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# Short-term and longer-term effects of brivaracetam on cognition and behavior in a naturalistic clinical setting—Preliminary data

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ABSTRACT

*Purpose:* To assess short-term and longer-term effects of brivaracetam (BRV) on cognition and behavior in a naturalistic clinical setting.

*Methods:* Analyses were based on 43 patients with epilepsy who had undergone a neuropsychological screening before adjunctive treatment with BRV and a follow-up evaluation either after 5 days or 25 weeks. The standard assessment focused on reaction times (Neurocog FX), attention and executive functions (EpiTrack), and verbal memory (short version of the VLMT). Self-perceived cognition and behavior was evaluated by an extended version of the Adverse Events Profile. In addition, health-related quality of life (QOLIE-10) was reassessed at the longer-term interval.

*Results:* Repeated measures analysis of variance revealed a significant improvement under BRV with regard to attention and executive functions ($p = .03$) without an interaction with the length of the observation interval. A statistical trend in the same direction was also seen for the reaction times ($p = .07$), but not for the unchanged verbal memory performance. Subjective measures indicated improvements in concentration ($p = .02$) and especially in comprehension ($p < .001$), and health-related quality of life ($p = .002$). Mood and aggression scores were unchanged. At the longer-term follow-up, an at least 50 percent reduction in seizure frequency was observed in 53% of the patients, 21% were seizure free.

*Conclusion:* These preliminary data point to a favorable cognitive profile of BRV similar to its precursor levetiracetam. Objective gains in attention and executive functions were accompanied by self-reported improvements in concentration and comprehension. Future studies with larger sample sizes and better control conditions are needed to confirm these findings.

## 1. Introduction

Brivaracetam (BRV) was approved in 2016 as a new antiepileptic drug (AED) for the adjunctive pharmacological treatment of focal-onset seizures with or without secondary generalization. Meanwhile BRV was also approved as monotherapy. BRV is a derivative of levetiracetam (LEV) with a 15- to 30-fold higher affinity to ubiquitous synaptic vesicle glycoprotein 2A [1].

A recent meta-analysis of randomized controlled trials on the adverse event profile of BRV reported a significant association between BRV treatment and dizziness, fatigue, and back pain without an obvious dose dependency [2]. Psychiatric problems were not found to be increased. In a preclinical model BRV treated rats showed no deviation in cognition and behavior compared to control rats, whereas LEV treated animals demonstrated significantly more aggressive and less social behaviors [3]. A favorable and superior adverse effect profile of BRV versus LEV was concluded. However, a more recent study found behavioral changes, predominantly aggressive behavior, in a relevant number of patients with intellectual disability and epilepsy treated with brivaracetam [4].

Regarding cognition, no negative effects of BRV have been seen in animal models when investigating spatial learning and memory [5]. In an Alzheimer's disease mouse model even positive effects of BRV on spatial memory have been reported [6].

Up to now only a single study has evaluated the neurocognitive effects of BRV in man, i.e. 16 healthy volunteers [7]. Objective and subjective cognition under BRV did not differ from placebo or treatment with LEV.

Up to now the objective cognitive effects of BRV have not been studied in people with epilepsy.

At the epilepsy center in Bonn we have established a routine monitoring of the cognitive and behavioral effects of drug treatment in in-

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and outpatients that is following a natural schedule as requested by the treating physician [8,9].

Data from these assessments were retrospectively examined in order to evaluate the short-term and longer-term effects of adjunctive BRV on cognition and behavior. Since BRV is a successor of LEV, we expected a comparable favorable cognitive profile. However, given that LEV may exert negative effects on mood and behavior [10,11], we also focused on behavioral side effects.

BRV is the very first antiepileptic drug (AED) that can provide an efficacious target dose already on titration day 1, offering the opportunity for exceptionally early cognitive follow-up evaluations.

## 2. Methods

### 2.1. Study design and participants

Retrospective analyses were based on 43 patients with epilepsy who had undergone a standardized cognitive screening before and after introduction of adjunctive treatment with BRV at our department. The follow-up evaluation was performed either after 5 ± 2 days (n = 24) or after 25 ± 13 weeks (n = 19). The demographic and clinical characteristics are presented in Table 1. There were no significant differences between the two follow-up conditions. However, there was a non-significant trend of a higher total antiepileptic drug load[1] at the short-term (vs. longer-term) follow-up (T = -1.9, p = .06; cf. Table 1). Concomitant AEDs and respective changes are listed in Table 2. At baseline the by far most common AEDs were LEV (77%) and lamotrigine (LTG; 51%).

### 2.2. Neuropsychological assessments

Neuropsychological routine assessment focused on attention and executive functions (*EpiTrack*), and verbal memory (short version of the *VLMT*). In addition to our routine battery we also assessed psychomotor speed and alertness via reaction times (subtest of the *NeuroCog FX*). Self-perceived cognition and behavior was evaluated by an extended version of the Adverse Events Profile (*AEP*). In addition, health-related quality of life (*QOLIE-10*) was reassessed at the longer-term interval.

