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ORIGINAL RESEARCH

Adjunctive Brivaracetam in People with Epilepsy and Intellectual Disability: Evidence from the BRIVAracetam Add-On First Italian netwoRk Study

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ABSTRACT

Introduction: Subjects with intellectual disability are usually excluded from clinical trials and there is limited evidence-based guidance for the choice of antiseizure medications in this vulnerable population. The study explored the effectiveness of brivaracetam (BRV) in people with epilepsy and intellectual disability.

Methods: BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST) was a 12-month

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retrospective, multicenter study including adults prescribed adjunctive BRV. Main outcomes included the rates of seizure-freedom, seizure response (≥ 50% reduction in baseline seizure frequency), and treatment discontinuation. The occurrence of adverse events (AEs) was also considered. Analyses by the presence and severity of intellectual disability were performed.

***Results*:** Subjects with intellectual disability were 253 (24.6%) out of 1029 participants. The 12-month rates of seizure freedom were 18.4% and 10.3% in participants without and with intellectual disability, respectively; the corresponding values for seizure response were 40.0% and 28.9%. Intellectual disability was not an independent predictor of seizure outcomes. The rates of treatment discontinuation were 25.8% and 26.4% in participants without and with intellectual disability. respectively. There were no statistically significant differences in the rates of any AEs, somnolence, nervousness/agitation, and aggressiveness by the presence and degree of intellectual disability.

***Conclusion*:** Brivaracetam can be a suitable treatment option and offer opportunities for clinical improvement in subjects with intellectual disability and uncontrolled seizures.

Keywords: Antiseizure medication; Brivaracetam; Focal seizures; Epilepsy; Intellectual disability

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Key Summary Points

Why carry out this study?

Subjects with intellectual disability are usually excluded from clinical trials, and little guidance exists about treatment of epilepsy in this vulnerable population.

This study aimed to explore the effectiveness and tolerability of adjunctive brivaracetam in people with epilepsy according to the presence and degree of intellectual disability

What was learned from the study?

Adjunctive brivaracetam was associated with seizure frequency reduction in people with intellectual disability

There was no major concern regarding the occurrence of neuropsychiatric effects with brivaracetam in people with intellectual disability

Brivaracetam can be a suitable treatment option in subjects with intellectual disability and uncontrolled seizures.

INTRODUCTION

Epilepsies are among the most common chronic disorders of the brain and affect around 55 million people worldwide in absence of geographical, social, or racial boundaries [1]. In people with an intellectual disability, epilepsy is significantly more common than in the general population. Community-based studies showed a prevalence of epilepsy in adults with intellectual disability of 16–26% [2], while the point prevalence of epilepsy in the general population has been identified at approximately 0.6% [3]. The prevalence of epilepsy increases with the severity of intellectual disability—being 10% in mild and 30–50% in moderate to profound intellectual disabilities [4]—and seizures are pharmacoresistant in more than two-thirds of the cases [2].

The treatment of epilepsy is mainly symptomatic and antiseizure medications (ASMs)

represent the mainstay of treatment. Subjects with intellectual disability are usually excluded from clinical trials, and little guidance exists about treatment of epilepsy in this vulnerable population. Of note, the management of epilepsy in people with intellectual disability is particularly challenging due to the global skills deficits and the high prevalence of drug-resistance, associated morbidities, and polypharmacy [2].

Brivaracetam (BRV) is a third generation, rationally developed ASM characterized by high-affinity binding to synaptic vesicle protein 2A [5]. The drug is indicated for the treatment of focal-onset seizures in patients 1 month of age and older in the US [6], and as adjunctive therapy in the treatment of focal-onset seizures in adults, adolescents and children from 2 years of age in Europe [7]. So far, the evidence about the clinical use of BRV in people with intellectual disability is limited and derives from a few real-world studies including small populations reporting conflicting findings.

The BRIVAracetam add-on First Italian network Study (BRIVAFIRST) evaluated the use of adjunctive BRV in a large population of adults with focal epilepsy treated following routine clinical practice [8, 9]. This analysis of BRIVAFIRST data aimed to explore the 1-year effectiveness and tolerability of adjunctive BRV according to the presence and severity of intellectual disability.

