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RESEARCH ARTICLE

Adjunctive brivaracetam and sustained seizure frequency reduction in very active focal epilepsy

Simona Lattanzi[1] | Laura Canafoglia[2] | Maria Paola Canevini[3,4] | Sara Casciato[5] | Emanuele Cerulli Irelli[6] | Valentina Chiesa[3] | Filippo Dainese[7] | Giovanni De Maria[8] | Giuseppe Didato[9] | Giancarlo Di Gennaro[5] | Giovanni Falcicchio[10] | Martina Fanella[6] | Edoardo Ferlazzo[11] | Massimo Gangitano[12] | Angela La Neve[10] | Oriano Mecarelli[6] | Elisa Montalenti[13] | Alessandra Morano[6] | Federico Piazza[14] | Chiara Pizzanelli[15,16] | Patrizia Pulitano[6] | Federica Ranzato[17] | Eleonora Rosati[18] | Laura Tassi[19] | Carlo Di Bonaventura[6] | on behalf of BRIVAFIRST (Brivaracetam Add-On First Italian Network Study) Group Membership[†]

[1]Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

[2]Department of Epileptology, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[3]Epilepsy Center, Child Neuropsychiatry Unit, AAST Santi Paolo Carlo, Milan, Italy

[4]Department of Health Sciences, Università degli Studi, Milan, Italy

[5]IRCCS Neuromed, Pozzilli, Italy

[6]Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy

[7]Epilepsy Center, Neurology Unit, Venice, Italy

[8]Clinical Neurophysiology Unit, Epilepsy Center, Spedali Civili, Brescia, Italy

[9]Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

[10]Department of Basic Medical Sciences, Neurosciences and Sense Organs, University Hospital of Bari A. Moro, Bari, Italy

[11]Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy

[12]Department of Biomedicine, Neuroscience, and Advanced Diagnostics, University of Palermo, Palermo, Italy

[13]Epilepsy Center, AOU Città della Salute e della Scienza di Torino, Turin, Italy

[14]Rita Levi Montalcini Department of Neurosciences, University of Turin, Turin, Italy

[15]Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

[16]Neurology Unit, Pisa University Hospital, Pisa, Italy

[17]Epilepsy Center, UOC Neurology, AULSS 8 Vicenza, Vicenza, Italy

[18]Department of Neurofarba, University of Florence, Florence, Italy

[19]C. Munari Epilepsy Surgery Center, Niguarda Hospital, Milan, Italy

[†]A complete list of the BRIVAFIRST Group Membership investigators can be found at the end of the article.

Correspondence
Simona Lattanzi, Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Via Conca 71, 60020 Ancona, Italy.
Email: alfierelattanzisimona@gmail.com

Abstract

Objective: This study aimed to explore the effectiveness of brivaracetam (BRV) according to baseline seizure frequency and past treatment history in subjects with focal epilepsy who were included in the Brivaracetam Add-On First Italian Network Study (BRIVAFIRST).

Methods: BRIVAFIRST was a 12-month retrospective, multicenter study including adults prescribed adjunctive BRV. Study outcomes included sustained seizure response (SSR), sustained seizure freedom (SSF), and the rates of treatment discontinuation and adverse events (AEs). Baseline seizure frequency was stratified as <5, 5–20, and >20 seizures per month, and the number of prior antiseizure medications (ASMs) as <5 and ≥6.

Results: A total of 994 participants were included. During the 1-year study period, SSR was reached by 45.8%, 39.3%, and 22.6% of subjects with a baseline frequency of <5, 5–20, and >20 seizures per month ($p < .001$); the corresponding figures for the SSF were 23.4%, 9.8%, and 2.8% ($p < .001$). SSR was reached by 51.2% and 26.5% participants with a history of 1–5 and ≥6 ASMs ($p < .001$); the corresponding rates of SSF were 24.7% and 4.5% ($p < .001$). Treatment discontinuation due to lack of efficacy was more common in participants with >20 seizures compared to those with <5 seizures per month (25.8% vs. 9.3%, $p < .001$), and in participants with history of ≥6 prior ASMs compared to those with history of 1–5 ASMs (19.6% vs. 12.2%, $p = .002$). There were no differences in the rates of BRV withdrawal due to AEs and the rates of AEs across the groups of participants defined according to the number of seizures at baseline and the number of prior ASMs.

Significance: The baseline seizure frequency and the number of previous ASMs were predictors of sustained seizure frequency reduction with adjunctive BRV in subjects with focal epilepsy.

KEYWORDS
antiseizure medication, brivaracetam, epilepsy, focal seizures

1 | INTRODUCTION

Antiseizure medications (ASMs) represent the mainstay of the treatment of people with epilepsy. Despite the introduction of many ASMs in the past decades, the rate of uncontrolled epilepsy remains high and there remains the need to develop new therapeutic options that are effective and safe.

Brivaracetam (BRV) is a third-generation ASM characterized by high-affinity binding to synaptic vesicle protein 2A and a chemical structure similar to levetiracetam (LEV).[1] In the European Union, BRV is approved for the add-on treatment of focal onset seizures in patients >2 years of age.[2]

Studies based on data generated in a real-life context can complement the evidence coming from the randomized, controlled trials and provide original insights on issues not captured in regulatory trials. The Brivaracetam Add-On First Italian Network Study (BRIVAFIRST) is the largest study to have assessed the 1-year effectiveness

Key points

- Baseline seizure frequency and number of previous treatments predicted sustained seizure frequency reduction with brivaracetam
- Sustained seizure frequency reduction was observed in brivaracetam-treated subjects with very active focal epilepsy
- No differences in tolerability of brivaracetam emerged according to baseline seizure frequency and number of prior treatments

and tolerability of BRV as adjunctive treatment of focal seizures in people with epilepsy treated according to daily clinical practice.[3,4] This analysis of the BRIVAFIRST data aimed to explore the response to adjunctive BRV according to the baseline seizure frequency and as a function of the number of previous ASMs.

2 | MATERIALS AND METHODS

2.1 | Participants

BRIVAFIRST was a retrospective study that involved 63 Italian centers. Adult (age ≥ 16 years) subjects who were prescribed add-on BRV (March 2018 to March 2020) and were on stable treatment with one or more ASMs during the prior 90 days were retrospectively identified. Participants with focal epilepsy, 12-month follow-up after initiating BRV, and ≥1 seizure during the 3 months before starting BRV were considered in the current analysis. Exclusion criteria were history of alcoholism, drug abuse, conversion disorders, and other nonepileptic ictal events.

