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Efficacy and tolerability of Generic Brivaracetam (Bevanta) on Drug Resistant Epilepsy patients in Babil Neurology Center (A single Center experience)

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Abstract :

Background: Brivaracetam (BRV) a third-generation Antiseizure medication (ASM) from a Racetam group structurally related to its predecessor Levetiracetam but has a higher affinity and selectivity to synaptic vesicle protein 2A (SV2A) with fewer psychiatric and behavioral adverse effects. It is primarily approved for focal seizures with or without generalization but more and more growing evidence about its efficacy in Primary generalized seizures as well, and owing to its favorable pharmacokinetic properties, low drug-drug interactions and its unique mechanism of action that makes it a favorable option in patients with drug-resistant epilepsy (DRE).

Objective: To evaluate the effectiveness, tolerability, treatment retention, and impact on quality of life of generic Brivaracetam (Bevanta) in patients with DRE in routine clinical practice in Iraq.

Methods : Retrospective clinically based real-world Study were records of 68 patients with drug-resistant epilepsy treated with generic BRV in Babil Neurology

Center/Epilepsy Clinic between January 2025 and May 2026 were collected. 63 Patients were included and followed for up to 15 months. Treatment response was defined as a ≥50% reduction in seizure frequency from baseline. Seizure freedom, treatment retention, treatment-emergent adverse events (TEAEs), previous Levetiracetam (LEV) exposure and intolerance, and quality-of-life changes were assessed.

Results: Sixty-three patients were included, 54.0% female, with a median age of 24 years (range, 3–80). The mean number of previous and current ASMs was 3.9 and 2.4, respectively. Focal-onset seizures were predominant (68.3%), and 95.2% of patients had previous LEV exposure. Response rate ≥50% among patients retained on BRV were 43.6%, 46.7%, 44.6%, and 48.9% at 3, 6, 12, and 15 months, respectively. Seizure freedom was achieved in 4.8%, 6.8%, 10.7%, and 10.6%. BRV retention rates were 93.7%, 82.5%, 58.7%, and 57.1%, respectively. Overall, 34.9% of patients reported at least one Treatment Emergent Adverse Events (TEAE), most commonly non Psychiatric Adverse Events 16 (25.4%), while psychiatric adverse events were less frequent 6 (9.5%). Quality of life improved in 58.7% of patients, with significantly greater improvement among responders ($p<0.0001$). Treatment response was significantly associated with mental status ($p=0.005$), epilepsy etiology ($p=0.003$), and neuroimaging findings ($p=0.02$), but not seizure type ($p=0.52$).

Conclusions: The generic Brivaracetam (Bevanta) has noticeable efficacy in DRE whether Focal or Generalized types with low potentials for serious side effects and good Retention Rates and positive impact on quality of life and considered as a good alternative to Levetiracetam Psychiatric Adverse Effects, or Failure, and the main limitations in its wide use due to its coast and affordability and availability issues. And its best synergistic combination is with Lacosamide.

Keywords: Brivaracetam, Drug-resistant epilepsy, Real-world experience, Levetiracetam

INTRODUCTION

Epilepsy is one of the most common neurologic diseases, affecting over 65 million .People worldwide.(1) Despite advances in pharmacotherapy, nearly 30% of patients continue to experience seizures despite adequate treatment with at least two appropriately chosen ASMs, thereby fulfilling the definition of drug-resistant epilepsy (DRE).(2) DRE is associated with cognitive decline, reduced quality of life, and increased mortality, underscoring the urgent need for effective therapeutic alternatives.(٣, 4) Furthermore,

many patients suffer from side effects of AEDs, which are responsible for the poor adherence and discontinuation of therapy, resulting in increased risk of uncontrolled seizures and death Therefore, research aimed at developing new AEDs with improved efficacy and tolerability profiles continues.(5)Brivaracetam (BRV) is a third- generation ASM developed as a prolyl analogue of its predecessor Levetiracetam (LEV).(6) BRV was identified in a large drug discovery effort to develop molecules with greater binding affinity and selectivity to SV2A than LEV. (7, 8) BRV has approximately 15- to 30-fold higher affinity to SV2A than LEV and its ability to inhibit vesicle release is superior to LEV.(9,10) Its action is more selective than that of LEV because it does not affect any other targets, unlike LEV, which also acts at the AMPA glutamatergic postsynaptic receptor and at the presynaptic calcium channel.(11) BRV has a favorable PK profile and is rapidly absorbed after single and multiple oral doses, with a median time to maximum concentration of approximately 1 h.(12,13) It has a Rapid Blood-Brain Barrier (BBB)Penetration due to its high lipophilicity it crosses the BBB extremely quickly via passive diffusion . It engages with its target –synaptic vesicle protein 2A (SV2A) - within minutes of administration, resulting in a rapid onset of clinical effect. (14, 15) It exhibits linear and dose-proportional PK across a range of doses which far exceed the therapeutic ones. (12, 16) It has little protein binding (< 20%), and its distribution volume is slightly lower than the total volume of body water. (13, 17) This significantly reduces the risk of competitive displacement interactions with highly protein-bound medications. (18, 14) It has a favorable Half-Life and Clearance with a terminal elimination half –life of approximately 7 to 9 hours, which remains stable regardless of the dose size. Clearance is mainly driven by hepatic metabolism (14, 19) unlike some other ant seizure medications (ASMs) BRV is bio transformed primarily through CYP-independent hydrolysis into three completely inactive metabolites. Only about 8% to 11% is excreted unchanged in the urine. (18, 14).Because of its high bioavailability, predictable linear kinetics, and early tolerability, BRV can be safely initiated directly at its therapeutic target dose without the need for a gradual titration schedule (15).

Low Drug-Drug Interaction Potential: BRV does not significantly induce or inhibit major cytochrome P450 enzymes or drug transporters at standard doses. This makes it highly compatible with other ASMs and ideal for polytherapy regimens (14, 15) In Renal Impairment no dosage adjustment are required for patients with any degree of renal impairment or those undergoing hemodialysis, as the metabolites excreted by the kidneys are inactive. (14) Because hepatic pathways dominate its metabolism, moderate-to-severe liver disease increases BRV plasma exposure by 50% to 60% and extends its half-life to

roughly 17 hours. A lower starting dose and a maximum daily ceiling of 150 mg are recommended (14,20) It gained initial FDA approval on February 18,2016 as adjunctive therapy for treating partial-onset seizures (POS) in patients aged 16 years and older with epilepsy and it relied on data from three pivotal phase III clinical trials (Studies N01252,N01253,and N01358)involving over 2,400 adult patients, demonstrating a significant reduction in seizure frequency compared to placebo.(20,21) And in September 2017 expanded the indication to include monotherapy treatment for partial-onset seizures in patients 16 years and older.(21) In May 10,2018 the indications expanded to include both monotherapy and adjunctive therapy for pediatric patients aged 4 years and older. And in August 27, 2021: the age limit was drastically lowered, approving the drug for infants as young as 1 month of age. (22)

Efficacy in DRE: Several pivotal randomized placebo-controlled trials evaluated BRV as adjunctive therapy in patients with refractory focal epilepsy and consistently demonstrated significant reductions in seizure frequency and improved responder rates compared with placebo. (23, 24).

