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Expert Opinion: Brivaracetam in Management of Epilepsy

A. V. Srinivasan[1], Kumar Gaurav[2, *], Arundhati Ghosh[2], Sukhpreet Singh[2]

[1]Department of Neurology, MGR Medical University, Tamilnadu, India

[2]Medical Affairs, Dr. Reddy's Laboratories Ltd, Hyderabad, India

Email address:

kumargaurav2@drreddys.com (K. Gaurav)

[*]Corresponding author

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Abstract: Epilepsy is prevalent with about 50 million patients affected worldwide. There are many treatment gaps in the management of epilepsy in India. Within Anti-epileptic drugs (AED), Brivaracetam, which is a high-affinity, selective, and reversible ligand for synaptic vesicle 2A is approved by the Food and Drug Administration for monotherapy as well as adjunctive treatment of focal seizures. A series of meeting occurring during April 2020 inviting neurologist across India as panel members, reviewed the efficacy and safety of brivaracetam and discussed the use of brivaracetam in clinical settings and the drivers and barriers for the use of brivaracetam in the management of epilepsy. Brivaracetam has good efficacy and tolerability as adjunctive therapy in the treatment of focal (partial onset) seizures in patients 16 years of age and older. Brivaracetam is safe for prolonged use in patients with epilepsy and in children with epilepsy. The most common adverse events with brivaracetam are related to central nervous system and include fatigue, dizziness, and somnolence; these may improve or resolve during treatment. A consensus was sought for the use of brivaracetam in epilepsy management in routine neurology practices Brivaracetam is a safer AED with lesser behavioral AEs, lack of cognitive impairment, and no clinically relevant drug-drug interactions or dose adjustment for renal patients.

Keywords: Brivaracetam, Epilepsy, Fecal-onset Seizures, Adjunctive Therapy, Antiepileptic Drugs

1. Introduction

Epilepsy is widely prevalent with about 50 million and 10 million people affected worldwide and in India, respectively. There are wide treatment gaps ranging from 22% to 90% in the management of epilepsy in India. [1, 2] Treatment of epilepsy with antiepileptic drugs (AEDs) are the mainstay of epilepsy therapy and 70-80% patients who are treated with monotherapy or combination therapy achieve remission. However, 20-30% patients continue to have chronic recurrent seizures despite treatment with optimal doses of AEDs. Monotherapy is the initial and preferred approach to management of newly diagnosed epilepsy. In the event of intolerance or ineffectiveness of monotherapy with an AED, the next step is to either add or switch to another AED. In a drug utilization study in 134 patients with epilepsy being treated in an outpatient setting in a National hospital in India, more than 68% patients of epilepsy received polytherapy for management of seizures. The most commonly used conventional AEDs included valproic acid (37.8%), carbamazepine (31.1%), and phenytoin (20%). The most frequently prescribed newer AEDs included clobazam (50.6%), levetiracetam (21%), and lamotrigine (18%). [3] Introduced over a period of time, newer AEDs have a more favorable adverse event (AE) profile when compared to the traditional AEDs. [4] Safety is a key attribute that guides the choice of AEDs in the management of epilepsy. About 60% of patients experience adverse effects with AED therapy and 33% have to change drugs. [5] Adverse effects of AEDs, which are dose-dependent and reversible, are detrimental to quality of life and can lead to noncompliance and discontinuation of treatment. [6]

New AEDs are needed with improved efficacy and better tolerability.

Brivaracetam is a propyl analog of levetiracetam with high-affinity binding to the synaptic vesicle protein 2A (SV2A). [7] It is approved by the Food and Drug Administration (FDA) for monotherapy as well as adjunctive

treatment of focal seizures in patients aged 16 years and older. In 2018, brivaracetam was approved as monotherapy and adjunctive therapy in the treatment of partial onset (focal) seizures in patients age ≥4 years. In the European Union, brivaracetam is only approved as an adjunctive therapy for focal-onset seizures with or without secondary generalization in patients from 16 years and older. [8] In India, brivaracetam is approved as an adjunctive therapy for the treatment of partial epilepsy in patients who are 16 years of age and older. It has been used in the management of epilepsy for the last 1.5 years. This paper presents the opinions of experts for the management of epilepsy with brivaracetam.

