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Zonisamide – An Overview

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1. Introduction

Zonisamide, a 1,2 benzisoxazole derivative is a structurally novel antiepileptic drug (AED) with a broad spectrum of antiseizure activity. [1,2] Zonisamide has been available in Japan since 1989, where it is widely used both as monotherapy and adjunctive therapy (i.e. as Add on) for various seizure types and syndromes in adults and children.[3,4]

In the United States, clinical trials of zonisamide began in the early 1980s. These studies provided clear evidence of zonisamide's promise as an effective adjunctive therapy for refractory partial seizures. Leppik et al. observed a 52% reduction in seizure frequency in a historical-control, open-label, multicenter study. However, development of kidney stones in 3.7% of patients enrolled in this study led to the temporary termination of US development efforts. Testing resumed in the 1990s, and zonisamide was approved by the US Food and Drug Administration (FDA) in March 2000 as adjunctive treatment for refractory partial-onset seizures in adults (aged >16 years).⁵

Results from placebo-controlled, short-term studies, as well as baseline- or historical-controlled, long-term studies, demonstrate that zonisamide is an effective adjunctive treatment for refractory partial-onset seizures. Zonisamide efficacy did not decline over time, suggesting that most patients do not develop tolerance to the anticonvulsant effects of zonisamide. Findings from one of the long-term studies indicate that, for some patients, zonisamide can be effective as monotherapy.^[7]

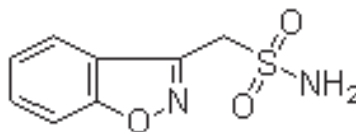
Zonisamide was well-tolerated; most adverse events were mild to moderate, and their incidence declined as treatment continued. The few serious adverse events were all reversible with zonisamide dose reduction or discontinuation or the passage of time. US clinical trials show that zonisamide is a safe and effective AED for the treatment of refractory partial-onset seizures. Further studies are needed to establish monotherapy efficacy in epilepsy.

The potential use of zonisamide in non epileptic conditions like neuropathic pain, migraine prophylaxis [2] and Parkinsonism [6] are briefly touched in this review.

2. Basic structure and chemistry⁵⁸

1-(1, 2-Benzoxazol-3-yl) methanesulphonamide

Molecular Structure



Molecular Formula	C ₈ H ₈ N ₂ O ₃ S
Molecular Weight	212.23
Appearance	White powder
pKa	10.2
Solubility	moderately soluble in water (0.80 mg/mL)
Melting point	161-163 oC
Isoelectric Point	10.2

Phase 1. Metabolising Enzyme (1-st Step of Metabolism) CYP3A4

3. Overview of pharmacodynamic properties

A brief overview of pharmacodynamic properties including mechanism of action is discussed here.^[1,3, 6]

Mechanism of action: The precise mechanism is still unclear^[5] but various proposed mechanisms based on various animal and cellular studies are listed below.

A. Membrane stabilisation through,

1. Blockade of voltage-dependent T-type calcium channels and
2. Blockade of voltage-sensitive sodium channels.

B. Neuro modulation by

1. Blockade of potassium-evoked glutamate response
2. Reduction of glutamate-mediated synaptic excitation
3. Increased γ -amino butyric acid (GABA) release and
4. Facilitation of Dopaminergic and serotonergic transmission and

C. Neuroprotection By free radical scavenging.^[2,3,6]

Despite the presence of a sulphonamide group in its chemical structure, zonisamide is only a weak inhibitor of carbonic anhydrase ^[3]and it is 100–200 times less potent than acetazolamide^[5,8]. In contrast to acetazolamide, this effect does not contribute to the antiepileptic activity of zonisamide.^[8]

4. Overview of pharmacokinetic properties

The pharmacokinetic profile is extensively studied from healthy volunteers from U.S, Japan and Europe. The data are published in various reviews ^[1,3,7,9-12] as well as in conference abstracts.^[13-16]