Data on demographics, clinical history, type of seizures and epilepsy,[5] etiology, baseline seizure frequency (monthly seizure frequency during the 3 months before adding BRV), and prior and concomitant ASMs were collected. Following the classifications adopted in prior studies, baseline seizure frequency was stratified as <5, 5–20, and >20 seizures per month,[6,7] and the number of previous ASMs was grouped as <5 or ≥6.[8] Data on seizure occurrence, adverse events (AEs), and drug withdrawal were retrieved from clinical records of follow-up visits performed at 3, 6, and 12 months as standard practice when a new ASM is initiated.

Study outcomes were sustained seizure response (SSR) and sustained seizure freedom (SSF), defined as ≥50% (SSR) and 100% (SSF) reduction in baseline seizure frequency that continued without interruption from the first time it was achieved through 12 months without BRV discontinuation.[9] The time of achievement of SSF and SSR was established using data at visits at 3, 6, and 12 months. The rate and reasons for treatment discontinuation and the rate of AEs considered BRV-related by physicians were also considered.

2.2 | Statistical analysis

Values were presented as median (interquartile range [IQR]) for continuous variables and number (percentage) of subjects for categorical variables. Comparisons were made using the Mann–Whitney test, Dunn test, or chi-squared test, as appropriate. Simple and multivariate logistic regression models were performed to evaluate whether baseline seizure frequency (<5, 5–20, and >20 seizures per month) and number of prior ASMs (<5 and ≥6) were associated with SSF and SSR. Age, duration of epilepsy, and number of concomitant ASMs were selected as independent variables of the multivariate models for their well-known association with seizure outcomes.[9–11] Data analysis was performed using Stata/IC 13.1 (StataCorp). The study is reported according to STROBE guidelines.[12]

2.3 | Standard protocol approval

The study was approved by the ethical committee of Sapienza University, Rome, Italy and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient or a legal representative.

3 | RESULTS

A total of 1325 participants were initially identified. After the exclusion of participants with a diagnosis of generalized, combined, or unknown epilepsy ($n = 71$), follow-up of <1 year ($n = 225$), or no seizures at baseline ($n = 35$), 994 subjects were included. The median age of the participants was 45 (IQR = 32–56) years, and 469 (47.2%) were men. Baseline characteristics of the included participants are reported in Table 1.

Participants with <5, 5–20, and >20 seizures per month at baseline numbered 441 (44.4%), 336 (33.8%), and 217 (21.8%). Subjects with >20 seizures per month were younger, had a younger age at epilepsy onset, had history of a greater number of prior ASMs, and were receiving more concomitant ASMs than subjects with <5 and 5–20 seizures per month. Baseline characteristics of participants according to baseline seizure frequency are shown in Table S1.

Participants with history of ≥6 prior ASMs were younger at epilepsy onset, had a longer duration of epilepsy, more commonly presented both focal onset and focal to bilateral tonic–clonic seizures, more commonly had a history of prior or concomitant use of LEV, were being treated with a higher number of concomitant ASMs, and had a higher baseline seizure frequency compared to participants who had history of 1–5 previous ASMs. Baseline characteristics of participants according to the number of prior ASMs are summarized in Table S2.

In the study cohort, the median BRV dose was 100 (IQR = 100–200) mg/day at 3 months, 150 (IQR = 100–200) mg/day at 6 months, and 150 (IQR = 100–200) mg/day at 12 months.

During the 1-year study period, SSR was reached by 202 of 441 (45.8%), 132 of 336 (39.3%), and 49 of 217 (22.6%)

TABLE 1 Baseline characteristics of patients.

Characteristics	Patients, $N=994$
Age, years	45 (32–56)
Male sex	469 (47.2)
Age at epilepsy onset, years, $N=993$[a]	13 (5–24)
Duration of epilepsy, years, $N=993$[a]	25 (14–38)
Type of seizures, $N=884$[a]	
Focal onset	657 (74.3)
Focal to bilateral tonic–clonic	165 (18.7)
Focal onset and focal to bilateral tonic–clonic	62 (7.0)
Etiology	
Structural	532 (53.5)
Genetic	38 (3.8)
Immune	10 (1.0)
Infectious	27 (2.7)
Unknown	387 (39.0)
Number of prior ASMs, $N=988$[a]	6 (3–8)
Number of prior ASMs, $N=988$[a]	
1–5	482 (48.8)
≥6	506 (51.2)
Levetiracetam status, $N=987$[a]	
Never used	260 (26.3)
Prior use/prescribed at baseline	727 (73.7)
Number of concomitant ASMs, $N=993$[a]	2 (1–3)
Baseline monthly seizure frequency[b]	6 (3–20)
Number of seizures per month at baseline[b]	
<5	441 (44.4)
5–20	336 (33.8)
>20	217 (21.8)

Note: Data are median (interquartile range) for continuous variables, and *n* (%) for categorical variables.

Abbreviation: ASM, antiseizure medication.

[a]*N* refers to the total number of patients for whom data in question were available.

[b]Based on the number of seizures during the 90 days before starting adjunctive brivaracetam.

of subjects with a baseline frequency of <5, 5–20, and >20 seizures per month ($p<.001$); the corresponding figures for the SSF were 103 of 441 (23.4%), 33 of 336 (9.8%), and six of 217 (2.8%, $p<.001$; Figure 1). Proportions of participants reaching SSR and SSF who were seizure responders and seizure-free from Day 1, Month 4, and Month 7 to Month 12 according to the number of seizures per month at baseline are reported in Table 2.

SSR was reached by 247 of 482 (51.2%) and 134 of 506 (26.5%) participants with a history of 1–5 and ≥6 ASMs ($p<.001$); the corresponding rates of SSF were 119 of 482 (24.7%) and 23 of 506 (4.6%, $p<.001$; Figure 1). The proportions of participants reaching SSR and SSF at the different time points according to the number of prior ASMs are reported in Table 3.

The rates of SSR and SSF according to the number of baseline seizures in the function of the number of prior ASMs are shown in Figure 2.

Older age (odds ratio [OR] =1.02, 95% confidence interval [CI] =1.01–1.03 for unitary increase, $p=.001$) was associated with increased odds of SSR, and number of prior ASMs of ≥6 (OR = .44, 95% CI = .33–.60, $p<.001$) and baseline frequency of >20 seizures per month (OR = .48, 95% CI = .32–.71, $p<.001$) were associated with decreased odds of SSR (Table 4).

Older age (OR=1.02, 95% CI=1.01–1.04 for unitary increase, $p=.001$) was associated with increased odds of SSF, and longer epilepsy duration (OR = .97, 95% CI = .96–.99 for unitary increase, $p<.001$), number of prior ASMs of ≥6 (OR = .26, 95% = CI .16–.44, $p<.001$), and baseline seizure frequency of 5–20 seizures per month (OR = .43, 95% CI = .27–.67, $p<.001$) and >20 seizures per month (OR = .16, 95% CI = .07–.38, $p<.001$) with decreased odds of SSF (Table 5).

