REPORT

Noninvasive Vagus Nerve Stimulation in a Primary Care Setting: Effects on Quality of Life and Utilization Measures in Multimorbidity Patients With or Without Primary Headache

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ABSTRACT

A patient audit was conducted in the UK to evaluate the impact of gammaCore use in multimorbidity patients on quality of life and healthcare resources utilization measures. A total of 233 patients were enrolled and their data was examined over a 1-year period after their gammaCore prescription. Of these patients, 132 (56%) had primary headache disorders while 101 (44%) were patients without a headache disorder (nonheadache patients). The mean age was 49 years, 169 (72%) were female, the mean number of comorbid conditions was 3.1, and the mean baseline EQ-5D score was 0.581. The mean paired difference in EQ-5D index for persistent gammaCore users (ie patients who used gammaCore for at least 40 weeks) was +0.156 at week 40. The mean percentage reductions in number of general practice consults (doctor's office appointments) was –28.5% from baseline mean of 7.31 and, 40.0% from baseline mean of 3.52 for medical codes used. This evidence demonstrates that a significant proportion of these multimorbidity patients on gammaCore remained compliant with the prescribed treatment regimen for an extended period. GammaCore use in multimorbidity patients may be associated with lower costs of care and provide opportunities for pay-for-performance coverage policies.

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For author information and disclosures, see end of text.

The FDA cleared gammaCore (noninvasive vagus nerve stimulator, nVNS; electroCore Medical, LLC, Basking Ridge, NJ) for treatment of episodic cluster headache in 2017 and for the acute treatment of migraine in January 2018.[1,2] GammaCore also has 5 Conformité Européenne (CE) marks for primary headache disorders, bronchoconstriction, epilepsy, gastric motility disorders, depression, and anxiety. These are symptoms associated with medically unexplained symptoms (MUS) in adults.[3,4] GammaCore has shown efficacy in numerous pilot and double-blind, sham-controlled studies in episodic cluster headache and episodic migraine populations. The device is safe, practical, and convenient.[5,6] Patients with primary headache disorders have associated multiple comorbidities at a higher rate than those without headache disorders. Their overall medical costs are between 2 and 3 times the average patient without headaches.[7-9] Guidelines published by The National Institute for Health and Care Excellence (NICE) describe the need to optimize care of patients with multiple comorbid conditions to improve patient quality of life (QOL) and reduce healthcare utilization.[10] In the United Kingdom (UK), approximately 25% of all general practice (GP) consults (doctor's office appointments), and 25% of all hospital referrals (to specialists) are generated by 10% of the adult population with MUS or "functional disorders."[10,11] These patients typically suffer from 3 or more concurrent illnesses falling into the following categories: primary headache disorders, gastric motility disorders, anxiety, depression, and widespread chronic pain.[11] GammaCore may have the potential to treat multiple MUS symptoms.[12-14] We conducted an audit of patients with multiple symptoms who were prescribed gammaCore and their data examined for up to 1 year, documenting their experiences, QOL, and healthcare utilization measures, including EQ-5D index, GP consults, referrals, diagnosis codes, and need for sick notes. The aim of this audit was to evaluate the impact of gammaCore use in the real-world primary care setting.

Methods

An audit of medical records of patients who were invited to participate and subsequently prescribed gammaCore for multimorbidity disorders in the UK was conducted.

Patient Population and Exclusion Criteria

Seven primary care practices in northern UK participated. Eligible patients were adults aged 18 to 70 years diagnosed with and coded for 2 or more of the following conditions: primary headache; gastric motility disorders; anxiety and depression; chronic pain; sino-bronchial symptoms; tinnitus; epilepsy; and insomnia. Eligible individuals were identified and invited to participate via physical mail requests. Patients were excluded if they had metallic implants, including but not limited to stents, bone plates, or bone screws, at or near the treatment site; an active implantable medical device, such as a pacemakers, defibrillators, cochlear implants, and other implanted electronic devices; and a history of significant carotid atherosclerosis; cervical vagotomy. Also excluded were pregnant women (women were advised to discontinue treatment if they became pregnant during the course of the observation period); patients with active cancer or cancer in remission; and patients with clinically significant hypertension, hypotension, bradycardia, or tachycardia.

Definitions

The following definitions are used in the context of this publication: *gammaCore* refers to the use of a proprietary externally applied device that stimulates the vagus nerve noninvasively (transcutaneously); *gammaCore dose* refers to 2 stimulations of gammaCore (nVNS) administered bilaterally (one on each side). Patients used 3 doses a day; *persistent gammaCore users* refer to patients who were prescribed and adhered to gammaCore regimen consistently for at least 40 weeks (n = 61); *QOL measures* refer to EQ-5D index; *healthcare resources utilization measures (*or *"utilization")*, refers to numbers of GP consults, referrals and diagnosis codes used; *productivity measures* refers to number of sick notes issued; *last observation carried forward (LOCF) analysis* refers to longitudinal analysis of all patients (n = 233) qualified to participate in the audit (given device and attended 2 in-person visits at baseline and at 4 weeks) comparing *QOL, utilization*, and *productivity* measures of the last observed visit up to week 40 to baseline; and *persistent gammaCore user analysis* refers to longitudinal analysis of only the patients meeting the *persistent gammaCore users* definition above (n = 61) comparing *QOL, utilization*, and *productivity* measures at week 40 to baseline.

