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REVIEW

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Zonisamide: Review of Recent Clinical Evidence for Treatment of Epilepsy

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SUMMARY

Zonisamide is an orally administered antiepileptic drug that was first approved for clinical use in Japan in 1989. Since then, it has been licensed in Korea for a broad spectrum of epilepsies in adults and children, and in the USA for adjunctive therapy of adults with partial seizures, and in Europe for monotherapy of adults with newly diagnosed partial seizures and adjunctive therapy of adults and adolescents and children aged ≥6 years with partial seizures with or without secondary generalization. Zonisamide is a benzisoxazole derivative with a unique chemical structure, predictable dose-dependent pharmacokinetics, and multiple complementary mechanisms of action. Treatment with zonisamide is well tolerated and is not known to be associated with clinically significant drug–drug interactions, including with oral contraceptives or other antiepileptic drugs. There have been >2 million patient-years of experience with zonisamide for treatment of epilepsy, and this drug has International League Against Epilepsy level A evidence for efficacy/effectiveness as initial monotherapy for adults with partial-onset seizures. This review presents the evidence for zonisamide across the spectrum of epilepsy, with emphasis on real-world clinical practice and special populations of patients (children, elderly patients, and women of childbearing age) who are likely to be treated in daily clinical practice.

Introduction

Zonisamide is an orally administered antiepileptic drug (AED) that was first approved for clinical use in Japan in 1989, where it is licensed as monotherapy or adjunctive therapy for partial onset and generalized epilepsy in adults and children [1,2]. Since then, it has been licensed in South Korea for a broad spectrum of epilepsies in adults and children, and in the USA and Europe for adjunctive treatment of adults with partial seizures, with or without secondary generalization [2,3]. In Europe, zonisamide is also licensed as adjunctive therapy in the treatment of partial seizures with or without secondary generalization in adolescents and children aged 6 years and older and as monotherapy for adults with newly diagnosed partial seizures [2,4].

Zonisamide is a benzisoxazole derivative with a unique chemical structure [2]. Zonisamide acts through multiple complementary mechanisms, including blocking voltage-gated sodium channels (providing activity against partial-onset seizures), inhibiting T-type calcium channels (providing activity against absence seizures) [1,3,5], and enhancing γ-aminobutyric acid release and inhibiting glutamate release [1,5]. Zonisamide also weakly alters acetylcholine, dopamine, and serotonin metabolism and inhibits carbonic anhydrase activity [4,6], although it is uncertain whether these actions contribute to its clinical efficacy [4].

Zonisamide has predictable dose-dependent pharmacokinetics. Peak plasma concentration is achieved in approximately 2–4 h, and the half-life is approximately 60 h [2,6,7], allowing once-daily dosing [1]. Zonisamide is rapidly absorbed after ingestion and has an oral bioavailability of ≥90% [8] that is unaffected by food, although food causes a slight delay to peak plasma concentration (4–6 h) [4,7]. Steady state is reached in approximately 14 days with stable dosing [7]. Zonisamide is predominantly metabolized via cytochrome P450 (CYP) 3A4 [6] and is primarily excreted in urine [4].

Poorly controlled epilepsy is often treated with combination therapy, so the potential for interactions with other AEDs is important [8,9]. Zonisamide is not highly bound to plasma protein (approximately 40–50%) [4] and does not affect protein binding

of other highly protein-bound AEDs. Protein binding of zonisamide is not affected by phenytoin, carbamazepine, or phenobarbital at therapeutic concentrations [4,6,7]. Clinically significant interactions with sodium valproate, lamotrigine, or oral contraceptives have not been shown [1,2,8–10]. Zonisamide does not inhibit key CYP enzymes, so is not expected to interact with other CYP-mediated drugs, although dose adjustment may be needed if administration of concomitant CYP3A4 drugs is changed [4,7]. Caution is advised for patients with mild renal or hepatic impairment in the form of slower dose titration.

There have been more than 2 million patient-years of experience with zonisamide for treatment of epilepsy. Zonisamide has been widely studied among pediatric and adult patients in Japan [6]. There appear to be only modest differences in efficacy between adults and young [11] or elderly [12] patients, and zonisamide has a good tolerability and safety profile in these populations [4,6]. It also appears that race does not affect the pharmacokinetics of zonisamide [4].

