Therapeutic Role of Zonisamide in Neuropsychiatric Disorders

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Abstract: Zonisamide (ZNS), a sulfonamide antiepileptic drug, is indicated as an adjunct therapy for partial seizure disorders with and without secondary generalization. ZNS has a favorable pharmacokinetic profile because of its rapid absorption and high bioavailability. Its activity is related to the blockade of voltage gated sodium and calcium channels, modulation of central dopaminergic, GABAergic, and serotonergic functions, as well as inhibition of carbonic anhydrase and monoamine oxidase B. ZNS has potential efficacy for an array of neuropsychiatric disorders including migraine and other headache syndromes, neuropathic pain, Parkinson's disease, essential tremor, stroke, obesity, anxiety, bipolar and binge-eating disorders.

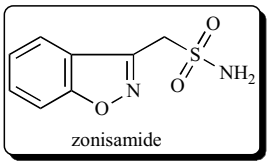
Key Words: zonisamide, seizure disorders, migraine, pain syndromes, movement disorders, neuroprotection, bipolar and anxiety disorders.

INTRODUCTION

Zonisamide (ZNS) is an antiepileptic drug (AED), which has been available in Japan since 1989 and received FDA approval for the United States in March of 2000 [1]. It is a broad-spectrum AED, initially indicated only as an adjunct therapy for the treatment of partial seizures. ZNS potentially has a wider domain of utility in both epileptic and non-epileptic disorders (Tables **1**-**4**).

PHARMACOKINETICS

ZNS is a synthetic 1,2- benzisoxazole derivative with the molecular formula $C_8H_8N_2O_3S$ and molecular weight of 212 [2]. It is classified as a sulfonamide with 1, 2-benzisoxazole-3-methanesulfonamide as an active ingredient.



zonisamide

Absorption and Distribution

ZNS has relatively rapid and complete absorption from the gastrointestinal tract with a T_{max} of approximately three hours and 95% bioavailability [3]. Age and food have demonstrated no effect on the bioavailability of ZNS [3]. It has relatively low protein binding (35-40%) and readily crosses the blood brain barrier [2, 3]. It is extensively distributed in erythrocytes. Half life was reported to be 63-69 hours in healthy adult volunteers who received 400mg /day of ZNS [4, 5]. Zonisamide exhibits linear pharmacokinetics up to daily doses of 10-15mg/kg and is extensively metabolized by acetylation and hepatic conjugation [11].

Metabolism

It is primarily metabolized through cytochrome P450 isoenzyme 3A4 (CYP3A4). It undergoes acetylation and reduction, forming N-acetyl ZNS, and the open-ring metabolite 2–sulfamoylacetyl phenol, respectively [2]. Its elimination is *via* renal (30%) and hepatic (70%) routes [2]. Animal studies have shown that it crosses the placenta and breast tissues, and its transfer rates *via* placenta and breast milk were reported to be 92% and 41-57% respectively [6].

ZNS neither induces nor inhibits hepatic cytochrome P450 (CYP450) isoenzymes and does not induce its own metabolism [7]. However, inhibiting or inducing the CYP3A4 isoenzyme may effect its plasma concentration [5]. Children require higher doses in mg/kg to attain equivalent serum concentrations as adults [11].

ZNS can be administered once a day because of its long, 63 hour, half-life [7]. The dose of ZNS should be increased slowly using a stepwise titration at 2-week intervals [7]. Its 63 hour half life is decreased by phenytoin, phenobarbitol, carbamazepine, and valproic acid to 27 hours, 38 hours, 38 hours, and 46 hours respectively [7]. Several clinical studies have indicated there are no significant drug-drug interaction of ZNS and phenytoin, lamotrigine and valproate [8-10] indicating that there is no dosage adjustment needed when used concurrently. Currently there is no clear association between ZNS serum levels and clinical response. There is a considerable overlap between responders and non-responders, as well as those who have and do not have adverse effects. The therapeutic range is between 10-38 micrograms per milliliter [11].