Approach

All eligible patients were invited by mail to present to participating clinics. After explanations on procedures and providing informed consent, patients willing to use gammaCore as an adjunct to their current treatment regimens were prescribed and trained to use gammaCore, given the device to take home, and advised to administer a stimulation bilaterally for 3 times a day for a total of 6 stimulations in 12 minutes. Participating patients completed a health-related QOL (EQ-5D-5L) questionnaire at baseline. A second in-person clinic visit 4 weeks after baseline while on gammaCore was required to complete eligibility. During the second visit, stimulation technique was verified and corrected accordingly, adherence to therapy was assessed, and an opportunity to address any questions that patients may have was given. Details of GP consults, referrals, diagnosis codes used during provider engagements, and sick notes issued were collected from patient records. Patients completed the EQ-5D-5L questionnaire every 4 weeks. Changes in QOL, utilizations, and productivity measures were calculated by comparing EQ-5D entries, numbers of GP consults, referrals, diagnosis codes used, and sick notes issued during the last 4-week observation interval and baseline 4-week interval.

Statistical Analyses

Descriptive statistics were used to compare patient reported health outcomes before and after gammaCore use. Means (standard deviation) and frequency (percentage) were used to characterize continuous variables and binary/categorical variables respectively for baseline characteristics. Paired differences of the EQ-5D index, EQ-5D individual components, number of GP consults, referrals, diagnosis codes used, and sick notes issued were calculated using paired T-test for *LOCF analyses* (n = 233) and *persistent gammaCore user analyses* (n = 61) as defined previously in this paper. Statistical significance for the paired t-test was set at $P < .05$. Analyses were performed for all patients as well as sub-group analyses for patients with primary headache diagnosis (n = 132 for *LOCF analysis* and n = 37 for *persistent gammaCore user analysis*) and nonheadache patients (n = 101 for *LOCF analysis* and n = 24 for *persistent gammaCore user analysis*). No formal comparisons were made between the primary headache and nonheadache patient subgroups.

