OPEN ACCESS

Molecular Medicine Communications

DOI: 10.55627/mmc.004.002.0580

Systematic Review

Clinical Pharmacokinetics of Brivaracetam: A Systematic Review

Attia Qayyum[1], Ammara Zamir[2], Imran Imran[1], Muhammad Fawad Rasool[2*]

[1]Department of Pharmacology, Faculty of Pharmacy, Bahauddin Zakariya University, 60800, Multan, Pakistan
[2]Department of Pharmacy Practice, Faculty of Pharmacy, Bahauddin Zakariya University, 60800, Multan, Pakistan
***Correspondence:** fawadrasool@bzu.edu.pk

Abstract

Brivaracetam (BRV) is an antiepileptic drug (AED) used to treat focal seizures. It can be administered through oral and intravenous (IV) routes. In this review, the main objective is to present a thorough analysis of reported pharmacokinetics (PK) information on BRV in humans. Five electronic databases were used to execute a systematic literature search, i.e. Google Scholar, EBSCO, Science Direct, Cochrane, and PubMed. All articles containing information on the PK of BRV in humans were searched. This review process was officially filed in the PROSPERO database under the registration number CRD42023451328. Thirteen papers were finally included in this systematic review after applying eligibility criteria to 1508 publications from all included databases. A dose-dependent increase in C_{max} and $AUC_{0-\infty}$ was seen after oral application of BRV. A slight increase in the $AUC_{0-\infty}$ of BRV was observed in severe renal impaired patients as compared to healthy controls. The co-administration of BRV with carbamazepine and rifampicin resulted in a significant rise in oral clearance (CL/F) from 0.92 ml/min to 1.30 ml/min and 0.80 ml/min to 1.45 ml/min, respectively, emphasizing the importance of medication interactions in clinical settings. The bioavailability and serum half-life ($t_{1/2}$) of BRV were reduced when administered with drugs. This comprehensive overview not only improves our understanding of the drug's PK behavior but also provides valuable insights for researchers and clinicians to optimize BRV therapy. The presented results may help clinicians understand the PK parameters ($AUC_{0-\infty}$, C_{max}, and $t_{1/2}$) of BRV in foreseeing its adverse drug reactions and drug-drug interactions.

Keywords: Antiepileptic drug; Brivaracetam; Healthy control; Pharmacokinetic; Systematic review; Severe renal impairment.

1. Introduction

Brivaracetam (BRV) is a third-generation antiepileptic drug approved by the United States Food and Drug Administration (US FDA) in 2016 for adjunctive treatment of patients with focal seizures (Klein et al. 2018, Khaleghi and Nemec 2017), and status epilepticus (Aicua-Rapun et al. 2019). Its precise mechanism of action is unknown, but in the brain, the effects of anticonvulsants are due to their greater affinity for "synaptic vesicle protein" (SV2A) (Khaleghi and Nemec 2017). By stimulating vesicle fusion and maintaining a reserve of secretory vesicles, BRV is supposed to play an essential part in regulating neurotransmission. It is regarded as the master regulator of neurotransmitter release (Gillard et al. 2011, Löscher et al. 2016, Madeo, Kovács, and Pearce 2014). It may be administered orally (Srinivasan et al. 2022) and intravenous (IV) route (Aicua-Rapun et al. 2019). The "Biopharmaceutics classification system" (BCS) categorized BRV as a class 1, having high permeability and solubility (Poposka et al. 2013). The plasma–protein–binding (PPB) of BRV with albumin is < 20% (Tiwari), with an oral absorption rate of 96.8% and a maximum time concentration (T_{max}) of about an hour (von Rosenstiel 2007). The main pathway of BRV metabolism involves the non-CYP-dependent enzyme amidase converting the amide function

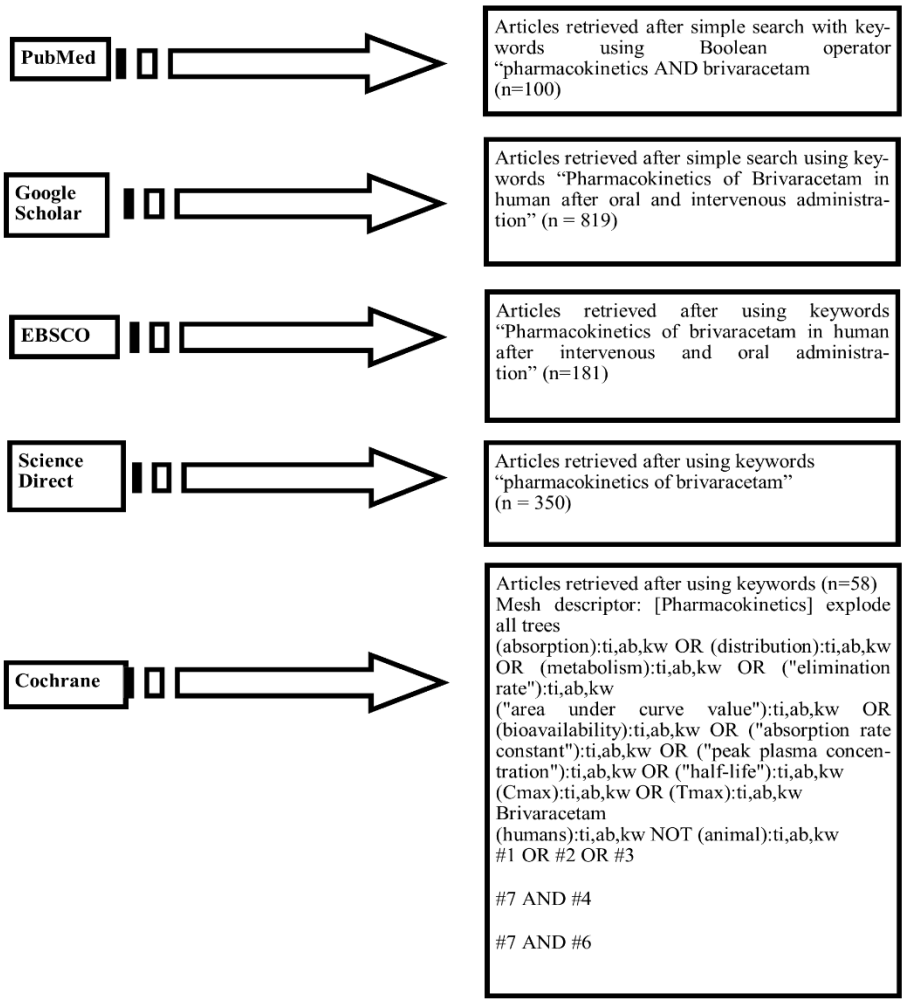

Figure 1. Literature Search Strategy

into a carboxylic acid, whereas the other one is related to CYP2C19-mediated hydroxylation of the propyl side chain (Otoul et al. 2017). Within 72 hours, approximately 95% of BRV is excreted in the urine, and 8.6% remains unchanged. The mean half-life ($t_{½}$) and plasma clearance of BRV are 7 to 8 hrs and 3.4 L/ hr, respectively (Rolan, Sargentini-Maier, et al. 2008).