Clinically, the advantages of monotherapy for epilepsy include convenient dosing, increased compliance, reduced potential for drug–drug interactions, and cost savings [3]. However, combination therapy may have the advantage of targeting multiple epilepsy mechanisms, particularly in patients refractory to initial treatment [3]. Zonisamide is effective as monotherapy for partial-onset seizures and as adjunctive treatment for refractory partial-onset seizures [5].

This review presents the evidence for zonisamide, with an emphasis on real-world clinical practice and the special populations of patients (children, elderly patients, and women of childbearing age) who are likely to be treated in daily clinical practice.

Methods

For this nonsystematic literature review, data for the past 10 years (from 2005 to 2014) were collected from MEDLINE®/PubMed® and EMBASE® using specified search criteria based on efficacy and safety of zonisamide in defined clinical settings. The search terms were combinations of the following search terms: "anticonvulsants," "zonisamide," "epilepsy," "seizures," "efficacy," and "safety." Only articles published in English were considered for this review. If a title or abstract described a high-quality study that was likely to be eligible for inclusion, the full article was obtained and assessed for relevance according to predefined criteria. We reviewed the published randomized controlled clinical trials of zonisamide used for regulatory approvals, as well as their open-label extension studies. We also collated the data for zonisamide in real-world clinical practice and in special populations of older and younger (pediatric) patients that lead to treatment-related practices. Age-related search terms were added to the predefined terms, and articles obtained were assessed for relevance.

Zonisamide for Partial Seizures

Clinical trials and experience in clinical practice have established zonisamide as an efficacious adjunctive treatment for partial epilepsy, and it has been shown to be effective as initial monotherapy for newly diagnosed patients with partial seizures [13]. Zonisamide is one of only four AEDs to have International League Against Epilepsy (ILAE) level A evidence as initial monotherapy for adults with partial-onset seizures (the other three being carbamazepine, phenytoin, and levetiracetam) [14]. This section describes the ILAE evidence [13] and three other phase 3 randomized controlled trials (RCTs) of zonisamide in adult patients with partial seizures: two as monotherapy [13,15] and two as adjunctive therapy to other AEDs [16,17].

Monotherapy

In a multicenter RCT of adults with newly diagnosed partial epilepsy, performed according to the ILAE guidelines, Baulac et al. [13] compared zonisamide 300 mg/day with carbamazepine 600 mg/day for 26–78 weeks. In the per protocol population, 79.4% and 83.7% of patients in the zonisamide and carbamazepine groups, respectively, were free of seizures for 26 weeks or more (Table 1). These results were echoed in the intent-to-treat (ITT) population, with 69.4% and 74.7% of patients in the zonisamide and carbamazepine groups being free of seizures for 26 weeks (Table 1). The zonisamide dose to achieve 26-week seizure freedom was 300 mg (range, 200–500 mg). The incidence of treatment-emergent adverse events (TEAEs) was similar for zonisamide (n = 170; 60%) and carbamazepine (n = 185; 62%), as was the incidence of treatment-related TEAEs of 102 (36%) for zonisamide and 115 (38%) for carbamazepine. The most frequent TEAEs were headache, decreased appetite, somnolence, dizziness, and weight loss, and most were mild or moderate in severity. The relative treatment difference of −5.4% for seizure freedom at 26 weeks was greater than the relative −20% margin in the ILAE guidelines for epilepsy monotherapy; thus, this study met the ILAE's criteria for a successful noninferiority trial (class I) [14]. The authors concluded that zonisamide could be useful as an initial monotherapy for patients with newly diagnosed partial epilepsy given its apparent lack of interaction with other drugs, including hormonal contraceptives, and its once-daily dosing advantage [13].

The long-term safety of zonisamide was evaluated in an extension to this study, which confirmed that the tolerability was maintained over the long term [15]. Both zonisamide and carbamazepine were well tolerated, with similar rates of TEAEs (52.6% and 46.2%, respectively), and low rates of serious TEAEs (5.1% and 4.4%) or TEAEs leading to discontinuation (1.5% and 0.6%). Retention rates were similar for both drugs at 12 and 18 months (Table 1). This long-term study confirmed the efficacy and tolerability of zonisamide.