Participants who discontinued BRV treatment numbered 259 (26.1%), and the reasons for treatment withdrawal were poor efficacy ($n=159/259$, 61.4%), poor tolerability ($n=93/259$, 35.9%), and a combination of both ($n=5/259$, 1.9%); in one participant, BRV was discontinued due to the subject's request, and one participant died from a cause not related to treatment. According to LEV status, the rate of treatment withdrawal for any cause was 21.9% ($n=57/260$) in participants who were LEV naïve and 27.8% ($n=202/727$) in participants with history of LEV use ($p=.065$). Drug discontinuation due to poor efficacy occurred in 13.5% ($n=35/260$) of participants who had never tried LEV and in 17.1% ($n=124/727$) of participants who had used LEV ($p=.176$). The rates of BRV withdrawal for AEs were 8.1% and 9.9% in participants without and with history of LEV use ($p=.387$).

Treatment discontinuation due to lack of efficacy was more common in participants with 5–20 seizures per month at baseline compared to those with <5 seizures per month (18.5% vs. 9.3%, $p<.001$), and in participants with >20 seizures per month compared to those with <5 seizures per month (25.8% vs. 9.3%, $p<.001$); there were no differences in the rates of BRV withdrawal due to AEs across the different groups based on the number of seizures at baseline.

Treatment discontinuation due to lack of efficacy was more common in participants with history of ≥6 prior ASMs compared to those with history of 1–5 ASMs (19.6% vs. 12.2%, $p=.002$), whereas there were no differences in the rates of BRV withdrawal due to AEs.

AEs were reported by 30.1% of the participants and rated as mild (74.8%), moderate (24.8%), and severe (.4%).

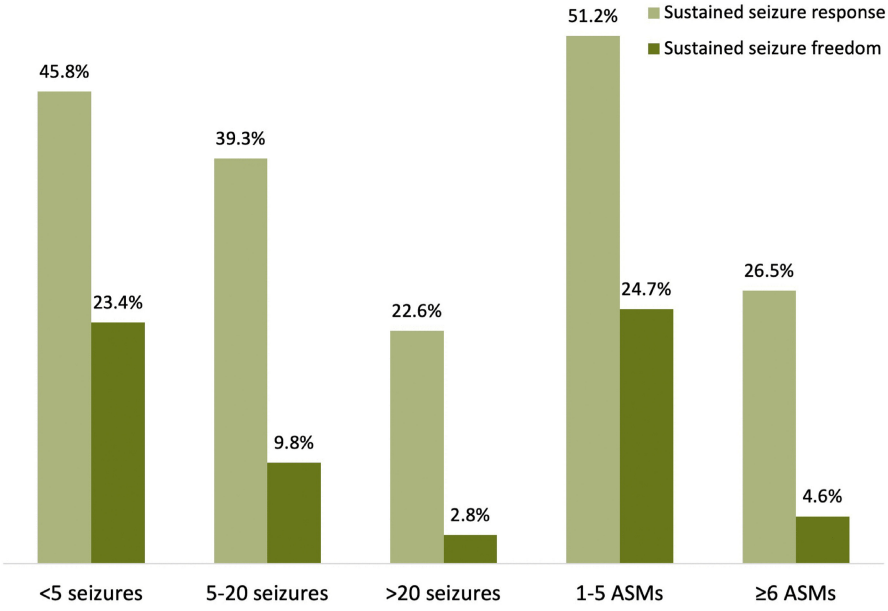

FIGURE 1 Sustained seizure response and sustained seizure freedom according to baseline seizure frequency and prior antiseizure medications (ASMs). Proportions of participants who achieved sustained seizure response and sustained seizure freedom during the 12-month follow-up are shown according to the number of monthly seizures at baseline and the number of prior ASMs.

TABLE 2 Sustained seizure response and sustained seizure freedom outcomes according to baseline seizure frequency.

	During the study period	From Day 1 to Month 12	From Month 4 to Month 12	From Month 7 to Month 12
Sustained seizure response				
<5 seizures	202/441 (45.8)	135/202 (66.8)	46/202 (22.8)	21/202 (10.4)
5–20 seizures	132/336 (39.3)	73/132 (55.3)	35/132 (26.5)	24/132 (18.2)
>20 seizures	49/217 (22.6)	28/49 (57.1)	13/49 (26.5)	8/49 (16.3)
Sustained seizure freedom				
<5 seizures	103/441 (23.4)	59/103 (57.3)	27/103 (26.2)	17/103 (16.5)
5–20 seizures	33/336 (9.8)	9/33 (27.3)	17/33 (51.5)	7/33 (21.2)
>20 seizures	6/217 (2.8)	4/6 (66.7)	2/6 (33.3)	0 (.0)

Note: Data are *n* (%) of participants. Proportions of participants reaching sustained seizure response and sustained seizure freedom who were seizure responders and seizure-free from Day 1, Month 4, and Month 7 to Month 12 according to the number of seizures per month at baseline are reported. Participants reaching sustained seizure response and sustained seizure freedom during the study period are equal to the sum of participants who were seizure responders and seizure-free from Day 1, Month 4, and Month 7 to Month 12.

TABLE 3 Sustained seizure response and sustained seizure freedom outcomes according to the number of prior antiseizure medications.

	During the study period	From Day 1 to Month 12	From Month 4 to Month 12	From Month 7 to Month 12
Sustained seizure response				
1–5 antiseizure medications	247/482 (51.2)	160/247 (64.8)	53/247 (21.5)	34/247 (13.8)
≥6 antiseizure medications	134/506 (26.5)	74/134 (55.2)	41/134 (30.6)	19/134 (14.2)
Sustained seizure freedom				
1–5 antiseizure medications	119/482 (24.7)	61/119 (51.3)	37/119 (31.1)	21/119 (17.7)
≥6 antiseizure medications	23/506 (4.6)	11/23 (47.8)	9/23 (39.1)	3/23 (13.0)

Note: Data are *n* (%) of participants. Proportions of participants reaching sustained seizure response and sustained seizure freedom who were seizure responders and seizure-free during the study period and from Day 1, Month 4, and Month 7 to Month 12 according to the number of prior antiseizure medications are reported. Participants reaching sustained seizure response and sustained seizure freedom during the study period are equal to the sum of participants who were seizure responders and seizure-free from Day 1, Month 4, and Month 7 to Month 12.