BRV is a chemical derivative of butanamide, having a molecular mass of 212.15 g/mol and the chemical formula $C_{11}H_{20}N_2O_2$ (Hung, Wu, and Huang 2021, Oster 2018). It has a pKa value of 7.07 and is soluble in aqueous fluids at a solubility of around 0.85 g/ml at pH 7.4 (Yang et al. 2022). The values for octanol-to-water partition coefficient (Log P), blood/plasma ratio (B/P), and fraction unbound to plasma proteins (fu. p) are 1.04, 1.0, and 0.79, respectively (Brochot, Zamacona, and Stockis 2010).

BRV falls under Schedule V and pregnancy Category C (Oster 2018). Because of its lipophilic characteristics, it penetrates the blood-brain barrier more rapidly than levetiracetam, which elaborates it as an efficacious drug in emergencies. Therefore, the fast penetration through the blood-brain barrier discloses its new treatment plan possibilities in the early stages of status epilepticus (Kalss et al. 2018). Drug-

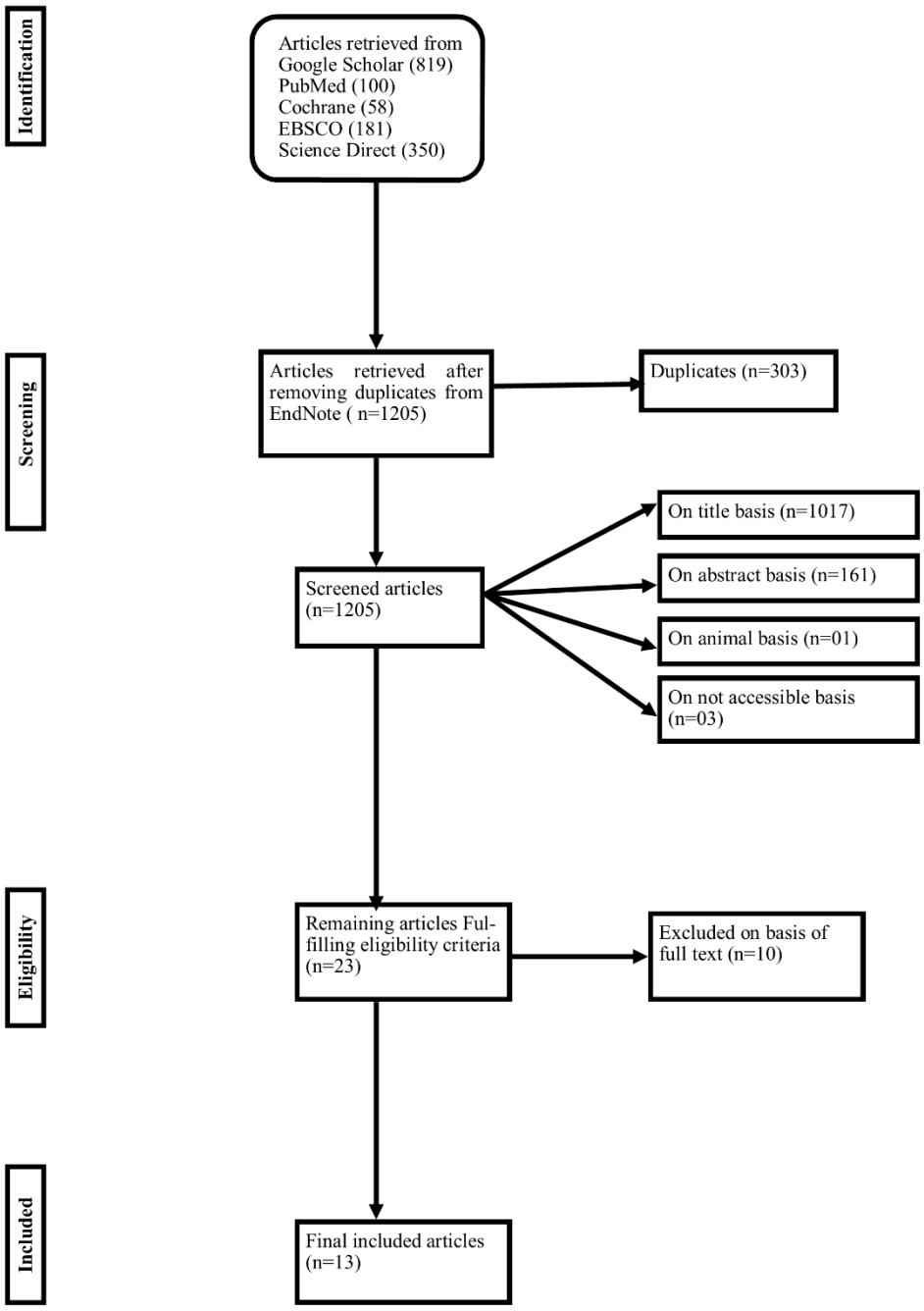

Figure 2: BRV PRISMA flow chart

induced adverse effects are found in patients with temporal lobe epilepsy with higher sensitivity to the drug (Klitgaard et al. 2016). The major adverse effects of BRV are somnolence (Meador et al. 2020), drowsiness (Visa-Reñé et al. 2020), dizziness (Meador et al. 2020), exhaustion (Siddiqui et al. 2023), nausea or vomiting, hypersensitivity reactions like bronchospasm (Brandt et al. 2020), angioedema (Kwan et al.), psychotic symptoms like paranoia,

Table 1. Demographic characteristics of the included Pharmacokinetic Studies.