Results

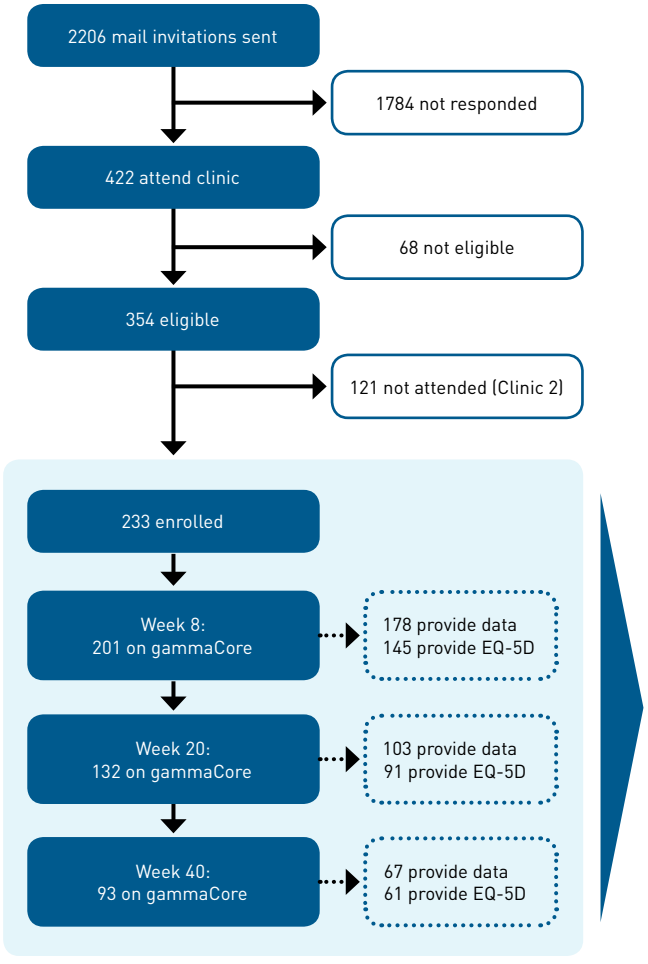
Patient Attrition

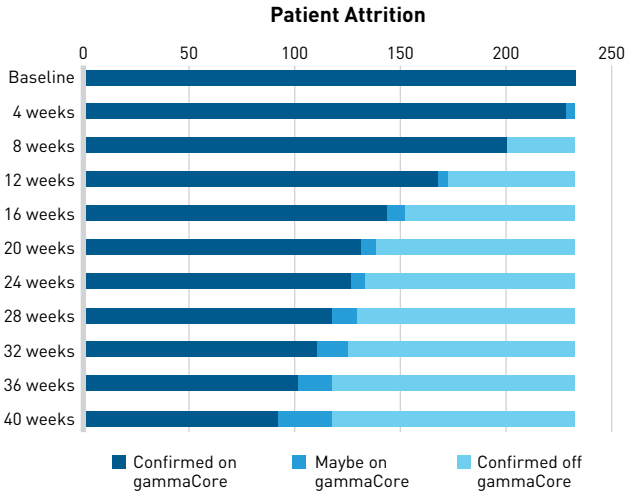
A total of 2206 mail invitations were sent to potential participants that were identified via chart review as adults diagnosed with 2 or more disorders of interest. Of these, 422 (19.1%) patients attended the first clinic visit, with 354 (83.9%) of these patients being eligible to participate and prescribed gammaCore therapy. Of the 354 patients, 233 (65.8%) attended the second (at week 4) in-person clinic visit while on gammaCore and were included. At week 8 and week 40 after initiating gammaCore, 201 (86.3%) and 93 (39.9%) patients remained on gammaCore treatment, respectively, and 145 (62.2%) and 61 (26.2%) patients reported their EQ-5D-5L outcomes, respectively, with 134 (58%) patients continuing therapy beyond 6 months.[15] Patient attrition is illustrated in **Figures 1a** and **1b** for procedures and gammaCore use, respectively.

Baseline Characteristics

At the time of their baseline evaluation (n = 233), the mean age was 49 years, 169 (72%) were female and 132 (56%) were multimorbidity patients that included a primary headache diagnosis code, while 101

FIGURE 1A. Patient Attrition in Procedures





(44%) did not include any primary headache diagnosis (nonheadache patients). Of the 233 patients, 83% had anxiety or depression, 47% had gastric motility disorders, 39% had chronic pain, 52% had sino-bronchial symptoms, 21% had insomnia, and fewer than 10% had tinnitus and epilepsy. The mean number of comorbid conditions was 3.1, with 78 (33%) patients having 1 to 2 comorbid conditions, 130 (56%) having 3 to 4 comorbid conditions, and 25 (11%) having 5 or more comorbid conditions. The mean baseline EQ-5D index for all patients was 0.581, and the total mean number of consults, referrals, codes used, and sick note requests between baseline and week 4 visits together with other patient baseline characteristics for primary headache, nonheadache, and all patients are shown in **Table 1**.

GammaCore Adherence and EQ-5D Index Trends

Participants were followed between 4 to 60 weeks with a median follow up duration of 28 weeks. Patient self-reported adherence to gammaCore use after the week 4 visit, who continued gammaCore

FIGURE 1B. Patient Attrition on gammaCore Treatment

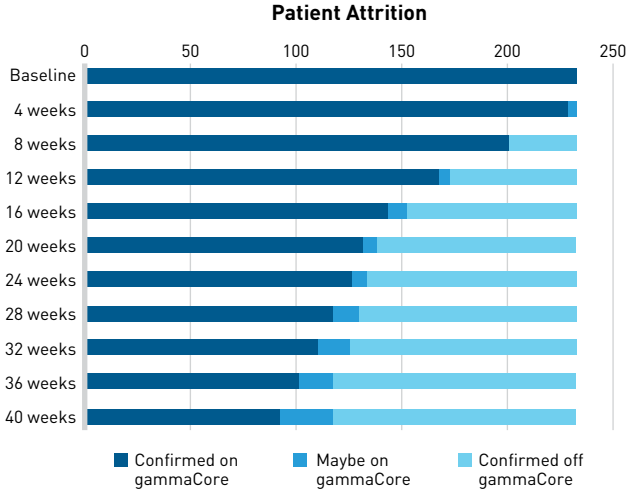


TABLE 1. Baseline Patient Characteristics, Occurrence of Comorbid Conditions, QOL Measures, and Utilization Measures

	Primary Headache Patients (n = 132)	Nonheadache Patients (n = 101)	All Patients (n = 233)
Age, mean	48.23 (12.13)	50.31 (12.05)	49.13 (12.11)
Female, n (%)	103 (78.03)	66 (65.35)	169 (72.53)
Comorbidities, n (%)			
Headache	132 (100)	—	132 (56.65)
Anxiety/depression	102 (77.27)	91 (90.10)	193 (82.83)
Sino-bronchial symptoms	63 (47.73)	57 (56.44)	120 (51.50)
Gastrointestinal disorders	58 (43.94)	52 (51.49)	110 (47.21)
Chronic pain	50 (37.88)	41 (40.59)	91 (39.06)
Insomnia	26 (19.70)	23 (22.77)	49 (21.03)
Tinnitus	7 (5.30)	10 (9.90)	17 (7.30)
Epilepsy	2 (1.52)	3 (2.97)	5 (2.15)
Comorbidity count, mean	3.33 (1.19)	2.74 (0.91)	3.08 (1.12)
Comorbidity count, n (%)			
1-2	34 (25.76)	44 (43.56)	78 (33.48)
3-4	75 (56.82)	55 (54.46)	130 (55.79)
>5	23 (17.42)	2 (1.98)	25 (10.73)
EQ-5D-5L index, mean	0.61 (0.25)	0.54 (0.28)	0.58 (0.27)
Utilization measures, first 4 weeks			
Total counts (mean)			
Consults	539 (4.08)	416 (4.12)	955 (4.10)
Referrals	107 (0.81)	74 (0.73)	181 (0.78)
Medical codes used	292 (2.21)	183 (1.81)	475 (2.04)
Sick notes issued	82 (0.62)	46 (0.46)	128 (0.55)

QOL indicates quality of life.