2. Methodology

A 'medical expert opinion' was developed based on meetings in April 2020 at several places in India, for the use of brivaracetam in epilepsy with invited experts who reviewed available evidence for brivaracetam and shared their clinical experience to synthesize state-of-the-art knowledge. Agreement of 80% of the panel was considered as unanimous for the development of expert opinion and formulation of a recommendation.

Recommendations of the expert panels and quality of evidence (High, medium, low) were graded in accordance with the US Preventive Services Task Force Ratings for the magnitude of net benefit with brivaracetam in clinical experience. The quality of evidence was graded as high, medium, and low (US preventive ratings).

A meeting of neurologists and epilepsy experts was held in cities of India on April 2020. The primary objective of this discussion was to develop an understanding about the utility of brivaracetam in the management of epilepsy. The panelists reviewed the efficacy and safety of brivaracetam and discussed the use of brivaracetam in clinical settings and the drivers and barriers for the use of brivaracetam in the management of epilepsy.

The details of panel members are listed in Table 1.

Table 1. *List of the panel members [92 members].*

Name of expert	Specialty	City
C S Agarwal	Neuro phy	Delhi
Rakesh Lalla	Neuro phy	Mumbai
Dr R Balakrishnan	Neuro Surg	Chennai
Dr. Sangeeta Rawat	Neuro phy	Mumbai
Dr. Nirmal Surya	Neuro phy	Mumbai
Dr. Jayanti mani	Neuro phy	Mumbai
Dr. Arun Shah	Neuro phy	Mumbai
Dr. S Sashank	Neuro phy	Mumbai
Dr. Girish Nair	Neuro phy	Mumbai
Dr. Rakesh Singh	Neuro phy	Mumbai
Dr. Fali poncha	Neuro phy	Mumbai
Dr. Nitin Dange	Neuro Surg	Mumbai
Dr. Paresh Doshi	Neuro Surg	Mumbai
Dr. Vivek agarwal	Neuro Surg	Mumbai
RAHUL KULKARNI	Neuro phy	ROM
Nandan Yardi	Neuro phy	ROM
Manoj Rajani	Neuro phy	Mumbai
Dr. V Nandmer	Neuro phy	MP
Dr. KK Bhoi	Neuro phy	MP
Dr. Pravar Passi	Neuro phy	MP
Dr. V V Nadkarni	Neuro phy	MP
Dr. Santosh Sontake	Neuro phy	ROM
Dr. Neeraj Baheti	Neuro phy	ROM
Dr. Sujit Jagtap	Neuro phy	ROM
Dr. KR Buch	Neuro phy	Gujarat
Dr. Bhadresh mangukiya	Neuro phy	Gujarat
Dr. Sita Jayalakshmi	Neuro phy	Hyderabad
Dr. Prashnat Utage	Neuro phy	Hyderabad
Dr. Afshan Jabeen	Neuro phy	Hyderabad
Dr. V N Mathur	Neuro phy	Hyderabad
Dr. Sudhir Kumar	Neuro phy	Hyderabad
Dr. Vikram Sharma	Neuro phy	Hyderabad
Dr. GRK Sarma	Neuro phy	Bangalore
Dr. Rajesh iyer	Neuro phy	Bangalore
Dr. JB Agadi	Neuro phy	Bangalore
Dr. A K Roy	Neuro phy	Bangalore
Dr. AV Srinivasan	Neuro phy	TN
Dr. Dinesh Nayak	Neuro phy	TN
Dr. Deepak Arjundas	Neuro phy	TN
Dr. K bhanu	Neuro phy	TN
Dr. Satish Kumar	Neuro phy	TN
Dr. Ashokan	Neuro phy	TN
Dr. Manjari Tripathi	Neuro phy	Delhi
Dr. R S Reddi	Neuro phy	Delhi
Dr. Sumit Singh	Neuro phy	Delhi
Dr. Parveen Gupta	Neuro phy	Delhi
Dr. Sushil Razdan	Neuro phy	Delhi
Dr. Atampreet Singh	Neuro phy	Delhi
Dr. Anshu Rohatgi	Neuro phy	Delhi
Dr. Arun Dhanuka	Neuro phy	Delhi
Dr. Atul Prasad	Neuro phy	Delhi
Dr. J D Mukherji	Neuro phy	Delhi
Dr. Atmaram Bansal	Neuro phy	Delhi
Dr. Sunit Shah	Neuro phy	Raj/UP
Dr. Anis Jhukkarwala	Neuro phy	Raj/UP
Dr. PK Sharma	Neuro phy	Raj/UP
Dr. Avinash chandra Singh	Neuro phy	Raj/UP
Dr. Vinay Agarwal	Neuro phy	Raj/UP
Dr. Suryaprakash Gora	Neuro Surg	Raj/UP
Dr. K K bansal	Neuro Surg	Raj/UP
Dr. Shamim Ahmed	Neuro Surg	Kolkata/NE
Dr. Arijit Chattopdhay	Neuro phy	Kolkata/NE
Dr. TK Banerjee	Neuro phy	Kolkata/NE
Dr. Pahari Ghosh	Neuro phy	Kolkata/NE
Dr. Amit Ghosh	Neuro Surg	Kolkata/NE
Dr. Subhayon Mandal	Neuro Surg	Kolkata/NE
Dr. Asit Senapati	Neuro Phy	Kolkata/NE
Dr. Sadananda Dey	Neuro phy	Kolkata/NE
Dr. P K Sachdeva	Neuro Surg	Delhi
Dr. Satosh Dash	Neuro phy	Kolkata/NE
Dr. Minhaj Momin	Neuro Surg	Kolkata/NE
Dr. Arindam Ghosh	Neuro phy	Kolkata/NE
Dr. Manas Panigrahi	Neuro Surg	Hyderabad
Dr. B Rohit	Neuro Surg	TN
Dr. Rakesh Redhu	Neuro Surg	Delhi
Dr. Puneet Agarwal	Neuro Phy	Delhi
Dr. Rajul Aggarwal	Neuro Phy	Delhi
Dr. C H Gopal	Neuro phy	Hyderabad
Dr. R C Mishra	Neuro Surg	Raj/UP
Dr. Puneet Agarwal	Neuro Phy	Raj/UP
Dr Vikas aggarwal	Neuro Phy	TN
Dr Chakaravarthi Avulla	Neuro Surg	TN
Dr Senthil Kumar	Neuro Phy	TN
A. K. PANDA	Neuro phy	Kolkata/NE
DEBABRATA BISWAL	Neuro Surg	Kolkata/NE