Sr. #	Study	Population	Gender	Age (years)	N	Drug	Dose (mg)	Dosage Form	Frequency	Primary goal	Primary outcome
1	(Stockis, Hartstra, et al. 2016)	Healthy	M/F	18–55	25	BRV	10, 50, 75, 100	PO	Single dose	PK	PK parameters
							100	IV			
2	(Stockis et al. 2015)	Healthy	M	18–55	14	BRV	200	PO	OD	PK	PK parameters
									BID		
						CBZ	300		BID		
3	(Sargentini-Maier et al. 2012)	9 Healthy, 9 with RD	M/F	N/M	18	BRV	200	PO	OD	PK	PK parameters
4	(Nicolas et al. 2012)	Healthy, diabetic	M	N/M	26	BRV	150	PO	OD	PK	PK parameters
						Gemfibrozil	600		BID		
5	(Stockis, Sargentini-Maier, and Horsmans 2013)	Healthy, patients with hepatic disease	M	N/M	42	BRV	100	PO	OD	PK	PK parameters
6	](Stockis, Watanabe, et al. 2016)	Healthy	M	18–55	26	BRV	150	PO	OD	PK	PK parameters
						Rifampin	600				
7	(Rolan, Sargentini-Maier, et al. 2008)	Healthy	M	28–30	36	BRV	200, 400 800	PO	OD, BID	PK	PK parameters
8	(Sargentini-Maier et al. 2007)	Healthy	M	18–55	35	BRV	Multiple	PO	OD	PK	PK parameters
9	(Otoul et al. 2017)	Healthy	M/F	18–55	NM	BRV	10**	PO	N/M	PK	PK parameters
							50				
10	(Sargentini-Maier et al. 2008)	Healthy	M	N/M	6	BRV	150	PO	Single dose	PK	Pk parameters
11	(Kruithof et al. 2017)	Healthy	M	18–55	18	BRV	200	PO	Single dose	PK	PK parameters
						Ethanol	0.6*	IV			
12	(Stockis et al. 2014)	Healthy	M	20–40	80	BRV	2.5–100	PO	Single doses	PK	PK parameters
							2.5–50		Multiple doses		
13	(Yamamoto, Ikeda, and Stockis 2022)	Healthy	M/F	20–55	24	BRV	100	IV Bolus	Single Dose	PK	PK parameters
								IV Infusion			
								PO			

PK pharmacokinetic, N/M not mentioned, M male, F female, PO per oral, IV intravenous, N number of participants, OD once a day, BID both in a day, BRV brivaracetam, CBZ carbamazepine, RD renal disease, * g/l gram/ liter, ** mg/ml O.S.

Table 2. PK parameters of BRV among intravenous studies in a healthy population.

S #	Reference	Drug	Dose (mg)	C_{max} (µg / ml)	$AUC_{0-\infty}$ (µg.h/ml)	T_{max} (h)	CL/F (ml/min/kg)	$t_{1/2}$ (h)
1	(Stockis, Hartstra, et al. 2016)	BRV	100	3.36	N/M	0.08	0.198	9.2
2	(Yamamoto, Ikeda, and Stockis 2022)	BRV IV bolus	100	7.40	37.6	0.083	0.164	9.0
		BRV IV infusion		6.07	36.8	0.25	0.165	9.0

$AUC_{0-\infty}$ "area under the plasma concentration-time curve", N/M not mentioned, C_{max} "maximum plasma concentration", BRV Brivaracetam, T_{max} "time to reach maximum plasma concentration", CL/F oral clearance.

hallucinations (Taj, Zuber, and Vidhyashree), and nonpsychotic symptoms like anxiety, mood swings, and irritability (Hussar and George 2016, Stephen and Brodie 2018). The chance of unfavorable neurologic events can be anticipated to rise due to potential drug interactions between BRV and other central nervous system depressants, such as alcohol. Patients with known hypersensitivity to BRV should not use the medication. (Hussar and George 2016).

A complete representation of BRV in terms of clinical efficacy and physiological parameters by utilizing IV and PO routes of administration in diseased and healthy individuals is elaborated in the existing systematic review. The described pharmacokinetics (PK) data of BRV in the present review may assist in evaluating the Physiologically based pharmacokinetic model (PBPK). The ultimate aim of the present review is to assist clinicians in optimizing BRV dosing after considering the presented PK data in both populations (healthy and unhealthy).

2. Methods

2.1 Research Design

The presented review followed the guidelines outlined in the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)" (Moher et al. 2009) and the Cochrane Handbook guidelines (Higgins 2011). The existing review protocol had been officially listed in the PROSPERO database with the registration number CRD42023451328.

2.2 Literature Search Strategy

A concise, systematic review search was performed till December 2023 after screening articles relevant to the PK of BRV by using different databases such as "PubMed, Google Scholar, EBSCO, Cochrane Library, and Science Direct". Keywords were identified by segmenting the research questions to start the search strategy. All reviewers scrutinized the outcomes of this systematic review. One reviewer identified the search following a thorough search of 5 databases. The titles, abstracts, and full texts of the included articles were independently reviewed by two evaluators using predefined inclusion and exclusion criteria. After finalizing the screening, one reviewer extracted the data, and this extraction was subsequently verified by the other reviewers. The applied strategies are illustrated in Figure 1.

Table 3. Studies of BRV via oral route in a healthy population.