Zonisamide is absorbed relatively rapidly from the gastrointestinal (GI) tract; a peak plasma concentration (C_{max}) of 3 micrograms/mL was reached 4–5 hours after a 200mg dose in healthy volunteers in Japan^[17,18]. In contrast, C_{max} values ranging from 2.3 micrograms/mL after a 200mg dose to 12.5 micrograms/mL after an 800mg dose were reached within 2.4–3.6

hours in healthy volunteers in the United States.^[20] The oral bioavailability of zonisamide is 100%^[19]. Food consumption does not influence the extent of zonisamide absorption, although the time to C_{max} is delayed, occurring at 4–6 hours.^[5]

Zonisamide steady-state plasma concentrations are achieved within 14 days.^[5] In patients with epilepsy in Japan, zonisamide steady-state plasma concentrations increased linearly with increasing dose in the zonisamide dosages of up to 13 mg/kg/day in children and 18.6 mg/kg/day in adults.^[22] On the other hand, zonisamide appeared to demonstrate non linear pharmacokinetics in healthy volunteers^[20] and patients with epilepsy in the US.^[23–25]

Zonisamide is distributed relatively evenly throughout the whole body; the apparent volume of distribution is 1.45 L/kg following a 400mg oral dose^[5]. The drug is not highly bound to plasma proteins (40–60%). However, zonisamide has a high affinity for erythrocytes, with concentrations in these cells exceeding those in plasma by 4- to 9-fold in healthy volunteers in Japan.^[7,18]

Zonisamide undergoes hepatic metabolism and its primary route of excretion is by the kidneys.^[5] After oral administration, inactive zonisamide metabolites identified in the urine, but not in the plasma, include *N*-acetyl-zonisamide and the glucuronide conjugate of the open isoxazole ring metabolite 2-sulphamoylacetyl phenol (SMAP). Acetylation of zonisamide is mediated by *N*-acetyltransferase,^[9] while reduction to SMAP is mediated by the cytochrome P450 isoenzyme 3A4.^[5]

Zonisamide has a long terminal elimination half-life (50–68 hours in plasma and 105 hours in erythrocytes) after administration of single oral 200–800mg doses in healthy volunteers in Japan and/or the US. Overall, 62% of the administered dose was recovered in the urine and 3% in the faeces. The pharmacokinetics of zonisamide were not altered to a clinically significant extent when compared in young (mean age 28 years) and elderly (mean age 69 years) healthy volunteers suggesting that dosage adjustment is not necessary in patients of advanced age.

Dosing data from a meta-analysis of 1008 patients in Japan (403 children and 605 adults) suggest that zonisamide clearance is moderately higher in children than in adults.^[57] In a single-dose study, the renal clearance of zonisamide decreased with decreasing renal function; marked renal impairment was associated with a 35% increase in the zonisamide area under plasma concentration curve. The US manufacturers' prescribing information recommends caution, but not dosage adjustment, in patients with hepatic or renal disease.

5. Therapeutic efficacy

5.1 Add-on therapy in adults

A Randomized, Double-blind, Placebo-controlled Study in Patients with Refractory Partial Seizures-Martin J. Brodie et al states that ZNS provides dose-dependent, effective, and generally well-tolerated adjunctive therapy in patients with partial seizures²⁶

Review of United States and European clinical trials of zonisamide in the treatment of refractory partial-onset seizures done by Edward Faught et al²⁷: Results from placebo-controlled, short-term studies, as well as baseline- or historical-controlled, long-term studies, demonstrate that zonisamide is an effective adjunctive treatment for refractory partial-onset seizures. Zonisamide efficacy did not decline over time, suggesting that most patients do not develop tolerance to the anticonvulsant effects of zonisamide. Findings from one of the long-term studies indicate that, for some patients, zonisamide can be effective as monotherapy. Zonisamide was well-tolerated; most adverse events were mild to moderate, and their incidence declined as treatment continued. The few serious adverse events were

all reversible with zonisamide dose reduction or discontinuation or the passage of time. US clinical trials show that zonisamide is a safe and effective AED for the treatment of refractory partial-onset seizures. Further studies are needed to establish monotherapy efficacy.

Practical prescribing and long-term efficacy and safety of zonisamide by Ilo E. Leppik et al²⁸: A range of clinical studies and extensive clinical experience have demonstrated the long-term efficacy and tolerability of zonisamide in the treatment of refractory partial seizures. Substantial patient benefit is maintained during continued administration of zonisamide, including sustained decreases in seizure frequency for many patients and attainment of seizure freedom for a substantial number of individuals. Careful patient management can optimise these benefits whilst minimising risks of any AEs. Clinical experience in the US indicates that the benefits of zonisamide may extend across a range of seizure types. These observations suggest that zonisamide is an efficacious and well tolerated treatment option for the long-term management of many types of epilepsy.