METHODS

Participants

BRIVAFIRST was a retrospective, multicenter study that included subjects aged ≥ 16 years who started adjunctive BRV while on stable treatment with ≥ 1 ASM; details of the study have been reported elsewhere [8, 9]. Subjects with focal epilepsy and 12-month follow-up were considered in the current analysis. Information on age, sex, types of seizures and epilepsy [10], aetiology, prior and concomitant drug regimen, and monthly seizure frequency at baseline (i.e., during the 3 months before starting BRV) were collected. Intellectual disability was categorized as mild, moderate, or severe/profound [11].

Effectiveness endpoints were the rates of short-term freedom from seizures, seizure response (reduction in baseline seizure frequency by 50% or greater), seizure worsening (increase in baseline seizure frequency by 25%) and discontinuation of BRV at 1 year. Additional analyses used information from the 3- and 6-month visits. Short-term seizure-freedom was defined as the lack of seizures since at least the previous visit. Unless patients were already seizure-free during the 3 months before starting BRV, we also considered the rates of sustained seizure freedom and sustained seizure response defined respectively as 100% and ≥ 50% reductions in baseline seizure frequency which continued without interruption from the first time it was achieved through the 12-month follow-up and without BRV withdrawal [12].

Tolerability endpoints were the rate of BRV discontinuation due to adverse events (AEs), the rate of any BRV-related AE and the rate of somnolence, nervousness/agitation, and aggressiveness as selected AEs of particular interest in people with intellectual disability.

Statistical Analysis

Continuous variables were presented as median (interquartile range) and categorical variables as number (percent) of participants. Comparisons were performed using the Mann–Whitney test, Dunn's test, or Chi-squared test. Bonferroni correction was adopted for multiple comparisons. Simple and multivariable logistic regression models were performed to evaluate whether intellectual disability was associated with 12-month seizure freedom and seizure response. Age, duration of epilepsy, number of prior and concomitant ASMs, and baseline monthly seizure frequency were pre-selected as independent variables [13, 14]. Results were considered significant for p values < 0.05 (two-sided). Data analysis was performed using Stata/IC 13.1 (StataCorp, TX, USA). The study is reported according to STROBE guidelines [15].

Ethical Approval

The BRIVAFIRST study was approved by the ethical committee at any participating site and conducted in accordance with the Declaration of Helsinki. Prior to participation in the study, informed consent (e.g., explanation of the purposes of the research, information about handling of personal data and results of the research, description of the procedures adopted for ensuring data protection) was obtained from any patient or from one of the parents or from the legal representative.

RESULTS

Of 1325 participants initially identified, 71 subjects were excluded as diagnosed with generalized, combined, or unknown epilepsy and 225 because follow-up was < 1 year at the data cut-off point. Accordingly, 1029 patients with focal epilepsy were included. Subjects with intellectual disability were 253/1029 (24.6%), whose 97 (38.3%) with mild, 84 (33.2%) with moderate, and 72 (28.5%) with severe/profound disability. Subjects with intellectual disability were younger, had epilepsy onset at a younger age, had a history of a higher number of prior ASMs, had more commonly a genetic aetiology of epilepsy, were treated with more concomitant ASMs, and had a higher seizure frequency at baseline than people without intellectual disability. Baseline characteristics of participants according to the presence and degree of intellectual disability are shown in Table 1.

The median BRV dose at 12 months was 150 (100–200) mg/day in subjects without intellectual disability and 200 (100–200) mg/day, 150 (100–200) mg/day, and 200 (100–200) mg/day in subjects with mild, moderate, and severe/profound intellectual disability, respectively ($p = 0.299$).

At 12-month, the rate of short-term seizure freedom was 143/776 (18.4%) in participants without intellectual disability, 15/97 (15.5%) in participants with mild, 9/84 (10.7%) in participants with moderate, and 2/72 (2.8%) in participants with severe/profound intellectual disability; the corresponding values for ≥ 50% seizure frequency reduction were 40.0%, 32.0%, 26.2%, and 27.8%. The rates of short-term seizure freedom, seizure response, and seizure worsening at 3, 6, and 12 months are summarized in Table 2 and shown in Fig. 1.