S #	References	Drug	Dose (mg)	C_{max} (µg/ml)	$AUC_{0-\infty}$ (µg.hr/ml)	T_{max} (hr)	CL/F (ml/min/kg)	$t_{1/2}$ (hr)
1	(Stockis, Hartstra, et al. 2016)	BRV	10	0.25	N/M	1	0.197	9.7
			50	1.28	N/M	1	0.196	9.4
			75	1.99	N/M	1	0.194	9.3
			100	2.63	N/M	1	0.196	9.0
2	(Rolan, Sargentini-Maier, et al. 2008)	BRV (D–1)	200	2.2	27.5	2	0.83	7.7
		BRV (D–7)		3.5	27.7	2	0.83	N/M
		BRV (D–14)		3.5	28	2	0.82	7.3
		BRV (D–1)	400	4.7	56	2	0.82	7.3
		BRV (D–7)		7.3	55.2	2	0.82	N/M
		BRV (D–14)		7.7	55.4	2	0.82	6.8
		BRV (D–1)	800	9.0	104.1	2	0.83	7.8
		BRV (D–7)		12.4	93.1	1	0.93	N/M
		BRV (D–14)		13.3	90.8	1	0.95	6.3
3	(Sargentini-Maier et al. 2007)	BRV	10	0.31	2.54	0.5	0.88	8.06
		BRV	20	0.43	4.50	1	1.07	8.18
		BRV	40	0.95	9.74	1.26	0.95	8.05
		BRV	80	2.18	19.66	0.5	0.95	7.71
		BRV	150	4.24	43.12	0.75	0.82	8.04
		BRV	300	8.58	84.25	1	0.86	7.43
		BRV	600	16.15	170.0	0.75	0.83	7.26
		BRV	1000	28.46	316.9	1.25	0.73	7.41
		BRV	1400	41.28	464.6	1.75	0.70	7.31
4	(Otoul et al. 2017)	BRV	10*	1.42	15.9	0.63	0.202	8.90
		BRV	50	1.34	16.3	1	0.200	9.13
5	(Yamamoto, Ikeda, and Stockis 2022)	BRV	100	3.96	36.6	0.5	2.77	9.1
6	(Sargentini-Maier et al. 2008)	BRV	150	4.0	44.6	1.5	0.77	7.6
7	(Stockis et al. 2014)	BRV (single doses)	2.5	0 .087	0.865	0.5	0.82	9.3
			10	0.373	3.606	0.5	0.81	9.2
			25	9.0	7.649	0.5	0.85	8.5
			50	0.921	18.358	0.5	0.78	9.3
			100	3.083	32.203	0.5	0.85	8.8
		BRV (Multiple doses)	2.5	0.113	0.702	0.5	0.93	9.4
			10	0.508	2.785	0.5	1	8.7
			50	2.477	14.239	0.5	0.47	8.6

$AUC_{0-\infty}$ " area under the plasma concentration-time curve, N/M not mentioned", C_{max} "maximum plasma concentration", BRV Brivaracetam, T_{max} "time to reach maximum plasma concentration", D day, CL/F oral clearance, HC healthy control, SRI severe renal impairment, *mg/ml O.S

.2.3 Eligibility Criteria

This systematic review focused on English-published studies with at least one documented PK parameter for BRV plasma–concentration vs time profile in different populations (healthy & diseased), administered by either IV or PO route. Furthermore, there were no limitations regarding publication years till December 2023. The excluded articles are given in Supplementary Table S1.

2.4 Study Selection and Data Collection

All the comprehensive studies from five databases were exported to EndNote version 20, and the deletion of duplicates was done by using the option of "remove duplicates". The screening process was then carried out based on the titles, animal studies, abstracts, and accessibility. The phrase "exclusion based on title and abstract" refers to the first screening of potentially relevant research to assess its suitability for inclusion in this review. Book chapters and brief reviews were excluded. After extracting all the publications that met the eligibility requirements using full-text reading, the relevant studies were then added. The age, number of individuals, dosage, frequency, routes of administration, and PK parameters such as the "area under the plasma concentration-time curves (AUC), maximum plasma concentration (C_{max}), T_{max}, $t_{1/2}$, and CL" were obtained from the included articles. To maintain data consistency and uniformity in comparing outcomes, units of $AUC_{0-\infty}$ and C_{max} were standardized in some studies.

2.5 Quality Evaluation

For quality appraisal, various scoring systems, including the Oxford scoring system or Jadad (Berger and Alperson 2009), the "Critical Appraisal Skills Program (CASP)" (Al-Dirini, Thewlis, and Paul 2012), and "Critical Appraisal of Clinical Pharmacokinetics (CACPK)" (Soliman et al. 2022) were used to assess the articles, with one author screening the eligibility and two independently assessing quality and risk of bias. The quality of each pertinent study was then evaluated by using these tools. The Jadad scoring system, which focuses on blinding, randomization, and dropouts, was used for assessing the quality of clinical trials. The Jadad grading system uses a five-point rating scale to rate the quality of publications, and studies are categorized as high, moderate, or low quality depending on which they receive a score of > 4, 3–4, and < 3, respectively. The CASP method is commonly used to evaluate the quality of multiple research like controlled trials, systematic reviews, and case-control. This technique consists of 10 questions with a rating scale score for each article, i.e., low quality (< 4), moderate quality (4–6), and high quality (> 6). The CACPK is a quality evaluation tool designed for PK investigations focusing on aspects such as study design, sample selection, and data processing. Its questionnaire comprises 21 questions with a rating scale for each question, i.e., studies scoring high (> 13), moderate (12–13), and poor quality (> 12). Furthermore, the "Cochrane Collaboration Tool (CCT)" (Peng et al. 2014) consisting of seven questions was used to assess the risk of bias, in which data is evaluated by the final scoring method in terms of unclear risk (UR), high risk (HR), and low risk (LR). Good quality is indicated by a score of more than 6, moderate quality by 4–6, and poor quality by 4.

3. Results

3.1 Literature Search Characteristics

After thoroughly searching via five different databases, 1508 published articles were retrieved. Following the removal of 303 duplicates, 1205 articles were excluded based on abstract, title, animal-related, extensive reading, and inaccessible studies, among which 13 publications were finally used in this systematic review. Figure 2 describes a detailed

Table 4. Depiction of PK parameters of BRV among PO studies in diseased population.

S #	References	Drug	Dose	C_{max} (µg/ml)	$AUC_{0-\infty}$ (µg.hr/ml)	T_{max} (hr)	CL/F (ml/min/kg)	$t_{1/2}$ (hr)
1	(Sargentini-Maier et al. 2012)	BRV, (HC)	200	6.42	63.1	0.5	51.8	8.4
		BRV, (SRI)		6.40	76.5	1.5	42.3	9.8
		Acid Metabolite, (HC)		0.270	3.51	4	N/M	8.0
		Acid Metabolite, (SRI)		0.645	11.4	4	N/M	10.0
		Hydroxy Metabolite, (HC)		0.498	14.1	12	N/M	9.4
		Hydroxy Metabolite, (SRI)		0.978	57.6	24	N/M	23.8
		Hydroxy acid Metabolite (HC)		0.074	1.67	6	N/M	16.8
		Hydroxy acid Metabolite (SRI)		0.868	35.8	12	N/M	22.7
2	(Stockis, Sargentini-Maier, and Horsmans 2013)	BRV (HC)	100	2.86	N/M	1.0	0.71	9.8
		BRV (H.D), Mild		3.21	N/M	0.5	0.54	14.2
		BRV (H.D), Moderate		2.86	N/M	0.5	0.48	16.4
		BRV (H.D), Severe		2.62	N/M	0.5	0.46	17.4

$AUC_{0-\infty}$ "area under the plasma concentration-time curve", N/M not mentioned, C_{max} "maximum plasma concentration", BRV Brivaracetam, T_{max} "time to reach maximum plasma concentration", CL/F oral clearance, HC healthy control, SRI severe renal impairment, H.D hepatic disease,

comprehensive overview of the specific inclusion and exclusion criteria, summarizing the search results and study selection.