PHARMACODYNAMICS

The exact mechanism by which ZNS exerts its antiepileptic effects may be through its action at sodium and

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Table 1. Zonisamide and Adult Seizure Disorders

Study Name	Study Type	Number of Participants	Number Improved or Reduction in Seizure Frequency
Schmidt *et al*. [46]	Double-blind, multi-center	139	38 (27.7%)
Leppik *et al*. [36]	Open-label, multi-center	167	51.8%, 113 (67.7%)*
Wilensky *et al*. [42]	Open-label	8	5 (62.5%)
Faught E *et al*. [32]	Double-blind multicenter	203	20.5 - 24.7%
Brodie MJ *et al*. [28]	Double-blind multicenter	351	51.2

* Entered safety study.

calcium channels. ZNS inhibits voltage-gated sodium channels when action potentials are occurring at a high frequency [5, 7, 12-14]. ZNS also inhibits T-type calcium channels, thereby suppressing inward calcium currents resulting in reduction of cellular bursting and the subsequent spread of seizure discharge [5, 7, 12, 13, 15]. Other anti-seizure mechanisms include modulation of central dopaminergic, GABAergic and serotonergic functions [16-20]. It enhances dopaminergic and serotonergic transmission by increasing the extra-cellular levels of these neurotransmitters [16-20]. It has inhibitory effect on the excitatory glutamate-mediated transmission secondary to its effects on sodium and calcium channels and through its direct effects on the neuronal transport system [16-20]. ZNS inhibits carbonic anhydrase isoenzymes CA II, CA V, and CA IX but this mechanism is not thought to contribute to its anti-seizure properties [21, 22]. This inhibitory effect is 100-200 times less potent than that of acetazolamide [23]. In summary, ZNS utilizes multiple mechanisms for broad anti-epileptic effects by: (1) inhibiting glutaminergic neurons through voltage-gated sodium and T-type calcium channels, (2) increasing the extracellular concentrations of dopamine and serotonin. The recommended initial dosage for adults is 50-100mg/day with a slow increase every 2 weeks, the usual maintenance dose is 200-400mg /day, and the maximum dose is 600mg/day [24]. The initial pediatric dose is 2-4 mg/kg/day, the maintenance dose is 4-8mg/kg/day, and the maximum dose is 12mg/kg/day [24].

CLINICAL SAFETY

The most common side effects are central nervous system related: including confusion, memory impairment, somnolence, and dizziness [1, 7]. It can also cause a decrease in appetite, weight loss, kidney stones and hyperthermia due to oligohydrosis [7, 25]. Oligohydrosis is especially common in children. ZNS should be avoided in patients allergic to sulfa [7].

Central nervous system and psychomotor symptoms are more common at doses of 300-500mg per day. If patients develop renal stones, therapy should be discontinued. Extreme caution in this regards should be exercised if topiramate is used with ZNS as both are carbonic anhydrase inhibitors [26].

Table 2. Zonisamide and Pediatric Seizure Disorders

Study Name	Study Type	Number of Participants	Number Improved or Reduction in Seizure Frequency
Kumagai *et al*. [51]	Open-label, prospective	44	29 (65.9%)
Wilfong [52]	Retrospective chart review as monotherapy	131	101 (77.0%)
Wilfong and Schultz [53]	Retrospective chart review of absence seizures' patients	45	23 (51.1%)
Suzuki *et al*. [54]	Open-label monotherapy for infantile spasms	11	4 (36.4%)
Lotze *et al*. [55]	Open-label therapy for infantile spasms	23	6 (26%)
Suzuki [56, 57]	Open-label therapy for West syndrome	11	7 (63.6%)

Table 3. Zonisamide in Migraine, Pain Disorders and Parkinson's Disease

Study Name	Study Type	Number of Participants	Number Improved
Zonisamide and migraines			
Darke *et al*. [62]	Open-label, prospective	34	30 (88.2%)
Ashkenazi *et al*. [63]	Retrospective chart review	33	No statistical significance
Pakalnis *et al*. [68]	Retrospective chart review of pediatric patients	12	8 (66.7%)
Zonisamide and pain syndromes			
Krusz *et al*. [70]	Open-label, prospective	42	15 (35.7%) with > 50% improvement; 10 (23.8%) with 25-50% improvement
Hasegawa *et al*. [72]	Retrospective chart review	27	17 (63.0%)
Atli *et al*. [73]	Randomized, double-blind, placebo-controlled	42	Not statistically significant
Takahashi *et al*. [74]	Case presentation	2	2
Zonisamide and Parkinsonism			
Murata *et al*. [75]	Open-label prospective	9	7 (77.8%)
Murata *et al*. [76]	Randomized, double-blind, placebo-controlled	347	Significant improvement in motor function

Patients with hepatic dysfunction, renal dysfunction and patients on sedatives, alcohol and multiple AEDs are more vulnerable to side effects. Safety and efficacy have not been established in children <16 years of age and its role in pregnancy has yet to be established [26].