Name of expert	Specialty	City
HARISH OJHA	Neuro Surg	Kolkata/NE
PRASANJEET DEKA	Neuro phy	Kolkata/NE
Dr. Dinesh Khandelwal	Neuro Phy	Raj/UP
Hardik Rajyaguru	Neuro Surg	Kolkata/NE
Amit Haldar	Neuro phy	Kolkata/NE
Dr. Manoj Satyawani	Neuro phy	Gujarat
Dr. Deepika Joshi	Neuro Phy	Raj/UP

Neuro phy = Neuro physician
Neuro surg = Neuro surgeon

3. Discussion

3.1. Pharmacology of Brivaracetam

Brivaracetam has a distinct mechanism of action when compared to other antiepileptic drugs.

It has 15- to 30-fold higher affinity for SV2A than levetiracetam. [7] Brivaracetam has no direct effect on α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), γ-aminobutyric acid (GABA), glycine, or kainic acid-gated currents. There is however a minor inhibition of N-methyl d-aspartate (NMDA)-receptor activity at supratherapeutic concentrations. [9] At therapeutic concentrations, there is no effect on ionic channels including the voltage-gated potassium and calcium channels. [10, 11]

Brivaracetam is well absorbed after oral dosing with a near 100% bioavailability and has a linear and dose-dependent kinetics with low interindividual variability. [12, 13] It has a median time to maximum concentration (tmax) of approximately 1-2 hours and elimination t1/2 of 7-8 hours. It is metabolized in the liver by hydrolysis and CYP2C19 and CYP2C9 mediated hydroxylation to three inactive metabolites. [14] The steady-state concentration of brivaracetam is typically achieved after 2 days of repeated dosing. [15] No dose adjustments of Brivaracetam required in elderly or patients with renal impairment. However, dose reductions by one third up to a maximal daily dose of 150 mg are needed in patients with severe hepatic impairment. [16, 17]

