Quality of life at 6 months in the Idiopathic Intracranial Hypertension Treatment Trial

Beau B. Bruce, MD, PhD
Kathleen B. Digre, MD
Michael P. McDermott, PhD
Eleanor B. Schron, PhD
Michael Wall, MD
On behalf of the NORDIC Idiopathic Intracranial Hypertension Study Group

Correspondence to Dr. Bruce: bbbruce@emory.edu

ABSTRACT

Objective: To examine the changes in vision-specific and overall health-related quality of life (QOL) at 6 months in participants with idiopathic intracranial hypertension (IIH) and mild visual loss enrolled in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) and to determine the signs and symptoms of IIH that mediate the effect of acetazolamide on QOL.

Methods: We assessed QOL using the National Eye Institute Visual Function Questionnaire–25 (NEI-VFQ-25), the 10-Item NEI-VFQ-25 Neuro-Ophthalmic Supplement, and the 36-Item Short Form Health Survey (SF-36). We examined associations among changes in QOL measures over 6 months, treatment status, and changes in signs and symptoms using linear and structural equation models.

Results: Among the 165 participants with IIH (86 randomized to acetazolamide, 79 to placebo), beneficial effects of acetazolamide were seen on all QOL scales evaluated, as well as on the Near Activities (5.60 points, $p = 0.03$), Social Functioning (3.85 points, $p = 0.04$), and Mental Health (9.82, $p = 0.04$) subscales of the NEI-VFQ-25. Positive acetazolamide-related effects on QOL appeared to be primarily mediated by improvements in visual field, neck pain, pulsatile tinnitus, and dizziness/vertigo that outweighed the side effects of acetazolamide.

Conclusions: The marked reductions in baseline QOL seen among patients with mild visual loss from IIH are improved by treatment with acetazolamide. When combined with acetazolamide-associated improvements in visual field and other aspects of IIH, our findings with respect to QOL provide further support from the IIHTT in favor of acetazolamide to augment a dietary intervention in the treatment of IIH with mild visual loss (clinicaltrials.gov: NCT01003639). ***Neurology*®** **2016;87:1871–1877**

GLOSSARY

BMI = body mass index; **CI** = confidence interval; **HIT-6** = 6-item Headache Impact Test; **IIH** = idiopathic intracranial hypertension; **IIHTT** = Idiopathic Intracranial Hypertension Treatment Trial; **NEI-VFQ-25** = 25-item National Eye Institute Visual Function Questionnaire; **MCS** = Mental Component Summary; **PCS** = Physical Component Summary; **PMD** = perimetric mean deviation; **QOL** = quality of life; **SF-36** = Short Form–36; **TVO** = transient visual obscurations.

Idiopathic intracranial hypertension (IIH) is a syndrome of elevated intracranial pressure of unknown etiology that frequently affects young, obese women. In addition to the potential for severe visual loss and the often debilitating related symptoms (e.g., headache, back and neck pain, pulsatile tinnitus, and photophobia), poor quality of life (QOL) has emerged as a key morbidity for patients with IIH.[1]

The Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) was the first study to prospectively assess the QOL of patients with mild visual loss at the time of their IIH diagnosis and after 6 months of treatment with acetazolamide or placebo, with all participants also receiving a low-sodium, weight-reduction diet.[2,3] We previously reported the vision-specific and overall health-related QOL in IIHTT participants at the baseline visit in the context of prior work on QOL in IIH.[1,4,5] The purpose of this article is to report the effects of

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From the Departments of Ophthalmology, Neurology, and Epidemiology (B.B.B.), Emory University, Atlanta, GA; Departments of Neurology and Ophthalmology (K.B.D.), Moran Eye Center, University of Utah, Salt Lake City; Departments of Biostatistics and Computational Biology and Neurology (M.P.M.), University of Rochester Medical Center, NY; Division of Extramural Research (E.B.S.), National Eye Institute, Bethesda, MD; and Department of Ophthalmology and Visual Sciences (M.W.), University of Iowa Carver College of Medicine, Iowa City.

Coinvestigators are listed at Neurology.org.