The rate of sustained seizure freedom with adjunctive BRV during the 1-year study period was 16.4% in participants without and 7.7% in participants with intellectual disability ($p = 0.001$); the corresponding rates of sustained seizure response were 41.4% and 29.7% ($p < 0.001$). Groupwise, 50.4% and 52.6% of the participants without and with intellectual disability reaching SSF were free from seizures from day 1 of treatment; the corresponding proportions of sustained seizure response maintained for 12 months were 61.9% and 60.3%.

Older age, a shorter duration of epilepsy, a lower number of previous ASMs, and a lower baseline monthly seizure count were independent predictors of 12-month seizure freedom; the number of previous ASMs and baseline seizure frequency were similarly predictors of 12-month seizure response (Table 3).

During the 1-year study period, 265 (25.8%) subjects of the cohort discontinued BRV; the rates of treatment discontinuation were 25.8% and 26.4% in participants without and with intellectual disability, respectively. The corresponding figures for the discontinuation of treatment due to insufficient efficacy were 15.1% and 16.7%, and those for the discontinuation of treatment due to AEs were 10.1% and 8.3%. Discontinuation for both reasons occurred in 5 (0.6%) participants without intellectual disability; in one case, BRV was discontinued due to the patient's request, and one patient died due to a cause unrelated to the treatment. There were no statistically significant differences in the rates of treatment discontinuation, any adverse events, somnolence, nervousness/agitation, and aggressiveness according to the presence and degree of intellectual disability (Table 4).

Table 1 Baseline characteristics of patients according to the presence and degree of intellectual disability

Characteristics	No intellectual disability (*n* = 776)	Mild intellectual disability (*n* = 97)	Moderate intellectual disability (*n* = 84)	Severe/profound intellectual disability (*n* = 72)
Age	46 (35–57)	43 (34–54)	40 (28.5–52)*	32 (25.5–46)*,‡
Male sex	352 (45.4)	51 (52.6)	46 (54.8)	38 (52.8)
Age at epilepsy onset, years ([a]*n* = 1028)	15 (8–31)	10 (4–20)*	8 (4–15)*	1 (0–5.5)*,‡,!
Duration of epilepsy, years ([a]*n* = 1028)	24 (12–37)	28 (14–39)	27.5 (16.5–39.5)	29.5 (20.8–44.5)*
Aetiology				
Structural	419 (54.0)	56 (57.7)	47 (56.0)	31 (43.1)
Genetic	9 (1.2)	9 (9.3)*	6 (7.1)*	16 (22.2)*,!
Immune	9 (1.2)	1 (1.0)	1 (1.2)	–
Infectious	15 (1.9)	5 (5.2)	7 (8.3)*	1 (1.4)
Unknown	324 (41.8)	26 (26.8)*	23 (27.4)	24 (33.3)
Number of previous ASMs ([a]*n* = 1023)	5 (3–8)	7 (4–9)*	7 (4–9)*	7 (4–9)*
Number of concomitant ASMs ([a]*n* = 1028)	2 (1–3)	2 (2–3)*	2 (2–3)*	2 (2–3)*
[b]Baseline monthly seizure frequency	5 (2–14)	3 (7–17)	9 (3–28)*	10 (4–30)*

Data are median (IQR) for continuous variables, and *n* (%) for categorical variables

ASM anti-seizure medication, *IQR* interquartile range

*$p < 0.05$ versus no intellectual disability

‡$p < 0.05$ versus mild intellectual disability

!$p < 0.05$ versus moderate intellectual disability

[a]*n* 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 BRV

DISCUSSION

This subgroup analysis of BRIVAFIRST data provided interesting insights into the use of BRV in people with epilepsy and intellectual disability. Adjunctive BRV was associated with a lower seizure frequency reduction in people with intellectual disability compared to people without. The biggest differences across subgroups were identified in the rates of seizure freedom at all time points throughout the 12-month follow-up; a similar trend was also observed in the proportions of seizure responders. Further, an inverse relationship between the likelihood of seizure control and the severity of intellectual disability emerged. In this regard, however, it is worth noticing that participants with intellectual disability had history of a higher number of prior ASMs, had a more common genetic aetiology of epilepsy, and were treated with more concomitant ASMs than people without intellectual disability. The more severe the intellectual disability and the younger the age at epilepsy onset, the