Changes in Utilization and Productivity Measures

In *LOCF analysis*, the mean percentage changes observed for all patients in number of consults and referrals were -19.3% (P <.001) from baseline mean of 4.10, and -23.2% (P =.02) from baseline mean of 0.78, respectively. The mean percentage change observed for primary headache patients in number of GP consults was -20.4% (P =.004) from baseline mean of 4.08. The mean percentage changes observed for nonheadache patients in number of GP consults and referrals were -17.8% (P = .05) from baseline mean of 4.12, and -36.5% (P = .04) from baseline mean of 0.73, respectively.

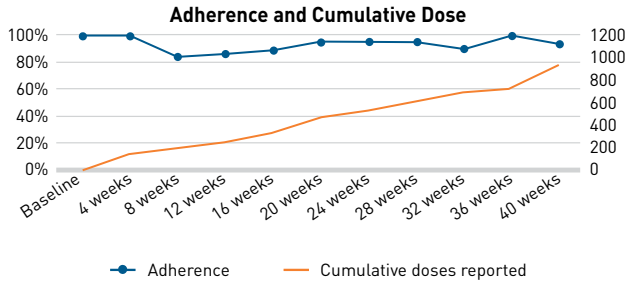
In *persistent gammaCore user analysis*, mean percentage changes observed for all patients in number of GP consults and medical codes used were -28.5% (P = .002) from baseline mean of 7.31 and -40.0% (P = .002) from baseline mean of 3.52, respectively. The mean percentage changes observed for primary headache patients in number of GP consults, medical codes and sick notes issued were -29.5% (P = .01) from baseline mean of 6.41, -38.8% (P = .04) from baseline mean of 3.41, and -34.6% (P = .06) from baseline mean of 0.78, respectively. The mean percentage changes observed for nonheadache patients in the number of GP consults and medical codes were -37.3% (P = .06) from baseline mean of 8.71 and -41.5% (P = .01) from baseline mean of 3.71, respectively. These findings are shown in **Table 2**.

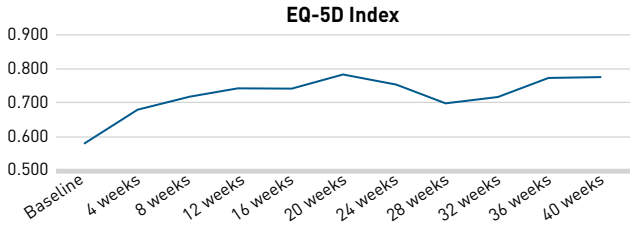
treatment was between 84% and 100% of patients complying to the prescribed gammaCore regimen as evaluated at the respective timepoints with the mean cumulative doses of gammaCore used, increasing to 955 doses at 40 weeks. In the *LOCF analysis*, the mean difference in EQ-5D index was +0.114 (P <.001) for all patients (n = 233), +0.113 (P <.001) for primary headache patients (n = 132), and +0.114 (P <.001) for nonheadache patients (n = 101). In the *persistent gammaCore user analysis*, the mean EQ-5D index increased from 0.58 at baseline to 0.74 at 12 weeks (n = 125) after which the index plateaued and was 0.77 at week 40 (n = 61). The increase in the EQ-5D index at week 40 (n = 61) was +0.156 (P <.001) for all patients, was +0.151 (P <.001) for primary headache patients (n = 37) and was +0.164 (P <.001) for nonheadache patients (n = 24). These findings for all primary headache and nonheadache patients are shown in **Figures 2a**, **2b**, and **2c**.

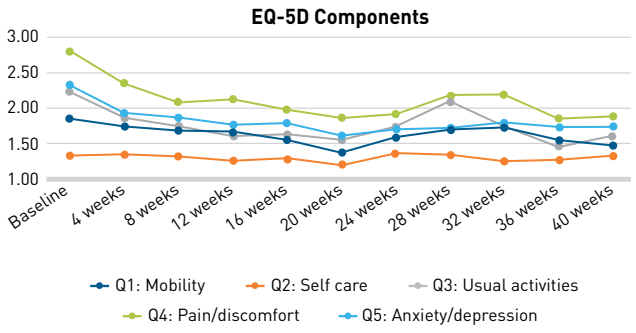
Changes in Utilization Measures by GammaCore Use Patterns