3.2 Characteristics of Included PK Studies

The characteristics of the articles included, encompassing details such as age demographics, gender distribution, population specifics, author names, participant numbers, dosage forms, administered doses, frequency, primary goals, and primary outcome, are mentioned below in Table 1.

3.3 Quality Assessment Results

To assess the quality and risk of bias, 13 studies were evaluated using "Jadad grading, CASP, CACPK, and CCT". It is vital to highlight that there is no single tool for judging quality and assessment. Each tool has advantages and disadvantages, and the ideal strategy is to employ a variety of methods to gain a thorough understanding of quality study. It is equally critical to understand the setting in which the scores are used. When examining the specific characteristics of quality measured by each tool, the Jadad scale may be significant, particularly in terms of the relevance of a certain research question or context. The ultimate goal of quality evaluation is to identify a study's strengths and limitations, allowing for appropriate interpretation and implementation of its findings in clinical practice or guiding future research. According to Jadad's grading, 3 articles were rated as high quality, 4 as moderate quality, and 6 as low quality. When assessed with the CASP tool, 1 article was of "low quality", 3 were of "moderate quality", and 9 were of "high quality". Within the framework of the CACPK tool, 9 articles were of high quality, 3 were of moderate quality, and 1 was of low quality. In CCT scoring, 2 articles were at HR having poor quality, 8 were at moderate risk having moderate quality, and 3 were at LR of bias having good quality. The results of these quality scoring methods are provided in supplementary tables S2, S3, and S4. The findings of the CCT for evaluating the "risk of bias" are represented in supplementary table S5.

3.4 Healthy Population

3.4.1 Intravenous Route of Brivaracetam

From the total 13 studies, merely two involved IV infusion, and notably, one of these studies also discussed IV bolus administration with a constant dose of 100 mg of BRV. After infusing the 100 mg dose, the mean C_{max} was reported to be 3.36 µg/ml (Stockis, Hartstra, et al. 2016). Another study reported that at the same dose of 100 mg of BRV, the values of $AUC_{0-\infty}$ were 37.6 µg.hr/ml and 36.8 µg.hr/ml for both IV infusion and IV bolus, respectively. (Yamamoto, Ikeda, and Stockis 2022). The remaining PK parameters are shown in Table 2.

3.4.2 Oral Route of Brivaracetam

Out of the 13 pertinent research articles, a total of 7 oral studies were reported. For one reported study, the C_{max} values increased from 0.25 µg/ml, 1.28 µg/ml, and 1.99 µg/ml, to 2.63 µg/ml with BRV doses of 10 mg, 50 mg, 75 mg, and 100 mg, respectively (Stockis, Hartstra, et al. 2016). In another reported study, on doubling the dose of BRV to 200 mg, the values of C_{max} and $AUC_{0-\infty}$ were found to be increased 2-fold (Rolan, Sargentini-Maier, et al. 2008). One of the published studies has displayed an increase in values of $AUC_{0-\infty}$ from 0.865 µg.hr/ml to 32.203 µg.hr/ml and 0.702 µg.hr/ml to 14.239 µg.hr/ml for single doses and multiple doses accordingly (Stockis et al. 2014). The other PK parameters, including T_{max}, CL/F, and $t_{1/2}$ are depicted in Table 3.

3.5 Diseased Population

3.5.1 Oral Administration of BRV

Only two studies out of 13 included articles, describe the disease pattern with impaired renal function and hepatic disease. In patients with severe renal impairment (SRI), while administering a BRV dose of 200mg, the values of C_{max} decreased as compared to healthy volunteers from 6.42 µg/ml to 6.40 µg/ml, and T_{max} increased, i.e. 1.5 hr vs. 0.5 hr (Sargentini-Maier et al. 2012). In 1 of the studies, the CL/F values of HC were found to decrease from 0.71 ml/min/kg to 0.54 ml/min/kg, 0.48 ml/min/kg, and 0.46 ml/min/kg in mild to moderate and severe hepatic disease, respectively (Stockis, Sargentini-Maier, and Horsmans 2013) and the additional PK parameters including $t_{1/2}$, CL/F, $AUC_{0-\infty}$ are mentioned in Table 4.

3.6 Drug-Drug Interactions of BRV

Four studies from systematic research have described the BRV-drug interactions. When rifampicin and BRV were administered together, the AUC decreased from 41.2 µg.hr/ml to 22.8 µg.hr/ml (Stockis, Watanabe, et al. 2016). No significant increase in C_{max} was noted from 4.15 µg/ml to 4.16 µg/ml when BRV was given in combination with gemfibrozil (Nicolas et al. 2012). Following an oral administration of BRV with carbamazepine, the decrease in C_{max} was found from 4.51 µg/ml to 3.92 µg/ml, and a substantial increase in CL/F (ml/min/kg) of BRV was seen, rising from 0.92 to 1.32 (Stockis et al. 2015) and further, PK parameters are depicted in Table 5.