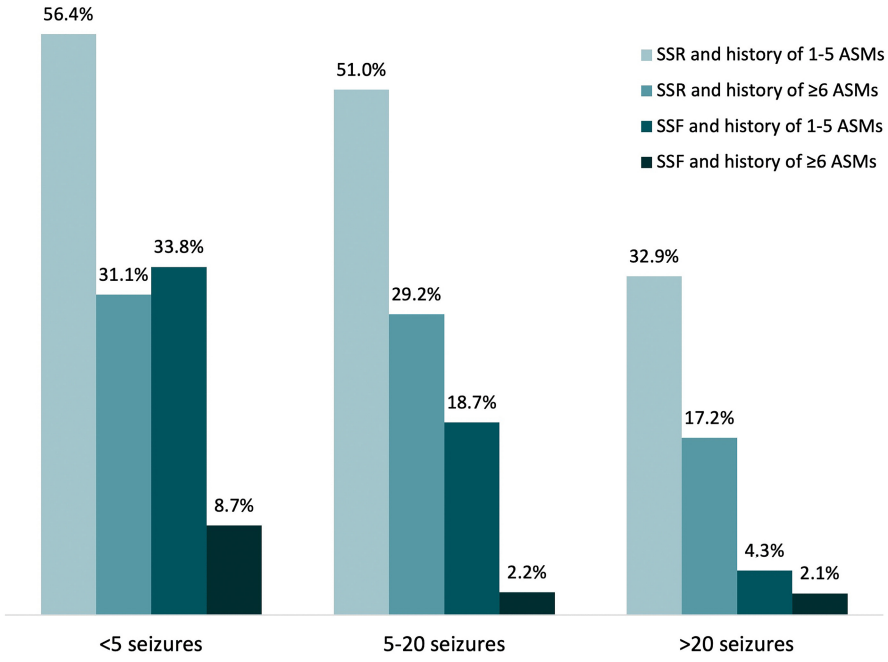

FIGURE 2 Sustained seizure response (SSR) and sustained seizure freedom (SSF) according to baseline seizure frequency and in relation to prior antiseizure medications (ASMs). Proportions of participants who achieved SSR and SSF during the 12-month follow-up are shown according to the number of monthly seizures at baseline and as a function of the number of prior ASMs.

TABLE 4 Association between baseline characteristics and sustained seizure response.

	Unadjusted		Adjusted[a]	
Dependent variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	1.02 (1.01–1.02)	<.001	1.02 (1.01–1.03)	.001
Duration of epilepsy	.99 (.98–.99)	.001	.99 (.98–1.00)	.072
Number of concomitant ASMs	.69 (.60–.80)	<.001	.91 (.77–1.08)	.248
Number of prior ASMs[b]				
≥6	.34 (.26–.45)	<.001	.44 (.33–.60)	<.001
Number of seizures per month at baseline[c]				
5–20	.77 (.57–1.02)	.069	.89 (.66–1.21)	.470
>20	.35 (.24–.50)	<.001	.48 (.32–.71)	<.001

Note: Values are from logistic regression models.

Abbreviations: ASM, antiseizure medication; CI, confidence interval; OR, odds ratio.

[a]Adjustment for age, duration of epilepsy, number of concomitant ASMs, number of prior ASMs, and baseline monthly seizure frequency.

[b]Reference is 1–5 ASMs.

[c]Reference is <5 seizures.

The most common AEs included somnolence (6.7%), nervousness and/or agitation (5.7%), vertigo (3.4%), and fatigue (3.2%; Table S3). There were no differences in the rates of AEs across the groups of participants defined according to the number of seizures at baseline and according to the number of prior ASMs.

4 | DISCUSSION

In this exploratory, post hoc analysis of BRIVAFIRST data, the seizure frequency before starting treatment with add-on BRV in subjects with focal onset seizures was a predictor of both SSR and SSF, a lower seizure count being associated with increased odds of sustained seizure frequency reduction. It is noteworthy that a sustained reduction in baseline seizure frequency that continued without interruption throughout the 12-month follow-up was observed also in participants with very active epilepsy; approximately 13% and 2% of the participants with >20 monthly seizures at baseline achieved SSR and SSF from the first day of treatment.

The number of seizures that occurred prior to treatment is a well-recognized predictor of seizure outcome.

TABLE 5 Association between baseline characteristics and sustained seizure freedom.

	Unadjusted		Adjusted[a]	
Dependent variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age	1.02 (1.01–1.04)	<.001	1.02 (1.01–1.04)	.001
Duration of epilepsy	.96 (.95–.97)	<.001	.97 (.96–.99)	<.001
Number of concomitant ASMs	.47 (.37–.59)	<.001	.84 (.64–1.09)	.192
Number of prior ASMs[b]				
≥6	.15 (.09–.23)	<.001	.26 (.16–.44)	<.001
Number of seizures per month at baseline[c]				
5–20	.36 (.23–.54)	<.001	.43 (.27–.67)	<.001
>20	.09 (.04–.22)	<.001	.16 (.07–.38)	<.001

Note: Values are from logistic regression models.

Abbreviations: ASM, antiseizure medication; CI, confidence interval; OR, odds ratio.

[a]Adjustment for age, duration of epilepsy, number of concomitant ASMs, number of prior ASMs, and baseline monthly seizure frequency.

[b]Reference is 1–5 ASMs.

[c]Reference is <5 seizures.

Several studies have reported that a heavier seizure burden at baseline reduces the response to ASMs,[8,13–15] and is linked to a higher risk of developing drug-resistant epilepsy.[16,17] A high number of pretreatment seizures can represent a hallmark of severe epilepsy, which is more likely to have poor response to ASMs[18]; the hypothesis that a large number of seizures is one of the causes or determinants of intractability through a mechanism similar to the experimental phenomenon of kindling, however, has also been proposed.[19,20] Of note, in a cohort of 1795 subjects with newly diagnosed epilepsy who started treatment at the Epilepsy Unit of the Western Infirmary in Glasgow, each increase in the number of seizures in the year prior to treatment was associated with a decrease by 6% in the probability of being seizure-free at the last clinic visit.[7] The level of >20 seizures per month has been linked to a very unfavorable outcome after ASM trials; epilepsy was uncontrolled in 47% of patients who reported having >20 seizures before the initiation of therapy, as compared with 33% of patients who had 20 seizures or fewer.[7] More recently, a retrospective study analyzed data related to consecutive adults who attended the epilepsy center at Beaumont Hospital in Dublin, and received cenobamate for at least 3 months through an Early Access Program.[21] Among 38 patients with highly active epilepsy, defined as the presence of ≥20 seizures per month at baseline, two (5.3%) were classified as seizure-free at the end of the study.[21] It is noteworthy that seizure freedom was defined as "freedom from seizures for a minimum of three times the longest preintervention inter-seizure interval or 12 months, whichever is longer,[22] and the actual periods of freedom from seizures in these cases were 5 and 7 months."[21]