Of the 233 participants, the mean number of baseline GP consults were 7.3 versus 4.0 versus 1.0, respectively (P <.001) for persistent gammaCore users (n = 61), patients who used gammaCore for more than 4 weeks but less than 40 weeks (n = 111), and patients who used gammaCore for just 4 weeks (n = 61) respectively; number of baseline referrals were 1.1 versus 0.9 versus 0.2, respectively (P <.001); and number of baseline diagnosis codes used were 3.5 versus 2.0 versus 0.6, respectively (P <.001). The observed mean changes among persistent gammaCore users who used gammaCore for more than 4 weeks but less than 40 weeks and patients who used gammaCore for just 4 weeks were –2.08 versus –0.36 versus –0.27 respectively for number of GP consults (P = .003); –0.30 versus –0.21 versus 0.00 (no change) respectively for number of referrals (P = .33); and –1.41

FIGURE 2A. Clockwise: Patient Adherence and Cumulative Doses of gammaCore; EQ-5D Index Trend, EQ-5D Components Trends and Changes in EQ-5D Index and EQ-5D Components From Baseline to Week 40 for All Patients



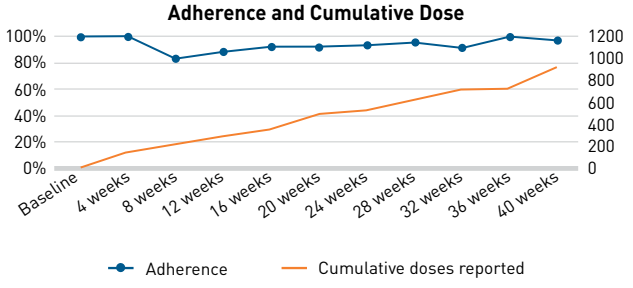


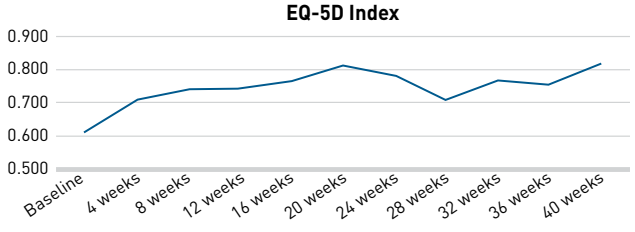


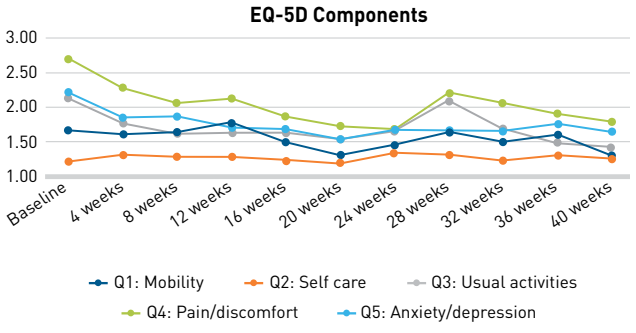
EQ-5D Index (n = 61)	Mean Changes	*P*
Ql: Mobility	-0.13	.21
Q2: Self-care	0.08	.36
Q3: Usual activities	-0.52	.01
Q4: Pain/discomfort	-0.77	<.001
Q5: Anxiety/depression	-0.38	.01
EQ-5D score	+0.156	<.001

*Ql-Q5 based on scale 1 (best) to 5 (worst);
**Paired T-test of baseline to 40 weeks

FIGURE 2B. Clockwise: Patient Adherence and Cumulative Doses of gammaCore; EQ-5D Index Trend, EQ-5D Components Trends and Changes in EQ-5D index and EQ-5D Components From Baseline to Week 40 for Primary Headache Patients



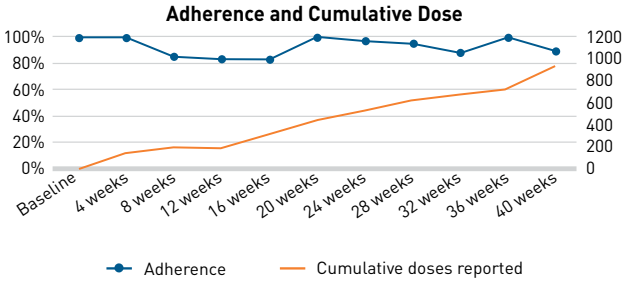


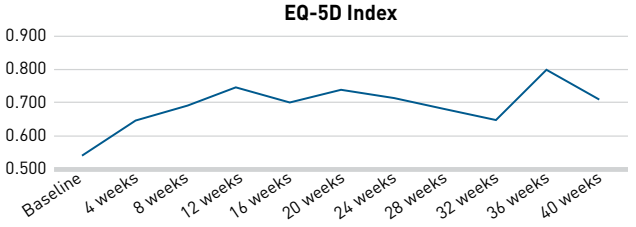


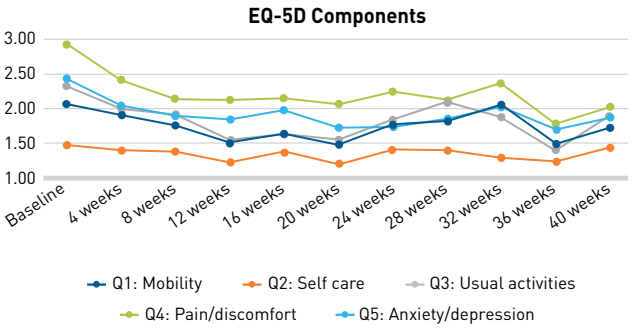
EQ-5D Index (n = 37)	Mean Changes	*P*
Ql: Mobility	-0.05	.49
Q2: Self-care	0.03	.79
Q3: Usual activities	-0.54	.02
Q4: Pain/discomfort	-0.81	<.001
Q5: Anxiety/depression	-0.27	.07
EQ-5D score	+0.151	<.001