Table 2 Seizure outcomes in the study cohort

	No intellectual disability ($n = 776$)	Mild intellectual disability ($n = 97$)	Moderate intellectual disability ($n = 84$)	Severe/profound intellectual disability ($n = 72$)
Seizure freedom				
3-Month	14.8%	12.4%	10.7%	2.8%*
6-Month	18.2%	16.5%	9.5%	4.2%*
12-Month	18.4%	15.5%	10.7%	2.8%*,‡
Seizure response				
3-Month	31.6%	22.7%	22.6%	26.4%
6-Month	38.5%	35.1%	26.2%	30.6%
12-Month	40.0%	32.0%	26.2%	27.8%
Seizure worsening				
3-Month	4.0%	4.1%	7.1%	5.6%
6-Month	2.8%	4.1%	7.1%	–
12-Month	1.8%	4.1%	4.8%	1.4%

*$p < 0.05$ versus no intellectual disability

‡$p < 0.05$ versus mild intellectual disability

higher the seizure frequency at baseline. When the analyses were adjusted for these indicators of epilepsy severity, intellectual disability was no longer a significant predictor of seizure freedom and response. Importantly, there was no signal that BRV may have had a negative impact and worsened seizure frequency in this vulnerable population. The median doses of adjunctive BRV were also comparable across the different subgroups of the study cohort.

During the 1-year study period, the rates of treatment discontinuation were similar irrespective of the presence and degree of intellectual disability, and the proportions of participants who experienced any AE were similar also . There were also no statistically significant differences in the rates of somnolence, nervousness/agitation, and aggressiveness, which may represent important tolerability issues and main concerns for caregivers in this selected people with epilepsy.

So far, only three real-world studies including a few subjects compared the use of BRV in people with and without intellectual disability by providing data according to the level of the impairment in cognitive functioning and skills. A retrospective study analyzed data collected from 12 centers in England [16]. Among 139 recruited subjects, 37 had a diagnosis of intellectual disability, which was mild in 17 and moderate–profound in 20. The BRV dose was slightly higher for the group of subjects without intellectual disability and increasingly lower with the severity of intellectual impairment. Changes in 12-month seizure frequency were simply categorized into two categories, namely "at least 50% improvement" and "no/less than 50% improvement". The observed efficacy proportions were higher in both groups of people with intellectual disability (mild: 35.3%; moderate/profound: 30.0%) compared to participants without intellectual disability (29.4%). The 12-month withdrawal rate for BRV was 27.0% in people without intellectual disability and higher than the rates in people with mild (23.5%) and moderate (20.0%) intellectual impairment. Behavioral side effects were more prevalent among people with intellectual disability. However, none of the