Neurological Disorders

Adult Seizure Disorders

ZNS is a treatment for partial seizures (simple or complex, with or without secondary generalization) in adults and provides dose-dependent, effective, well-tolerated adjunctive therapy in these patients [27-37]. It has also been used as an adjunct therapy for the treatment of refractory seizures in patients with compound/combination seizures, progressive myoclonic epilepsy (PME), juvenile myoclonic epilepsy (JME), Lennox-Gastaut syndrome (LGS), Unverricht-Lundborgs disease (ULD) and Lafora disease [29, 38-41]. The best response to ZNS was achieved at doses approximately 6mg/kg/day, corresponding to plasma levels of 20-30 mg/L and most of the adverse effects including drowsiness, loss of appetite, gastrointestinal problems and central nervous side effects were noted with plasma concentrations >30mg/L [2, 29, 42].

Ito *et al.* and Masuda *et al.* demonstrated that ZNS has anti-seizure properties and can suppress epileptogenic focused activity in the cortex [43, 44]. Their studies demonstrated that ZNS has a propensity to block seizure propagation from the cortex to the subcortical structures [43]. Kamei *et al.* showed anti-seizure effects of ZNS on the neocortical and hippocampal seizures in rat brains [45].

To find the efficacy and safety of ZNS several placebo controlled double blind trials have been undertaken (Table **1**). Most of these trials were for ZNS use as an adjunctive therapy for refractory partial seizures. Different doses of ZNS, 100mg/day to 500mg/day, have been used in these trials. ZNS demonstrated dose dependant efficacy in all trials. The steady state follow-up until 24 weeks has been studied and several end points have been evaluated. Schmidt *et al.* studied 139 patients in which 27.7% experienced decreased seizure frequency compared to placebo ($P < 0.05$) [46]. The median rate dropped from 12 to 7.1 per month with no changes in the placebo group ($P < 0.007$). Adverse events reported were mostly fatigue, but also included somnolence, dizziness and ataxia; events occurred in 59.2% of the study population compared to 27.9% in the placebo group [46].

The efficacy of ZNS was tested in 167 adult participants who entered a open label multi-center study [36]. The median percent reduction from baseline for partial seizures was 51.8% [36]. Of the 167 participants, 113 patients successfully completed the efficacy study and entered a long-term safety study; 3.7 % patients developed kidney stones [36]. This is an important finding as previously, the development of ZNS in the US was stopped because of high percentage of kidney stones [36, 47]. Sackellares *et al.* demonstrated the efficacy of ZNS as an anti-seizure drug in 10 adults with

Table 4. Zonisamide in Psychiatric Disorders

Study Name	Study Type	Number of Participants	Number Improved
Zonisamide and bipolar disorders			
Anand *et al*. [90]	Open-label, prospective	10	5 improved
McElroy *et al*. [91]	Open-label, prospective	64	Improvement in depression and mania but also had behavioral side effects
Kanba *et al*. [92]	Open-label, prospective, add on therapy	21	15 (71.4%)
Baldassano *et al*. [89]	Retrospective chart review	12	6 (50.0%), not statistically significant
Zonisamide and binge-eating disorders			
McElroy *et al*. [94]	Open-label, prospective	15	8 (53.3%)
Wang *et al*. [95]	Open-label, prospective	25	Statistically significant weight loss but 11 patients dropped out because of mood disorders
Zonisamide and anxiety disorder			
Kinrys *et al*. [97]	Open-label, prospective	10	6 (60.0%)

refractory partial seizures [35]. In most patients, seizure frequency was reduced with a oral dose of 400mg/day without any significant side effects [35]. Another study of eight patients with uncontrolled partial seizures found definite antiepileptic activity of ZNS for five patients, while the other three had increased seizures [42].