*Ql-Q5 based on scale 1 (best) to 5 (worst);
**Paired T-test of baseline to 40 weeks

FIGURE 2C. Clockwise: Patient Adherence and Cumulative Doses of gammaCore; EQ-5D Index Trend, EQ-5D Components Trends and Changes in EQ-5D Index and EQ-5D Components From Baseline to Week 40 for Nonheadache Patients







EQ-5D Index (n = 24)	Mean Changes*	*P***
Ql: Mobility	-0.25	.3
Q2: Self-care	0.17	.33
Q3: Usual activities	-0.50	.12
Q4: Pain/discomfort	-0.71	.005
Q5: Anxiety/depression	-0.54	.06
EQ-5D Score	+0.164	.015

*Ql-Q5 based on scale 1 (best) to 5 (worst);
**Paired T-test of baseline to 40 weeks

TABLE 2. Changes in EQ-5D Index, Consults and Referrals for Last Observation Carried Forward Analysis (LOCF: n = 233) and Persistent gammaCore Users Analysis (n = 61) Compared With Baseline

	Last Observation Carried Forward Analysis (n = 233)					
	Primary Headache Patients (n = 132)		Nonheadache Patients (n = 101)		All Patients (n = 233)	
	Observed change	*P*	Observed change	*P*	Observed change	*P*
EQ-5D index, mean change	0.113	<.001	0.114	<.001	0.114	<.001
Utilization and productivity						
Mean at baseline						
Consults	4.08	—	4.12	—	4.10	—
Referrals	0.81	—	0.73	—	0.78	—
Medical codes used	2.21	—	1.81	—	2.04	—
Sick notes issued	0.62	—	0.46	—	0.55	—
Mean change* (% change)						
Consults	−0.83 (-20.4%)	.004	−0.73 (-17.8%)	.05	−0.79 (-19.3%)	<.001
Referrals	−0.11 (-14.0%)	.20	−0.27 (-36.5%)	.04	−0.18 (-23.2%)	.02
Medical codes used	−0.25 (-11.3%)	.33	−0.28 (-15.3%)	.18	−0.26 (-12.8%)	.13
Sick notes issued	−0.08 (-13.4%)	.58	−0.16 (-34.8%)	.50	−0.12 (-21.1%)	.38

(continued)

versus +0.31 versus -0.14 respectively for number of diagnosis codes used (P <.001). These findings are illustrated in **Figure 3**.

Discussion

This analysis shows that a significant proportion of multimorbidity patients with MUS were persistent and adherent with gammaCore for more than 6 months. It also demonstrated that those considered high-demand patients (ie, those who had the highest healthcare resource utilization at baseline) were more likely to become the persistent gammaCore users and experienced the most robust improvements in QOL and reductions in utilization. Therefore, the high-demand patents that needed gammaCore the most were self-selecting and benefited from the greatest reduction in symptoms and health resource utilization. The gammaCore response was rapid and observed within 2 to 3 months of initiating treatment. The impact of gammaCore in patients with multiple comorbid conditions were somewhat similar among those with or without a primary headache disorder, indicating its potential suitability for any patient with comorbidities. This observation may be due to an existing common, yet unexplained pathology associated with vagal tone insufficiency or some other latent causation, that is potentially highlighted in those who benefited most dramatically due to persistent gammaCore use. The significant reduction in the utilization measures (–29%) and symptom codes used (–40%) among persistent gammaCore users suggest that nVNS may result in significantly lower healthcare costs and allow the potential for an effective pay-for-performance (value-based) platform for insurance coverage policies in the United States and similar healthcare environments.