Brivaracetam is highly lipophilic and crosses the blood brain barrier by passive diffusion. When compared to levetiracetam, brivaracetam has a rapid entry into the brain and it engages with SV2A within minutes. [18]

Brivaracetam unlikely to cause clinically relevant drug-drug interactions. [19, 20] Coadministration of rifampin may reduce the brivaracetam exposure by 45% due to CYP2C19 induction and patients receiving rifampin are candidates for increased dosing of brivaracetam. [21]

Expert consensus: Brivaracetam has a favorable pharmacokinetic profile for use as monotherapy and add-on therapy in patients with epilepsy as well as those on concomitant treatment for other comorbidities. Brivaracetam has an early and sustained response which can be explained by the high lipophilicity leading to easy penetration of the blood brain barrier explains the early and sustained response with brivaracetam. It has high affinity for presynaptic SV2A proteins, greater occupancy of SV2A proteins, and a linear association between the SV2A affinity and anti-seizure properties.

3.2. Psychiatric Comorbidities in Epilepsy

Psychiatric disorders are a common comorbidity in patients with epilepsy with prevalence rates varying from 19%-62%. Common psychiatric conditions include depression, anxiety, mood disorders, psychosis, aggression, and suicidal ideations. [22] Please confirm this reference). Epilepsy is highly prevalent in people with intellectual disabilities, affecting more than 20% of such people. The prevalence rises with the increasing levels of intellectual disabilities. [23] In a cross-sectional study in 100 patients with epilepsy visiting a psychiatry outpatient clinic, 45% patients had psychiatric comorbidities. Mood disorders, anxiety disorders, and psychotic disorders were seen in 21%, 14%, and 28% patients, respectively. [24] In patients with psychiatric comorbidities, counselling, cognitive strategies, and behavioral countermeasures can help to improve quality of life and psychological well-being. [25] Patients with epilepsy should be screened for anxiety. Tools validated for screening for depression, including Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) and Emotional Thermometers (ET), have been used to identify moderate to severe anxiety in patients with epilepsy. [26]

Expert consensus: In patients with epilepsy, anxiety is seen in about 40-50% patients and depression in 35-38% patients. Patients with epilepsy should be screened for anxiety using tools that are used to screen for depression. In these patients, psychiatric comorbidities adversely impact quality of life. Levetiracetam therapy can further worsen anxiety, depression, and mood swings. Switch of therapy to brivaracetam can help to improve psychiatric conditions including suicidal tendencies. Psychological support and education are key to managing psychiatric comorbidities in patients with epilepsy.

3.3. Safety of Brivaracetam

Brivaracetam is well tolerated in patients with epilepsy. A meta-analysis of eight randomized controlled trials (n=2505) reported good safety and tolerability profile for brivaracetam with no significant risk for serious AEs, drug withdrawal, drug discontinuation due to AEs, or psychiatric AEs. With increasing doses, there was no significant risk of increase in AE-related withdrawal or psychiatric AEs. Brivaracetam was significantly associated with dizziness [Relative risk (RR) (99% CI) = 1.57 (1.13, 2.18), P = 0.008], fatigue [RR (95% CI) = 1.98 (1.32, 2.97), P = 0.001], and back pain [RR (95% CI) = 0.44 (0.20, 0.93), P = 0.03]. [27] Brivaracetam has been reported to have a higher probability of dizziness when compared to levetiracetam. [28]

Mild to moderate AEs have been reported with brivaracetam. The most common AEs include dizziness and euphoria which are known to resolve within the first day of treatment. No clinically relevant changes are reported in laboratory tests, physical examinations, vital signs or cardiac monitoring. [14] The safety of brivaracetam spares the need

for titration and allows initiation at target doses. [29]