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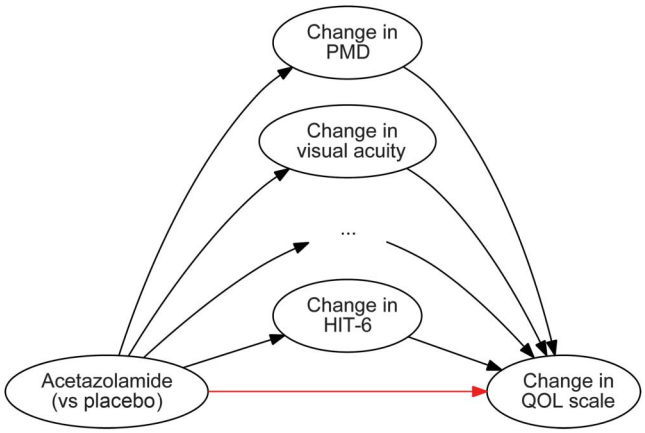
Figure 1 Construction of the structural equation model



The direct effect of acetazolamide on quality of life (QOL) is represented by the red arrow. The indirect effects of acetazolamide on QOL mediated through the signs and symptoms of idiopathic intracranial hypertension are represented by the black paths through each sign or symptom. Control for baseline QOL, which was included in the model, is not shown to simplify the graph. ... = Other mediating variables included but not shown; HIT-6 = 6-item Headache Impact Test; PMD = perimetric mean deviation.

acetazolamide on QOL scales and subscales at 6 months, examine associations between changes in QOL and symptom changes, and evaluate potential mediators of the effects of acetazolamide on QOL at 6 months using the IIHTT study cohort.

METHODS

Standard protocol approvals, registrations, and patient consents. We conducted this study in accordance with the Declaration of Helsinki. The institutional review board at each site approved this study, and all participants provided written informed consent.

Patients. This study was a longitudinal evaluation of the QOL characteristics of participants with IIH and mild visual loss enrolled in the IIHTT, a randomized, double-masked, placebo-controlled trial of acetazolamide. All participants received a low-sodium, weight-reduction diet. To be eligible for the study, participants satisfied the Modified Dandy Criteria for IIH[6] and had baseline computerized automated perimetric mean deviation (PMD) between −2 and −7 dB in the worst affected eye on a 24-2 SITA standard test (Humphrey; Carl Zeiss Meditec, Inc., Dublin, CA).

Visual function testing. A certified technician measured high-contrast visual acuity using retroilluminated Early Treatment Diabetic Retinopathy Study charts (Lighthouse International Low Vision Products, New York, NY). The technician also tested low-contrast letter acuity using retroilluminated, low-contrast Sloan letter charts (Precision Vision, La Salle, IL) at 2.5% and 1.25% contrast levels. Study team members performed an ocular examination, pupillary testing, and direct and indirect ophthalmoscopic evaluations at the screening and baseline visits and at months 1, 2, 3, 4.5, and 6. Automated perimetry with Humphrey Field Analyzer SITA standard program 24-2 was also performed at these visits. The site investigator and the Photographic Reading Center graded papilledema for each eye using the Frisén Scale at screening and at months 1, 2, 3, 4.5, and 6.[7,8]

QOL assessments. We administered QOL questionnaires at the baseline and month 6 visits, or at the time of treatment failure or withdrawal from the study. Participants completed the questionnaires on the NORDIC website up to 1 week before each visit, or completed the questionnaires during the visit. Vision-specific QOL was assessed with the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25).[9] This self-administered scale includes 25 questions with response gradings that use a Likert scale. Assessment also included administering the more recently designed 10-item Neuro-Ophthalmic Supplement to the NEI-VFQ-25.[10] The Short Form–36 (SF-36) was used to measure overall health-related QOL.[11] Each patient also completed the 6-item Headache Impact Test (HIT-6) questionnaire[12] to evaluate headache disability and the Berlin Sleep Apnea Questionnaire to discern the possibility of underlying sleep apnea, which would exclude the patient from participating. One participant's baseline QOL data were unavailable/incomplete, as was the Neuro-Ophthalmic Supplement for 2 other participants. At 6 months, data were unavailable/incomplete for the NEI-VFQ-25 in 28 participants, the Neuro-Ophthalmic Supplement in 29 participants, and the SF-36 in 30 participants.