4. Discussion

The primary objective of this systematic review was to compile, assess, and evaluate all the studies in humans that had been done on BRV PK. In total, relevant studies of BRV two were allocated with IV studies, seven with PO studies, two with diseased studies, and four with drug-drug interactions. The C_{max}, $AUC_{0-\infty}$, CL/F, T_{max}, and $t_{1/2}$ were the PK variables that were most frequently recorded in the related papers. (Schoemaker, Wade, and Stockis 2017). The PK characteristics of BRV, such as C_{max} and $AUC_{0-\infty}$, increased consistently with escalating dosages of 10 mg, 50 mg, 75 mg, and 100 mg, indicating a dose-dependent PK response. This tendency suggests that increased doses of BRV cause higher peak concentrations in the circulation, potentially influencing the therapeutic effectiveness and drug safety profile. One of the

Table 5. Studies of BRV regarding Drug-Drug Interactions

S #	References	Drug		Dose (mg)	C_{max} (µg/ml)	$AUC_{0-\infty}$ (µg.hr/ml)	T_{max} (hr)	CL/F (ml/min/kg)	$t_{½}$ (hr)
1		BRV	D1	200	4.51	48.3	N/M	0.92	7.5
		CBZ + BRV	D22	300 + 200	3.92	34.19	N/M	1.30	6.4
		CBZ-E + BRV	D35	300 + 200	5.07	33.73	N/M	1.32	6.1
2	(Stockis, Watanabe, et al. 2016)	BRV		150	4.22	41.2	0.75	0.80	8.19
		BRV + Rifampin		600	3.74	22.8	0.63	1.45	4.4
3	(Nicolas et al. 2012)	BRV		150	4.15	41.4	N/M	0.217	8.09
		BRV–OH			0.154	4.18	N/M	N/M	9.58
		BRV–AC			0.244	3.29	N/M	N/M	8.59
		BRV–OHAC			0.0476	0.966	N/M	N/M	11.2
		BRV + Gemfibrozil		150 + 600	4.16	39.2	N/M	0.229	7.64
		BRV–OH			0.183	4.94	N/M	N/M	9.25
		BRV–AC			0.285	3.61	N/M	N/M	7.99
		BRV–OHAC			0.0247	7.09	N/M	N/M	15.7
4	(Kruithof et al. 2017)	BRV		200	4.940	53.97	N/M	N/M	N/M
		BRV+ Ethanol		200+0.6**	4.369	54.82	N/M	N/M	N/M

studies have emphasized the importance of taking dose-dependent effects into account when adjusting BRV therapy for people with varying needs (Stockis, Hartstra, et al. 2016). The significant increase in $AUC_{0-\infty}$ values observed in this study indicates potential changes in the drug's PK profile, affecting its safety and efficacy at both single and multiple doses of BRV (Stockis et al. 2014).

The oral solution and tablet showed similar patterns of mean BRV plasma concentration over time, indicating rapid absorption. The median difference of 15 minutes in T_{max} values of 0.63 hr and 1.00 hr demonstrates that absorption was more rapid with the oral solution than with the tablet. The AUC and C_{max} values were observed to be remarkably similar in individual participants, which depicted that patients are not expected to experience any problems with PK, tolerability, or safety while switching between the two forms. Therefore, the patients who struggle to swallow pills now have another treatment choice with BRV oral solution, which may improve their likelihood of adhering to their prescribed course of treatment (Otoul et al. 2017).

In this study, the CL/F of HC decreased from 0.71 ml/min/kg to 0.54, 0.48, and 0.46 ml/min/kg when compared to individuals with mild, moderate, and severe hepatic disease, respectively. This decline in CL/F suggests that there is a need for dose adjustments in patients with varying degrees of liver dysfunction (Stockis, Sargentini-Maier, and Horsmans 2013). Doubling the BRV dose to 200 mg resulted in a two-fold rise in both Cmax and AUC0-∞ values, demonstrating a linear dose-response relationship. This suggests the necessity for cautious dosage adjustment to balance therapeutic efficacy and possible hazards (Rolan, Sargentini-Maier, et al. 2008).

A notable decrease in C_{max} was observed while administering BRV with carbamazepine, suggesting a possible PK interaction. Moreover, a significant rise in BRV CL/F showed that carbamazepine may affect BRV absorption or metabolism, potentially influencing its therapeutic levels. More investigation is required to assess the implications of these alterations when these medicines are administered concurrently (Moseley et al. 2019). When BRV was administered with gemfibrozil, no significant increase in C_{max} was noted, i.e., 4.15 µg/ml to 4.16 µg/ml. This suggests that gemfibrozil may not have a significant impact on BRV's peak plasma concentration because of limited PK interaction between the two drugs (Nicolas et al. 2012). The combination of rifampicin (CYP2C19 inducer) with the BRV resulted in a decrease in the plasma concentrations of the latter by 45%. Therefore, in such patients, it may be needed to adjust the dose of BRV to achieve the required therapeutic effect (Stockis, Watanabe, et al. 2016).

Moreover, there is a potential for publication bias. Age and sex ratios (males vs. females) in the included research were not taken into account. By searching several databases and incorporating published papers, an effort to reduce the likelihood of publication bias was made, but despite that, publication bias cannot be completely avoided.

The existing review's strength lies in its coverage of PK variables from studies conducted in both populations (healthy and diseased) in the English language till December 2023. There is less possibility of missing an article because 13 studies were retrieved from 5 different databases, which led to appropriate and reliable findings and trustworthy results. Only "English-language-based" papers were considered in the current review, therefore, it might be possible that a few papers may have been missed. There are currently no head-to-head trials, little information on long-term safety and efficacy, and high costs for BRV.

5. Conclusions

In the current review, all the available PK data of the BRV in both healthy and diseased populations are summarized. The C_{max} and AUC proportionally rose in healthy people with an increase in dose. The AUC was found to be higher in patients with renal disease. Additionally, the co-administration of other medicines dramatically decreases the bioavailability, thus affecting other PK parameters of BRV. This extensive literature search may be used to create PK drug-disease models by applying the available input parameters, and it will also benefit clinicians in estimating the dosage regimen and avoiding medication interactions in patients with different diseases. Moreover, in the future, it may also help to optimize clinical trials.

Conflict of Interest

The authors declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Funding

This study did not receive any internal or external funding.

Study Approval

NA

Consent Form

NA

Availability of Data and Material

All the data used for this publication is either presented in the main article or is available as supplementary information.

Authors' Contributions

Conceptualization: A.Q, I.I, M.F.R; Methodology: A.Q, A.Z, M.F.R; Formal analysis and investigation: A.Z, I.I, M.F.R, Writing - original draft preparation: A.Q, I.I, M.F.R; Writing - review and editing: A.Z, I.I, M.F.R, Supervision: M.F.R., I.I. All authors have made substantial contributions to the design, extraction, analysis, and interpretation of data and have actively participated in drafting and revising the article. All authors agreed to submit the final version to the journal and agreed to be accountable for all aspects of the work.