The analysis of BRIVAFIRST data suggested that BRV treatment was associated with higher rates of SSF and SSR when it was started in people with history of <5 prior ASMs compared to those with history of ≥6. These findings are consistent with many reports in the literature, which identified the number of ASMs that proved inefficient in the past as a significant independent prognostic factor for the response to a newly administered treatment.[16,17] Of note, the proposed definition of drug resistance as "the failure of adequate trials of two tolerated and appropriately chosen and used ASMs schedules to achieve sustained seizure freedom"[22] is primarily based on observational cohort studies of newly diagnosed epilepsy, suggesting that once a patient has failed trials of two appropriate drugs, the probability of achieving seizure freedom with subsequent treatments is modest.[6,14] There is, however, evidence supporting that drug-resistance is a graded process; the likelihood of seizure freedom decreases and the effect of additional seizure control diminishes with each successive ASM regimen tried.[8,23] In the 30-year longitudinal study in the Glasgow cohort, each additional ASM from the fourth therapeutic regimen onward added only an approximate 1% or less probability of seizure freedom.[7] The rate of 1-year seizure freedom with the sixth and seventh ASM regimens were .33% and .06% of the total study cohort, and none of the patients who tried eight or more successive drug regimens reached seizure freedom.[7] Schiller and Najjar suggested that drug resistance follows a monoexponential course with a half-decay constant of 1.5–2 ASMs, and "absolute" drug resistance requires failure of six ASMs; no patient was rendered seizure-free by the newly administered drug in participants with a history of failure of six or seven ASMs due to inefficacy or AEs when

seizure freedom was defined as no seizures since administration of the ASM or for the last 12 months of follow-up.[8] Notably, adjunctive BRV was associated with an SSF rate of 4.5% in patients with focal epilepsy and prior history of six or more therapeutic regimens, and seizure freedom was achieved on Day 1 of treatment in nearly half of the cases. In the original study by Schiller and Najjar, 26.5% of patients with prior failure of 6–7 ASMs due to inefficacy or AEs benefitted from a newly administered drug with >50% reduction in seizure frequency in the last 3 months of treatment compared to the 3-month baseline.[7] In the BRIVAFIRST cohort, 26.5% of patients with history of six or more lifetime ASMs reached a sustained reduction in baseline seizure frequency of 50% or greater, and 55.2% achieved this improvement the first day of treatment. The term "ultrarefractory" epilepsy has recently been proposed to define the failure to control seizures after appropriate use of at least six epilepsy treatments, including well-tolerated ASM trials, epilepsy surgery, and vagus nerve stimulation.[21] In 54 patients with "ultrarefractory" epilepsy treated with add-on cenobamate, three (5.6%) seizure-free patients had periods of seizure freedom lasting between 5 and 7 months.[21]

The 1-year rate of BRV withdrawal was approximately 25%, which was consistent with the rates reported in other retrospective noninterventional studies of BRV and newer ASMs in clinical practice.[24–31] The main reason for treatment discontinuation was inadequate efficacy and, as expected, it was more common among patients with a higher baseline seizure frequency and a greater number of prior ASMs. Conversely, there were no differences in the rates of drug withdrawal due to poor tolerability according to the initial burden of seizures and prior ASMs. AEs were observed in 30% of the included patients, and at similar rates in the different subgroups; they were mostly mild in intensity, and the most common ones were somnolence, vertigo, fatigue, and headache. These findings confirmed the overall favorable tolerability profile of adjunctive BRV across a wide range of epilepsy activity and severity, and matched data from prior randomized and nonrandomized studies.[24–33]

Sustained seizure freedom and sustained seizure response represent rigorous metrics of treatment efficacy. By excluding those patients who presented only transient periods of seizure frequency reduction or discontinued the drug, these outcomes can account for the "honeymoon effect" that has been reported with many ASMs,[34] and provide more reliable information about the actual response to treatment. The findings of this analysis supported prior evidence suggesting that BRV may have an early and sustained action, and a subset of responders may benefit from the very beginning of the treatment. According to the international definition of drug resistance, seizure freedom is considered as "freedom from seizures for a minimum of three times the longest pre-intervention inter-seizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer." Although in a population of people with very active focal epilepsy, the preintervention interseizure interval is likely to be short and, hence, the three times longest preintervention interseizure interval <12 months, the "rule of three" definition of seizure freedom could represent an additional perspective to consider in future studies. Other strengths of the study include the recruitment at multiple sizes, the large sample size, and the real-world design, which can offer high external validity and address issues left unanswered by randomized, controlled trials. Of note, in regulatory trials of BRV, the treatment phases lasted only 12 weeks and the median baseline seizure frequencies of participants ranged from six to 10 seizures per month, leaving uncertainties about the generalizability of the results over the long term and in populations with more severe seizure activity.[35] Some limits also need to be acknowledged, including potential sources of biases, like the open-label design and retrospective nature. In this regard, the assessment of seizure frequency data by an external expert panel could allow confirmation of the rates of SSR and SSF and act as a quality control; of note, a similar approach has already been shown to be feasible to retrospectively confirm or refute the patient's drug-resistant status,[36] and could also be useful in studies evaluating the effect of ASMs in the reduction of seizure frequency. Although the baseline seizure frequency and number of previous ASMs were stratified following the thresholds of 20 seizures and six treatments proposed in prior seminal papers,[6–8] alternative classifications and their informative value need to be further explored in future studies. The reporting of AEs based on the records of clinical visits rather than standardized questionnaires may have underestimated their actual rate. As changes in therapeutic regimens during follow-up have not been consistently reported, the influence of any variations in concomitant drug load, including the introduction of new or the increase in the dose of concomitant ASMs, could not be explored. Furthermore, the interval of 3 months before starting BRV as baseline may have been short to provide a reliable seizure frequency reduction for people with only one or two seizures a year; it could have been coincidence that some participants had a seizure in the baseline interval and then stayed seizure-free for the 12-month follow-up. In addition, although the data look convincing, the lack of a control group does not allow comparisons with other ASMs and prevents any definitive conclusion about the comparative effectiveness of BRV. Should strict criteria be developed and adopted for grading drug resistance, it would become easier to make indirect comparisons of the efficacy of ASMs from real-world studies.

5 | CONCLUSIONS

Adjunctive BRV was associated with a clinical benefit in a subset of patients with very active and difficult-to-treat focal epilepsy. The sustained control of seizures is a meaningful goal in people with epilepsy, and the reporting of the duration of seizure frequency reduction over time in epilepsy studies can provide more reliable information about the actual effectiveness of ASMs. Studies including the assessment of patient-reported outcomes may further explore the impact of BRV treatment and offer more guidance for informed treatment decisions in clinical practice.