Real-world observational studies have largely confirmed the efficacy demonstrated in clinical trials with Retention rates generally range between 60% and 80%, reflecting both effectiveness and tolerability in routine practice.(25,26,27) In a real- world post marketing Canadian study in a highly refractory epilepsy population with a mean of 8.9 previously failed ASMs and current use of 2.5 concomitant ASMs, the 50% responder rates at 3, 6, 12, and 15 months were 36.1%, 32%, 41.2%, and 45.5%, respectively. Retention rates at corresponding time points were 75.0%, 72.0%, 59.2%, and 47.9%. These findings demonstrate that even among profoundly treatment-resistant patients, BRV achieves clinically meaningful seizure reduction in a substantial proportion. (28)

Several studies reported meaningful seizure reduction after switching patients from LEV to BRV, particularly in individuals who experienced behavioral adverse events with LEV with real-world cohorts suggest that BRV maintains seizure control while improving psychiatric tolerability in selected patients. (29, 30) In additional open-label studies, BRV demonstrated promising results

And high retention rates in patients with both focal-onset and genetic generalized Epilepsies. (31, 32) .According to a meta-analysis, the most common AEs associated with BRV are irritability, fatigue, somnolence, and dizziness. (33) In the largest study, psychiatric AEs occurred in 10.8% of patients, measured by open-ended questions. (34).BRV is generally well tolerated. And most adverse events are mild to moderate in

severity and often improve with dose adjustment or continued therapy. And it has a lower incidence of irritability, aggression, anxiety, and mood disturbance than LEV. (31, 32) .BRV is an effective and generally well-tolerated ASM for patients with DRE, clinical trials and real-world evidence consistently demonstrate significant seizure reduction, favorable retention rates, and an acceptable safety profile. And it may offer improved suicidal attempt tolerability compared with LEV, making it a useful alternative in patients with behavioral adverse effects.As there is a limited real-world long-term efficacy and tolerability studies on Generic form of BRV in our region in comparison to its predecessor LEV and there is a growing evidence from multiple studies about its broad spectrum efficacy on other Primarily Generalized forms of epilepsies and its approval on a wide range of age groups including infants of one month of age to geriatric population we conducted this study on DRE patients on a wide age group **(**Sixty-three patients with DRE aged 3–80 years were included and followed for up to 15 months), and on broader spectrum of seizure types to test this recently newly introduced drug.

The Aim of the study: Is to verify the effectiveness(Response Rates) and safety and Tolerability of BRV in controlling DRE Whether Focal onset with or without secondary generalization or in primarily generalized seizures, and to verify its Retention Rate and any treatment emergent Adverse effects (TEAE) and its effects on Quality of life (Qol)overall score.

Study Ethical and Scientific approval obtained According to the Research Committee of Babil Training and Developing Center/ Babil Health directory/ Ministry of Health. Numbered :- (30/2026/85/26/8/2026).

Study Design and Methods: A Retrospective real-world observational clinically based study were conducted in Babil Neurology Center, Hilla Babylon, Iraq. Where around 505 Epileptic patients registered in the Epilepsy clinic of Babil Neurology Center in Imam Al Sadiq Teaching Hospital from January 2025 to May 2026, around 190 DRE, 110 on VNS.

From the follow up Patients data 68 DRE are found taking Bevanta (BRV) only 63 patients with DRE were taking BRV with regular follow up at 3, 6, 12 and15 months after initiation of the drug From Jan. 2025 to May 2026. Patients without follow up or with incomplete records (4 patients) and those with non- epileptic events (1 patient) were excluded from the study.

Where patients demographic, Biometric and Clinical DATA were taking as Age, Gender, Occupation, Educational Level, Marital status and Residence. Type of Seizures (Epileptic syndrome) and Semiology of attacks and conformation of the diagnoses of DRE were

provided by a special committee of 2 specialist and one consultant in Epilepsy clinic , Duration of epilepsy, Previous ASM, Current ASM, Seizure freq. at base line 3months before the initiation of BRV and 3 months after (from patients seizure diary), Responder Rates (RR)and Retention Rates at 3 ,6, 12 and 15 months are calculated, (RR) ≥ 50% ,Seizure Freedom 100% ,Treatment Emergent Adverse Events (TEAE), Quality of life overall score Qol using the rapid 2-3 minutes Quality of life in Epilepsy Inventory-10 (QOLIE-10) score for adults and adolescent patients and (PedsQL Cognitive Functioning) Scale for younger children comparing at each visit to the base line categorized to positive impact, no change or worsening. Neuro Imaging Findings and Co morbidity and concomitant conditions also were noted. Where numerical variables are dealt with mean and average and Standard deviation, while non numerical variables are dealt with percentages. And the comparison between Responders and Non Responders and type of seizure and epileptic syndromes and combined treatments sub groups are dealt with Pearson chi square test for Qualitative variables. And Kaplan- Meier survival scale for retention rates.

Results

Patients Characteristics at Baseline

A total of 63 patients with drug-resistant epilepsy were included in the study. The median age was 24 years (range, 3–80 years), with 23.8% aged <18 years. Females represented 54.0% of the cohort, compared with 46.0% males. The most common educational level was primary education (30.2%), while housewives constituted the largest occupational group (28.8%) and married participants represented the most frequent marital-status category (41.3%) (Table 1).

Table 1. Baseline Demographic Characteristics of the Study Cohort (N=63).

Variables	Groups	Frequency	Percent
Age group	< 18 years	15	23.8%
	18 years and more	48	76.2%
	Median (Range)	24.00 (3-80)	

Sex	Male	29	46.0%
	Female	34	54.0%
Education	Illiterate	5	7.9%
	Primary	19	30.2%
	Secondary / High School	13	20.6%
	College or Institute	11	17.4%
	Special need	11	17.4%
	special need learning	4	6.5%
Occupation	Student	14	23.7%
	Housewife	17	28.8%
	Free Work / Self-employed	9	15.3%
	Employed	6	10.2%
	Retired	3	5.1%
	Unemployed	7	11.9%
	Child	3	5.1%
Marital status	Single	23	36.5%
	Married	26	41.3%
	Child / Minor	14	22.2%
Address	Babil	53	84.1%
	Kabala	4	6.3%
	Wasit /Swara	2	3.2%
	Al Najaf	2	3.2%
	Dewaine	1	1.6%
	Al Muthana/ Al Semawa	1	1.6%

* Note: Percentages were calculated based on the available observations for each variable. Missing values were excluded from the corresponding analysis.

45 (71.4%) patients had normal mental status (Table 2), while 18 (28.6%) had abnormal mental status. Focal seizures observed in 43 (68.3%) patients, including 23 with idiopathic epilepsy and 20 with symptomatic epilepsy. Generalized seizures in 19 (30.2%) patients, including 9 with idiopathic generalized epilepsy (7 with genetic generalized epilepsy and 2 with juvenile myoclonic epilepsy), 6 with symptomatic epilepsy, (2 with progressive myoclonic epilepsy, 1 with West syndrome, and 1 with Lennox–Gastaut syndrome (LGS). Two patients had generalized seizures associated with Homocystinuria and birth trauma). Four patients had cryptogenic epilepsy, including (1 with West syndrome, 1 with LGS, 1 with Dravert syndrome, and 1 with another cryptogenic epilepsy), while 1 (1.6%) patient had unknown epilepsy .{in total 32 with idiopathic , 26 with symptomatic , 4 with cryptogenic and 1 with Unknown}. Four patients had previously undergone Vagus nerve

stimulation (VNS), 3 were scheduled for VNS, and 1 had undergone unsuccessful epilepsy surgery. The duration of epilepsy ranged from 2 to 52 years, with median 13 years. Regarding neuroimaging, 41 patients (65.1%) had normal findings, whereas 22 (34.9%) had abnormal findings.

Table 2. Baseline Clinical Characteristics of the Study Cohort (N=63).

