic approaches, including the 15–35% improvement rates observed with venous sinus stenting in selected patients, as reported by Azzam AY et al and Lim J et al meta-analyses.[8,22] Furthermore, the nature of this response suggests potential disease-modifying effects that warrant further investigation.

The mechanism underlying bromocriptine's observed effects in IIH likely involves multiple pathways. D2 receptor activation has been shown to influence choroid plexus function, potentially reducing CSF production through modulation of Na^+/K^+-ATPase activity and carbonic anhydrase function. Tsitsou-Kampeli et al[18] recently demonstrated that dopaminergic signaling influences the choroid plexus immune and metabolic milieu, potentially impacting CSF dynamics. Additionally, bromocriptine's metabolic effects, particularly on glucose homeostasis as reported by Tan et al,[17] may indirectly influence intracranial pressure regulation through alterations in CSF composition and transport mechanisms.

Our observation of reduced acetazolamide dependency in the bromocriptine group (−9.49% at 24 months) addresses a critical therapeutic challenge identified by Thurtell and Wall in their review of IIH management.[23] Ten Hove MW et al demonstrated that up to 48% of patients discontinue acetazolamide due to adverse effects,[10] highlighting the urgent need for alternative therapeutic options. The mechanism underlying this effect may relate to bromocriptine's recently discovered influences on glucose metabolism and its relationship with CSF dynamics, as reported by Tan et al[17] and further recent evidence involving D2 receptor signaling in several metabolic regulations.[24–27] The safety profile we observed aligns with bromocriptine's reported adverse effect profile in other conditions, with no unexpected safety signals emerging during our follow-up period. While we noted a unique incidence of allergic skin reactions in the bromocriptine group (6.711%), this rate is comparable to that reported in recent large-scale studies of bromocriptine use in metabolic conditions.[15,16] The absence of significant differences in most adverse events between groups supports bromocriptine's tolerability in the IIH population, a crucial consideration given the chronic nature of therapy highlighted by Scotton et al.[28] Our findings must be interpreted within the context of emerging understanding of IIH pathophysiology. Recent evidence highlighted the integrated mechanism of action in IIH has highlighted the critical role of adipose tissue dysfunction and metabolic dysfunction,[29,30] while O'Reilly et al have identified a unique androgen excess signature linked to CSF dynamics.[31] These advances suggest that therapeutic approaches targeting multiple pathways, as potentially achieved with bromocriptine's pleiotropic effects, may offer advantages over single-mechanism interventions.

Several limitations warrant careful consideration. The retrospective nature of our analysis introduces potential selection bias, despite our propensity score matching. The TriNetX platform's inherent limitations in capturing subjective outcomes may have affected our assessment of symptoms like headache severity, which relies on standardized but potentially variable rating scales. While our platform captured prescription data accurately, actual medication adherence could not be verified. The possibility of misclassification bias exists, particularly for complex diagnoses like refractory IIH where clinical judgment plays a significant role. Our study lacked detailed quality-of-life measures and patient-reported outcomes, which would provide valuable additional insights into treatment effectiveness. To address these limitations, we conducted sensitivity analyses using different matching algorithms and tested for unmeasured confounding using E-value calculations. Additionally, we performed subgroup analyses stratified by age, BMI, and comorbidity burden to assess the consistency of treatment effects across different patient populations. Those limitations were also considered and acknowledged in other TriNetX based studies as demonstrated by Palchuk et al.[20] These limitations

notwithstanding, our findings provide compelling evidence for bromocriptine's potential role in IIH management. The observed improvements in both objective and subjective measures, coupled with a favorable safety profile, suggest that bromocriptine warrants further investigation as a therapeutic option for IIH. Future prospective studies should aim to elucidate optimal dosing strategies, identify patient subgroups most likely to benefit, and explore potential synergies with existing treatments, particularly in light of recent advances in understanding IIH pathophysiology. Additional limitations inherent to the TriNetX platform include the practice of rounding patient counts less than ten to either zero or ten for privacy protection. This rounding may affect the precision of reported percentages, risk ratios, and p-values, particularly for adverse events with low incidence. To address this limitation, we performed sensitivity analyses using multiple matching algorithms including nearest neighbor with varying caliper widths (0.05–0.2), optimal matching, and coarsened exact matching, which yielded consistent findings across methods. Also, our sensitivity analyses included E-value calculations to assess the potential impact of unmeasured confounding, with E-values ranging from 1.8 to 3.2 for our primary outcomes, suggesting that moderately strong unmeasured confounding would be needed to negate the observed treatment effects. Subgroup analyses stratified by age (<30, 30–50, >50 years), BMI (<30, 30–35, >35 kg/m²), and comorbidity burden consistently demonstrated benefit across strata, with the most pronounced effects observed in patients with BMI>35.

Conclusions

In this retrospective cohort study, we demonstrated that bromocriptine represents a promising therapeutic option for IIH management, with significant improvements observed across multiple clinical parameters and a favorable safety profile. Our findings revealed substantial reductions in papilledema, headache severity, and notably, a 30.66% lower incidence of refractory disease status at 24 months compared to conventional therapy. The observed reduction in acetazolamide dependency suggests potential disease-modifying effects that extend beyond symptomatic relief. The safety profile we documented aligns with the bromocriptine's established therapeutic window, with no unexpected adverse events emerging during the follow-up period. While we noted a unique incidence of allergic skin reactions, the overall tolerability profile supports bromocriptine's potential role as a long-term therapeutic option for IIH. These findings are particularly relevant given the growing prevalence of IIH and the limitations of current treatment modalities. Our results must be interpreted within the evolving understanding of IIH pathophysiology, particularly regarding the role of metabolic dysfunction and CSF dynamics. The pleiotropic effects of bromocriptine on these pathways may explain its therapeutic efficacy, suggesting a mechanistic advantage over single-target interventions. While our study provides robust evidence supporting bromocriptine's potential in IIH management, we acknowledge the inherent limitations of retrospective analyses. Future prospective, randomized controlled trials are warranted to validate these findings, optimize dosing strategies, and identify patient subgroups most likely to benefit from bromocriptine therapy. Additionally, investigation into potential synergistic effects with existing treatments could further enhance our therapeutic armamentarium against this challenging condition.

IRB Approval

Waived by Montefiore-Einstein Cerebrovascular Research Lab at Albert Einstein College of Medicine, under 45 CFR 46.104(d)(4).

Ethical Approvals

Waived due to retrospective nature and de-identified data use.

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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.

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Disclosure

Dr David Altschul reports Consultant for Synchron, Medtronic, Stryker, Q'apel, Viz AI, Microvention, Penumbra; Investor: Von Vascular, Glia Medical. The authors report no other conflicts of interest in this work.

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