Adjunctive Therapy

In a pivotal European RCT of zonisamide as adjunctive therapy, 351 patients aged 12–77 years with refractory partial epilepsy, with or without secondary generalization, who were taking up to three AEDs were randomized to placebo or zonisamide 100, 300, or 500 mg/day [16]. The dose was titrated for 6 weeks and followed by fixed-dose assessment for 18 weeks. In the ITT population, reduction in frequency and response rates (≥50% reduction in seizure frequency) were significant for complex partial seizures, all partial seizures (simple and complex partial seizures), and all seizures for zonisamide 500 mg/day versus placebo (Table 1).

Table 1 Zonisamide in patients with partial seizures

Study	Design	Patients	Intervention	Duration	Results
Baulac et al., 2012 [13]	Phase 3 randomized double-blind parallel-group noninferiority trial	583 adults with newly diagnosed partial seizures from 120 centers globally	Zonisamide 200–500 mg/day or carbamazepine 400–1200 mg/day Monotherapy	26–78 weeks	Seizure-free at 26 weeks: PP population: Zonisamide: 79.4%; carbamazepine: 83.7% Absolute treatment difference: −4.5 (95% CI, −12.2 to 3.1) ITT population: Zonisamide 69.4%; carbamazepine 74.7% Absolute treatment difference: −6.1 (95% CI, −13.6 to 1.4) Seizure-free at 52 weeks: PP population: Zonisamide: 67.6%; carbamazepine: 74.7% Absolute treatment difference: −7.9 (95% CI, −17.2 to 1.5) ITT population: Zonisamide 55.9%; carbamazepine 62.3% Absolute treatment difference: −7.7 (95% CI, −16.1 to 0.7)
Baulac et al., 2014 [15]	Extension study to Baulac et al., 2012 [13]	295 adults with newly diagnosed partial seizures from 72 centers	Zonisamide 200–500 mg/day or carbamazepine 400–1200 mg/day Monotherapy	–	Retention rates at 12 months: Zonisamide 58.4%; carbamazepine 61.4% Retention rates at 18 months: Zonisamide: 27.7%; carbamazepine: 27.8%
Brodie et al., 2005 [16]	Phase 3 European RCT	351 patients with refractory partial seizures, with or without secondary generalization	Adjunctive therapy with zonisamide 100, 300, or 500 mg/day or placebo	18 weeks	Complex partial seizure: Reduction in frequency: Zonisamide 500 mg/day: −51.2%; placebo: −16.3%; $P < 0.0001$ Response rate[a]: Zonisamide 500 mg/day: 52.3%; placebo: 21.3%; $P < 0.001$ All partial seizure: Reduction in frequency: Zonisamide 500 mg/day: −50.6%; placebo: −19.4%; $P < 0.0001$ Response rate[a] Zonisamide 500 mg/day: 50.5%; placebo: 20.2%; $P < 0.001$ All seizure: Reduction in frequency: Zonisamide 500 mg/day: −51.3%; placebo: −18.1%; $P < 0.0001$ Response rate[a] Zonisamide 500 mg/day: 52.5%; placebo: 17.9%; $P < 0.001$

(continued)

Table 1 (Continued)

Study	Design	Patients	Intervention	Duration	Results
Mayer et al., 2005 [17]	Subanalysis of Brodie et al., 2005 [16]	82 patients with refractory partial seizures	Adjunctive therapy with zonisamide 100, 300, and 500 mg/day or placebo	18 weeks	All seizure frequency: ITT Zonisamide 300 mg/day: −57.5%; zonisamide 500 mg/day: -47.4%; placebo: −29.6% EE Zonisamide 300 mg/day: −57.5%; zonisamide 500 mg/day: −59.6%; placebo: −29.6% Response rate[a]: ITT Zonisamide 300 mg/day: 53.3%; zonisamide 500 mg/day: 48.3%; placebo: 22.7% EE Zonisamide 300 mg/day: 53.8%; zonisamide 500 mg/day: 63.2%; placebo: 27.8%

AED, antiepileptic drug; CI, confidence interval; EE, efficacy-evaluable; ITT, intent-to-treat; PP, per protocol; RCT, randomized controlled trial. [a]≥50% reduction in seizure frequency.