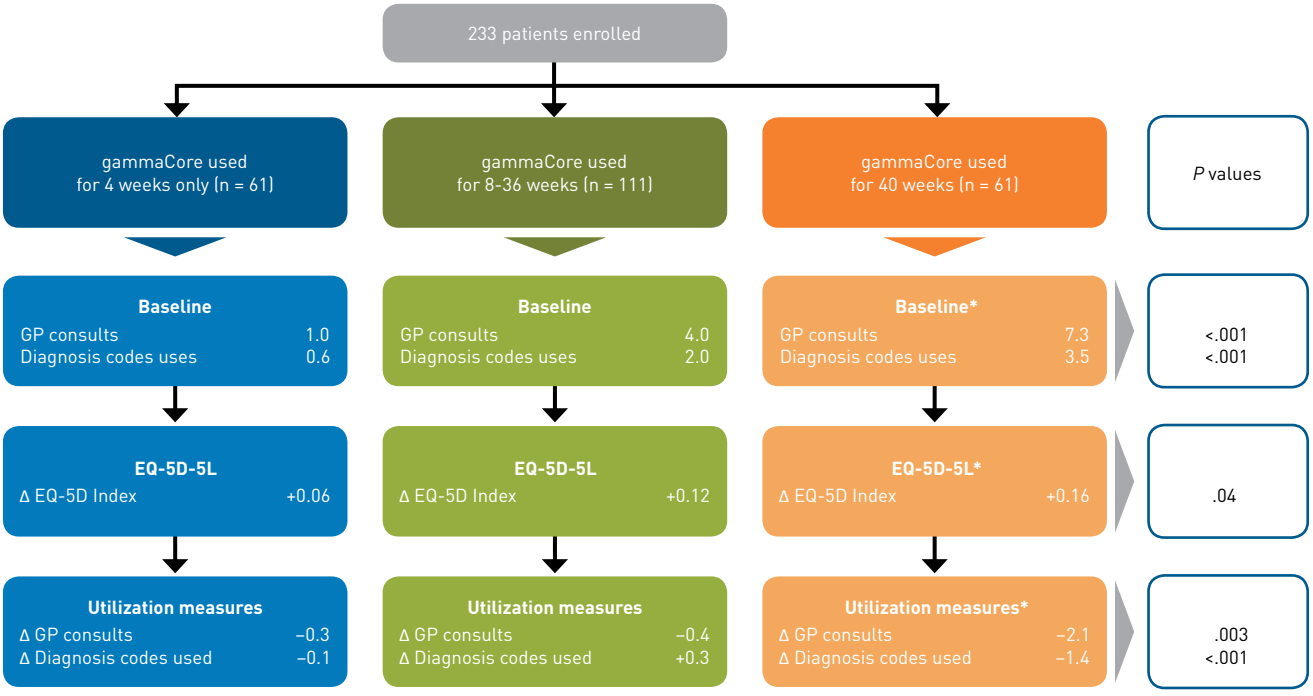
These findings represent real-world evidence based on practical observations without strict clinical study requirements and designed to show how patients will respond to gammaCore use now that the device is being launched more broadly. We believe this is the first piece of evidence characterizing the effect of gammaCore in documented multimorbidity patients. Multimorbidity patients with MUS, who typically represent high-demand patients, can cost payers up to 3 times than patients without MUS and related comorbidities.[7-9,16] The observed reduction in utilization (ie, the reduction in GP consults and number of diagnosis codes used) translates to a significant decrease in the costs associated with fewer GP visits, fewer laboratory tests, fewer requests for imaging diagnostic tests, and a decrease in a range of other related costs. The choice to use the number of GP consults, referrals, diagnosis codes used, and sick notes issued as measures of utilization and productivity was dictated by previously published studies and the availability of data in these primary care clinics.[16] In considering the reduced GP consults (–30%) for which patients seek care for fewer diagnosis codes (–40%), it is reasonable to conclude that the additive effects could result in significantly lower future cost of care, reduced by as much as 50% (at least more than 30% or 40% in this case) and these savings may be more dramatic if there are subsequent reductions in laboratory and imaging test requests. This would be supported in findings by Polson et al (2018), demonstrating that in migraine

TABLE 2. *(Continued)* Changes in EQ-5D Index, Consults and Referrals for Last Observation Carried Forward Analysis (LOCF: n = 233) and Persistent gammaCore Users Analysis (n = 61) Compared With Baseline

	Persistent gammaCore User Analysis ** (n = 61)					
	Primary headache patients (n = 37)		Nonheadache patients (n = 24)		All patients (n = 61)	
	Observed change	*P*	Observed change	*P*	Observed change	*P*
EQ-5D index, mean change	0.151	<.001	0.164	.015	0.156	<.001
Utilization and productivity						
Mean at baseline						
Consults	6.41	—	8.71	—	7.31	—
Referrals	1.001	—	1.29	—	1.11	—
Medical codes used	3.41	—	3.71	—	3.52	—
Sick notes issued	0.78	—	0.29	—	0.59	—
Mean change* (% change)						
Consults	–1.89 (-29.5%)	.01	–2.38 (-27.3%)	.06	–2.08 (-28.5%)	.002
Referrals	–0.16 (-16.0%)	.35	–0.50 (-38.8%)	.17	–0.30 (-27.0%)	.09
Medical codes used	–1.32 (-38.8%)	.04	–1.54 (-41.5%)	.01	–1.41 (-40.0%)	.002
Sick notes issued	–0.27 (-34.6%)	.06	0.17 (-58.6%)	.56	–0.10 (-16.9%)	.48

*LOCF last 4 weeks period frequencies compared to first 4 weeks; ** Week 40 assessment

FIGURE 3. *Persistent gammaCore Users Who Adhered to Treatment Were High-demand Patients at Baseline With Mean 3 Comorbidities, Highest Rates of GP Consults and Seeking Treatment for Highest Number of Symptoms but Experienced the Most Robust Benefit



GP indicates general practitioner.

patients with other MUS, there were higher utilization rates and the costs associated with the individual utilization events (eg, doctors' visits, laboratory tests, imaging tests, emergency department [ED] visits) were higher for migraine/MUS patients than controls.

