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Brivaracetam (Brivact®): A New Adjunctive Treatment for Partial-Onset Seizures

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Epilepsy affects 1.3 to 2.8 million people in the United States alone[1] and as many as 30% of these patients develop refractory epilepsy.[2] Even worse, only about 5% of patients with treatment-resistant epilepsy are able to achieve being seizure-free for one year using newer and older anti-epileptic drugs (AEDs).[3] Generally, epilepsy is a disorder where the brain is continuously predisposed to generating epileptic seizures. This definition of epilepsy also includes the psychological, cognitive, and social consequences of the disorder.[4] Seizures are defined as a fleeting occurrence of signs and/or symptoms as a result of abnormal excessive or synchronous neuronal activity in the brain.[5]

There are currently many treatment options for epilepsy including carbamazepine, gabapentin, lamotrigine, and levetiracetam, which are particularly useful in patients with newly-diagnosed generalized or partial epilepsy.[5] Many of these medications work by acting on sodium or calcium channels or on the GABA system.[6] Brivaracetam (Brivact®) was approved by the Food and Drug Administration (FDA) in 2016 as adjunctive therapy in the treatment of partial-onset seizures (POS) in patients sixteen years of age or older. This article is intended to discuss the pharmacology, kinetics, and administration of brivaracetam.

Pharmacology

The exact mechanism of brivaracetam is unknown, but it does display a high affinity for synaptic vesicle protein 2A (SV2A) in the brain which may contribute to its anticonvulsant effect.[7] The only other AED displaying this mechanism of action is levetiracetam. Giving clinicians more treatment options can be especially helpful in treating patients with epilepsy who do not respond to other, more typical treatments.

Brivaracetam is highly permeable and is quickly and nearly completely absorbed after oral administration. It is rapidly and evenly distributed in most tissues. It exhibits dose-proportional pharmacokinetics with the time to peak plasma concentration being 1 hour when taken without food. Brivaracetam given with high-fat meals may slow absorption, but does not change the extent of absorption. When 50 mg of brivaracetam was given with a high-fat meal, the maximum plasma concentration was decreased by 37% and the time to peak plasma concentration was postponed three hours,[7] however, the area under the curve (AUC) remained unchanged. Brivaracetam is weakly-bound to plasma proteins, and its plasma half-life is about 9 hours.

Brivaracetam is metabolized primarily by CYP2C19, therefore, in patients with a genetic variation in CYP2C19, or in patients taking medications which induce CYP2C19 such as rifampin, dose increases may be warranted. In these patients, blood levels of brivaracetam are generally increased – in some cases as much as 42% which could potentially lead to an increased chance of side effects.[7] Brivaracetam is mainly eliminated via metabolism and via excretion in the urine. Drug interactions with other AEDs are noted in Table 1. Some notable medications that are safe to use with brivaracetam are lamotrigine, levetiracetam, and valproic acid.

Clinical Trials

The initial studies involving brivaracetam included 1550 participants in total and were all randomized, double-blind, and pla-

Table 1 | Interactions Between Brivaracetam and other Antiepileptic Drugs[7]

Antiepileptic Drug	Influence of AED on brivaracetam	Influence of brivaracetam on AED
Carbamazepine	26% decrease	None; increase in metabolite
Lacosamide	No data	None
Lamotrigine	None	None
Levetiracetam	None	None
Oxcarbazepine	None	None on the active metabolite
Phenobarbital	19% decrease	None
Phenytoin	21% decrease	Up to 20% increase
Pregabalin	No data	None
Topiramate	None	None
Valproic acid	None	None
Zonisamide	No data	None

AED = antiepileptic drug

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Table 2 | Summary of Clinical Trials for Brivaracetam