Compared with placebo, zonisamide 300 mg/day also significantly reduced the frequency of all partial seizures (−19.4% vs. −46.4%; $P = 0.0007$) and all seizures (−18.1% vs. −41.8%; $P = 0.0005$). There was a significant dose–response relationship for all seizure types ($P < 0.0001$). Zonisamide was well tolerated, with the most common adverse events (AEs) being somnolence, headache, dizziness, and nausea during titration and headache and pharyngitis during fixed-dose treatment.

A subanalysis of the European phase 3 trial evaluated zonisamide as first-line adjunctive therapy in patients with refractory partial epilepsy taking only one concomitant AED [17]. Efficacy data were determined for two patient populations: the ITT population (all patients who received ≥1 dose of zonisamide [$n = 81$]) and the efficacy-evaluable (EE) population (all patients who received ≥10 weeks of treatment [$n = 65$]). Zonisamide was superior to placebo in reducing the frequency of all seizures in the ITT and EE populations (Table 1), and in improving responder rates to zonisamide 100, 300, and 500 mg/day, which were dose-dependent at 46.7%, 53.8%, and 63.2%, respectively, in the EE population. In the ITT population, freedom from all seizures was achieved by 13.8% of patients receiving zonisamide 500 mg/day compared with 4.5% of patients taking placebo. Zonisamide was well tolerated, with insomnia, somnolence, and dizziness occurring most frequently during titration, and infection and pharyngitis occurring during treatment.

Zonisamide in Special Populations

Epilepsy is common in children, and the incidence is increasing in older adults. Management of these special populations, including women of childbearing age, often requires greater consideration of the risks and benefits of pharmacotherapy. The following three summaries present the evidence for zonisamide in these groups of patients with partial seizures [11,12,18,19].

Pediatric Patients

A phase 3 RCT found that adjunctive therapy with zonisamide was significantly more effective for controlling seizures than placebo in 183 pediatric patients (age 6–18 years) with partial seizures who were taking one or two AEDs [11]. Zonisamide was started at 1 mg/kg/day and titrated to 8 mg/kg/day, which was maintained for 12 weeks. Response rates (defined as ≥50% reduction in seizure frequency) during maintenance therapy were greater for zonisamide than for placebo in the ITT-last observation carried forward (LOCF) population ($P = 0.0044$), ITT-observed cases population ($P = 0.0143$), and per protocol-LOCF population ($P = 0.0046$) (Table 2). Median reductions in 28-day seizure frequency in the ITT-LOCF population were greater for zonisamide than for placebo during maintenance therapy and during the joint titration and maintenance phases. The incidence of TEAEs was similar for both treatments at 55.1% and 50.0% for zonisamide and placebo, respectively. Zonisamide was effective and well tolerated as adjunctive therapy in this group of pediatric patients with partial epilepsy.

An open-label extension study in this group of patients concluded that zonisamide had an acceptable long-term safety profile for children in this age group [18,19]. Patients already receiving

Table 2 Zonisamide in special populations

Study	Design	Patients	Intervention	Duration	Results
Guerrini et al., 2013 [11]	Phase 3 RCT Pediatric	183 patients aged 6–18 years with partial seizures	Zonisamide 1 mg/kg/day titrated to 8 mg/kg/day or placebo Adjunctive therapy	12 weeks	Response rate[a]: ITT population: LOCF: Zonisamide: 50%; placebo: 31%; $P = 0.0044$ OC: Zonisamide: 48%; placebo: 31%; $P = 0.0143$ PP: Zonisamide: 51%; placebo: 31%; $P = 0.0046$ Median reduction in 28-day seizure frequency: Maintenance phase: Zonisamide: 50.0%; placebo: 24.5%; $P < 0.0001$ Titration and maintenance phase: Zonisamide: 42.2%; placebo: 20.4%; $P < 0.0001$ Seizure freedom during maintenance phase: Zonisamide: 14%; placebo: 3%; $P = 0.0049$
Guerrini et al., 2013 [18] Guerrini et al., 2014 [19]	Long-term open-label extension to Guerrini et al., 2013 [11] Pediatric	144 patients aged 6–18 years with partial seizures	Zonisamide 1–8 mg/kg/day Adjunctive therapy	45–57 weeks	108 patients (75.0%) received zonisamide for ≥1 year Mean dose: 7.5 mg/kg/day (standard deviation, 1.1 mg/kg/day; range, 3.8–10.6 mg/kg/day) Drug-related TEAEs: 39 (27.1%) 92.3% were mild or moderate
Trinka et al., 2013 [12]	Pooled analysis Elderly	95 patients aged 65 years or older with partial seizures	Zonisamide 200 mg/day (range, 25–600 mg/day Monotherapy or adjunctive therapy	4.2 months (range, 0.1–18.4 months)	TEAE incidence: elderly: 82%; adult: 84% Drug-related TEAEs: elderly: 56%; adult: 73% Severe TEAEs: elderly: 12%; adult: 21% Serious TEAEs: elderly: 13%; adult: 17% Serious treatment-related TEAEs: elderly: 3%; adult: 7% TEAEs leading to withdrawal: elderly: 18%; adult: 23%