Of the 233 patients prescribed gammaCore, 93 patients (40%), a significant proportion, who persisted on gammaCore for up to 40 weeks with associated benefits, suggest clinical effectiveness. The voluntary persistence and adherence to gammaCore among the patients are indications that patients identified and appreciated measurable clinical and QOL benefits. The patients who persisted on and adhered to gammaCore were self-driven and self-selective and not dictated by a study protocol. This suggests that the observed rate of persistent use was very high and likely facilitated by the alleviation of symptoms together with ease of use, safety, practicality of gammaCore use, and offers robust evidence supporting the persistent use of gammaCore in the real world. This has been documented in primary headache studies.[13,17-19] Patients benefited in a range of meaningful ways, including improvements in QOL measured using the validated EuroQol EQ-5D-5L index instrument.[15] Patients showed significant benefits in questions in the EQ-5D instrument pertaining to usual activities, pain and discomfort, and anxiety and depression, but not in mobility or self-care. These observations align well with illness profiles of the patients included and further validate the patterns elicited for this population. These patients typically are relatively healthy physically and can take care of themselves. Therefore, even at baseline, these patients understandably scored well on mobility or self-care. Typically, the symptoms for these comorbid functional disorders of MUS predominantly affect activities of daily living, such as employment, exposure to pain, or anxiety/depression. Accordingly, at baseline, these patients scored poorly on usual activities, pain and discomfort, and anxiety and depression. This is consistent in our results, in which a significant response to gammaCore use was observed. Our interpretation is that persistent gammaCore use resulted in improved symptoms to the extent that it reduced the need for patients to seek as many GP consults and to seek treatment for fewer symptoms in their last 4 weeks compared to their respective initial 4 weeks and required fewer sick notes. Persistent gammaCore users benefited the most in those measures and even though the numbers of patients (n = 61 for all patients; n = 37 for primary headache patients; and n = 24 for nonheadache patients) were small, the findings were even more clinically and statistically significant. Of note, the improvements in QOL among the persistent gammaCore users were rapid and most dramatic in the initial 2 to 3 months and then sustained, thus, perpetuating the voluntary persistence and adherence to gammaCore. Those not experiencing the benefit within this time frame likely opted to stop treatment.

Our findings have implications for primary headache indications. The rapid responses observed among both primary headache and nonheadache patients for QOL and healthcare resource utilization measures were similar. This observation aligns with the hypothesis that many primary headache patients, such as those suffering from migraine and cluster headache, have an underlying pathology associated with vagal insufficiency or other latent causation. Patients with migraine and cluster headache seek more medical services (physician and ED visits and laboratory and imaging testing) than the general population, and the average cost of each of these visits and tests cost more for patients with migraine.[8] When gammaCore treatment is used, even for primary headache indications, and enhances vagal tone, these multiple comorbidities are improved, resulting in a reduction in healthcare utilization and the cost of care. Both primary headache and nonheadache patients self-identified through symptom relief within 2 to 3 months and uniquely for gammaCore. The lack of response within this period was associated with treatment termination. Nonresponders are identified early and can stop treatment, and associated costs, within 2 months, saving payers unnecessary costs and are considered for cost-saving pay-for-performance insurance coverage policies. Additionally, the significant improvements in QOL is associated with better long-term quality adjusted life years, a key metric for utilities in cost effectiveness analyses as recognized by NICE and payers in the United States and globally. This new evidence demonstrates gammaCore treatment that can save payer costs and reduce future costs. This will be critical in supporting cost-effectiveness analyses and budget impact models for assessing the economic value of gammaCore use in practice and coverage policies, and could form the basis of future practice guides, policy, and research.

The strengths of these analyses are that these are real-world data on persistent gammaCore users and were gathered from patients with no strict or limiting research criteria. The sample size that used gammaCore was reasonable (N = 233), allowing for relevant analyses and inferences to be drawn about gammaCore treatment and were based on statistically significant findings. Multimorbidity MUS patients with and without primary headache diagnoses were included to allow into the unknown latent causation associated with the multiple comorbid conditions. These findings offer new evidence to support future practice guides, policy decisions, and research into the economic benefits of persistent gammaCore use. One of the limitations is the relatively small sample size that may not allow extensive examination of predictors, but nonetheless, provided robust, statistically significant findings.

Conclusions

This evidence suggests that gammaCore may be an effective treatment in functional / MUS multimorbidity patients with or without primary headache that likely suffer from vagal tone insufficiency or a pathology responsive to vagus nerve stimulation. Persistent gammaCore users were high-demand patients with high healthcare resource utilization at baseline who benefited the most with significant reductions in symptoms and utilization. This evidence supports findings of the clinical studies in cluster headache and migraine patients, mode of action models, and the proposition for gammaCore's value on cost reduction. Further study of the economic impact of gammaCore in a randomized, controlled environment is needed to assess the cost-effectiveness of gammaCore and associated budget impact, if adopted in health insurance coverage policies in multimorbidity patients. ■

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