Long-term efficacy and safety of monotherapy and adjunctive therapy with zonisamide - William A. Tosches et al²⁹: In this study, zonisamide, when used as monotherapy or concomitant therapy, proved effective as an anticonvulsant and was well tolerated over time.

According to a Cochrane data base review done in 2005³⁰, Zonisamide has efficacy as an add-on treatment in people with drug-resistant partial epilepsy. Minimum effective and maximum tolerated doses cannot be identified. The trials reviewed were of 12 week duration and results cannot be used to confirm longer periods of effectiveness in seizure control. The results cannot be extrapolated to monotherapy or to people with other seizure types or epilepsy syndromes.

In four short-term (24 weeks), placebo-controlled trials conducted in the US or Europe (n = 138–351), once- or twice-daily administration of zonisamide at dosages of >300 mg/day was mostly effective in the treatment of patients with medically refractory partial seizures, with or without secondary generalisation to tonic-clonic seizures, based on significantly greater reductions in median seizure frequency for all partial seizures, for complex partial seizures only and for all seizure types. The corresponding responder rates (i.e. patients achieving a >50% reduction from baseline in seizure frequency) in zonisamide >400 mg/day recipients were generally significantly greater than with placebo. When assessed in two of the above-mentioned trials, twice-daily administration of zonisamide 100 or 200 mg/day was mostly effective in one study, whereas 100 mg/day was not effective in the other.

Longer term, the antiepileptic efficacy of zonisamide was maintained in patients who continued therapy for up to 2 years, with no evidence of tachyphylaxis or pharmacological tolerance.

The efficacy of zonisamide at mean dosages of 5.9–8.8 mg/kg/day was demonstrated in a total of 1008 adults or children in Japan with various types of epilepsy mainly refractory to treatment who were recruited to a series of predominantly non-comparative clinical trials. In the only active comparator-controlled study performed to date, zonisamide (mean dosage 330 mg/day) was judged to be as effective as carbamazepine (mean dosage 600 mg/day) in Japanese patients with predominantly partial epilepsies.

5.2 Add-on therapy in children

There has been extensive clinical trial and clinical practice experience with zonisamide therapy in Japanese children. Open-label data from pediatric clinical trials conducted in Japan suggest that zonisamide is well tolerated and effective against partial- and

generalized-onset seizures in children. Despite this wealth of open-label data, no formal pharmacokinetic studies and only one well-controlled trial of zonisamide's efficacy and safety in Japanese children have been completed to date. No controlled clinical trials of zonisamide in children have been completed in the United States or Europe³¹

5.3 Monotherapy in children

Tohru Sekia³² did a study on seventy-seven children with epilepsy (ages 8 months–15 years) who were treated with zonisamide. Nine patients were withdrawn early because of side effects; these patients were included in side effect but not efficacy analyses. Zonisamide dosages were initiated at approximately 2 mg/kg per day and adjusted for each patient individually to a maximum of 12 mg/kg per day. Among 44 patients with cryptogenic/symptomatic partial epilepsy, 36 (82%) became seizure free; 4 (9%) had a $\geq 50\%$ reduction in seizure frequency; and 4 (9%) had no change in seizures with zonisamide treatment. Of 11 patients with cryptogenic/symptomatic generalized epilepsy, 10 (91%) became seizure free, and 1 experienced no change with zonisamide treatment. Similarly, 4 patients (100%) with idiopathic partial epilepsy, and 8 of 9 patients (89%) with idiopathic generalized epilepsy became seizure free with zonisamide treatment; in the last group, 1 experienced no change. Thirty patients (39%) reported side effects, including somnolence (11.7%), decreased spontaneity (7.8%), anorexia (6.5%), and rash (6.5%). Thus, zonisamide is effective for partial seizures with or without secondarily generalized seizures in children and should be considered a broad-spectrum antiepilepsy agent.