Variables	Groups	Frequency	Percent
Mentality	Normal	45	71.4%
	Mental Retardation	18	28.6%
Seizure type	Focal Onset	43	68.3%
	Generalized Onset	19	30.2%
	Unknown	1	1.6%
Underlying Etiology of Epilepsy	Idiopathic	٣٢	50.8%
	Symptomatic	٢٦	41.3%
	Cryptogenic/Unknown	5	7.9%
Duration of Epilepsy (Years)	Median (Range)	13 (2-52)	
Neuroimaging	Normal	٤١	٦٥.١%
	Abnormal	٢٢	٣٤.٩%
Prior ASMs	Mean ± SD	3.9 ± 1.14	
Current ASMs	Mean ± SD	2.4 ± 0.70	

*ASMs= Antiseizure medication; SD= Standard deviation. mean ± SD where appropriate.

Brivaracetam Treatment Characteristics

Brivaracetam was administered as adjunctive therapy in 59 patients (93.7%), while only 4 patients received BRV as monotherapy. Dual therapy consisting of BRV plus one additional ASM was the most common treatment regimen, used in 34 patients (54.0%), whereas 25 patients (39.7%) received BRV as part of polytherapy with two or more concomitant ASMs.

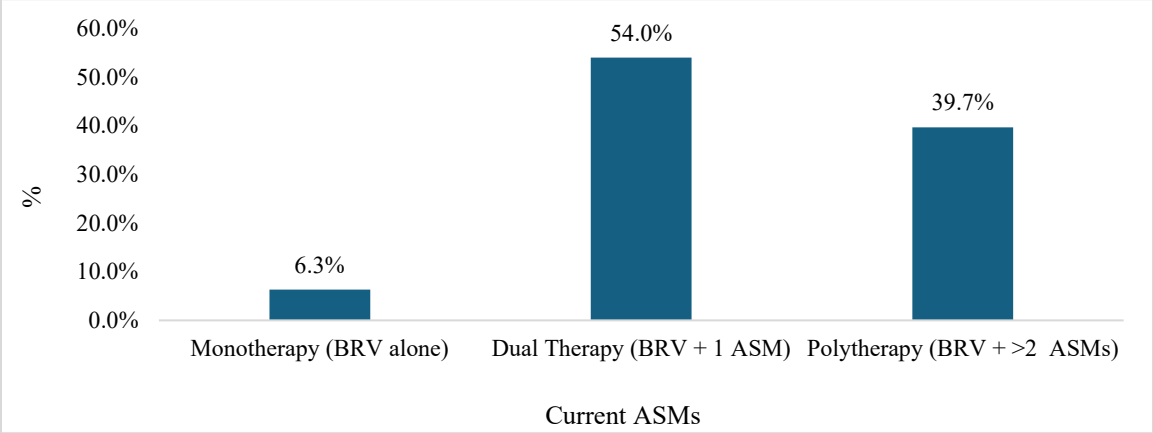

Figure 1. Distribution of patients by current ASMs (N=63).

The most frequently used BRV dose was 200 mg/day, administered to 52 patients (82.5%). Lower doses included 150 mg/day in 6 patients (9.5%), 100 mg/day in 4 patients (6.3%), and 50 mg/day in 1 pediatric patient (1.6%).

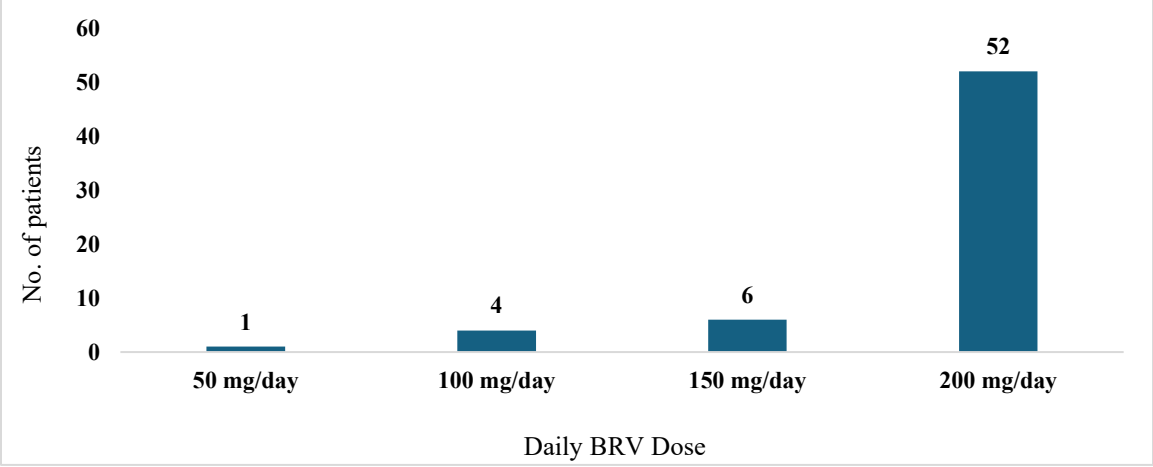

Figure 2. Distribution of Daily Brivaracetam (BRV) Dose across the study cohort (N=63).

Efficacy Analysis

Responder Rate: ≥ 50% at 3, 6, 12 and 15 months were 43.55%, 46.66%, 44.64% and 48.94% as in Table 3.

Table 3. BRV Responder Rates (≥ 50%) in the Study Cohort (N=63).

Time-point	Retained on BRV	No. of Responders	RR (among retained)	95% CI	RR (ITT, mITT) N=63	95% CI
3 months	62	27	43.٥٥%	31.8-55.9%	42.9 %	31.4-55.1%
6 months	60	28	46.٦٦%	34.4-59.3%	44.4%	32.8-56.7%
12 months	56	25	44.6٤%	32.4-57.5%	39.7%	28.5-52%
15 months	47	23	48.9٤%	35.3-62.8%	36.5%	25.7-48.9%

*95%CI for proportion were computed using the Wilson score method.
* ITT= Intention to treat; mITT= Modified Intention to treat. ITT analysis includes all enrolled patients (N=63) in the denominator across all time-points.
*No.= Number; CI= confidence interval

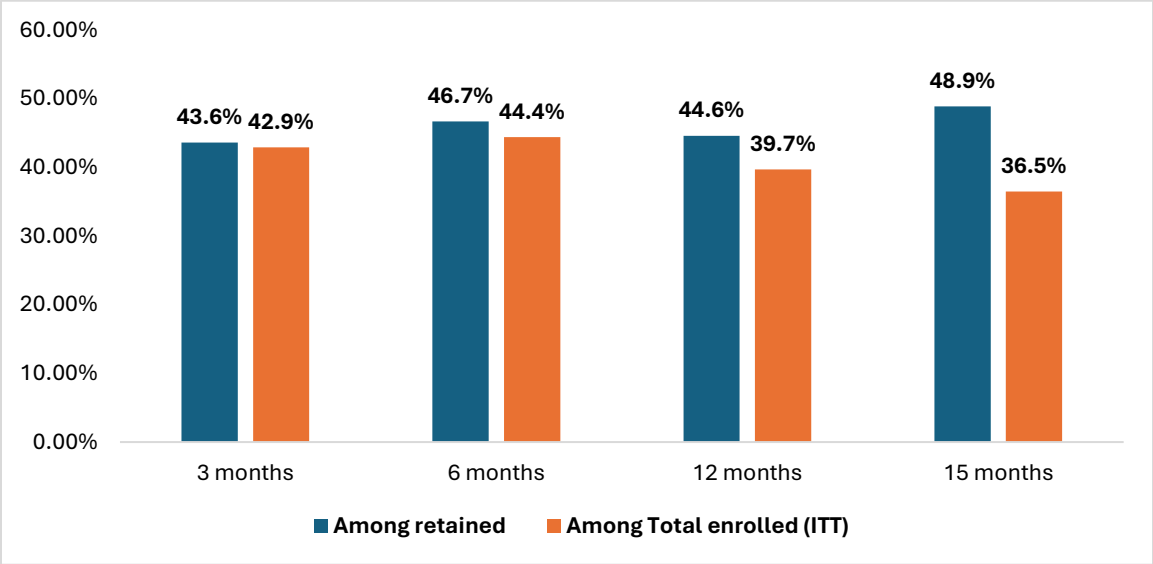

Figure 3. Responder rates (≥ 50%) over time points.