Trial	Design	Intervention	Primary Outcome	Findings	Authors' Conclusions
Binton, et al (2007)[8]	2-year, Phase III RCT	Brivaracetam 5 mg/day, 20 mg/day, 50 mg/day, or placebo	Percent reduction in POS frequency per week over placebo	The 50 mg/day group showed a statistically-significant reduction in seizure frequency/week of 12.8%	These results demonstrate efficacy for the 50 mg/day dose, but not other groups
Ryvlin, et al (2007)[9]	2-year, Phase III RCT	Brivaracetam 20 mg/day, 50 mg/day, 100 mg/day, or placebo	Percent reduction in focal seizure frequency per week over placebo over the treatment period	The 100 mg/day group showed a statistically-significant reduction in seizure frequency/week of 11.7%	The efficacy results are inconclusive, but these data may be useful in determining the lowest effective dose of brivaracetam
Klein, et al (2010)[10]	2-year, Phase III RCT	Brivaracetam 100 mg/day, 200 mg/day, or placebo	Co-primary outcomes: 1) Percent reduction over placebo in 28-day adjusted POS frequency and 2) ≥50% responder rate	Both outcomes were statistically-significant. Decrease in adjusted seizure frequency of 22.8% for BRV 100 mg/day and 23.2% for BRV 200 mg/day. ≥50% responder rate of 38.9% in BRV 100 mg/day group and 37.8% in BRV 200 mg/day group.	The data demonstrate that BRV 100 mg/day and 200 mg/day had a robust, statistically-significant effect for both co-primary efficacy outcomes

BRV = brivaracetam; **POS** = partial-onset seizure; **RCT** = randomized controlled trial

cebo-controlled. All studies discussed are Phase III clinical trials and are summarized in **Table 2.**

Binton et al. conducted a study from 2007 to 2009 comparing brivaracetam 5 mg, 20 mg, or 50 mg to placebo.[8] Participants were recruited from 85 sites in several countries: Australia, Brazil, Canada, Mexico, and the United States. The study was designed to have an 8-week prospective baseline period followed by a 12-week treatment period followed either by a 1-week down-titration period or optional entry into a long term open-label follow-up study. Participants were not randomized until the end of the 8-week prospective baseline period. Participants studied were aged 16 to 70 with well-characterized partial epilepsy defined as two or more partial-onset seizures per month during the 3 months prior to the initial screening, and eight or more partial-onset seizures during the 8-week prospective baseline period. In addition, participants were uncontrolled on at least one or two AEDs at optimal dosages for more than one month. The vast majority in each group were on two concomitant AEDs, while a much smaller proportion were receiving one or three concomitant AEDs. Carbamazepine and lamotrigine were the two most common concomitant AEDs. The main exclusion criteria were nonmotor simple partial seizures as the sole seizure type. Other exclusion criteria included either presence or history of status epilepticus or pseudoseizures, among others. The primary efficacy outcome was the frequency of partial-onset seizures per week over the 12-week treatment period, as measured by percent reduction over placebo. Five hundred potential participants were identified however only 400 patients were randomized. Of these 400 patients, four were excluded due to one of them failing to take the study medications and the other three due to randomization errors. The remaining 396 participants were randomized in a 1:1:1:1 ratio to the placebo, brivaracetam 5 mg/day, 20 mg/day, and 50 mg/day groups, respectively. Only the 50 mg/day group showed statistically significant reductions in seizure frequency per week and per 28 days compared to placebo at 12.8% ($p = 0.025$) and 22% ($p = 0.004$), respectively.[8] The 5 mg/day group showed a 0.9% increase ($p = 0.885$) in seizure frequency per week while the 20 mg/day group showed a 4.1% decrease ($p = 0.492$) in seizure frequency per week compared to placebo.

Ryvlin et al. compared brivaracetam 20 mg, 50 mg, or 100 mg/day to placebo.[9] Similar to the previous trial, this study was designed to have an 8-week prospective baseline period followed by a 12-week treatment without up-titration. Participants included were aged 16 to 70 years and were diagnosed with focal epilepsy or epileptic syndrome. Inclusion criteria were well-characterized focal epilepsy with a history of focal seizures with or without secondary generalization.[9] In addition, participants were included if they had two or more focal seizures per month for 3 months prior to screening and eight or more focal seizures during the 8-week baseline period. Like the previous study, participants were receiving at least one or two concomitant AEDs at stable and optimal dosages from at least one month prior to screening and throughout the entirety of the study. The vast majority of patients in each group were receiving two concomitant AEDs while a much smaller proportion were receiving one or three AEDs. Carbamazepine and valproic acid were the two most common concomitant AEDs. Some of the key exclusion criteria included nonmotor simple focal seizures as the only seizure type, a history of seizures occurring only in clusters before randomization, and the presence of status epilepticus during the 12 months prior to screening or during baseline.[9] The primary efficacy variable was the frequency of focal seizures per week over the treatment period of 12 weeks. Out of 398 participants, 367 were randomized to brivaracetam 20 mg/day, 50 mg/day, 100 mg/day and placebo. There were rough-