There has been extensive clinical trial and clinical practice experience with zonisamide therapy in Japanese children. Open-label data from paediatric clinical trials conducted in Japan suggest that zonisamide is well tolerated and effective against partial- and generalized-onset seizures in children. Despite this wealth of open-label data, no formal pharmacokinetic studies and only one well-controlled trial of zonisamide's efficacy and safety in Japanese children have been completed to date. No controlled clinical trials of zonisamide in children have been completed in the United States or Europe.

5.4 Monotherapy in adults

Angus A. Wilfong^[33] in his several small, open-label studies have indicated that it may be safe and effective as monotherapy. This present chart review study was conducted to evaluate the safety and effectiveness of zonisamide monotherapy in a paediatric and young adult patient group. Patient records at the Blue Bird Circle Clinic for Paediatric Neurology were reviewed to identify patients receiving zonisamide monotherapy. Efficacy was assessed from seizure diaries and patients' subjective evaluations. Safety and tolerability were evaluated by analysis of adverse events and change in body weight. The study included 131 patients aged 1 to 21.8 years with a broad spectrum of seizure types and epilepsy syndromes. A total of 101 patients (77.1%) achieved a 50% or greater decrease in seizure frequency, including 39 patients who achieved seizure freedom. Zonisamide monotherapy was well tolerated, with three patients (2.3%) discontinuing for adverse events. These results support open-label studies from Japan reporting that zonisamide monotherapy is safe and effective in paediatric and young adult patients.

Pooled analyses of open-label studies³⁴ specifically in young adults and/or children showed zonisamide to be effective as adjunctive therapy for refractory partial seizures (dosage of 2.0–18.6 mg/kg/day) and as monotherapy for newly diagnosed or refractory partial seizures (dosage of 1–12 mg/kg/day).

6. Specific categories of seizures

1. Post-operative seizures - Zonisamide, an agent with antiepileptogenic, free radical scavenging and neuroprotective actions in experimental animals, showed promising effects against postoperative epilepsy in a randomized double blind controlled trial.³⁶
2. Myoclonic epilepsy - zonisamide may be useful in the treatment of patients with PME. Studies have found it to be useful in Unverricht-lundborg disease³⁷.
3. West syndrome
4. Brain tumour related epilepsy³⁸

7. Tolerability and adverse effects

Zonisamide was generally well tolerated as adjunctive therapy in patients (n = 499) with refractory partial seizures enrolled in placebo-controlled trials conducted in the US and Europe³⁵, and as adjunctive therapy or monotherapy in adults or children in Japan (n = 1008) with various types of epilepsy recruited in predominantly non-comparative clinical trials. The most frequently occurring adverse events common to these studies were somnolence, anorexia, ataxia, gastrointestinal discomfort/abdominal pain, mental slowing, weight loss and skin rash/itch.

Adverse events usually occurred early during treatment (within 4 weeks), were generally of mild-to-moderate intensity, and decreased with time in the US and European studies. Patient tolerability of zonisamide was optimised during slow titration from low initial dosages to therapeutic dosages over 4–8 weeks.

The tolerability profile of zonisamide in a Japanese study was generally similar to that of carbamazepine, although anorexia occurred more frequently with zonisamide, and ataxia was noted more frequently with carbamazepine.

Patients mainly in the US and Europe appear to be at increased risk of developing kidney stones (incidence equivalent to 18 cases per 1000 patient-years of exposure), while paediatric patients, in particular, appear to be at increased risk of zonisamide-associated oligohydrosis/hyperthermia (estimated reporting rate 1–2 cases per 10 000 patient-years of exposure).

7.1 Adverse effects

All seizure medicines affect the amount of activity by brain cells, and carry dose-related risks of:

- fatigue/somnolence (usually within the first month of treatment and at higher doses)
- psychiatric symptoms
- depression
- psychosis
- cognitive symptoms
- impaired concentration
- speech problems (especially word-finding difficulties)
- psychomotor slowing

7.2 Allergy and hypersensitivity

Zonisamide is a sulfonamide medication. Life-threatening allergies to sulfonamide medications can occur, including

- Stevens-Johnson syndrome

- toxic epidermal necrolysis
- aplastic anaemia
- agranulocytosis
- other blood dyscrasias
- fulminant hepatic necrosis

Zonisamide should be discontinued immediately in any patient with signs of hypersensitivity reaction. Any rash that develops during zonisamide treatment should be monitored carefully, and discontinuation should be strongly considered. Deaths due to serious rashes have been reported. Rash is most common in the first 2-16 weeks of treatment.