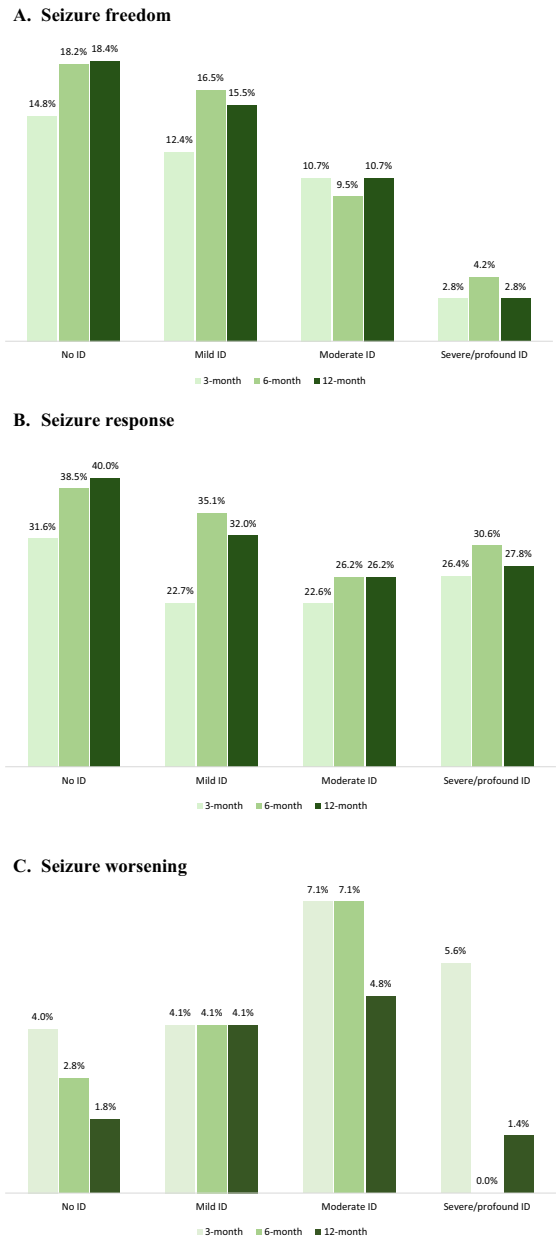

Fig. 1 Seizure outcomes according to the presence and degree of intellectual disability. Rates of *seizure response*, *seizure freedom*, and *seizure worsening* at 3, 6, and 12 months are reported. *Seizure response* was defined as a ≥ 50% reduction in seizure frequency in comparison to baseline seizure frequency. *Seizure worsening* was defined as an increase in seizure frequency of > 25% in comparison to baseline seizure frequency. *ID* intellectual disability

above reported differences reached a statistically meaningful difference suggesting that participants responded similarly to BRV irrespective of whether they had an intellectual disability or its severity [16].

A retrospective study performed at one single tertiary epilepsy center in The Netherlands included 116 in-patients and out-patients with epilepsy and intellectual disability treated with BRV [17]. Most (57.8%) subjects had borderline/mild, 12.9% moderate, and 29.3% severe/profound intellectual disability. Changes in seizure frequency were categorized into three, rather crude groups as seizure frequency reduction, no change, or increase in seizure frequency, and analyses were purely descriptive. All subjects had complete data of 3-month follow-up, while only 76 and 39 had 6- and 12-month follow-up. A decrease in seizure frequency was found in 50.9% of participants at 3 months, in 41.2% at 6 months, and in 41% at 12 months; no information was provided about the antiseizure activity of BRV across the degree of intellectual impairment. The 1-year retention rate for BRV was 58.1%, and adverse effects were experienced by 45.7% of all subjects. There was no statistically significant difference between the group with or without side effects concerning the level of intellectual disability [17]. Andres and colleagues retrospectively evaluated the efficacy and tolerability of BRV treatment during 6 and 12 months in a cohort of residential patients with intellectual disability and drug-resistant epilepsy [18]. The study was performed at one epilepsy center in Germany and included 33 participants aged between 17 and 63 years. There were 9 responders at 6 months out of 32 (28.1%) participants for whom data were available, distributed as 3/12, 3/8, and 3/6 according to borderline/mild, moderate, and severe intellectual disability, respectively; after 12 months, 5 of 27 (19%) participants were responders. The retention rates were 56% at 6 months and 37% at 12 months. Adverse events were documented in 16 of 33 (48%) subjects, behavioral changes being the commonest. Discontinuation of BRV treatment due to behavioral changes was

Table 3 Association between baseline characteristics and seizure outcomes at 12 months