Pediatric Seizure Disorders

Most of the data about the use of ZNS in children are from the studies done in Japan. No controlled, double-blinded, clinical trials for the use of ZNS in pediatric patients are available from the US. Open label trails done in Japanese children suggest that ZNS is efficacious and well tolerated against partial and secondary generalized seizures in the pediatric population [48-50].

ZNS was administered to 44 children, their ages ranging from 8 months to 15 years; 6 children were eliminated due to side effects, and 29 children had a positive outcome [51]. The main side effect was drowsiness, especially during the introduction [51]. ZNS was started at the dose of 2-4 mg/kg/day and increased to 12 mg/kg/day unless a satisfactory response was achieved at a lower dose [51]. Most of the patients had good response to ZNS without any significant side effects.

Wilfong *et al.* in their retrospective study of 131 patients, aged 1 to 21.8 years, with a spectrum of different seizure types and epilepsy syndromes showed that 101 patients (77.1%) achieved a 50% or greater decrease in seizure frequency, including 39 patients who achieved seizure freedom [52]. ZNS monotherapy was well tolerated, with three patients (2.3%) discontinuing for adverse events [52].

Wilfong and Schultz conducted a chart review evaluating the efficacy and safety of ZNS for pediatric absence seizures and found good results [53]. Patients aged less than 18 years old with absence seizures were included and of the 45 included, 23 (51.1%) achieved freedom from absence seizures [53]. Two patients discontinued ZNS, one for increased seizures and the other for sleepiness and inefficacy [53].

Infantile spasms (IS) is an age-specific epileptic syndrome in infants. ZNS, because of its GABAergic effects, is emerging as a potentially effective treatment option for these children [58]. Yanai *et al.* determined its efficacy in 27 newly diagnosed pediatric patients with IS [59]. Nine (33.3%) out of the 27 patients who were administered ZNS exhibited the disappearance of seizures. ZNS was effective in all the cryptogenic cases and seven (28.0%) of the symptomatic cases. The mean time interval between the start of ZNS and the seizure disappearance was 5 days without an adverse reaction in any patient [59].

Suzuki *et al.* showed short-term efficacy of ZNS in 11 pediatric patients with IS; four infants had cessation of spasms and disappearance of the hypsarrhythmia [54]. Lotze *et al.* evaluated ZNS in 23 patients with infantile spasms and 6 (26%) had favorable results [55]. Kishi *et al.* and Traverse in their reports described epileptic infants with hypsarrhythmia who responded well to ZNS therapy [60, 61].

West syndrome, also known as infantile myoclonic encephalopathy with hypsarrhythemia, is one of the generalized epileptic syndromes. ZNS has been used as a therapy in patients with West syndrome with 7 out of 11 pediatric patients rapidly responding within two weeks [56, 57].

The current data supports that ZNS represents a valuable broad-spectrum AED for the treatment of many pediatric seizure disorders. Although, double blind and randomized studies would better support the cause and further assist in developing a pediatric safety profile.

Migraine and Headache Syndromes

Similar to other AEDs, ZNS may be beneficial in the treatment and prevention of headaches and migraine attacks in adults and pediatric populations [62-67]. Darke *et al.* used ZNS for an open label trial on 34 resistant migraine patients. They showed improvements in headache severity ($P < 0.01$), duration ($P < 0.05$), and frequency ($P < 0.05$) after 1 month of therapy [62]. ZNS was well tolerated, with 4 patients (11.8%) discontinuing for adverse events, including dysphoria (n=2) and difficulty concentrating (n=2). Other adverse events were transient and tolerable [62]. Ashkenazi *et al.* did a retrospective study by reviewing the charts of adult patients with International Headache Society-defined episodic migraine or with transformed migraine according to the Silberstein-Lipton criteria, who had been treated with ZNS at Jefferson Headache Center out-patient clinic for at least 60 days [63]. ZNS therapy did not result in a statistically significant beneficial effect on headache or on other associated symptoms in these migraine patients [63].