Statistical analysis. Statistical analyses were performed using R 3.2.1 (The R Foundation for Statistical Computing; r-project.org). The intention-to-treat principle was followed. If data were available after the baseline visit on a participant, these observations were carried forward to the 6-month timepoint. Missing data from the remaining patients were accommodated in the analyses by multiple imputation using fully conditional specification implemented by the multivariate imputation by chained equations algorithm (appendix e-1 at Neurology.org).[13]

Treatment effects on QOL subscales were estimated using linear models controlling for site, baseline Frisén scale in the study eye, and the baseline value of the relevant QOL scale or subscale (analogous to models performed in the main 6-month report).[3] Associations between changes in symptoms/signs (Frisén grade, PMD, visual acuity, CSF opening pressure, body mass index [BMI], HIT-6 total score, back pain, neck pain, binocular diplopia, cognitive dysfunction, dizziness/vertigo, photophobia, radicular pain, pulsatile tinnitus, nonpulsatile tinnitus, and transient visual obscurations) and change in QOL were evaluated with linear models controlling for treatment assignment and the baseline values of the symptom/sign and QOL measure. With respect to changes in binary symptoms, these were coded as improved vs remained the same or worsened.

Mediation analysis was performed using structural equation models fit using diagonally weighted least squares with robust standard errors via the lavaan package for R, version 0.5.18. For each QOL scale, the structural equation model contained several indirect effects of acetazolamide on QOL mediated through changes in signs or symptoms of IIH and a direct effect of acetazolamide (figure 1). For these analyses, baseline QOL was also included in the model.

RESULTS

Demographics. A total of 161 women and 4 men met all eligibility criteria and enrolled in the trial.[3] The age range was 18–52 years. Most participants (65%) self-identified as white/Caucasian while 25% were African American, 2% were Native American, and 8% were of other races or did not report their race; also, 13% were Hispanic/Latino.

All were overweight, and obesity (i.e., BMI >30 kg/m^2) was present in 88% of patients.

Effect of treatment on QOL scales and subscales. The primary IIHTT article[3] reported acetazolamide-associated improvements at 6 months on all 4 main QOL measures used in the study: NEI-VFQ-25 total score (6.4 points; $p = 0.003$), NEI-VFQ-25 Neuro-Ophthalmic Supplement total score (8.2 points; $p = 0.001$), SF-36 Physical Component Summary (PCS) (3.0 points; $p = 0.03$), and SF-36 Mental Component Summary (MCS) (3.5 points; $p = 0.03$). For the present article, we extended this analysis to the subscales (NEI-VFQ-25 and SF-36) and individual questions (NEI-VFQ-25 Neuro-Ophthalmic Supplement) of these QOL scales (tables 1 and e-1). Both groups experienced improvements in almost all of the subscales/individual questions of the QOL scales, and the mean improvement in the acetazolamide group was larger than the mean improvement in the placebo group for several subscales/individual questions. Treatment effects on the NEI-VFQ-25 were apparent on the Near Activities subscale (5.60 points; 95% confidence interval [CI] 0.42–10.78; $p = 0.03$), Social