Dependent variable	Unadjusted		Adjusted[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Seizure freedom				
Age	1.03 (1.02–1.04)	< 0.001	1.02 (1.01–1.03)	0.001
Duration of epilepsy	0.96 (0.94–0.97)	< 0.001	0.98 (0.96–0.99)	0.001
Number of previous ASMs	0.67 (0.62–0.72)	< 0.001	0.76 (0.69–0.83)	< 0.001
Number of concomitant ASMs	0.44 (0.36–0.56)	< 0.001	0.92 (0.71–1.20)	0.556
Baseline monthly seizure frequency	0.90 (0.87–0.93)	< 0.001	0.93 (0.90–0.96)	< 0.001
[b]Intellectual disability				
Mild	0.81 (0.45–1.45)	0.475	1.26 (0.64–2.48)	0.503
Moderate	0.53 (0.26–1.09)	0.083	0.99 (0.44–2.21)	0.983
Severe/profound	0.13 (0.03–0.52)	0.004	0.32 (0.07–1.39)	0.128
Seizure response				
Age	1.01 (1.004–1.021)	0.004	1.01 (1.00–1.02)	0.120
Duration of epilepsy	0.990 (0.982–0.998)	0.012	1.00 (0.99–1.01)	0.679
Number of previous ASMs	0.82 (0.78–0.86)	< 0.001	0.83 (0.79–0.88)	< 0.001
Number of concomitant ASMs	0.73 (0.63–0.84)	< 0.001	0.98 (0.83–1.16)	0.815
Baseline monthly seizure frequency	0.986 (0.980–0.993)	< 0.001	0.99 (0.985–0.998)	0.008
[b]Intellectual disability				
Mild	0.71 (0.45–1.11)	0.130	0.87 (0.54–1.40)	0.575
Moderate	0.53 (0.32–0.89)	0.015	0.70 (0.41–1.19)	0.182
Severe/profound	0.58 (0.34–0.99)	0.045	0.87 (0.49–1.54)	0.623

Values are from logistic regression models

ASM antiseizure medications, *CI* confidence interval, *OR* odds ratio

[a]Adjustment for age, duration of epilepsy, number of previous ASMs, number of concomitant ASMs, baseline monthly seizure frequency, and intellectual disability status

[b]No intellectual disability as reference

necessary in almost one-quarter of the study population. Aggressive behavior was the most frequently reported AE and a main reason for BRV discontinuation. There was no significant influence of the grade of intellectual disability in subjects developing behavioral deterioration or other AEs [18].

This subgroup analysis of the BRIVAFIRST data offered new insights into a clinically relevant issue not addressed by pivotal trials and left largely unanswered by the currently available, weak, and limited real-world evidence. The study allowed exploring the effectiveness of adjunctive BRV in the largest cohort of people with epilepsy and intellectual disability ever described. The analyses provided the opportunity to appreciate potential differences in the efficacy and tolerability profile of the drug across the spectrum

Table 4 Treatment discontinuation and adverse events

	No intellectual disability (*n* = 776)	Mild intellectual disability (*n* = 97)	Moderate intellectual disability (*n* = 84)	Severe/profound intellectual disability (*n* = 72)
Treatment discontinuation, *n* (%)				
Any reason	200 (25.8)	20 (20.6)	26 (31.0)	19 (26.4)
Insufficient efficacy	117 (15.1)	13 (13.4)	17 (20.2)	12 (16.7)
Adverse events	78 (10.1)	7 (7.2)	8 (9.5)	6 (8.3)
Both reason	5 (0.6)	–	–	–
Any adverse events, *n* (%) ([a]*n* = 877)	208/654 (31.8)	29/87 (33.3)	15/73 (20.6)	12/63 (19.1)
Somnolence, *n* (%) ([a]*n* = 852)	47/632 (7.4)	5/86 (5.8)	1/72 (1.4)	3/62 (4.8)
Nervousness/agitation, *n* (%) ([a]*n* = 852)	39/632 (6.2)	7/86 (8.1)	3/72 (4.2)	1/62 (1.6)
Aggressiveness, *n* (%) ([a]*n* = 852)	14/632 (2.2)	2/86 (2.3)	2/72 (2.8)	2/62 (3.2)