Brivaracetam is safe for long-term use in patients with epilepsy. In an open label, flexible-dose, uncontrolled long-term study, adjunctive brivaracetam was well tolerated in adult patients (≥16 years) with focal (n=652) or primary generalized (n=15) seizures who were followed up for up to 11 years (About 50% patients with exposure of at least 48 months). [30] Treatment−emergent adverse events (TEAEs) occurred in 91.2% of all patients. Drug−related TEAEs and serious TEAEs were seen in 56.7% and 22.8% patients, respectively and 14.8% patients discontinued brivaracetam due to TEAEs. The most common TEAEs were headache (24.9%) and dizziness (21.4%). Psychiatric TEAEs were reported in 31.8% patients; the commonest ones being depression (10.6%), insomnia (7.3%), and anxiety (6.7%). Psychiatric TEAEs led to discontinuation of brivaracetam in about 5% patients. Overall, the incidence of TEAEs was the highest in the first 1-3 months and diminished over further follow-up.

Brivaracetam may also be considered for elderly patients with epilepsy who experience AEs with other AEDs like lacosamide and valproate. Though both these AEDs allow rapid titration, therapy in elderly may be challenging due to AEs like dizziness and arrythmias with lacosamide and tremor and encephalopathy with valproate. Levetiracetam, a broad spectrum and high efficacy AED, may be a good choice in elderly due to rapid titration and low tendency for cognitive AEs. However, the psychiatric AEs and dose adjustments in renal compromise can be challenging. [31] In a pooled analysis from the three Phase III studies, involving patients aged ≥65 years (n=32), brivaracetam (50 to 200 mg/day) showed good efficacy which was consistent with that reported in larger populations. The ≥50% responder rate was 14.3% for placebo when compared to 25.0%, 50.0%, and 66.7% for brivaracetam 50, 100, and 200 mg/day, respectively. [32]

Brivaracetam helps to improve quality of life in patients with epilepsy. In aa large pooled analysis (n=2186), improvements were reported for health-related quality of life assessed by Quality of Life in Epilepsy Inventory-31 (QOLIE-31) in patients receiving adjunctive brivaracetam over long term for partial-onset seizures. Brivaracetam therapy for ≥2 months improved total QOLIE−31P scores over the first 42 months of treatment. Clinically meaningful improvements were seen for seizure worry subscale and daily activities/social functioning subscales in approximately 59% and 55% of patients, respectively. [33]

Expert Opinion: Brivaracetam has few behavioral AEs and is a preferred choice for patients with epilepsy who are engaged in jobs that require high intellectual abilities or are students. Brivaracetam is a good choice in elderly patients with epilepsy and does not need dose adjustments according to glomerular filtration rates.

3.4. Efficacy of Brivaracetam

Adjunctive brivaracetam is effective in reducing seizure frequency in adults aged 16–80 years with focal seizures at the dose range of 50–200 mg/day. [34] Brivaracetam also has good efficacy children. Efficacy of brivaracetam is comparable to that of levetiracetam in refractory focal seizures. [28] Brivaracetam is also reported to have efficacy in emergency events such as status epilepticus. [35]

Brivaracetam has an early and sustained efficacy. In three phase III studies, time to onset of sustained ≥50% responder status was assessed for patients (n=1160) with focal (partial-onset) seizures who received placebo or adjunctive brivaracetam 50 mg/day, 100 mg/day, or 200 mg/day. [36] Sustained ≥50% responder status on day 1 was seen in 6.7% patients receiving placebo, and 15.5%, 18.1%, and 19.4% patients receiving the three doses of brivaracetam, respectively (all $P < 0.001$ vs placebo).

The effects of brivaracetam are sustained over long term. In a long-term (follow-up up to 11 years) flexible-dose study of brivaracetam in 652 patients with focal seizures, 170 (30.3%) and 114 (20.3%) patients were continuously seizure−free for at least 6 months and 12 months, respectively. These rates of seizure freedom improved with each exposure duration cohort through to the 84-month cohort and then stabilized. [30]

Brivaracetam therapy reduces the need for other AEDs. A retrospective study in 575 adult patients with focal epilepsy (most having received ≥4 AEDs) showed that brivaracetam reduced the need for concomitant AEDs over 12 months. At baseline, median number of AEDs was three and this reduced to two AEDs at 12 months and 21 patients (3.7%) were on monotherapy. At 12 months, mean reduction in seizure frequency was 36.0%, 39.7% of patients were ≥50% responders, and 17.5% were seizure-free. [37] It may be possible to discontinue any other AEDs and continue brivaracetam as monotherapy (50 to 100 mg/day) in adults with focal seizures with or without secondary generalization. [38]