References

Aicua-Rapun, Irene, Pascal André, Andrea O Rossetti, Laurent A Decosterd, Thierry Buclin, and Jan Novy. 2019. "Intravenous brivaracetam in status epilepticus: correlation between loading dose, plasma levels and clinical response." *Epilepsy Research* no. 149:88-91.

Al-Dirini, Rami Mohamad Ameer, Dominic Thewlis, and Gunther Paul. 2012. "A comprehensive literature review of the pelvis and the lower extremity FE human models under quasi-static conditions." *Work* no. 41 (Supplement 1):4218-4229.

Berger, Vance W, and Sunny Y Alperson. 2009. "A general framework for the evaluation of clinical trial quality." *Reviews on Recent Clinical Trials* no. 4 (2):79-88.

Brandt, Christian, Pavel Klein, Vincent Badalamenti, Teresa Gasalla, and John Whitesides. 2020. "Safety and tolerability of adjunctive brivaracetam in epilepsy: In-depth pooled analysis." *Epilepsy & Behavior* no. 103:106864.

Brochot, Anne, Miren Zamacona, and Armel Stockis. 2010. "Physiologically based pharmacokinetic/pharmacodynamic animal-to-man prediction of therapeutic dose in a model of epilepsy." *Basic & Clinical Pharmacology & Toxicology* no. 106 (3):256-262.

Gillard, Michel, Bruno Fuks, Karine Leclercq, and Alain Matagne. 2011. "Binding characteristics of brivaracetam, a selective, high affinity SV2A ligand in rat, mouse and human brain: relationship to anti-convulsant properties." *European Journal of Pharmacology* no. 664 (1-3):36-44.

Higgins, JP. 2011. "Cochrane handbook for systematic reviews of interventions. Version 5.1. 0 [updated March 2011]. The Cochrane Collaboration." *www. cochrane-handbook. org*.

Hung, Te-Yu, Sheng-Nan Wu, and Chin-Wei Huang. 2021. "The integrated effects of brivaracetam, a selective analog of levetiracetam, on ionic currents and neuronal excitability." *Biomedicines* no. 9 (4):369.

Hussar, Daniel A, and Jerry Rachel George. 2016. "Brivaracetam, lumacaftor/ivacaftor, and deoxycholic acid." *Journal of the American Pharmacists Association* no. 56 (4):474-477.

Kalss, Gudrun, Alexandra Rohracher, Markus Leitinger, Georg Pilz, Helmut F Novak, Caroline Neuray, Rudolf Kreidenhuber, Julia Höfler, Giorgi Kuchukhidze, and Eugen Trinka. 2018. "Intravenous brivaracetam in status epilepticus: A retrospective single-center study." *Epilepsia* no. 59:228-233.

Khaleghi, Farbod, and Eric C Nemec. 2017. "Brivaracetam (briviact): a novel adjunctive therapy for partial-onset seizures." *Pharmacy and Therapeutics* no. 42 (2):92.

Klein, Pavel, Anyzeila Diaz, Teresa Gasalla, and John Whitesides. 2018. "A review of the pharmacology and clinical efficacy of brivaracetam." *Clinical pharmacology: advances and applications* no. 10:1.

Klitgaard, Henrik, Alain Matagne, Jean-Marie Nicolas, Michel Gillard, Yves Lamberty, Marc De Ryck, Rafal M Kaminski, Karine Leclercq, Isabelle Niespodziany, and Christian Wolff. 2016. "Brivaracetam: Rationale for discovery and preclinical profile of a selective SV 2A ligand for epilepsy treatment." *Epilepsia* no. 57 (4):538-548.

Kruithof, Annelieke C, Shikiko Watanabe, Pierre AM Peeters, Marieke L de Kam, Rob GJA Zuiker, Jasper Stevens, Joop MA van Gerven, and Armel Stockis. 2017. "Pharmacological interactions between brivaracetam and ethanol in healthy males." *Journal of Psychopharmacology* no. 31 (7):915-926.

Kwan, P, E Trinka, W Van Paesschen, I Rektor, ME Johnson, and S Lu. "Brand Name: Briviact."

Löscher, Wolfgang, Michel Gillard, Zara A Sands, Rafal M Kaminski, and Henrik Klitgaard. 2016. "Synaptic vesicle glycoprotein 2A ligands in the treatment of epilepsy and beyond." *CNS drugs* no. 30:1055-1077.

Madeo, Marianna, Attila D Kovács, and David A Pearce. 2014. "The Human Synaptic Vesicle Protein, SV2A, Functions as a Galactose Transporter in Saccharomyces cerevisiae*♦." *Journal of Biological Chemistry* no. 289 (48):33066-33071.

Meador, Kimford J, Cedric Laloyaux, Sami Elmoufti, Teresa Gasalla, Jesse Fishman, Melinda S Martin, and Pavel Klein. 2020. "Time course of drug-related treatment-emergent adverse side effects of brivaracetam." *Epilepsy & Behavior* no. 111:107212.

Moher, David, Alessandro Liberati, Jennifer Tetzlaff, Douglas G Altman, and PRISMA Group*. 2009. "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement." *Annals of Internal Medicine* no. 151 (4):264-269.

Moseley, Brian D, Christian Otoul, Ludovicus Staelens, and Armel Stockis. 2019. "Pharmacokinetic interaction of brivaracetam on other antiepileptic drugs in adults with focal seizures: pooled analysis of data from randomized clinical trials." *Epilepsy Research* no. 158:106218.

Nicolas, J-M, Hugues Chanteux, Maria Rosa, Shikiko Watanabe, and Armel Stockis. 2012. "Effect of gemfibrozil on the metabolism of brivaracetam in vitro and in human subjects." *Drug Metabolism and Disposition* no. 40 (8):1466-1472.

Oster, Joel M. 2018. "Brivaracetam: a newly approved medication for epilepsy." *Future Neurology* no. 14 (3):FNL23.

Otoul, Christian, Shikiko Watanabe, Suzanne McCabe, and Armel Stockis. 2017. "Relative bioavailability and bioequivalence of brivaracetam 10 mg/ml oral solution and 50-mg film-coated tablet." *Clinical Pharmacology in Drug Development* no. 6 (3):313.

Peng, Weijun, Jingjing Yang, Yang Wang, Weihao Wang, Jianxia Xu, Lexing Wang, and Zhihua Xing. 2014. "Systematic review and meta-analysis of randomized controlled trials of xingnaojing treatment for stroke." *Evidence-Based Complementary and Alternative Medicine* no. 2014.