Table 1 Treatment effect by quality of life subscale

Scale	Subscale	Treatment effect[a] (95% CI)	p Value
NEI-VFQ-25	General health	1.45 (−8.10 to 11.01)	0.76
	General vision	6.08 (−0.29 to 12.45)	0.06
	Near activities	5.60 (0.42 to 10.78)	0.03
	Distance activities	3.32 (−1.85 to 8.49)	0.20
	Driving	4.18 (−3.59 to 11.95)	0.29
	Peripheral vision	7.18 (−1.40 to 15.75)	0.10
	Color vision	1.63 (−0.22 to 3.49)	0.08
	Ocular pain	5.61 (−1.40 to 12.61)	0.12
	Role difficulties	5.25 (−2.24 to 12.74)	0.17
	Dependency	3.63 (−1.70 to 8.97)	0.18
	Social functioning	3.85 (0.23 to 7.47)	0.04
	Mental health	9.82 (3.51 to 16.14)	0.003
NEI-VFQ-25 NOS	Difficulty with tasks when eyes tired	7.52 (−1.38 to 16.42)	0.10
	Difficulty performing tasks in bright sunlight	8.76 (0.53 to 17.00)	0.04
	Difficulty parking car	−0.70 (−11.64 to 10.24)	0.90
	Difficulty using computer	5.53 (−0.33 to 11.39)	0.06
	Feeling eyes see differently	10.95 (−2.99 to 24.89)	0.12
	Feeling my eye or eyelid appearance is unusual	2.53 (−7.20 to 12.26)	0.61
	Vision blurry, not clear, or fuzzy	14.67 (4.88 to 24.45)	0.004
	Trouble focusing on moving objects	3.49 (−4.14 to 11.12)	0.37
	Binocular double vision	5.03 (−0.78 to 10.84)	0.09
	Eyelids droop	4.14 (−2.32 to 10.60)	0.21
SF-36	Physical functioning	2.67 (−0.21 to 5.55)	0.07
	Role-physical	3.44 (−0.17 to 7.05)	0.06
	Bodily pain	0.05 (−3.66 to 3.75)	0.98
	General health	0.07 (−3.33 to 3.46)	0.97
	Vitality	1.91 (−1.88 to 5.69)	0.32
	Social functioning	3.33 (−0.15 to 6.81)	0.06
	Role-emotional	2.37 (−1.25 to 6.00)	0.20
	Mental health	3.02 (−0.08 to 6.11)	0.06

Abbreviations: CI = confidence interval; NEI-VFQ-25= 25-item National Eye Institute Visual Function Questionnaire; NOS = Neuro-Ophthalmic Supplement; SF-36= Short Form-36.
[a] Difference (acetazolamide − placebo) of month 6 change adjusted for site, baseline quality of life value, and baseline Frisén grade in the study eye.

Functioning subscale (3.85 points; 95% CI 0.23–7.47; $p = 0.04$), and Mental Health subscale (9.82 points; 95% CI 3.51–16.14; $p = 0.003$). Treatment effects on the Neuro-Ophthalmic Supplement included those on the question about difficulty with activities in bright sunlight (8.76 points; 95% CI 0.53–17.00; $p = 0.04$) and the question about vision being blurry, not clear, or fuzzy (14.67 points; 95% CI 4.88–24.45; $p = 0.004$).

Changes in symptoms and signs associated with QOL changes at 6 months. Changes in several symptoms and signs were associated with changes in the QOL measures at 6 months after controlling for baseline QOL measure, treatment assignment, and baseline value of the relevant symptom/sign. Improvements in the NEI-VFQ-25 were associated with improvements in PMD in both the worst eye (1.5 points/dB; 95% CI 0.07–2.7; $p = 0.04$) and best eye (3.5 points/dB; 95% CI 1.0–6.0; $p = 0.006$). Comparing those with resolution of a symptom/sign present at baseline to those who developed the symptom/sign or remained stable, improvements in the NEI-VFQ-25 were associated with resolution of self-reported cognitive dysfunction (23.5 points, 95% CI 4.4–42.6; $p = 0.02$), dizziness/vertigo (10.5 points, 95% CI 0.4–42.6; $p = 0.04$), and transient visual obscurations (11.6 points, 95% CI 2.6–20.6; $p = 0.01$).

Improvements in the Neuro-Ophthalmic Supplement were associated with improvements in PMD in the worst eye (1.7 points/dB; 95% CI 0.2–3.2; $p = 0.03$) and best eye (3.1 points/dB, 95% CI 0.4–5.8; $p = 0.02$), resolution of transient visual obscurations (TVO) (9.9 points, 95% CI 1.1–18.8; $p = 0.03$), and improvement in the HIT-6 score (8.8 points, 95% CI 0.7–16.9; $p = 0.04$).