Table 3 | Adverse Reactions in Pooled Placebo-Controlled Adjunctive Therapy Studies in Patients with Partial-Onset Seizures[11]

Adverse Reactions	Brivaracetam (N= 803) %	Placebo (N= 459) %
Nausea/vomiting symptoms	5	3
Constipation	2	0
Somnolence and sedation	16	8
Dizziness	12	7
Fatigue	9	4
Cerebellar coordination and balance disturbances	3	1
Irritability	3	1

ly equal amounts of participants in these groups. Only the 100 mg/day group in this study showed a statistically-significant reduction in baseline seizure frequency per week and per 28 days at 11.7% ($p = 0.037$) and 20.5% ($p = 0.010$), respectively. The 20 mg/day group showed a 6.8% reduction ($p = 0.239$) in baseline seizure frequency per week and a 10.2% reduction ($p = 0.222$) in seizure frequency per 28 days. The 50 mg/day group showed a 6.5% ($p = 0.261$) and a 9.2% ($p = 0.274$) reduction in seizure frequency per week and per 28 days, respectively.

Klein, et al conducted a study using brivaracetam 100 mg/day and 200 mg/day compared to placebo.[10] Similar to the two previous studies, this study was designed to have the same 8-week prospective baseline, 12-week treatment, 4-week down-titration, and 2-week drug-free periods as the other studies. Participants could also opt into a long-term follow up study after the down-titration period. The participants were of a wider age range, 16 to 70 years of age, than the other studies, but also had well-characterized focal epilepsy or epileptic syndrome and were uncontrolled with one or two AEDs at consistent dosages at least a month prior to visit. Like the two previous studies, the vast majority of patients in each group were receiving two concomitant AEDs during the study while a much smaller proportion were receiving one or three concomitant AEDs. Carbamazepine and lamotrigine were the two most common concomitant AEDs. One notable difference in this study in comparison to the two other previous studies is that participants must have had an electroencephalography reading compatible with the diagnosis of focal epilepsy within the last 5 years. They must also have had a brain magnetic resonance imaging or computed tomography scan within the last 2 years.[10] Participants needed to have 8 or more POSs during the baseline period of 8 weeks and 2 or more POSs per month during the 3 months before the first visit. Seventy-eight participants in 27 countries were then randomized in a 1:1:1 ratio to brivaracetam 100 mg/day, 200 mg/day, or placebo. The co-primary efficacy outcomes were percent reduction in POSs over placebo per 28 days and ≥50% responder rate based on percent reduction in seizure frequency from baseline to the treatment period. Both co-primary outcomes were statistically significant for both brivaracetam doses ($p < 0.001$ vs. placebo). The 100 mg/day group saw a 22.8% reduction in 28-day seizure frequency while the 200 mg/day group saw a 23.2% reduction. The ≥50% responder rate was 38.9% for the 100 mg/day group, 37.8% for the 200 mg/day group, and 21.6% for the placebo group.

The three trials discussed above show promise in the efficacy of brivaracetam. All three trials combined either showed statistically-significant efficacy at 50 mg, 100 mg, or 200 mg per day. The results seem to be clinically-significant as well with a 22.8% and 23.2% decrease in seizures per week for 100 mg and 200 mg per day, respectively.