AED, antiepileptic drug; ITT, intent-to-treat; LOCF, last observation carried forward; OC, observed cases; PP, per protocol; RCT, randomized controlled trial; TEAE, treatment emergent adverse event. [a]≥50% reduction in seizure frequency.

zonisamide continued at the same dose, while the placebo group started zonisamide at 1 mg/kg/day, titrated to 8 mg/kg/day. The open-label period lasted for 45–57 weeks, during which the zonisamide dose could be titrated up or down to control seizures and minimize AEs (Table 2). Thirty-nine patients (27.1%) had treatment-related TEAEs, with the most common being nasopharyngitis, headache, weight loss, bronchitis, and decreased appetite. Most of the treatment-related TEAEs (92.3%) were mild or moderate in intensity. Small-to-moderate decreases in bicarbonate levels of >3.5 mmol/L were noted in 64 patients (44.4%). Zonisamide was considered to have acceptable safety for pediatric patients when given long term as adjunctive treatment for partial seizures.

Elderly Patients

Elderly people are the fastest growing group with epilepsy as life expectancies increase and epilepsy rates increase in later life [12]. Approximately 25% of new diagnoses of epilepsy are in elderly people. Management of epilepsy in this population involves consideration of the greater burden of comorbidities and associated medications, as well as physiological changes related to aging.

There are few reports of AED use among elderly people because of the challenges of treating this population, particularly with the older AEDs. However, pooled data from the zonisamide clinical trial program were evaluated to ascertain the safety and tolerability of zonisamide in elderly patients (aged 65 years or older) compared with younger patients (aged 18–65 years). Elderly patients received zonisamide as adjunctive therapy (n = 59) or monotherapy (n = 36) for partial seizures. Among the elderly patients, the final zonisamide dose was 200 mg/day (range, 25–600 mg/day), which was taken for a median duration of 4.2 months (range, 0.1–18.4 months). The total incidence of TEAEs was similar for elderly and adult patients at 82% and 84%, respectively, but fewer elderly patients than adult patients had drug-related, severe, serious, and serious treatment-related TEAEs or TEAEs leading to withdrawal (Table 2). More than 75% of TEAEs in both groups were mild or moderate. TEAEs that were more frequently reported by elderly patients than by adult patients were constipation, vomiting, fatigue, peripheral edema, asthenia, urinary tract infection, nasopharyngitis, oropharyngeal pain, and pruritus. Peripheral edema, pruritus, and oropharyngeal pain, in particular, were reported in elderly patients at 2-fold the rate in adult patients. Serious TEAEs reported by ≥2% of elderly patients were "convulsions," which was at a rate similar to that in adult patients of 4%. There were minimal changes in clinical laboratory parameters and, as for other studies, no significant changes from baseline for alanine transaminase, aspartate aminotransferase, creatinine, or creatine phosphokinase levels. There were no reports of respiratory alkalosis or metabolic acidosis, and no significant weight changes. Overall, zonisamide had a good safety/tolerability profile in this group of patients, owing to its good pharmacokinetic and pharmacodynamic profile, including its apparent lack of drug interactions.

Women and Childbearing

For women of childbearing age with epilepsy, contraception and pregnancy are important issues [20]. While most women with epilepsy can have normal pregnancies and bear healthy children, fertility issues include drug interactions with hormonal contraceptives and the risks of medication during pregnancy and breastfeeding. Ideally, childbearing should be planned to allow for treatment adjustments before conception.