AUTHOR CONTRIBUTIONS

Simona Lattanzi designed and conceptualized the study, coordinated and supervised the data collection, carried out the data analyses, and drafted the manuscript. Valentina Chiesa, Edoardo Ferlazzo, Angela La Neve, Elisa Montalenti, and Carlo Di Bonaventura designed and conceptualized the study, and coordinated and supervised the data collection. Laura Canafoglia, Maria Paola Canevini, Sara Casciato, Emanuele Cerulli Irelli, Filippo Dainese, Giovanni De Maria, Giuseppe Didato, Giancarlo Di Gennaro, Giovanni Falcicchio, Martina Fanella, Massimo Gangitano, Oriano Mecarelli, Alessandra Morano, Federico Piazza, Chiara Pizzanelli, Patrizia Pulitano, Federica Ranzato, Eleonora Rosati, and Laura Tassi were involved in the acquisition of data. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript for submission and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

S.L. has received speaker or consultancy fees from Angelini, Eisai, GW Pharmaceuticals, and UCB Pharma, and has served on advisory boards for Angelini, Arvelle Therapeutics, Bial, Eisai, GW Pharmaceuticals, and Rapport Therapeutics. L.C. has received consultancy fees from Eisai. M.P.C. has received speaker or consultancy fees from Bial, Eisai, Italfarmaco, Sanofi, and UCB Pharma. S.C. has participated in pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma, and Lusofarmaco. V.C. has received speaker or consultancy fees from Eisai and UCB Pharma. E.F. has received speaker or consultancy fees from Angelini, Arvelle Therapeutics, Eisai, GW Pharmaceuticals, and UCB Pharma. A.L.N. has received speaker or consultancy fees from Angelini, Arvelle Therapeutics, Bial, Eisai, GW Pharmaceuticals, Mylan, Sanofi, and UCB Pharma. P.P. has received consulting fees or speaker honoraria from UCB Pharma and Eisai. F.R. has received speaker fees from Eisai, UCB, and LivaNova. E.R. has received fees for participation on advisory boards or scientific consultation from Eisai, GW Pharmaceuticals, Bial, and UCB Pharma. L.T. has received speaker or consultancy fees from Arvelle Therapeutics, Eisai, and UCB Pharma. C.D.B. has received consulting fees or speaker honoraria from UCB Pharma, Eisai, GW Pharmaceuticals, Bial, and Lusopharma. None of the other authors has any conflict of interest to disclose.

LIST OF INVESTIGATORS

BRIVAFIRST Group Membership: Angela Alicino, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University Hospital of Bari A. Moro; Michele Ascoli, Department of Medical and Surgical Sciences, Magna Græcia University of Catanzaro, Catanzaro, Italy; Giovanni Assenza, Dipartimento di Neurologia, Neurofisiopatologia, Neurobiologia, Università Campus Bio-Medico, Rome, Italy; Federica Avorio, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Valeria Badioni, Neurology Unit, Maggiore Hospital, ASST Lodi, Lodi, Italy; Paola Banfi, Circolo Hospital, Fondazione Macchi, ASST Settelaghi, Varese, Italy; Emanuele Bartolini, USL Central Tuscany, Neurology Unit, Nuovo Ospedale Santo Stefano, Prato, Italy; Luca Manfredi Basili, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Vincenzo Belcastro, Neurology Unit, Maggiore Hospital, ASST Lodi, Lodi, Italy; Simone Beretta, San Gerardo Hospital, ASST Monza, Italy; Irene Berto, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Martina Biggi, Department of Neurofarba, University of Florence, Florence, Italy; Giuseppe Billo, Epilepsy Center, UOC Neurology, AULSS 8 Vicenza, Vicenza, Italy; Giovanni Boero, Complex Structure of Neurology, SS Annunziata Hospital, Taranto, Italy; Paolo Bonanni, IRCCS Medea Scientific Institute, Epilepsy Unit, Conegliano, Treviso, Italy; Jole Bongiorno, Neurology Unit, Giovanni Paolo II Hospital, Ragusa, Italy; Francesco Brigo, Department of Neurology, Hospital of Merano (SABES-ASDAA), Merano-Meran, Italy; Emanuele Caggia, Neurology Unit, Giovanni Paolo II Hospital, Ragusa, Italy; Claudia Cagnetti, Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy; Carmen Calvello, Dipartimento di Neurologia, Ospedale Santa Maria della Misericordia, Università di Perugia, Perugia, Italy; Edward Cesnik, Neurology Unit, AOU Ferrara, Ferrara, Italy; Gigliola Chianale, Neurology Unit, San Giovanni Bosco Hospital, Turin, Italy; Domenico Ciampanelli, Institute of Clinical Neurophysiology, Department of Neuroscience, Policlinico Riuniti, Foggia, Italy; Roberta Ciuffini, Department of Life, Health, and