Improvement in the SF-36 PCS was associated with resolution of TVO (6.9 points; 95% CI 1.6–12.2, $p = 0.01$). No changes in symptoms/signs were associated with changes in the SF-36 MCS.

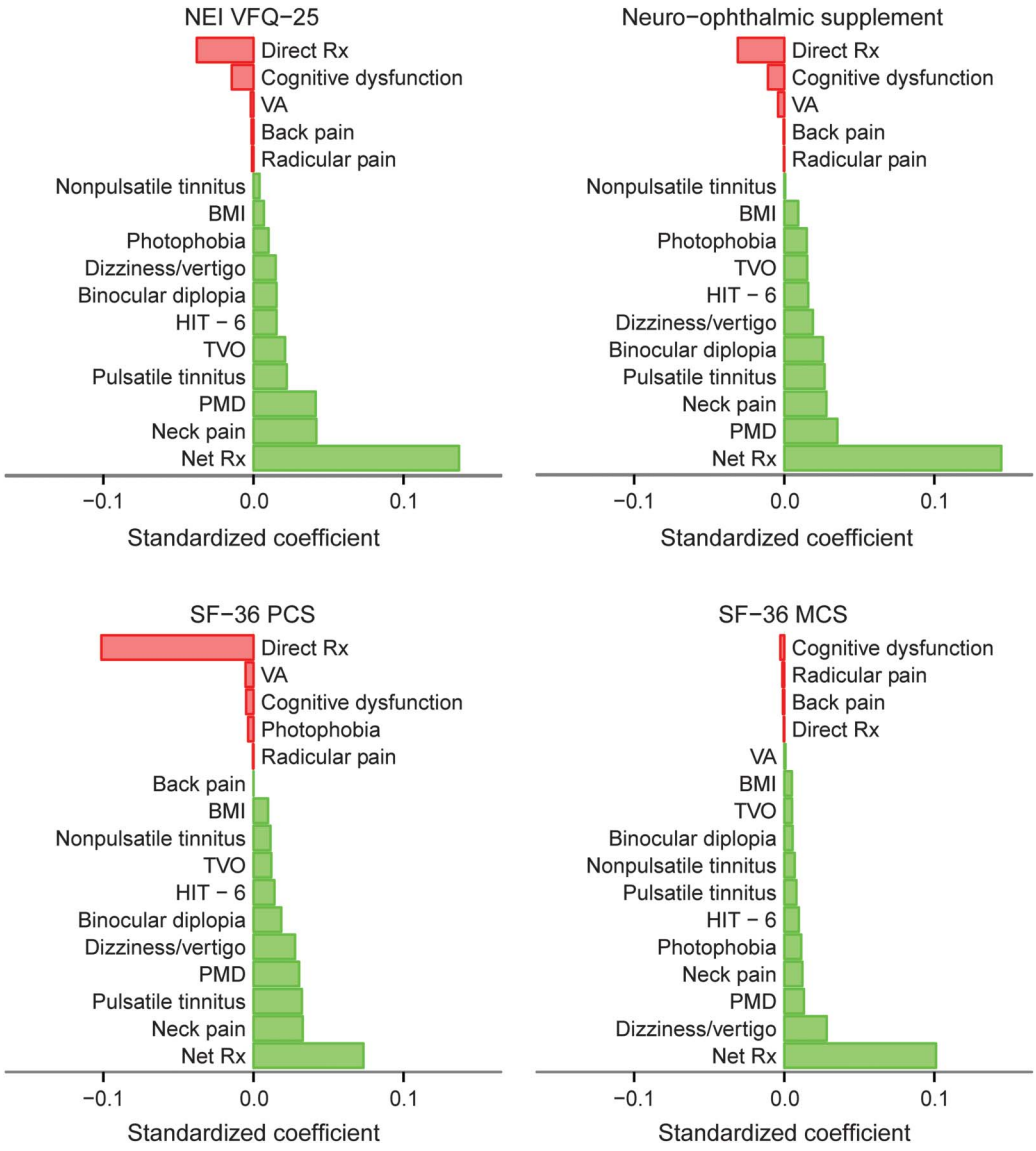
Changes in Frisén scale, BMI, back pain, neck pain, radicular pain, photophobia, tinnitus (pulsatile or nonpulsatile), binocular diplopia, and visual acuity were not significantly associated with QOL changes, nor were changes in CSF opening pressure, although only about half of our participants agreed to a lumbar puncture at 6 months.