Seizure freedom (100% reduction in seizure frequency) was achieved in 4.8%, 6.8%, 10.7%, and 10.6% of retained patients at 3, 6, 12, and 15 months, respectively. The ITT (mITT) seizure-freedom rates were 4.8%, 6.3%, 9.5%, and 7.9%, respectively (Table 4).

Table 4. Seizure Freedom (100% reduction) in the Study Cohort (N=63).

Time point	Retained on BRV	No. of Responders (100%)	SF (among retained)	95% CI	SF (ITT, mITT) N=63	95% CI
3 months	62	3	4.8%	1.7-13.3%	4.8%	1.6-13.1%
6 months	60	4	6.8%	2.6-15.9%	6.3%	2.5-15.2%
12 months	56	6	10.7%	5.0-21.5%	9.5%	4.4-19.3%
15 months	47	5	10.6%	4.6-22.6%	7.9%	3.4-17.3%

*95%CI for proportion were computed using the Wilson score method.

* ITT= Intention to treat; mITT= Modified Intention to treat. ITT analysis includes all enrolled patients (N=63) in the denominator across all timepoints.

*No.= Number; CI= confidence interval

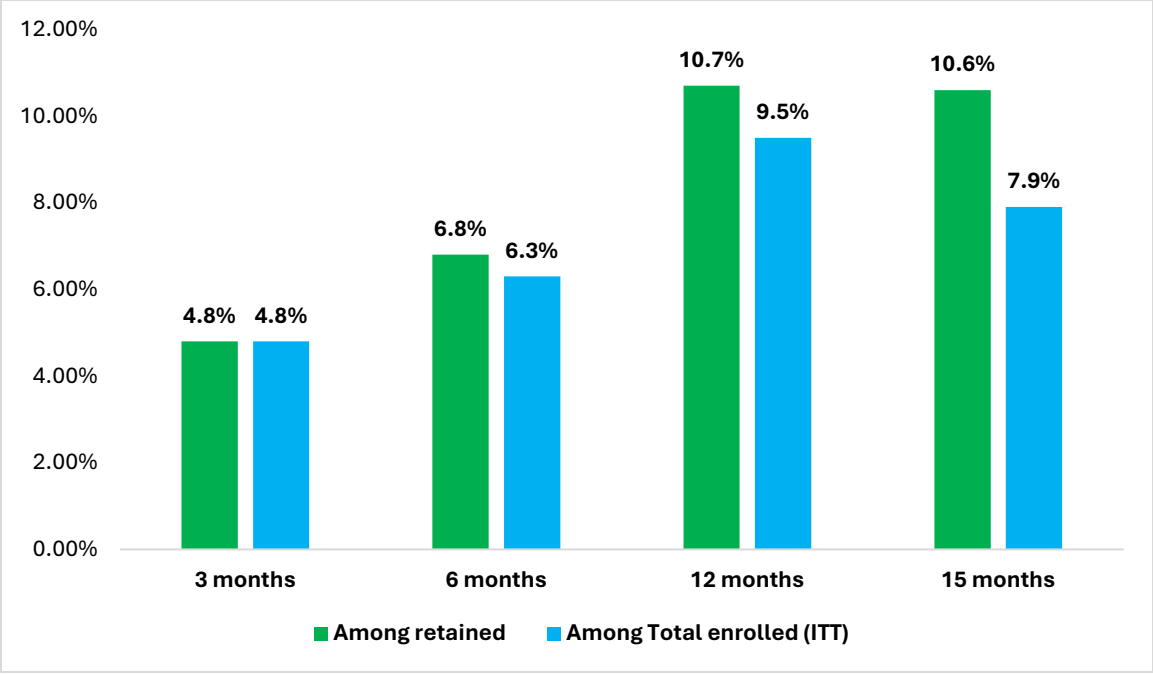

Figure 4. Seizure Freedom (100% reduction) over time points.

The mean reduction in seizure frequency among patients retained on BRV was 43.4 ± 22.6% at 3 months, 51.3 ± 23.5% at 6 months, 62.4 ± 23.6% at 12 months, and 61.6 ± 22.2% at 15 months (Table 5).

Table 5. Mean Percentage Reduction in Seizure Frequency across Follow up Time points among retained Patients

Time point	No.	Mean Reduction % ± SD
3 months	٦٢	43.4 ± 22.6
6 months	٦٠	51.3 ± 23.5
12 months	٥٦	62.4 ± 23.6
15 months	٤٧	61.6 ± 22.2

No.= Number; SD= Standard Deviation

Seizure reduction significantly improved over follow-up, except between 12 and 15 months (adjusted p = 0.56) (Table 11).

Adverse Events

Treatment-emergent adverse events (TEAEs) were in 22 of 63 patients (34.9%), while 41 patients (65.1%) completed follow-up without reported TEAEs as in Figure 5. The adverse events were divided into **Non Psychiatric Adverse Events (PAE):16 (25.4%)**: (Dizziness 6 (9.5%), Drowsiness 6 (9.5%), Seizure worsening 3(4.8%), Insomnia 1 (1.6%) and **PAE: 6 (9.5%)** (Depression 3 (4.8%), Nervousness 1(1.6%), Rage 1(1.6%), Suicidal attempt 1(1.6%))

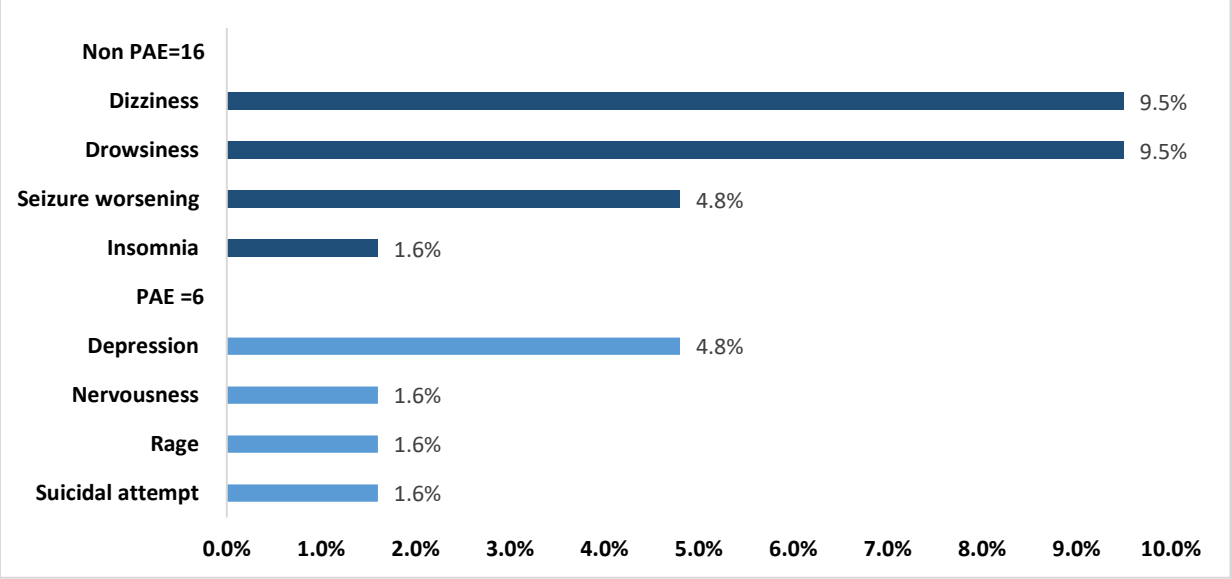

Figure 5. Treatment-Emergent Adverse Events (TEAEs) among patients receiving Brivaracetam (N=63)