The effects of adjunctive BRV were evaluated on cognition and behavior in 43 patients with epilepsy in a naturalistic clinical setting with follow-up either after 5 days or after 25 weeks. There was a significant improvement in attention and executive functions ($p = 0.03$) without an interaction with the length of the observation interval. At the longer-term follow-up, 53% of the patients showed at least 50 percent reduction in seizure frequency and 21% were seizure free. [39]

In a 3-week, phase IIa, open-label, single-arm study, add-on treatment with brivaracetam oral solution was well tolerated by children (n=100) aged 1 month to < 16 years with epilepsy. The ≥50% responder rates were 21.3% and 36.4% in all patients (n=80) and those with focal seizures (n=22), respectively. [40]

Expert consensus: Adjunctive brivaracetam (50-200 mg/day) is effective in reducing seizure frequency in adults aged 16-80 years with partial onset seizures. Brivaracetam has shown good efficacy for antiepileptic activity for prolonged periods. Dose modifications are not needed for monotherapy with brivaracetam.

3.5. Switch to Brivaracetam

The favorable pharmacokinetics of brivaracetam allows an

easy and safe switch from other AEDs. In a retrospective study in patients with focal epilepsy (n=575) who were followed up for one year, 228 (39.7%) patients were receiving levetiracetam at baseline and most switched to brivaracetam (dose ratio 1:10-15). Among patients who switched from levetiracetam to brivaracetam due to psychiatric AEs (n = 53), 9 (17%) reported psychiatric AEs on brivaracetam and 3 (5.7%) discontinued brivaracetam due to psychiatric AEs. [37] An open-label, prospective, phase III study (n=29) evaluated nonpsychotic behavioral AEs in patients receiving levetiracetam who switched to brivaracetam 200 mg/day without titration. After treatment over 12 weeks, 27/29 (93.1%) patients had clinically meaningful reductions in BAEs with the switch. [41]

Expert consensus: Patients of epilepsy who experience behavioral AEs with levetiracetam can be safely switched over to brivaracetam without the need for titration.

3.6. Brivaracetam as Add-on Therapy

Brivaracetam is used as add-on therapy with various other traditional and newer AEDs. A pooled analysis of three phase III, placebo-controlled studies of adjunctive brivaracetam in patients with uncontrolled focal seizures suggested no dose adjustments for brivaracetam with concomitant carbamazepine. [42] However, there have been concerns for dose-dependent and reversible elevation of brivaracetam-induced carbamazepine-10,11-epoxide with concomitant treatment with carbamazepine. [43] Brivaracetam does not affect steady-state plasma concentrations of levetiracetam, lamotrigine, lacosamide, phenobarbital, phenytoin, pregabalin, valproate, topiramate, or zonisamide. [19]

Brivaracetam may be used as add-on either early in the course of management of epilepsy or in refractory epilepsy. An early addition of brivaracetam may be considered as add-on therapy is reported to be more effective when started immediately after first AED failure than after failure of second AED. [44] Seizure characteristics, drug profiles, and patient factors should be considered before initiation of add-on therapy. In clinical studies evaluating efficacy and safety, brivaracetam was administered to patients with uncontrolled epilepsy who had received 0-1, 2-4, and ≥5 AEDs. [45-47] In a real-world study in 101 patients being treated for epilepsy in a tertiary referral center, median number of AEDs used prior to brivaracetam treatment was 10 (Range 2 to 18). [48]

In a meta-analysis of five randomized controlled trials (n=1639), brivaracetam had good clinical efficacy as adjunctive therapy for adults with refractory partial seizures. When compared to placebo, the pooled RR was 1.80 (95% CI 1.43-2.26, P < 0.00001) for 50% responder rates, 4.11 (95% CI 1.39-12.21, P = 0.01) for seizure free rates, 1.08 (95% CI 0.73-1.59; P = 0.70) for withdrawal rates. [49] Similar results were reported in another meta-analysis of six trials (n=2399). [50] In a sub analysis by levetiracetam status, there were no significant differences in 50% responder rates when comparing brivaracetam with placebo in patients with concomitant therapy with levetiracetam.