Environmental Sciences, University of L'Aquila, Epilepsy Center, Ospedale San Salvatore, L'Aquila, Italy; Dario Cocito, Presidio Sanitario Major, Istituti Clinici Scientifici Maugeri, Turin, Italy; Donato Colella, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Italy; Margherita Contento, Department of Neurofarba, University of Florence, Florence, Italy; Cinzia Costa, Dipartimento di Neurologia, Ospedale Santa Maria della Misericordia, Università di Perugia, Perugia, Italy; Eduardo Cumbo, Neurodegenerative Disorders Unit, Azienda Sanitaria Provinciale di Caltanissetta, Caltanissetta, Italy; Alfredo D'Aniello, IRCCS Neuromed, Pozzilli, Italy; Francesco Deleo, Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Jacopo C. DiFrancesco, San Gerardo Hospital, ASST Monza, Monza, Italy; Roberta Di Giacomo, Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Alessandra Di Liberto, Neurology Unit, San Giovanni Bosco Hospital, Turin, Italy; Elisabetta Domina, Neurology Unit, Maggiore Hospital, ASST Lodi, Lodi, Italy; Fedele Dono, Department of Neuroscience, Imaging, and Clinical Science, G. D'Annunzio University of Chieti-Pescara, Chieti, Italy; Vania Durante, Neurology Unit, Perrino Hospital, Brindisi, Italy; Maurizio Elia, Oasi Research Institute, IRCCS, Troina, Italy; Anna Estraneo, IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy; Giacomo Evangelista, Department of Neuroscience, Imaging, and Clinical Science, G. D'Annunzio University of Chieti-Pescara, Chieti, Italy; Maria Teresa Faedda, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Ylenia Failli, Department of Neurofarba, University of Florence, Florence, Italy; Elisa Fallica, Neurology Unit, AOU Ferrara, Ferrara, Italy; Jinane Fattouch, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Alessandra Ferrari, Division of Clinical Neurophysiology and Epilepsy Center, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; Florinda Ferreri, Department of Neurosciences, University of Padua, Padua, Italy; Giacomo Fisco, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Davide Fonti, University of Cagliari, Cagliari, Italy; Francesco Fortunato, Dipartimento di Neurologia, Università Magna Græcia, Catanzaro, Italy; Nicoletta Foschi, Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy; Teresa Francavilla, Department of Basic Medical Sciences, Neurosciences, and Sense Organs, University Hospital of Bari A. Moro, Bari, Italy; Rosita Galli, Neurology Unit, Department of Cardioneurovascular Sciences, San Donato Hospital, Arezzo, Italy; Stefano Gazzina, Clinical Neurophysiology Unit, Epilepsy Center, Spedali Civili, Brescia, Italy; Anna Teresa Giallonardo, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Filippo Sean Giorgi, Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy and Neurology Unit, Pisa University Hospital, Pisa, Italy; Loretta Giuliano, Department of Medical and Surgical Sciences and Advanced Technologies G. F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy; Francesco Habetswallner, Department of Clinical Neurophysiology, Cardarelli Hospital, Naples, Italy; Francesca Izzi, Epilepsy Center, Neurology Unit, Department of Systems Medicine, Policlinico Tor Vergata, University of Rome Tor Vergata, Rome, Italy; Benedetta Kassabian, Department of Neurosciences, University of Padua, Padua, Italy; Angelo Labate, Dipartimento di Neurologia, Università Magna Græcia, Catanzaro, Italy; Concetta Luisi, Department of Neurosciences, University of Padua, Padua, Italy; Matteo Magliani, Department of Neurofarba, University of Florence, Florence, Italy; Giulia Maira, Department of Medical and Surgical Sciences and Advanced Technologies G. F. Ingrassia, Section of Neurosciences, University of Catania, Catania, Italy; Luisa Mari, Epilepsy Center, Neurology Unit, Department of Systems Medicine, Policlinico Tor Vergata, University of Rome Tor Vergata, Rome, Italy; Daniela Marino, Neurology Unit, Department of Cardioneurovascular Sciences, San Donato Hospital, Arezzo, Italy; Addolorata Mascia, IRCCS Neuromed, Pozzilli, Italy; Alessandra Mazzeo, Institute of Clinical Neurophysiology, Department of Neuroscience, Policlinico Riuniti, Foggia, Italy; Stefano Meletti, Department of Biomedical, Metabolic, and Neural Science, University of Modena and Reggio Emilia, Modena, Italy; Chiara Milano, Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy and Neurology Unit, Pisa University Hospital, Pisa, Italy; Annacarmen Nilo, Clinic of Neurology, Department of Head, Neck, and Neurosciences, University Hospital S. Maria della Misericordia, Udine, Italy; Biagio Orlando, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Francesco Paladin, Epilepsy Center, Neurology Unit, Venice, Italy; Maria Grazia Pascarella, Neurology Unit, Maggiore Hospital, ASST Lodi, Lodi, Italy; Chiara Pastori, Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Giada Pauletto, Neurology Unit, Department of Head, Neck, and Neurosciences, University Hospital S. Maria della Misericordia, Udine, Italy; Alessia Peretti, Epilepsy Center, UOC Neurology, AULSS 8 Vicenza, Vicenza, Italy; Gabriella Perri, Neurology Unit, ASST Rhodense, Milan, Italy; Marianna Pezzella, Department of Clinical

Neurophysiology, Cardarelli Hospital, Naples, Italy; Marta Piccioli, Dipartimento di Neurologia, Ospedale San Filippo Neri, Rome, Italy; Pietro Pignatta, Neurology and Epilepsy Unit, Humanitas Gradenigo Hospital, Turin, Italy; Nicola Pilolli, Complex Structure of Neurology, SS Annunziata Hospital, Taranto, Italy; Francesco Pisani, Neurology Unit, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; Laura Rosa Pisani, Neurology Unit, Cutroni-Zodda Hospital, Barcellona, Messina, Italy; Fabio Placidi, Epilepsy Center, Neurology Unit, Department of Systems Medicine, Policlinico Tor Vergata, University of Rome Tor Vergata, Rome, Italy; Patrizia Pollicino, IRCCS Centro Neurolesi Bonino-Pulejo, Messina, Italy; Vittoria Porcella, AOU Sassari, Sassari, Italy; Silvia Pradella, USL Central Tuscany, Neurology Unit, Nuovo Ospedale Santo Stefano, Prato, Italy; Monica Puligheddu, University of Cagliari, Cagliari, Italy; Stefano Quadri, Neurology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; Pier Paolo Quarato, IRCCS Neuromed, Pozzilli, Italy; Rui Quintas, Epilepsy Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Rosaria Renna, Epilepsy Outpatient Clinic for Adults, A. Cardarelli Hospital, Naples, Italy; Giada Ricciardo Rizzo, Epilepsy Center, Neurology Unit, Venice, Italy; Adriana Rum, Dipartimento di Neurologia e Neurofisiopatologia, Aurelia Hospital, Rome, Italy; Enrico Michele Salamone, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Ersilia Savastano, Department of Human Neurosciences, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; Maria Sessa, Neurology Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; David Stokelj, Neurology Clinic, ASUGI, Trieste, Italy; Elena Tartara, Epilepsy Center, IRCCS Mondino Foundation, Pavia, Italy; Mario Tombini, Dipartimento di Neurologia, Neurofisiopatologia, Neurobiologia, Università Campus Bio-Medico, Rome, Italy; Gemma Tumminelli, Epilepsy Center, Child Neuropsychiatry Unit, AAST Santi Paolo Carlo, Milan, Italy; Anna Elisabetta Vaudano, Department of Biomedical, Metabolic, and Neural Science, University of Modena and Reggio Emilia, Modena, Italy; Maria Ventura, Neurology Unit, Giovanni Paolo II Hospital, Ragusa, Italy; Ilaria Viganò, Epilepsy Center, Child Neuropsychiatry Unit, AAST Santi Paolo Carlo, Milan, Italy; Emanuela Viglietta, Neurology and Epilepsy Unit, Humanitas Gradenigo Hospital, Turin, Italy; Aglaia Vignoli, Department of Health Sciences, Università degli Studi, Milan, Italy; Flavio Villani, Division of Clinical Neurophysiology and Epilepsy Center, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; Elena Zambrelli, Epilepsy Center, Child Neuropsychiatry Unit, AAST Santi Paolo Carlo, Milan, Italy; Lelia Zummo, Neurology and Stroke Unit, P.O. ARNAS-Civico, Palermo, Italy.