Retention Rate

The BRV retention rates were 93.65%, 82.54%, 58.73%, and 57.40% as in Table ٦ . Respectively. Main causes of discontinuation at 3 months; 3 drop outs (2 due to worsening, and 1 due to affordability availability (aff/av) issues) , at 6 months; 8 drop outs (5 form lack of efficacy (LOE), 1 from (TEAE) and 2 due to (aff/av) issues), at 12 months; 19 drop outs (11 (LOE), 1 due (TEAE), and 7 due to (aff/av) issues), and at 15 months; 11 drop outs; (6 (LOE), 3 TEAE, and 2 due to (aff/av) issues)..

Table ٦. Comparison of primary and sensitivity retention rate across follow-up intervals.

Timepoint	Primary retention%	Sensitivity retention %	Difference
3 months	93.7%	95.2%	+ 1.5%
6 months	82.5%	87.3%	+4.8%
12 months	58.73%	74.6%	+14.3%
15 months	57.1%	76.2%	+ 19.1%

*Primary retention considers any cessation. Sensitivity retention right-censors patients withdrawing strictly for non-clinical reasons (purely medical / clinical discontinuation).

Retention According to Clinical Subgroups

Kaplan–Meier analysis showed no significant difference in BRV retention between patients with focal and generalized seizure types (log-rank $\chi^2 = 0.00$, $p = 0.9616$)..

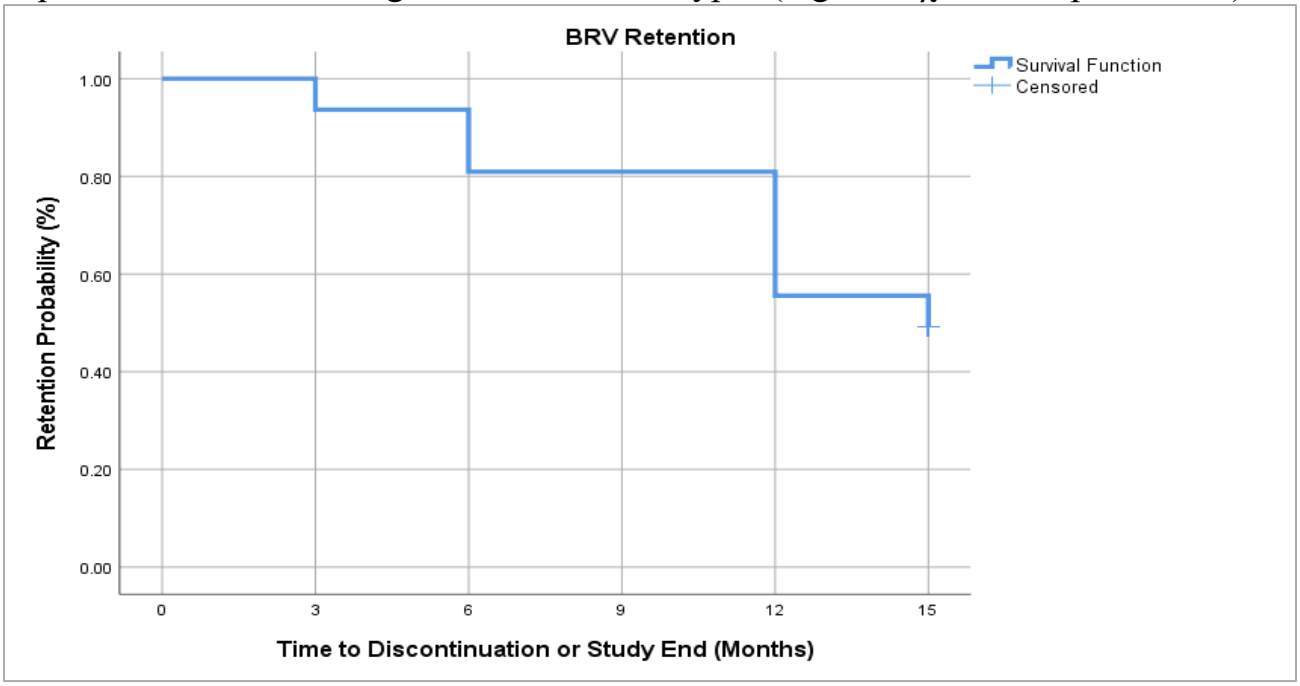

Figure 5. Kaplan-Meier Analysis of Brivaracetam (BRV) Retention Over 15 Months (N=63).

Previous Levetiracetam Exposure

Nearly all the patient except 3(4.8%) had previously exposed to LEV before they switched to BRV, From the 60 (95.2%) patient who exposed to LEV 50(83.3%) were currently on it and 10 (16.7%) were previously exposed. 31 out of 60 (49.2%) are due to Psychiatric AE of LEV. And 9 (14.3 %) are due to LEV failure & Psychiatric AE, 20 (31.7%) due to LEV failure as in Table 7.
20 from the responders (71.43%) are due to Psychiatric AE of LEV. And 7 (25%) are due to LEV failure and 1(3.57%) not used before.

Table 7. Distribution of patients' Previous Levetiracetam Exposure in the Study Cohort (N=63).

Prior LEV status	Frequency	Percent
Due to Psychiatric Adverse Effects (PAE)	31	49.2%
Due to Failure	20	31.7%
Both PAE and Failure	9	14.3%
Not Used LEV before	3	4.8%
Total	**63**	**100.0%**

Table 8: Baseline characteristic by History of Prior Levetiracetam use.

Variable	group	LEV-PAE	LEV-Failure	LEV-Both	Not used	P - value
Mentality	Normal	21 (46.7%)	16 (5.6%)	5 (11.1%)	3 (6.7%)	0.53
	Mental Retardation	10 (55.6%)	4 (22.2%)	4 (22.2%)	0 (0.0%)	
Seizure type	Focal Onset	19 (44.2%)	15(34.9%)	6(14.0%)	3 (7.0%)	0.88
	Generalized	11 (57.9%)	5(26.3%)	3(15.8%)	0 (0.0%)	
	Unknown	1 (100.0%)	0(0.0%)	0 (0.0%)	0 (0.0%)	
Underlying Etiology of Epilepsy	Idiopathic	18 (56.3%)	8 (25.0%)	3(9.4%)	3 (9.4%)	0.56
	Symptomatic	11 (42.3%)	10(38.5%)	5 (19.2%)	0 (0.0%)	
	Cryptogenic	2 (40.0%)	2 (40.0%)	1 (20.0%)	0 (0.0%)	
Neuroimaging	Normal	24 (57.1%)	11(26.2%)	5(11.9%)	2 (4.8%)	0.37
	Abnormal	7 (33.3%)	9 (42.9%)	4(19.0%)	1 (4.8%)	
Duration of disease	Median(range)	11 (3-45)	19 (2-52)	11 (6-23)	13(2-46)	0.28

*Pearson Chi-square test (χ^2-test) at p-value < 0.05
*Fisher's exact test used for cells have expected countless than 5.
*Kruskal-Wallis Test

As shown in **Table 9** response rates differ significantly according to the History of Prior Levetiracetam use ($p<0.001$). The highest responder rate was observed among patients who had discontinued levetiracetam because of psychiatric adverse effects (65%, 20/31), and those with no prior use of levetiracetam (33.3% [1/3]). Of the patients who stopped levetiracetam due to treatment failure, 35.0% (7/20) were responders; compared with no responders out of a total of 9 subjects who discontinued levetiracetam because both psychiatric AEs and treatment failure.