#### 2.2.1. Reaction times

Simple reaction times on visual stimuli were measured via the respective subtest of the Neurocog FX, a computerized test battery developed for neurological settings and patients with epilepsy in particular [12,13]. Every time a blue circle is presented on the screen patients had to push a key as fast as they could. The relevant parameter is the median reaction time in milliseconds. Neurocog FX provides normative data from 244 healthy controls and reliable change indices (RCIs) to determine significant intraindividual change. Regarding the simple reaction times, the cutoff for a significant increase or decrease is > 80 ms or < 80 ms, respectively.

#### 2.2.2. Attention and executive function

The EpiTrack® (second edition with extended and revised norms) is a screening tool devised for the tracking of adverse cognitive effects of antiepileptic medication [14,15]. The test comprises six subtests on response inhibition, visuo-motor speed, mental flexibility, visual motor planning, verbal fluency and working memory. Based on the subtest results, an age-corrected total score is calculated. Application and evaluation of this test is simple and thus guarantees objectivity. Age-corrected norms from 689 healthy individuals (age range 16–87) and RCIs for reassessments are provided. Patients can achieve a maximum score of 49 points. The interval for mild impairment is 29–31 points, and the cutoff for significant impairment is ≤28 points. Practice corrected RCIs indicate a significant change with a gain of > 3 points, and a loss of > 2 points. Studies demonstrated the usefulness of the EpiTrack with regard to cognitive monitoring of pharmacological treatments [8,9,16,17] and its sensitivity in regard to the overall drug load, i.e. the number of concurrent AEDs [18].

#### 2.2.3. Verbal memory

Episodic memory was assessed via a short version of the Verbaler Lern- und Merkfähigkeitstest (VLMT) [19], the German adaption of the Rey Auditory Verbal Learning Test (RAVLT) and the most commonly applied verbal learning and memory test in German epilepsy centers [20]. The applied version consists of two consecutive trials of learning and immediate recall of a 15-item word list before performing the EpiTrack. Delayed free recall of the learned items is requested after the EpiTrack. Thus the Epitrack represents the distraction condition for memory testing. Memory performance was normalized with results from 383 healthy individuals. Scores for learning (learning trials 1 + 2), memory (delayed recall trial 3), and loss of learned items over time (trial 2 minus trial 3) were converted into a scale ranging from 1 to 7 according to the norm data of the healthy subjects and merged into a total memory score ranging from (3–21). After age correction, total memory scores from 14 to 18 were rated as normal, scores from 11 to 13 as mild impairment, and scores of ≤10 as significant impairment. According to practice corrected RCI (p < .10) a change was considered to be significant with a gain of > 3 points and a loss of > 5 points. This short version of the VLMT had been applied together with EpiTrack in previous studies on the cognitive effects of LEV vs. carbamazepine (CBZ) monotherapy [16], lacosamide (LCM) vs. topiramate (TPM) vs. lamotrigine (LTG) [9], and perampanel (PER) vs. LCM [8].

#### 2.2.4. Side effects

Self-perceived side effects of AEDs were assessed by an extended version of the Adverse Events Profile (AEP) [9,21] covering the three domains (1) cognition (vigilance, psychomotor speed, attention, fluent speech, word finding comprehension, remote memory, recent memory, spatial orientation), (2) behavior (energy, depression, anxiety, aggression, irritability), and (3) physical/physiological symptoms (vestibular disorder, dizziness, drowsiness, sleepiness, nervousness, tremor, headache, upset stomach/nausea, trouble with mouth or gums, hair loss, skin problems, double or blurred vision, weight gain or loss, sexual dysfunction, altered libido, disturbed sleep). Patients were asked to rate the presence and strength of impairments on a four-tiered scale ranging from not at all (0) to strong (3).

#### 2.2.5. Health-related quality of life

Health-related quality of life was assessed via the German adaptation of the Quality of Life in Epilepsy (QOLIE)-10 questionnaire [9] which is a widely used and validated instrument developed specifically to screen aspects of health-related quality of life for individuals with epilepsy [22]. The QOLIE-10 covers different epilepsy- and treatment-related issues including energy, mood, mobility, work and social limitations, cognitive problems, physical and cognitive treatment effects, seizure worries, and general quality of life. In contrast to the original version, the German adaptation comprises 13 items. Each item includes a 5-tiered rating scale (1–5) so that total scores between 13 and 65 can be achieved with greater values reflecting worse quality of life. Since on item level values of 1 indicate no impairment, and values of 2 the mildest form of impairment, total scores exceeding half of the possible

[1] The total antiepileptic drug load was quantified according to the defined daily doses (DDD) of concurrent AEDs. The DDD is provided by the Collaborating Centre for Drug Statistics Methodology of the World Health Organization (WHO) and reflects the "assumed average maintenance dose per day" for drugs used in different medical areas, in this context the treatment of epileptic seizures (http://www.whocc.no/atc_ddd_index/). Regarding individual patients, the actual daily dose of a specific AED is related to the respective DDD by calculating the respective ratio (daily dose/DDD). The cumulative or total DDD is the sum of this ratio for all AEDs of the individual regimen.