Enzyme-inducing AEDs can reduce the effectiveness of hormonal contraceptives by enhancing their metabolism, thereby reducing their plasma concentrations [9,10,20]. However, zonisamide has not been shown to interact with the ethinylestradiol or norethisterone components of hormonal contraception or with circulating luteinizing hormone, follicle-stimulating hormone, or progesterone [9,10].

During pregnancy, continuing treatment is important to avoid risks to the mother and the effects that maternal seizures might have on the fetus. However, the risks and benefits need to be weighed to reduce the effects of seizures or AEDs on the fetus. Treatment of epilepsy during pregnancy aims to minimize teratogenic effects while maintaining seizure control [20]. The recommended strategy is to address treatment before conception and to start with the most appropriate drug at the lowest effective dose. Measurement of the serum concentration of the selected AED before pregnancy can act as a reference value during the pregnancy. After delivery, breastfeeding is possible as few drugs is passed to a breastfed infant than to a fetus, although AEDs can be transferred to breastmilk [20].

Zonisamide in Real-World Clinical Practice

As RCTs are conducted under controlled conditions, it can be difficult to translate the results to "real-world" clinical practice [21]. The following six studies show that zonisamide as monotherapy or adjunctive therapy for partial seizures, refractory partial seizures, and generalized seizures is effective when prescribed in the clinic, with safety and tolerability profiles similar to those of the RCTs [22–27].

The Zonegran in the European Union Study was an open-label multicenter noncomparative study to assess adjunctive zonisamide in a diverse population with refractory partial-onset seizures in a clinical practice setting [22]. The trial was conducted in 281 patients in nine European countries to evaluate zonisamide as adjunctive therapy at doses of 200–500 mg/day. There were two fixed-dose periods of zonisamide 400 mg/day (period 1: weeks 10–13) and 500 mg/day (period 2: weeks 16–19). The mean daily dose of zonisamide was 246 mg (median, 255 mg; range, 50–369 mg). The median reductions in seizure frequency from baseline to fixed-dose period 1 and fixed-dose period 2 are shown in Table 3. From baseline to fixed-dose period 2, >40% of patients achieved ≥50% reductions in seizure frequency and ≥15% of patients achieved seizure freedom. Zonisamide was generally well tolerated, with a real-world safety profile similar to that reported in the RCTs, with no clinically significant changes in laboratory variables, vital signs, or physical and neurological examinations.

The multicenter phase 4 Zonisamid im Alltag der Epilepsiepatienten study evaluated the efficacy and tolerability of adjunctive zonisamide in 365 patients with partial seizures in clinical practice [23]. Efficacy was evaluated according to the monotherapy at