Table 9. Responder rates according to History with Prior Levetiracetam.

History of Prior Levetiracetam use	Non-Responder		Responder		P-value
	No.	%	No.	%	
Due to Psychiatric Adverse Effects (PAE)	11	35.5%	20	64.5%	**<0.001**
Due to Failure	13	65.0%	7	3∘.0%	
Both PAE and Failure	9	100.0%	0	0.0%	
Not Used LEV before	2	66.7%	1	33.3%	

*Fisher's exact test used for cells have expected countless than 5.

Quality of Life

Over all Qol score (QOLIE-10) & (PedsQL Cognitive Functioning) 37/63 (58.73 %) improved, and 22/63 (34.92 %) no change, 4(6.35 %) with worsening as in Table 10 . The association between treatment response and quality-of-life change was statistically significant ($\chi^2 = 23.95$, df = 2; $p < 0.0001$).

Table10. Association between Responder rates (≥ 50 reduction) and patient reported Quality of Life change.

Quality of Life	Non-Responder		Responder		p-value
	No.	%	No.	%	
Improved	11	29.7	26	70.3	**$X^2 \approx 23.95$, df=2 P < 0.0001**
No Change	20	90.9	2	9.1	
Worsened	4	100.0	0	0.0	

*Fisher's exact test used for cells have expected countless than 5 at p-value < 0.05.

Predictors of Treatment Response

Responders were younger than non-responders (25.11 ± 10.03 vs. 34.00 ± 22.67 years), had a shorter duration of epilepsy (13.43 ± 8.32 vs. 18.03 ± 13.10 years), and had fewer previous ASMs (3.61 ± 0.69 vs. 4.14 ± 1.38); however, none of these differences reached statistical significance (p = 0.329, p = 0.220, and p = 0.115, respectively) as in Table 11.

Table 11. Continuous Demographic, Clinical Characteristics and subgroup analysis of responder status (≥ 50% reduction)

Subgroup\predictor	Total cohort N=63	Non-responders N=35	Responders N=28	P-value
Age	30.05 ± 18.58	34 ± 22.67	25.11 ± 10.03	0.329
Epilepsy duration	15.95 ± 11.38	18.03 ± 13.1	13.43 ± 8.32	0.220
Number of prior ASMs	3.90 ± 1.15	4.14 ± 1.38	3.61 ± 0.69	0.115

*Differences between responders and non-responder were compared via Mann-Whitney U test. *Significant level at p <0.05

Regarding responders as in Table 12, Response status was statistically associated with mental status (p = 0.006). 55.6% with normal mentality and 16.7% with mental retardation. 21/43 (48.84%) were focal-onset and 8/19 (42.11%) were generalized-onset. By etiology, 21 (65.6%) were idiopathic, 8 (30.8%) symptomatic, and 1 (20.0%) unknown. Underlying etiology was statistically associated with treatment response (P=0.01). Neuro imaging: 23 (54.8%) normal and 5 (23.8%) with abnormalities. Normal neuroimaging was also associated with treatment response (p = 0.02). No significant association was observed between responder status and seizure type (p = 0.52).

Table 12. Comparison of clinical Characteristics between Responders and Non-responders.

Variables	Group	Non-Responders		Responders		p-value
		No.	%	No.	%	
Mentality	Normal	20	44.4%	25	55.6%	**0.005**
	Mental Retardation	15	83.3%	3	16.7%	
Seizure type	Focal Onset	22	51.2%	21	48.8%	0.68
	Generalized Onset	11	57.9%	8	42.1%	
	Unclassified/Unknown	0	0.0%	1	100.0%	
Underlying Etiology of Epilepsy	Idiopathic	11	34.4%	21	65.6%	**0.01**
	Symptomatic	18	69.2%	8	30.8%	
	Cryptogenic / Unknown	4	80.0%	1	20.0%	
Neuroimaging	Normal	19	45.2%	23	54.8%	**0.02**
	Abnormal	16	76.2%	5	23.8%	

*Pearson Chi-square test (χ^2-test) at p-value < 0.05
*Fisher's exact test used for cells have expected countless than 5.

Concomitant Antiseizure Medications among Responders

Best combinations in responders were with Lacosamide (LCM) 13 times in responder group (46.4 %), VPA 6 and CBZ 5 times (21.4 %),(17.9 %), LTG 4 (14.3 %), OXC and PER each 3 (10.7 %),TPM 2 (7.1 % %) and CLB 1(3.6 % %).

Table 13: Prior and Current ASMs Profile among responders (N=28).

ASMs	Responders (n)	Responders (%)

LCM (Lacosamide)	13	46.4 %
VPA (Valproic Acid)	6	21.4 %
CBZ (Carbamazepine)	5	17.9 %
LGT (Lamotrigine)	4	14.3 %
OXC (Oxcarbazepine)	3	10.7 %
PER (Perampanel)	3	10.7 %
TPM (Topiramate)	2	7.1 %
CLB (Clobazam)	1	3.6 %

٢٥ patients (٣٩,٧ %) had comorbidity among all enrolled patients and Most participants (n=38, 60.3%) had no comorbidities demonstrated that as in Figure 6

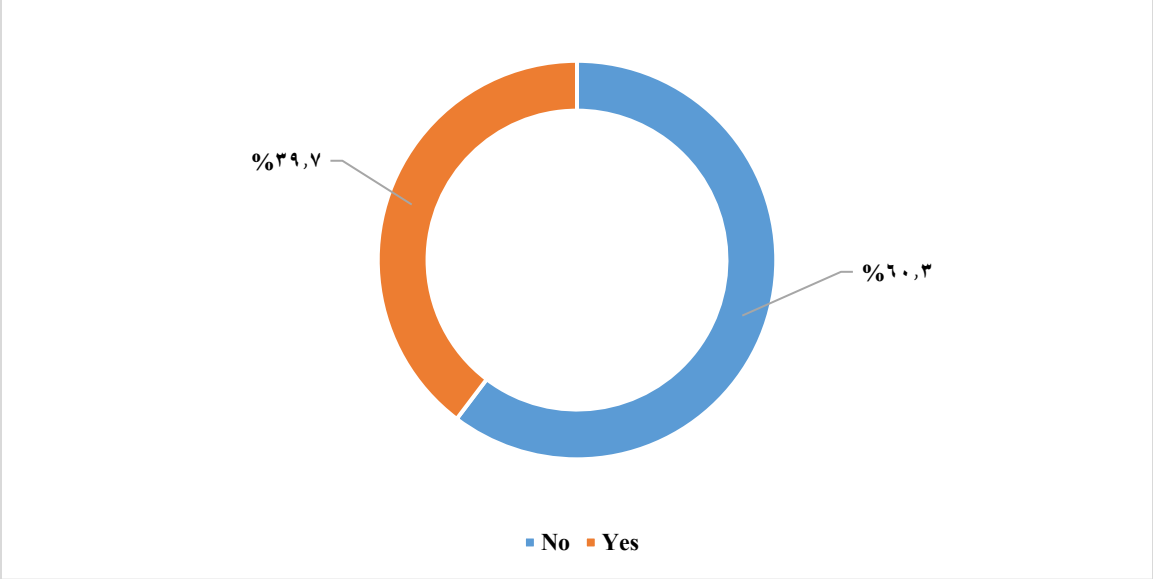

Figure 6. Distribution of patients by comorbidity (n=63).