Evaluation of which factors mediate the effect of acetazolamide on QOL. Exploratory analyses of symptoms and signs that potentially mediate the effect of acetazolamide on QOL were performed using structural equation models. Root mean square errors of approximation were <0.05 and the comparative fit indices were >0.95 for all of these models. Although none of the mediation effects were significant, net positive effects of treatment with acetazolamide on QOL were seen for all QOL measures, despite a negative direct effect of acetazolamide on QOL after accounting for the mediation of acetazolamide through the symptoms and signs of interest (figure 2 and table e-2). Effects of acetazolamide on neck pain, PMD, and pulsatile tinnitus were consistently the main positive mediators of acetazolamide's effects on QOL except with respect to the SF-36 MCS, for which effects on dizziness and vertigo were more important mediators of acetazolamide's positive effect on QOL than effects on pulsatile tinnitus. Acetazolamide's negative effects on cognitive function were relatively important for the NEI-VFQ-25 and Neuro-Ophthalmic Supplement in addition to the already noted negative direct effects of acetazolamide.

DISCUSSION In addition to the acetazolamide-related improvements in the 4 main QOL scales previously reported, we found positive effects of acetazolamide on the Near Activities, Social Functioning, and Mental Health subscales of the NEI-VFQ-25 and the questions about activities in bright sunlight and about blurry vision in the Neuro-Ophthalmic Supplement (table 1). The acetazolamide-related improvements in QOL appear most likely to be primarily mediated through improvements in visual field, neck pain, pulsatile tinnitus, and dizziness/vertigo. Although we were unable to identify any significant specific mediators of the effect of acetazolamide on QOL, our exploratory mediation analyses support the net positive effect of acetazolamide on QOL (figure 2) and suggest that this effect is mediated through positive effects of acetazolamide on most of the IIH-related symptoms and signs examined. These effects on the symptoms and signs of IIH outweighed the negative direct effects of acetazolamide on QOL (i.e., the effects of acetazolamide on QOL that remain after accounting for the effects of acetazolamide on IIH-related symptoms and signs). The negative direct effects are likely related to side effects of acetazolamide including paresthesia, dysgeusia, vomiting, diarrhea, and fatigue.[14–16] Side effects related to fatigue (experienced by 17% of participants on acetazolamide vs only 1% of the placebo group[16]) may partly explain the contribution that negative effects of acetazolamide had on QOL mediated by cognitive dysfunction and may also partly explain the negative direct effect of acetazolamide on the SF-36 PCS as physical functioning accounts for a considerable part of that scale's questions.

The most important mediating symptoms and signs were among those we found to be associated

Figure 2 Mediation of acetazolamide's effect on quality of life



Standardized coefficients of key symptoms and signs potentially affected by acetazolamide. In all cases, the net effect of acetazolamide (Net Rx) is positive (green), despite negative (red) direct effects (Direct Rx) that would generally be expected from the side effects of acetazolamide. BMI = body mass index; HIT-6 = 6-item Headache Impact Test; MCS = Mental Component Summary; NEI-VFQ-25 = 25-item National Eye Institute Visual Function Questionnaire; PCS = Physical Component Summary; PMD = perimetric mean deviation, best eye; TVO = transient visual obscurations; VA = visual acuity, worst eye.

with the NEI-VFQ-25 at baseline[1]: PMD, neck pain, and pulsatile tinnitus. In addition, dizziness/vertigo emerged as the most important mediator of acetazolamide-related improvement in the SF-36 MCS. While dizziness/vertigo was not a part of the final multivariate model at baseline for the NEI-VFQ-25, it had strong univariate associations with all the QOL scales at baseline,[1] and dizziness and vertigo have been found to lead to surprisingly large impairments in the SF-36 MCS.[17]