7.3 Metabolic acidosis

The FDA identified that zonisamide can cause metabolic acidosis in some patients. The acidosis is characterized by:

- Elevated serum chloride and reduced serum bicarbonate
- Greater apparent risk early in treatment (but it can arise later)
- Greater risk with increased dose (but acidosis has been observed with doses as low as 25 mg daily)
- Children are at greater risk of acidosis than adults.

Risk factors include

- Kidney disease
- Severe respiratory disorders
- Diarrhoea
- Ketogenic diet
- Drug interactions

Metabolic acidosis may be asymptomatic, but can be accompanied by symptoms of:

- Hyperventilation
- Fatigue
- Anorexia
- Cardiac arrhythmias

Identification and treatment of metabolic acidosis is important, because it can increase the risk of:

- Kidney stones
- Nephrocalcinosis
- Bone abnormalities (with increased risk of fracture)
- Growth delay
- Abnormal foetal development.

The FDA recommends treatment of acidosis if it occurs:

- Consider either reducing the dose or discontinuing the drug and modifying the patient's anti-epileptic treatment
- If a patient with metabolic acidosis is to continue on zonisamide, consider treatment with alkali.

7.4 Oligohydrosis/hyperthermia

Oligohydrosis, characterised by decreased sweating and elevation in body temperature above normal, has been noted in rare cases. Risk factors appear to be the paediatric age group, a high level of physical activity and a high ambient temperature. The occurrence of oligohydrosis during treatment may be related to weak inhibition of carbonic anhydrase by

zonisamide as similar effects have been described following treatment with topiramate and acetazolamide, which are known to possess this mechanism. Cautioning parents of this rare effect, combined with monitoring in warm climates or hot weather, and ensuring that patients remain cool and well hydrated, should help to minimise the risk of oligohydrosis

7.5 Kidney stones

The rate of new kidney stones is approximately 18 per 1000 patient-years; with a relative risk five to nine times that of the general population. The risk of renal stones appears to be greater with higher doses and longer duration of treatment. Increased fluid intake is likely to reduce the risk of renal stones through limitation of tubular precipitation and aiding passage of any calculi, and fluid intake should be encouraged to get specific gravity to 1.010.

7.6 Appetite/weight loss

Mean weight loss was <1.7 kg and the majority of weight decreases are <5 kg in pivotal studies. The changes in body weight did not appear to be progressive in the clinical trial population, and remain stable over periods of up to 2 years. Weight loss has been confirmed by clinical experience with women losing more weight than men. Weight loss has been observed even when zonisamide is used in conjunction with valproate

7.7 Suicide

The FDA has issued a general warning regarding anticonvulsants and suicide, which applies to zonisamide. Children (especially adolescents and young adults) taking zonisamide should be monitored closely by their parents for any notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression

7.8 Teratogenicity

Women of child bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryo-lethal in monkeys when administered during the period of organogenesis. A variety of foetal abnormalities, including cardiovascular defects, and embryo-foetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of Zonisamide Capsules during pregnancy in humans may present a significant risk to the foetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus

8. Dosage and administration³⁹

8.1 Infants and children

Initial: 1-2 mg/kg/day given in two divided doses/day (although in more urgent settings, up to 4 mg/kg/d to start may be tolerated)

Increase by 0.5-1 mg/kg/day every 2 weeks

Goal dose: 5-8 mg/kg/day

Max dose: ~12 mg/kg/day

(Glauser 2002; Leppik, 1999; Oommen, 1999)

8.2 Adolescents and adults

Initial: 100 mg once daily for 1 week, then 200mg once daily

Titration: Increase in increments of 100 mg/day if needed for seizure control, with a minimum of 2 weeks between adjustments

Usual effective dose: 100-600 mg/day

There is no evidence of increased benefit with doses >400 mg/day

Once vs. twice daily dosing:

Once daily dosing keeps steady-state serum concentrations within 27%

Twice daily dosing keeps concentrations within 14%

Patient with an effective dose which is near the maximum tolerated dose may benefit from twice daily dosing

8.3 Dosage adjustment in renal/hepatic disease

Slower dosage titration and more frequent monitoring are recommended in patients with renal or hepatic disease. It should be used with extreme caution if creatinine clearance is less than 50 mL/minute.