25 patients with concomitant co-morbidities: 7(28%) with concomitant medical or surgical comorbidities: 2(8%) with type 2 DM, 1(4%) with pulmonary fibrosis Hypertension and renal impairment, 1(4%) with Hypertension and Hepatitis B (inactive), 1(4%) with old CVA, 1(4%) Large CPA Meningioma with CP Shunt, and 1(4%) with Post traumatic SDH with gliosis.

And 18 (72%) with co-morbid intellectual impairment: (3(12%) with Birth asphyxia and Cerebral palsy, 2(8%) with Autism and ADHD, 1(4%) with Homocystinuria, 1(4%) with Autosomal recessive Sialidosis, and other 11(44%) with Mental Retardation) show that in Table -14

Table14: Distribution of medical, surgical, and intellectual impairment comorbidities among patients with comorbidities(N=25).

Category	Comorbidity	No.	%
Concomitant medical or surgical comorbidities	Type 2 DM	2	8%
	Pulmonary fibrosis Hypertension and renal impairment	1	4%
	Hypertension and Hepatitis B (inactive)	1	4%
	Old CVA	1	4%
	Large CPA Meningioma with CP Shunt	1	4%
	Post traumatic SDH with gliosis	1	4%
	Total	**7**	**28%**
intellectual impairment	Mental Retardation	11	44%
	Birth asphyxia and Cerebral palsy	3	12%
	Autism and ADHD	2	8%
	Homocystinuria	1	4%
	Autosomal recessive Sialidosis	1	4%
	Total	**18**	**72%**
Total		**25**	**100.0%**

Of the 38 patients without comorbidities, 26 (68.4%) responded to treatment, compared with only 2 (8.0%) of the 18 patients with comorbidities. On the other hand, non-response was significantly higher among patients with comorbidities (92.0%, n=23) compared to those without comorbidities (42.2%, n=12). This difference was statistically significant association between comorbidities and treatment response ($p < 0.001$).

Table: Association between Responder rates and Comorbidity.

	Non-Responder	Responder	P-value

		NO.	%	NO.	%	
Comorbidity	**No**	12	31.6%	26	68.4%	**$X^2 \approx 1٤.٥٨$ df=1 P <0.001**
	Yes	٢٣	٩٢,٠%	٢	٨,٠%	

*Fisher's exact test used for cells have expected countless than 5 at p-value < 0.05.

The majority of participants were from Babil ٥٣ (84.1%), while smaller proportions were from Kabala٤ (6.3%), Wasit/Swara ٢(3.2%), Al-Najaf٢ (3.2%), Dewaine١ (1.6%), and Al-Muthana/Al-Semawa١ (1.6%).

Discussion

The present study included 63 patients with drug-resistant epilepsy, with a median age of 24 years (range, 3–80 years) and a slight female predominance (54.0%) in Table 1. Compared with the Canadian study (28), our patients were younger, had a lower proportion of females (54.0% vs. 73.7%), focal-onset epilepsy (68.3% vs. 84.2%), and intellectual disability (28.6% vs. 36.8%). The inclusion of pediatric patients (23.8%) may partly account for the younger age distribution. Epilepsy was predominantly idiopathic (50.8%) or symptomatic (41.3%), with a disease duration of 2–52 years. Patients had previously received a mean of 3.9 ± 1.14 ASMs and were taking 2.4 ± 0.70 concomitant ASMs at BRV initiation, reflecting a longstanding and treatment-resistant population in Table 2.

In our retrospective study the Responder rates of ≥ 50% at 3, 6, 12 and 15 months were 43.55% (27/62), 46.66% (28/60) , 44.46% (2٥/56), and 48.94% (23/47) which shows a slightly higher rates than the previous Canadian study (٢٨) , 36.1% (13/36) , 32% (8/25), 41.2% (7/17) and 45.5% (5/11) but a less seizure freedom (3/62) 4.84%, (4/60) 6.7%, (6/56) 10.7%,and (5/47) 10.64%. Comparing to the Canadian study (5/38) 13.4%, (4/25) 8%, (2/17) 11.8% and (2/11) 18.2%. As their DRE patients cohort were more intractable, and more than one third had intellectual disability (36.8%) and more than half (57.9%) had pre-existent comorbid mental health issues, while in our cohort less than one third (28.57%) 18/63 had some form of intellectual disability, 8-2 pre-treatment ASMs average 3.9 and 5-1 current ASMs including BRV average 2.4 and 39.68% (25/63) were currently on ≥ 3 ASMs. While in the Canadian study the average pre-treatment were 8.9 and the current 2.5 and 50% (19/38) were currently on ≥ 3 ASMs. So our cohort appearing much

less intractable as only 4 (6.35%) patients were on VNS and 3 more scheduled for VNS and one failed Epilepsy surgery, while a third of patients in the Canadian study underwent unsuccessful epilepsy surgery and 6 (15.8%) had VNS. But it was in line and lessor than A Greek study (35) which involved more patients 61 with DRE ≥ 50% Responders were 62%, 22% of them reach seizure freedom. Also other previous real-world studies 5 from Germany (36, 37, 38, 39, and 40) and one from Spain (41) using a similar study design showed 50% responder rates ranging from (27.8% - 45%) at 3 months with seizure freedom ranging from (7%- 25%) also their cohort appear more intractable than the current study with a mean of previously failed ASMs of 5.9.

The BRV Responders Rates (≥ 50%) in the Study Cohort in Table 3 was 43.55% at 3 months, 46.66% at 6 months, 44.64% at 12 months, and 48.94% at 15 months. The intention rate ITT were 42.9%, 44.4%, 39.7%, and 36.5%, respectively. The relatively stable responder rates among patients who remained on treatment suggest sustained clinical benefit over time, while the lower ITT estimates provide a more conservative assessment of effectiveness across the entire cohort.

While in Table 4,Seizure freedom was achieved in a smaller proportion of patients, as expected in a highly refractory population. Among retained patients, seizure freedom was observed 4.8%, 6.8%, 10.7%, and 10.6% at 3, 6, 12, and 15 months, respectively, while the intention rate ITT were 4.8%, 6.3%, 9.5%, and 7.9%. Although complete seizure freedom was achieved in a limited proportion of patients, the rates among those retained on BRV increased over time and remained stable between 12 and 15 months.

seizure reduction supports the observed clinical benefit of BRV as in Table 5. Among retained patients, mean seizure-frequency reduction increased from 43.4 ± 22.6% at 3 months to 51.3 ± 23.5% at 6 months and 62.4 ± 23.6% at 12 months, with a slight decline to 61.6 ± 22.2% at 15 months. Longitudinal analysis demonstrated statistically significant reductions in seizure frequency at all follow-up time points compared with baseline ($p < 0.0001$). Significant differences were also observed between 3 and 6 months, 3 and 12 months, 3 and 15 months, 6 and 12 months, and 6 and 15 months, whereas the difference between 12 and 15 months was not significant (adjusted $p = 0.56$). This pattern suggests that the major improvement in seizure control occurred during the first year of treatment, followed by a relative stabilization of the therapeutic effect beyond 12 months.