Table 3 Zonisamide in clinical practice

Study	Design	Patients	Intervention	Duration	Results
Dupont et al., 2010 [22] Zonegran in the European Union Study (ZEUS)	Open-label multicenter noncomparative	281 patients with refractory partial seizures	Zonisamide 200–500 mg/day Adjunctive therapy	Fixed dose: Zonisamide 400 mg/day (period 1: weeks 10–13) Zonisamide 500 mg/day (period 2: weeks 16–19)	Median reduction in seizure frequency from baseline: Fixed-dose period 1: OC: 33.5% (95% CI, 25.0–48.4); LOCF: 32.1% (95% CI, 20.0–46.2) Fixed-dose period 2: OC: 41.1% (95% CI, 30.4–50.0); LOCF: 33.3% (95% CI, 23.1–42.9)
Stefan et al., 2011 [23] Zonisamid im Alltag der Epilepsiepatienten study	Multicenter phase 4	365 patients with partial seizures	Zonisamide Adjunctive therapy to carbamazepine, valproate, oxcarbazepine, lamotrigine, or levetiracetam	4 months	≥50% seizure frequency reduction: Range: 80.0% (levetiracetam) to 91.7% (carbamazepine) ≥75% seizure frequency reduction: Range: 40.0% (levetiracetam) to 79.3% (lamotrigine) Seizure freedom Range: 26.7% (levetiracetam) to 65.5% (lamotrigine) Decreased baseline AED dose: Range: 6.9% (lamotrigine) to 37.7% (carbamazepine)
Chung et al., 2007 [24]	Single-center retrospective database	479 patients (828 exposures) partial or generalized seizures	Lamotrigine, levetiracetam, oxcarbazepine, topiramate, or zonisamide	2 years	Retention rate: Lamotrigine: 186 (74.1%) Zonisamide: 77 (60.2%) Oxcarbazepine: 57 (58.8%) Levetiracetam: 105 (53.6%) Topiramate: 69 (44.2%)
Dupont et al., 2013 [25] OZONE study	Observational longitudinal naturalistic	Patients with complex partial epilepsy who had started zonisamide ≥3 months before inclusion	Zonisamide 300 mg/day (median) Adjunctive	Visit 1: inclusion Visit 2: 3–6 months	Seizure frequency reduction (from 16.0 seizures/month): Visit 1: 8.7 seizures/month Visit 2: 7.1 seizures/month Response rate Visit 1: 61.9% Visit 2: 65.9% Seizure freedom Visit 1: 31.1% Visit 2: 25.6%
Wroe et al., 2008 [26]	Long-term extension to Brodie et al., 2005 [16]	317 patients with refractory partial seizures	Zonisamide 100–600 mg/day	3 years	Retention rate: 1 year: 65.3% 2 years: 44.5% 3 years: 28.8% Median monthly reductions in seizure rates from baseline: 1 year: 45.0% 2 years: 45.7% 3 years: 47.0%
Catarino et al., 2011 [27]	Single-center clinic visits	417 patients with partial seizures, with or without secondary generalization, or generalized seizures	Zonisamide 25–1200 mg (median, 225 mg)	3 years	Retention rate: 1 year: 62% (95% CI, 57–67%) 2 years: 46% (95% CI, 40–51%) 3 years: 30% (95% CI, 24–36%)

AED, antiepileptic drug; CI, confidence interval; LOCF, last observation carried forward; OC, observed cases.

baseline (carbamazepine, valproate, oxcarbazepine, lamotrigine, or levetiracetam). Patients achieving ≥50% and ≥75% seizure frequency reduction after 4 months adjunctive zonisamide ranged from 80.0 to 91.7% and from 40.0 to 79.3%, respectively, while seizure freedom rates ranged from 26.7 to 65.5% (Table 3). The study showed that zonisamide was an effective early adjunctive treatment to a range of monotherapies in everyday clinical practice.

In a comparative trial of new AEDs in patients with partial or generalized seizures, retention of levetiracetam, lamotrigine, oxcarbazepine, topiramate, and zonisamide was compared by searching established medical databases [24]. At 2 years, retention was highest for lamotrigine at 74.1%, followed by zonisamide at 60.2% (Table 3). If an AED was discontinued, this usually occurred within 24 weeks (>80% of discontinuations). For zonisamide, 91.7% of patients who had been treated for 6 months without discontinuation continued for ≥2 years.

The OZONE study was an observational longitudinal naturalistic study conducted to describe the effectiveness and tolerability of zonisamide in everyday clinical practice [25]. Data were collected during routine consultations from patients who had started zonisamide at least 3 months before inclusion in the study. The median zonisamide maintenance dose was 300 mg/day. The seizure frequency was reduced from 16.0 seizures/month at initiation to 8.7 and 7.1 seizures/month at visits 1 (inclusion) and 2 (3–6 months), respectively. The response rates and proportions of seizure-free patients are shown in Table 3. In this study, zonisamide was generally given in association with other AEDs for the treatment of complex partial epilepsy in adults and was effective in improving seizure control in this real-world population.

An extension to the pivotal European phase 3 trial was performed to ascertain whether zonisamide was effective and well tolerated for long-term treatment of refractory partial epilepsy in clinical practice [26]. Retention rates for zonisamide over 3 years are shown in Table 3. Most patients were compliant throughout the study. The median duration of zonisamide treatment was 548 days (range, 31–1463 days) for patients previously given placebo in the phase 3 trial and 546 days (15–1582 days) for those treated with zonisamide during the fixed-dose study. Zonisamide treatment maintained reduction in seizure frequency, with some patients having long seizure-free periods (Table 3). Sixty-one patients attained seizure freedom for the last 6 months and 12 months, respectively. Twenty-nine and 21 patients attained seizure freedom during any 6- and 12-month period, respectively. Thirty-five patients (14.6%) were able to reduce their concomitant AED use.