ORCID

Simona Lattanzi https://orcid.org/0000-0001-8748-0083
Laura Canafoglia https://orcid.org/0000-0002-5385-761X
Giuseppe Didato https://orcid.org/0000-0002-4812-6310
Giovanni Falcicchio https://orcid.org/0000-0003-0745-5246
Chiara Pizzanelli https://orcid.org/0000-0001-5044-8944
Carlo Di Bonaventura https://orcid.org/0000-0003-1890-5409

REFERENCES

1. Rogawski MA. Brivaracetam: a rational drug discovery success story. Br J Pharmacol. 2008;154:1555–7.
2. European Medicines Agency. Brivaracetam. https://www.ema.europa.eu/en/documents/overview/briviact-epar-medicine-overview_en.pdf. Accessed 31 May 2023.
3. Lattanzi S, Canafoglia L, Canevini MP, Casciato S, Chiesa V, Dainese F, et al. Adjunctive brivaracetam in focal epilepsy: real-world evidence from the BRIVAracetam add-on first Italian netwoRk STudy (BRIVAFIRST). CNS Drugs. 2021;35:1289–301.
4. Lattanzi S, Canafoglia L, Canevini MP, Casciato S, Chiesa V, Dainese F, et al. Correction to: adjunctive brivaracetam in focal epilepsy: real-world evidence from the BRIVAracetam add-on first Italian netwoRk study (BRIVAFIRST). CNS Drugs. 2021;35:1329–31.
5. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
6. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342:314–9.
7. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol. 2018;75:279–86.
8. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology. 2008;70:54–65.
9. Lattanzi S, Ascoli M, Canafoglia L, Paola Canevini M, Casciato S, Cerulli Irelli E, et al. Sustained seizure freedom with adjunctive brivaracetam in patients with focal onset seizures. Epilepsia. 2022;63:e42–50.
10. Lattanzi S, De Maria G, Rosati E, Didato G, Chiesa V, Ranzato F, et al. Brivaracetam as add-on treatment in focal epilepsy: a real-world time-based analysis. Epilepsia. 2021;62:e1–6.
11. Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Lacosamide monotherapy for partial onset seizures. Seizure. 2015;27:71–4.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7.
13. Kwan P, Brodie MJ. Refractory epilepsy: a progressive, intractable but preventable condition? Seizure. 2002;11:77–84.
14. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol. 2006;13:277–82.
15. Sillanpää M. Remission of seizures and predictors of intractability in long-term follow-up. Epilepsia. 1993;34:930–6.

16. MacDonald BK, Johnson AL, Goodridge DM, Cockerell OC, Sander JW, Shorvon SD. Factors predicting prognosis of epilepsy after presentation with seizures. Ann Neurol. 2000;48:833–41.
17. Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. Neurology. 2001;57:2259–64.
18. Rogawski MA, Johnson MR. Intrinsic severity as a determinant of antiepileptic drug refractoriness. Epilepsy Curr. 2008;8:127–30.
19. Reynolds EH. Do anticonvulsants alter the natural course of epilepsy? Treatment should be started as early as possible. BMJ. 1995;310:176–7.
20. Berg AT, Shinnar S. Do seizures beget seizures? An assessment of the clinical evidence in humans. J Clin Neurophysiol. 1997;14:102–10.
21. Peña-Ceballos J, Moloney PB, Munteanu T, Doyle M, Colleran N, Liggan B, et al. Adjunctive cenobamate in highly active and ultra-refractory focal epilepsy: a "real-world" retrospective study. Epilepsia. 2023;64:1225–35.
22. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. Epilepsia. 2010;51:1069–77.
23. Gomez-Alonso J, Gil-Nagel A. A graded system to categorize drug-resistant epilepsy. Epilepsia. 2010;51:2360–1.
24. Villanueva V, Lo'pez-Gonza'lez FJ, Mauri JA, Rodriguez-Uranga J, Olivé-Gadea M, Montoya J, et al. BRIVA-LIFE-a multicenter retrospective study of the long-term use of brivaracetam in clinical practice. Acta Neurol Scand. 2019;139:360–8.
25. Adewusi J, Burness C, Ellawela S, Emsley H, Hughes R, Lawthom C, et al. Brivaracetam efficacy and tolerability in clinical practice: a UK based retrospective multicenter service evaluation. Epilepsy Behav. 2020;106:106967.
26. Hirsch M, Hintz M, Specht A, Schulze-Bonhage A. Tolerability, efficacy and retention rate of brivaracetam in patients previously treated with levetiracetam: a monocenter retrospective outcome analysis. Seizure. 2018;61:98–103.
27. Steinig I, von Podewils F, Möddel G, Bauer S, Klein KM, Paule E, et al. Postmarketing experience with brivaracetam in the treatment of epilepsies: a multicenter cohort study from Germany. Epilepsia. 2017;58:1208–16.
28. Lattanzi S, Cagnetti C, Foschi N, Ciuffini R, Osanni E, Chiesa V, et al. Adjunctive perampanel in older patients with epilepsy: a multicenter study of clinical practice. Drugs Aging. 2021;38:603–10.
29. Villanueva V, Holtkamp M, Delanty N, Rodriguez-Uranga J, McMurray R, Santagueda P. Euro-Esli: a European audit of real-world use of eslicarbazepine acetate as a treatment for partial-onset seizures. J Neurol. 2017;264:2232–48.
30. Wehner T, Mannan S, Turaga S, Vallabhaneni K, Yip HM, Wiggans C, et al. Retention of perampanel in adults with pharmacoresistant epilepsy at a single tertiary care center. Epilepsy Behav. 2017;73:106–10.
31. Villanueva V, López-Gomáriz E, López-Trigo J, Palau J, García M, Villarroya T, et al. Rational polytherapy with lacosamide in clinical practice: results of a Spanish cohort analysis RELACOVA. Epilepsy Behav. 2012;23:298–304.
32. Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Brivaracetam add-on for refractory focal epilepsy: a systematic review and meta-analysis. Neurology. 2016;86:1344–52.
33. Ben-Menachem E, Mameniškienė R, Quarato PP, Klein P, Gamage J, Schiemann J, et al. Efficacy and safety of brivaracetam for partial onset seizures in 3 pooled clinical studies. Neurology. 2016;87:314–23.
34. Löscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. Epilepsia. 2006;47:1253–84.
35. Lattanzi S, Trinka E, Zaccara G, Striano P, Russo E, Del Giovane C, et al. Third-generation Antiseizure medications for adjunctive treatment of focal-onset seizures in adults: a systematic review and network meta-analysis. Drugs. 2022;82:199–218.
36. Mula M, Zaccara G, Galimberti CA, Ferrò B, Canevini MP, Mascia A, et al. Validated outcome of treatment changes according to International League Against epilepsy criteria in adults with drug-resistant focal epilepsy. Epilepsia. 2019;60:1114–23.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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