[a]*n* the total number of patients for whom data in question were available

of intellectual disability. The actual impact of intellectual disability and baseline characteristics of the participants on seizure outcomes was investigated and independent outcome predictors were identified. Further, the real-world setting with clinical decisions based on the experience and judgment of the treating physician guaranteed a high degree of external validity and generalizability of the findings to everyday clinical practice. There are also limitations that need to be acknowledged. The open-label and retrospective study design may have introduced potential sources of biases, and the lack of a control group did not allow the drawing of any conclusion about the comparative efficacy and tolerability of BRV with other ASMs. Although statistical analyses were adjusted for common indicators of epilepsy severity, there may exist other differences clearly intrinsic to intellectual disability which were not included. The unavailability of data by seizure subtypes prevented an investigation of the antiseizure activity of BRV according to seizure semiology, while the collection of AEs through the records of clinical visits instead of standardized questionnaires might have resulted in possible underreporting. The unavailability of neuropsychological testing over time did not allow evaluation or drawing definitive conclusions about the impact of the therapy; of note, impairment in cognitive functioning would be much more noticeable and badly perceived in completely healthy subjects than in subjects with a pre-existing intellectual disability. In addition, the lack of statistical difference could not exclude a similar effect, either negative or positive, across the subgroups.

CONCLUSION

There is limited evidence-based guidance for the treatment choice of ASMs in people with epilepsy and intellectual disability. In the BRIVA-FIRST study, adjunctive BRV was associated with seizure frequency reduction, and differences across subgroups could be likely explained by the severity of underlying epilepsies rather than by the independent effect of intellectual disability. The treatment with BRV was tolerated similarly well irrespective of the concomitant intellectual impairment, and there was no major concern regarding the occurrence of neuropsychiatric effects. Brivaracetam can be a suitable treatment option and offer opportunities for clinical improvement in subjects with

intellectual disability and uncontrolled seizures. Additional research is needed to further explore the actual potential of BRV in this vulnerable population and to give more information for guiding clinical decisions.

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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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Declarations

Conflict of Interest. Simona Lattanzi has received speaker's or consultancy fees from Angelini, Eisai, GW Pharmaceuticals, NewBridge Pharmaceuticals, and UCB Pharma, and has served on advisory boards for Angelini, Arvelle Therapeutics, Bial, EISAI, GW Pharmaceuticals, Rapport Therapeutics, and UCB Pharma. Laura Canafoglia has received consultancy fee from Eisai. Maria Paola Canevini has received speaker's or consultancy fees from Bial, Eisai, Italfarmaco, Sanofi, and UCB Pharma. Sara Casciato has participated in pharmaceutical

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REFERENCES

1. Asadi-Pooya AA, Brigo F, Lattanzi S, Blumcke I. Adult epilepsy. Lancet. 2023;402:412–24.

2. McGrother CW, Bhaumik S, Thorp CF, Hauck A, Branford D, Watson JM. Epilepsy in adults with intellectual disabilities: prevalence, associations and service implications. Seizure. 2006;15:376–86.

3. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurolog. 2017;88:296–303.

4. Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: a systematic review. Seizure. 2015;29:46–62.

5. 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.

6. US Food and Drug Administration. Brivaracetam. Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205836s009,205837s007,205838s006lbl.pdf. Accessed Dec 2024.

7. European Medicines Agency. Brivaracetam. https://www.ema.europa.eu/en/documents/overview/briviact-epar-medicineoverview_en.pdf. Accessed Oct 2024.

8. Lattanzi S, Canafoglia L, Canevini MP, BRIVAFIRST Group Membership, 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.

9. Lattanzi S, Canafoglia L, Canevini MP, BRIVAFIRST Group Membership, 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.

10. 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.

11. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization. https://www.who.int/iris/handle/10665/37958. Accessed Oct 2024.

12. Lattanzi S, Ascoli M, Canafoglia L, et al. Sustained seizure freedom with adjunctive brivaracetam in patients with focal onset seizures. Epilepsia. 2022;63:e42-50.

13. 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.

14. Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Lacosamide monotherapy for partial onset seizures. Seizure. 2015;27:71–4.

15. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7.

16. Allard J, Henley W, Sellers A, et al. Efficacy and tolerability of Brivaracetam in people with intellectual disability compared to those without intellectual disability. Epilepsy Behav. 2024;158: 109906.

17. Gillis RME, Wammes-van der Heijden EA, Schelhaas HJ, et al. Efficacy and tolerability of brivaracetam in patients with intellectual disability and epilepsy. Acta Neurol Belg. 2021;121:677–84.

18. Andres E, Kerling F, Hamer H, Winterholler M. Behavioural changes in patients with intellectual disability treated with brivaracetam. Acta Neurol Scand. 2018;138:195–202.