Poposka, Zaklina, Shaban Memeti, Maja Shishovska, Zana Mustafa, Katerina Starkoska, and Zorica Arsova-Sarafinovska. 2013. "Identification of counterfeit medicines for erectile dysfunction by validated RP-HPLC method."

Rolan, P., M. L. Sargentini-Maier, E. Pigeolet, and A. Stockis. 2008. "The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men." *Br J Clin Pharmacol* no. 66 (1):71-5. doi: 10.1111/j.1365-2125.2008.03158.x.

Rolan, Paul, Maria Laura Sargentini-Maier, Etienne Pigeolet, and Armel Stockis. 2008. "The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy men." *British journal of clinical pharmacology* no. 66 (1):71-75.

Sargentini-Maier, Maria Laura, Pascal Espie, Alain Coquette, and Armel Stockis. 2008. "Pharmacokinetics and metabolism of 14C-brivaracetam, a novel SV2A ligand, in healthy subjects." *Drug metabolism and disposition* no. 36 (1):36-45.

Sargentini-Maier, Maria Laura, Paul Rolan, John Connell, Dominique Tytgat, Tom Jacobs, Etienne Pigeolet, Jean-Michel Riethuisen, and Armel Stockis. 2007. "The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males." *British Journal of Clinical Pharmacology* no. 63 (6):680-688.

Sargentini-Maier, Maria Laura, Antoni Sokalski, Pierre Boulanger, Tom Jacobs, and Armel Stockis. 2012. "Brivaracetam disposition in renal impairment." *The Journal of Clinical Pharmacology* no. 52 (12):1927-1933.

Schoemaker, Rik, Janet R Wade, and Armel Stockis. 2017. "Brivaracetam population pharmacokinetics in children with epilepsy aged 1 month to 16 years." *European Journal of Clinical Pharmacology* no. 73 (6):727-733.

Siddiqui, Fowzia, Bashir A Soomro, Mazhar Badshah, Ehsan U Rehman, Ahsan Numan, Amer Ikram, Muhammad Wazir Ali Khan, Sajjad Ali, Husnain Hashim, and Jawwad-us Salam. 2023. "Efficacy and Safety of Brivaracetam in Persons With Epilepsy in a Real-World Setting: A Prospective, Non-Interventional Study." *Cureus* no. 15 (12).

Soliman, Alaa Bahaa Eldeen, Shane Ashley Pawluk, Kyle John Wilby, and Ousama Rachid. 2022. "The use of a modified Delphi technique to develop a critical appraisal tool for clinical pharmacokinetic studies." *International Journal of Clinical Pharmacy*:1-10.

Srinivasan, Avathvadi Venkatesan, Lakshminarayanan Kannan, Vykunta Raju K Gowda, Lokesh Lingappa, Prashanth Utage, Shalin

Shah, Madhusudhan BK, Rakesh Lalla, Kumar Gaurav, and Rupali Vinodchandra Bandagi10. 2022. "Drug Corner Placement of Oral Formulations of Brivaracetam in Various Patient Profiles: An Indian Perspective." *Journal of Indian Medical Association* no. 120 (4):82-86.

Stephen, Linda J, and Martin J Brodie. 2018. "Brivaracetam: a novel antiepileptic drug for focal-onset seizures." *Therapeutic advances in neurological disorders* no. 11:1756285617742081.

Stockis, Armel, Hugues Chanteux, Maria Rosa, and Paul Rolan. 2015. "Brivaracetam and carbamazepine interaction in healthy subjects and in vitro." *Epilepsy Research* no. 113:19-27.

Stockis, Armel, Jan Hartstra, Muriel Mollet, and Salah Hadi. 2016. "Bioavailability and bioequivalence comparison of brivaracetam 10, 50, 75, and 100 mg tablets and 100 mg intravenous bolus." *Epilepsia* no. 57 (8):1288-1293.

Stockis, Armel, Maria Laura Sargentini-Maier, and Yves Horsmans. 2013. "Brivaracetam disposition in mild to severe hepatic impairment." *The Journal of Clinical Pharmacology* no. 53 (6):633-641.

Stockis, Armel, Shikiko Watanabe, Elisabeth Rouits, Kyoko Matsuguma, and Shin Irie. 2014. "Brivaracetam single and multiple rising oral dose study in healthy Japanese participants: influence of CYP2C19 genotype." *Drug Metabolism and Pharmacokinetics* no. 29 (5):394-399.

Stockis, Armel, Shikiko Watanabe, André J Scheen, Dominique Tytgat, Brigitte Gerin, Maria Rosa, Hugues Chanteux, and Jean-Marie Nicolas. 2016. "Effect of rifampin on the disposition of brivaracetam in human subjects: further insights into brivaracetam hydrolysis." *Drug Metabolism and Disposition* no. 44 (6):792-799.

Taj, Shifa, Mohammed Zuber, and BH Vidhyashree. "Behavioral and Psychiatric Adverse Events Induced by Brivaracetam: A Case Report."

Tiwari, Mahesh Narayan. "Brivaracetam: A 3rd Generation Anti-Epileptic With Higher Efficacy And Better Safety Profile."

Visa-Reñé, Núria, Miquel Raspall-Chaure, Fernando Paredes-Carmona, Júlia Sala Coromina, and Alfons Macaya-Ruiz. 2020. "Clinical experience with brivaracetam in a series of 46 children." *Epilepsy & Behavior* no. 107:107067. doi: https://doi.org/10.1016/j.yebeh.2020.107067.

von Rosenstiel, Philipp. 2007. "Brivaracetam (ucb 34714)." *Neurotherapeutics* no. 4 (1):84-87.

Yamamoto, Junichi, Kaori Ikeda, and Armel Stockis. 2022. "Bioavailability, safety and tolerability of intravenous brivaracetam in healthy Japanese participants." *Xenobiotica* no. 52 (2):146-151.

Yang, Hongyi, Leting Yang, Xiaofang Zhong, Xuehua Jiang, Liang Zheng, and Ling Wang. 2022. "Physiologically based pharmacokinetic modeling of brivaracetam and its interactions with rifampin based on CYP2C19 phenotypes." *European Journal of Pharmaceutical Sciences* no. 177:106258.