Expert consensus: Brivaracetam does not impact the plasma concentrations of other AEDs and is a good add-on option in the management of epilepsy. Early add-on treatment with brivaracetam should be considered after failure of first AED depending upon the patient and seizure characteristics. Brivaracetam may be considered as the first add-on agent in patients who have behavioral issues like depression and suicidal ideations. Brivaracetam is also suitable for patients with encephalopathy and idiopathic generalized epilepsy. Dual therapy may be continued for at least 6 months to 1 year before one of the AEDs is withdrawn to again get the patient on monotherapy.

Table 2. *Expert consensus for the use of brivaracetam in neurology practices.*

Statements	Agree	Neutral	Do not agree	Consensus	Alternate opinion, if any
Brivaracetam has faster onset of action	√				
Brivaracetam does not require dose titration				√	
Brivaracetam has broad spectrum of activity for seizures following neurosurgical procedures				√	
Brivaracetam has stronger affinity and potency than levetiracetam towards SV2a glycoproteins	√				
Brivaracetam has high retention	√				
Brivaracetam needs no dose adjustments in patients with deranged renal functions	√				
Brivaracetam has a good tolerability profile				√	
Brivaracetam is associated with lesser adverse events when compared to other antiepileptics				√	
Brivaracetam does not adversely impact cognitive functions				√	
No drug interactions are reported with brivaracetam				√	
Young college going female with POS and secondary generalisation is a candidate for brivaracetam therapy				√	
Middle aged male with localised epilepsy and high seizure frequency is a candidate for brivaracetam therapy				√	
An elderly patient with multiple comorbidities and receiving concomitant medications is a candidate for brivaracetam therapy				√	

4. Summary

There was consensus for the use of brivaracetam in epilepsy management in routine neurology practices (Table 2). Adjunctive brivaracetam reduces seizure frequency in adults aged 16–80 years with partial-onset seizures in daily doses of 50–200 mg. Candidates for switch to brivaracetam

are those patients who achieve seizure control with levetiracetam but cannot tolerate its behavioral adverse effects. An immediate switch from levetiracetam to brivaracetam at a 10:1–15:1 dose ratio is possible without titration. Adjunctive treatment with brivaracetam is associated with better effect on executive performance than levetiracetam. In a naturalistic clinical setting, brivaracetam was associated with a small (> 0.2) positive effect size (Cohen's d = 0.31) on executive performance while a neutral effect (positive effect sizes < 0.2) was seen for levetiracetam (Cohen's d = 0.14). [39] Brivaracetam is a safer AED with lesser behavioral AEs, lack of cognitive impairment, and no clinically relevant drug-drug interactions. No dose adjustments are needed for brivaracetam in patients with deranged renal functions. This makes it a good choice in elderly patients with epilepsy. Higher cost of treatment may limit the widespread use of brivaracetam in clinical practice.

Patient profiles for brivaracetam: Eligible patients for brivaracetam therapy in epilepsy include young female patients with concomitant oral contraceptives, young and anxious students, middle aged patients with high frequency of seizures despite polytherapy, patients with aggression and cognitive disabilities and psychiatric comorbidities, elderly patients with multiple comorbidities and concomitant medications. Early add-on brivaracetam may be considered for patients with behavioral issues like depression and suicidal tendencies. There is no experience for the use of brivaracetam in pregnant women. The non-availability of IV formulation and higher cost of therapy limit the use of brivaracetam in India.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

Declaration

We confirm that the manuscript has been read and approved by all the authors and there are no other persons who satisfied the criteria for authorship but are not listed. The order of authors listed in the manuscript has been approved by all of us.

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All named authors for this manuscript meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. All authors take full responsibility for the integrity of the work and have given final approval for the published version. The authors acknowledge Dr. Punit Srivastava and Dr. Tarveen Jandoo from Mediception Science Pvt. Ltd (www.mediception.com), Gurgaon, India for providing writing and editing assistance for this project. The fund for writing assistance was funded by Dr Reddy's Laboratories.

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