Adverse Reactions and Precautions

The main adverse reactions in patients taking brivaracetam are somnolence and sedation, which are dose-dependent. In all three clinical trials, the rate of these specific adverse reactions was 16% among patients taking brivaracetam. Dizziness was the second most common adverse reaction at 12%. Adverse reactions of brivaracetam can also include psychiatric non-psychotic symptoms such as irritability, anxiety, nervousness, and aggression. Psychotic symptoms may also occur including paranoia, acute psychosis, and psychotic behavior. Over the three studies discussed, the percentage of patients affected by these reactions, both psychotic and non-psychotic, was approximately 13% in those who received brivaracetam and 8% in those who received placebo.[7] **Table 3** summarizes important adverse reactions observed in the trials. Dizziness and somnolence/sedation account for most of the adverse reactions seen in patients taking brivaracetam.

Dosing and Administration

Brivaracetam is available as an oral and injectable medication and may be started at a dose of 50 mg twice daily. Gradual dose increases are not necessary. Based on patient response and tolerability, the dose may be adjusted down to 25 mg twice daily. Brivaracetam for injection is also available when oral administration is temporarily not possible. The dosage and frequency is the same regardless of route of administration. It is administered intravenously over 2 to 15 minutes and should not be used for more than 4 consecutive days.[7] Brivaracetam should not be abruptly discontinued in order to minimize the risk of increased seizure frequency and status epilepticus.

It should also be of note that brivaracetam is a Schedule V controlled substance, and that therapeutic and supratherapeutic doses were compared to alprazolam, a Schedule IV controlled substance, in a human abuse potential study. It was found that the recommended single dose of 50 mg caused fewer sedative and euphoric side effects than alprazolam, but in supratherapeutic doses of 200 mg and 1000 mg, brivaracetam was similar to alprazolam in terms of abuse potential.[7] Clinically, it seems that the worry for abuse would be low as the euphoric effects of the drug did not occur until higher-than-indicated doses.

Use in Special Populations

Brivaracetam can be used in patients who fall within specific populations. Brivaracetam is pregnancy category C[7], but no well-controlled studies have been performed in pregnant women. In animal studies, it has shown some developmental toxicity at exposures greater than typical clinical exposures. Brivaracetam should only be used in pregnant women when the benefits outweigh the risks. Brivaracetam has only been studied in patients 16 years of

age or older. Safety and effectiveness in patients less than this age have not been established. In the geriatric population there were insufficient numbers of patients aged 65 years or older in the three main clinical trials discussed above to adequately assess safety and efficacy in this population. In patients with impaired renal function, dosage adjustments are not required. Patients with end-stage renal disease and undergoing dialysis, however, should not take brivaracetam. For patients with any stage of hepatic impairment, the recommended starting dosage is 25 mg twice daily with a maximum of no more than 75 mg twice daily.[7]

Conclusion

Epilepsy is a complex condition affecting millions of people across the world, and a number of these individuals may develop refractory epilepsy. Brivacetam (Brivact®) has been shown to reduce seizure frequency among adult patients with partial-onset seizures uncontrolled on at least one AED. Although the results from the clinical trials are not generalizable to children and the elderly, brivaracetam (Brivact®) represents a new and effective adjunct therapy option for many patients with partial-onset seizures who have failed, or are not adequately controlled on, other conventional therapies.

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Editor's Corner

Off-label Dosing of Direct Acting Oral Anticoagulants in Clinical Practice

A recent study published in the *Journal of American College of Cardiology* assessed the prevalence of off-label dosing with direct acting oral anticoagulants (DOACs) in patients with non-valvular atrial fibrillation (AF). The study also evaluated the clinical outcomes associated with off-label dosing in community practice.

Utilizing patient data from the ORBIT-AF II trial, the authors included adult patients with a recent, new diagnosis of AF and/or who have been initiated on a DOAC for thromboembolism prevention. Enrolled patients were categorized into three groups based on appropriateness of DOAC dose: (1) dosing consistent with, (2) underdosed, and (3) overdosed according to U.S. FDA-approved package insert. Follow-up in the ORBIT-AF II trial was 12 to 24 months, at 6 month intervals. The clinical outcomes of this study were all-cause death, stroke or systemic embolism, myocardial infarction, hospitalization, and major bleeding.