Long-term retention of zonisamide was studied in 417 patients with epilepsy assessed for efficacy and tolerability during normal clinic visits at a tertiary referral center [27]. One-, 2-, and 3-year retention rates were 62%, 46%, and 30%, respectively (Table 3). A total of 131 patients (31%; 95% confidence interval [CI], 27–36%) had improvement with zonisamide for ≥6 months, of whom 73 (56%; 95% CI, 47–64%) had improvement for ≥12 months. Sixteen and seven people attained freedom from seizures for ≥6 months and ≥1 year, respectively. Overall, retention rates were similar to those previously reported for zonisamide, and to those of lamotrigine, topiramate, and pregabalin.

Safety and Tolerability, and Drug–Drug Interactions

Combination therapy is widely used to control epilepsy seizures [9]. While older AEDs are associated with pharmacokinetic interactions, zonisamide has no clinically evident effect on the pharmacokinetics of carbamazepine, phenytoin, sodium valproate, or lamotrigine, and there are no known clinically significant interactions between zonisamide and other drugs.

Zonisamide has been associated with kidney stones, oligohydrosis, weight loss, and hyperammonemia [28]. Kidney stones have been identified in 1.2% of patients, although this effect is more common in western than in Japanese populations. The incidence of kidney stones may be reduced by avoiding concomitant treatment with topiramate or a ketogenic diet, and by increasing fluid intake. Care should be taken if a patient has a history of kidney stones.

In the pivotal European phase 3 trial, most patients reported at least one AE, as follows: 82 patients (68.3%) receiving placebo; 38 patients (67.9%) receiving zonisamide 100 mg/day; 39 patients (70.9%) receiving zonisamide 300 mg/day; and 96 patients (81.4%) receiving zonisamide 500 mg/day [16]. Most AEs in each treatment group were mild or moderate. There were no clinically significant differences between zonisamide and placebo.

In a study of zonisamide compared with controlled-release carbamazepine for newly diagnosed partial epilepsy, the incidence of TEAEs was similar for the two groups (60% for zonisamide vs. 62% for carbamazepine), as well as serious TEAEs (5% vs. 6%) and TEAEs leading to withdrawal (11% vs. 12%) [13].

Comparison between RCTs, non-RCTs, and observational studies that analyzed the AE profile of zonisamide found that in the RCTs, no AEs were significantly associated with zonisamide, although there was an increased risk of AE-related study withdrawals [29]. In the non-RCT studies, there was a high incidence of weight loss and headache. There did not appear to be any major safety concerns related to zonisamide.

To assess the impact of zonisamide on body weight, weight changes after the start of treatment were evaluated [30]. Patients were categorized according to body mass index <20, 20–25, and >25 kg/m^2. Overall, body weight decreased by 3.7% (standard deviation, 9.1%; range, −36% to 32%). Weight loss >5% was noted in 35% of patients, and weight gain of >5% was seen in 14% of patients. Weight loss was greater in patients who were overweight prior to the start of treatment. Weight loss was reversible to pretreatment levels after discontinuation of zonisamide.

Conclusions

Zonisamide has a unique structure that is unrelated to any other AED. This agent has multiple mechanisms of action that provide for a broad spectrum of use across a wide range of epilepsies. Owing to its favorable safety and drug interaction profile, including with other AEDs and the oral contraceptive pill, zonisamide is an effective first-line adjunctive therapy for refractory epilepsy. Furthermore, the updated ILAE report has established level A efficacy/effectiveness evidence for zonisamide as initial monotherapy for adults with partial-onset seizures. Zonisamide has a good tolerability profile, resulting in high retention rates. The long half-life

of zonisamide enables a once-daily dosing regimen and assures steady therapeutic drug levels after titration.

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Conflict of Interest

The authors have not published or submitted the manuscript elsewhere. S.-Y. Kwan, Y.-C. Chuang, C.-W. Huang, T.-C. Chen, and S.-B. Jou declare no conflict of interest. A. Dash is an employee of Eisai Co. Ltd, Mumbai, India.

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