8.4 Levels

Plasma concentrations may be useful; with therapeutic levels usually between: 10-20 mcg/mL. Higher levels (up to 30 mcg/mL), may improve control, but are associated with adverse effects (Oommen, 1999 and Leppik, 1999).

8.5 Monitoring

Due to the risk of asymptomatic metabolic acidosis, the FDA recommends measuring serum bicarbonate before starting zonisamide and periodically thereafter (even in the absence of symptoms)

9. Current role of ZNS in the therapy of epilepsy

Zonisamide was approved by the US Food and Drug Administration (FDA) in March 2000 as adjunctive treatment for partial-onset seizures in adult. In Japan, it is approved for use as monotherapy and as adjunctive therapy for children and adults with both generalized and partial seizures

10. Use in non-epileptic indications

- The drug has recently hypothesized to be useful in autism⁴⁰.
- Zonisamide-induces long-lasting recovery of dopaminergic neurons from MPTP-toxicity. It has been found to be useful in managing impulse control disorders in Parkinson's disease⁴¹.
- Zonisamide can be used for migraine prophylaxis in topiramate-intolerant patients. It is also used in the preventive treatment of migraine^{42,43}
- SUNCT syndrome has been found to show response to zonisamide⁴⁴
- It is found to be effective in the treatment of alcohol dependence. It reduced ethanol self-administration by risky drinkers.^{45,46}
- Zonisamide ameliorates symptoms of secondary paroxysmal dystonia.⁴⁸
- It is used in the treatment of extrapyramidal and psychotic symptoms in patients suffering from dementia with lewy bodies⁵⁰

- Zonisamide Combined with Cognitive Behavioural Therapy has been useful in the treatment of Binge Eating Disorder⁵³
- Idiopathic hemifacial spasm has been found to be responsive to zonisamide⁵⁴
- Zonisamide is used in the treatment of neuropsychiatric disorders⁵⁵.
- Zonisamide suppresses pain symptoms of formalin-induced inflammatory and streptozotocin-induced diabetic neuropathy⁵⁶.

11. Conclusion

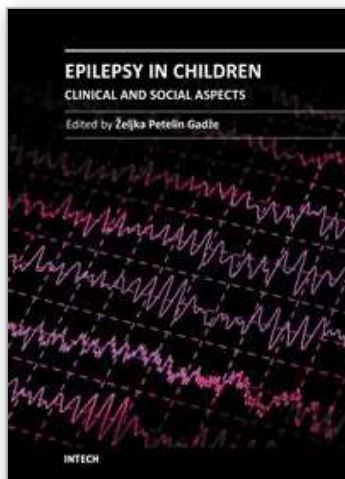
In conclusion, the new-generation AED zonisamide, either as adjunctive therapy or as monotherapy, effectively reduces the frequency of partial seizures, with or without secondary generalisation to tonic-clonic seizures, in adults and children with epilepsy. The drug is generally well tolerated and, additionally, has a favourable pharmacokinetic profile permitting once- or twice-daily administration. Direct head-to-head comparisons with other AEDs would be beneficial in fully defining the place of zonisamide in therapy. In the meantime, adjunctive therapy or monotherapy with zonisamide is a convenient, useful option for the management of partial seizures, including those refractory to other AEDs.

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Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book “On The Sacred Disease”. Classically, epilepsy has been defined as a chronic condition characterized by an enduring propensity to generate seizures, which are paroxysmal occurring episodes of abnormal excessive or synchronous neuronal activity in the brain. Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits, because the symptoms of epileptic seizures are not the result of usual loss of function that accompanies many disease that affect the brain. I am therefore extremely honoured to present this book. The 15 very interesting chapters of the book cover various fields in epileptology – they encompass the etiology and pathogenesis of the disease, clinical presentation with special attention to the epileptic syndromes of childhood, principles of medical management, surgical approaches, as well as social aspects of the disease.

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