Other symptoms and signs at baseline that were associated with the NEI-VFQ-25, such as visual acuity, HIT-6 (headache), TVO, and binocular diplopia, were less frequently among the top symptoms and signs mediating acetazolamide-related changes in QOL in this study. The relatively low effect of headache as a mediator (based on the HIT-6) is explained by the lack of effect that acetazolamide had on headache in the IIHTT since similar improvements in headache were experienced by both the acetazolamide and placebo groups.[3] Even though the effect of acetazolamide on QOL did not appear to be mediated through its effect on TVO, improvements in TVO were associated with improvements in the NEI-VFQ-25, the Neuro-Ophthalmic Supplement, and the SF-36 PCS at 6 months, controlling for treatment. As in

the case of headache, this discrepancy between the symptom's association with QOL controlling for treatment vs its mediation of acetazolamide-related improvements in QOL is likely due to similar rates of improvement in TVO in the acetazolamide (49%) and placebo groups (43%).

Although obesity has been shown to be associated with lower QOL, we did not find BMI to be associated with the QOL of IIH patients either at baseline or at 6 months.[1] However, while the mean weight loss experienced by both groups was notable (−7.5 kg acetazolamide, −3.5 kg placebo), patients in both groups remained obese at the conclusion of this relatively short study (100.22 kg acetazolamide, 104.27 kg placebo), likely attenuating any mediating effects that improvements in weight would have had on QOL in the context of this study.[3]

Limitations of our study, in addition to those discussed above, include that multiple testing correction was not performed as part of our analyses. Likewise, none of the mediation effects of acetazolamide through signs and symptoms were significant. Thus, our results should be interpreted cautiously and will require further validation. However, the data provided by the IIHTT represent the highest quality evidence available concerning the effects of acetazolamide on various aspects of QOL in patients with mild visual loss. Finally, while the validated QOL questionnaires included many questions relevant to the visual and overall QOL of patients with IIH, they generally did not address typical side effects of acetazolamide (such as paresthesias, gastrointestinal symptoms, or changes in taste) that could have resulted in lower QOL at month 6 among treated patients if they had been assessed in the questionnaires. However, the maximum dosage administered was defined by protocol as that dosage for which side effects did not interfere with activities of daily living. Thus, we would expect the influence of side effects on QOL to be mild, because the dosage of acetazolamide would have been reduced in participants whose QOL was substantially affected.

QOL is markedly affected in untreated patients with mild visual loss from IIH at baseline, but treatment with acetazolamide results in marked improvements in QOL that appear to be primarily mediated through its effects on visual field, neck pain, pulsatile tinnitus, and dizziness/vertigo. The acetazolamide-related improvements in QOL outweigh its smaller negative effects on QOL, presumably from the side effects of the medication. When combined with improvements in visual field and other important aspects of IIH that are associated with acetazolamide treatment, our findings further strengthen the already substantial support from the IIHTT in favor of acetazolamide to augment dietary interventions in the treatment of IIH with mild visual loss.

AUTHOR CONTRIBUTIONS

Beau B. Bruce: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, statistical analysis, and obtaining funding. Kathleen B. Digre: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Michael P. McDermott: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Eleanor B. Schron: drafting/revising the manuscript, study concept or design, final approval, study supervision, and obtaining funding. Michael Wall: drafting/revising the manuscript, study concept or design, final approval, study supervision, and obtaining funding.

STUDY FUNDING

NIH 1U10EY017281-01A1 and 1U10EY017387-01A1; ARRA for NORDIC 3U10EY017281-01A1S1 and DCBC 1U10EY017387-01A1S1; supplements for NORDIC 3U10EY017281-01A1S2. Dr. Bruce was supported by K23EY019341 and by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY, to the Department of Ophthalmology at Emory University. Dr. Digre was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, NY, to the Department of Ophthalmology and Visual Sciences, University of Utah, Salt Lake City.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received February 8, 2016. Accepted in final form July 18, 2016.

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