Also the current study reveals very good Retention rates 93.7%, 82.5%, 58.7%, and 57.1% at 3, 6, 12, and 15 months in Table 6, respectively. Comparing with the previous Canadian study (28) 75.50%, 72.0%, 59.2% and 47.9%.And higher retention rates of 95.2%, 87.3%, 74.6%, and 76.2% at the intention to treat (ITT).
Also the study reveals that the best combination occur with Lacosamide in 13(**46.4 %**) of responders mostly due to synergistic complementary mechanisms and least interaction between the two as in Table 13 (26).

Also the study found no statistical deference in responders regarding seizure type whether focal or Primarily generalized type, 8/19 (42.1%) of Generalised are Responders 2 of them with seizure freedom, while 21/43 (48.84%) from the Focal with or without generalisation are responders.as in previous multicentre retrospective study of 61 patients with genetic generalised epilepsy (GGE) and BRV treatment 50% responder rate of 36%, 25% seizure free for 3 months (42)

There is a low incidence of adverse events in the current study as only (22/63) 34.92% had adverse events and most of them are non-serious 12 with drowsiness / dizziness specially occur with the concomitant use of Carbamazepine as it might leeds to a dose-dependent reversible inhibition of CBZ epoxide hydrolase (43) and most are transient improved within 2 weeks and sometimes managed with gradual dose titration. One female patient had unexplained intractable to treat insomnia that only disappeared by discontinuing BRV and she was on concomitant LTG, 3 patients had seizure worsening and one patient pass into status on overnight switch form LEV that improved on returning back to LEV, also there is a lessor Psychiatric Adverse events (PAEs) in this study 6/63 (9.52%) 3 with depression, 1 with Nervousness, 1 with uncontrollable rage and one with serious suicidal attempt in figure 5. And all those with PAEs had it with LEV before. Comparing to the Canadian study (28) which showed an exceptional very high AEs 60.5% from medical reports and 85.7% from self-report questionnaire, with a total PAEs 31.6% form medical reports and 47.4% from questionnaire mostly attributable to the more degree of intractable epilepsy and more numbers of ASMs and the possibility of drug interactions. The incidence of AE in the current study were in line with other previous retrospective real-life studies ranging from 16- 39.8% (36 – 41). As the U.S FDA include in the latest Prescribing information of BRV worn for Steven Johnson and TEN (44) there is no any skin allergy in our patient cohort from BRV, as in our cohort 2 patients had previous skin allergy one male with 75 years with co-morbid pulmonary fibrosis had allergy to LCM

and one 29 years female with previous allergy to LTG and they were on BRV > than 12 - 15 months without any complaint from skin allergy.

An important finding of the present study was the association between clinical characteristics and BRV response in Table 12. Patients with normal mental status had a significantly higher response rate than those with intellectual disability, 55.6% versus 16.7%, respectively ($p = 0.005$). Response also differed significantly according to epilepsy etiology ($p = 0.003$), with the highest response observed among patients classified as having idiopathic epilepsy (65.6%), compared with 23.1% among those with symptomatic epilepsy and 20.0% among those with cryptogenic or unknown etiology. Normal neuroimaging was also associated with a higher response rate than abnormal neuroimaging (54.8% versus 23.8%; $p = 0.02$). These findings suggest that patients without major structural or neurological abnormalities may have a greater likelihood of achieving substantial seizure reduction with BRV.

The improvement in quality of life provides an important patient-centred perspective on the findings. Overall, 58.7% of patients reported improved quality of life in Table 10, while 34.9% reported no change and 6.3% reported worsening. Among responders, 92.9% reported improved quality of life compared with 31.4% of non-responders, and the association between seizure response and quality-of-life change was highly significant ($\chi^2 = 23.95$, $df = 2$; $p < 0.0001$). These findings indicate that seizure reduction with BRV was not statistical outcome but was associated with a substantial perceived improvement in patients' quality of life.

Baseline characteristics were comparable across the different categories of prior LEV use, with no significant differences in mental status, seizure type, epilepsy etiology, neuroimaging findings, or disease duration as in Table 8.

A significant difference in BRV response was observed according to the reason for previous LEV discontinuation ($p < 0.001$). The highest response rate was found among patients who had discontinued LEV because of psychiatric adverse effects (64.5%), compared with 35.0% among those who discontinued LEV because of treatment failure. No response was observed among patients who had experienced both psychiatric adverse effects and treatment failure as in Table 9.

Regarding Previous LEV use and Switching to BRV 60 patients in our cohort were exposed to LEV 50 (83.3%) were currently on it and they switched rapidly and safely (over-night switch) without titration to BRV in 10-15:1 ratio (37, 41) and only 1 patient

pass into status that improved on switching back to LEV and 10 (16.7%) patients were on LEV in the past and currently not on it when they start BRV

The reason of giving BRV in 31/60 (51.67%) were due to PAEs from LEV and 9 (15%) due to both PAEs and Failure and 20/60 (33.33%) were due to LEV failure in Table 7. And most of the PAEs that present with LEV not persist with BRV in only 6 (10%) had persistent PAEs and that is mostly due the difference between the two drugs in that BRV has no modulatory effects on alfa – amino-3-hydroxy-5-methyl-4-isoxazoleproionic acid (AMPA) receptors than LEV and that might explains the different psychotropic effects between the two (45,46)

The most common causes of drug discontinuation in this study were lack of efficacy and affordability/availability issues (due to cost-effectiveness) rather than AEs. The increasing difference between primary and sensitivity estimates over time suggests that access and affordability contributed substantially to long-term treatment discontinuation in this cohort, in addition to clinical factors.

Taken together, the findings suggest that BRV provided clinically meaningful seizure reduction in a substantial proportion of patients with DRE, including individuals with extensive previous ASM exposure and a high prevalence of prior LEV intolerance. The progressive improvement in seizure reduction during the first 12 months, together with the stabilization observed thereafter, suggests a sustained benefit among patients who remained on treatment. The relatively favorable TEAE profile and the low frequency of psychiatric adverse events are also notable, particularly given the substantial history of LEV-related behavioral or psychiatric intolerance in this cohort.

The main limitations of this study are its retrospective design and reliance on patient seizure logs to calculate seizure frequency, as well as its reliance on medical records and reported treatment-related adverse events. Additionally, data were collected from a single site (Babil Neurology Center/Epilepsy Clinic).

And the main strength points are its long follow-up duration (15 months) and the utilization of (QOLIE -10 & PedsQL Cognitive Functioning) rapid brief scores which focuses on capturing and detection of PAEs.

Conclusion:

In this real-world study adjunctive generic BRV (Bevanta) has noticeable efficacy in DRE whether Focal or Generalized types with low potentials for serious side effects and good Retention Rates and positive impact on quality of life and considered as a good alternative to Levetiracetam Psychiatric Adverse Effects, or Failure, and the main limitations in its

wide use due to its coast and affordability and availability issues. And the best synergistic combination is with Lacosamide.

Recommendations

BRV might be considered early in the treatment strategy for focal DRE particularly when rapid titration is required or when behavioural and Psychiatric intolerance limits LEV use. Larger prospective multicenter studies are recommended in future researches with longer follow-up periods to evaluate quality of life improvements, cost-effectiveness, and optimal ASM regimens as in synergistic combinations and more trials on Primarily Generalized types of epilepsies.

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