The total study cohort consisted of 5,738 patients who were treated with a DOAC, which included dabigatran (7.4%), rivaroxaban (53.6%), and apixaban (39%). Overall, 87% of the patients were receiving doses consistent with the FDA label, whereas only 9.4% were receiving a dose lower than recommended and 3.4% were receiving a dose higher than recommended per package insert. Compared to those whose doses were appropriate, patient who received under– and overdoses of DOACs were significantly older, more likely to be female, more likely to have CHA_2DS_2-VASc score ≥2, and more likely to have high ORBIT bleeding scores.

After a median follow-up of roughly one year, patients stratified to the overdosing group were associated with an increased risk of all-cause mortality compared to patients with appropriately dosed DOAC (8.1% vs 3.0%; HR 1.91, p=0.0438). Patients stratified to the underdosing group were associated with increased risk of cardiovascular hospitalization relative to the appropriately dosed group (26.1% vs 24.2%; HR 1.26, p=0.0065).

The results of this study indicate that a significant minority of patients with AF are receiving off-label doses of DOACs. Underdosing and/or overdosing appeared to occur more frequently in patients with intermediate renal dysfunction; potential reasons included variable calculations of creatinine clearance and unfamiliarity with dosing guidelines. The study also highlights the possibility of intentional off-label dosing among physicians, given that patients who received off-label dosing were likely to have higher CHA_2DS_2-VASc and ORBIT bleeding risk scores. Overall, this study underscores the importance of adhering to appropriate doses of DOACs among patients with AF as off-label doses have been associated with increase risk of mortality and hospitalizations.

For additional information:
Steinberg BA, Shrader P, Thomas L, et al. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. *J Am Coll Cardiol* 2016;68:2597-604.

Personalized Medicine Corner

Genetic Test Shows Promise for Improved Cardiovascular Outcomes Post-PCI

Clopidogrel is an antiplatelet medication used post-percutaneous coronary intervention (PCI) to prevent major adverse cardiovascular events (MACE).[1] Clopidogrel is activated by the *CYP2C19* enzyme, whereas other P2Y12 inhibitors (i.e., ticagrelor, prasugrel) are not dependent on *CYP2C19* for activation. Clopidogrel activation and effectiveness after PCI are reduced in patients with a *CYP2C19* genetic polymorphism that decreases enzyme activity, also referred to as a loss-of-function (LOF) allele.[2] Post-hoc analyses of randomized controlled trials and patient registries have shown a higher risk for MACE in clopidogrel-treated patients with a *CYP2C19* LOF allele.[3]

Results of a collaboration among 7 U.S. institutions that implemented *CYP2C19* genotype-guided therapy post-PCI as part of clinical care and examined outcomes with this approach were presented at the November 2016 American Heart Association Scientific Sessions.[4] Alternative antiplatelet therapy (i.e., prasugrel, ticagrelor) was recommended in patients at each institution with a *CYP2C19* LOF allele.

Of 1,815 total patients, 572 (31.5%) carried a *CYP2C19* LOF allele, with 346 of these patients (60.5%) prescribed an alternative to clopidogrel. Clinicians received genotype test results and implemented alternative therapy at a median of 1 day (interquartile range 1–6 days) after PCI across all sites. Patients with a *CYP2C19* LOF allele who received clopidogrel were more likely to experience MACE in the 12 months post-PCI than those who received alternative therapy (adjusted hazard ratio [HR] 2.21, 95% confidence interval [CI] 1.13–4.33; p=0.021). The risk of MACE was similar in patients with a *CYP2C19* LOF allele who received alternative therapy and those without a LOF allele (adjusted HR 0.81, 95% CI 0.48–1.35; p=0.41).

These data show that use of pharmacogenetic testing to guide antiplatelet drug therapy decisions post-PCI is feasible in a real-world environment across multiple institutions. Study findings also suggest that a genotype-guided approach can lead to improved outcomes when genotype is made available early after PCI and alternative antiplatelet therapy is started in patients with a *CYP2C19* LOF allele.

For questions about these data, or ordering and interpreting a pharmacogenetic test, contact the UF Health Personalized Medicine Program (PMP-HELP@ctsi.ufl.edu).

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