ZNS has also been studied as a possible headache and migraine prophylactic agent in pediatric population. Pakalnis *et al.* performed a retrospective chart review and demonstrated ZNS had some efficacy in headache reduction in twelve pediatric headache patients [68]. Eight out of the 12 patients in this study showed positive response to ZNS therapy with more than 50% reduction in their headaches [68]. These studies suggest ZNS beneficence for both adult and pediatric migraine headaches, but further prospective and double blind studies would help confirm these findings.

The current data do not support the use of ZNS as first line therapy for headache and migraine prophylaxis. It can be considered in patients with seizure disorder who also have cephalgia.

Neuropathic and Central Pain Syndromes

There are similarities in the underlying pathophysiology of neuropathic pain and seizure disorders [69, 70]. ZNS, like other new AEDs possesses the potential role in the treatment of neuropathic pain such as post herpetic neuralgia, and diabetic polyneuropathy [67, 69, 71]. Krusz conducted an open label prospective study in 55 patients demonstrating the beneficial effects of ZNS in patients with chronic neuropathic pain [70]. Most of the patients had a beneficial effect without any significant side effects. Forty-two patients had efficacy data available: fifteen (35.7%) had a >50% improvement in daily pain scores; 10 (23.8%) had a 25% to 50% improvement [70]. ZNS was also well tolerated; only 5 patients discontinued its use secondary to adverse events (drowsiness, nausea, and itching) [70]. Hasegawa in a retrospective study, showed that ZNS might be an effective adjunct therapy in patients with chronic pain not responsive to analgesics [72]. Atli *et al.* conducted a randomized, double blind, placebo controlled trial to analyze the safety and efficacy of ZNS in patients with painful diabetic neuropathy. In this trial, pain scores decreased more for the ZNS group compared with the placebo group but these differences did not reach statistical significance [73].

ZNS can be one of the treatment options for central pain syndromes like central post stroke pain [74]. Takahashi *et al.* presented two cases of intractable central post stroke pain after posterolateral thalamic infarcts who responded well to ZNS [74]. The possible mechanisms of action for central pain control include the blockage of voltage gated calcium channels and increase gamma-aminobutyric acid (GABA) release resulting in suppression of abnormal activities of thalamic sensory neurons [74].

There are other AEDs including gabapentin and pregabalin which have shown more efficacy in the management of both neuropathic and other pain syndromes, therefore it is not recommended to use ZNS as first line treatment for these disorders. There is a need for more randomized and larger placebo controlled studies, which would clarify the efficacy and tolerability of ZNS in these disorders.

Movement Disorders

ZNS has some beneficial effects in patients with Parkinson's disease (PD) [75-77]. Its exact mechanism of action in this disorder could involve the activation of dopamine synthesis, monoamine oxidase B (MAO B) inhibition, and its action on the T-type calcium channels [78]. Murata *et al.* conducted an open trial of ZNS on nine patients with PD after noticing beneficial effects of ZNS in a PD patient whose convulsive attacks and Parkinsonian symptoms improved [75]. Seven patients experienced improved PD symptoms with the most beneficial effect on the wearing-off phenomenon when adding ZNS to their PD medication regimen [75]. Murata *et al.* also conducted a randomized double blind study of 347 patients with PD to evaluate the effect of ZNS on motor functions [76]. This study showed improvement in the primary endpoint change from baseline in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS) in the 25-mg and 50-mg groups *vs*. placebo. ZNS also has an anti-tremor effect and has shown some efficacy in treating essential, oxotreorine, and tacrine-induced tremulous jaw movements [79-82].

Conversely, a few reports have linked ZNS to induced movement disorders, e.g. restless leg syndrome [83, 84]. The biphasic effect of ZNS on dopaminergic system might be a possible explanation of these symptoms [83]. In summary, ZNS acts on the activation of dopamine synthesis, MOA-B inhibition and T-type calcium channels and appears to lessen Parkinsonian tremors. Further controlled data is necessary to elucidate the role of ZNS in Parkinson`s and related disorders.

Neuroprotection and Stroke

Newer AEDs have been studied for their potential role as neuroprotective agents and animal studies have shown promising neuroprotective effects [85]. Minato *et al.* assembled an ischemic rat model and demonstrated that the pre or post-ischemic treatment with ZNS reduced cerebral damage in the cortical and sub-cortical regions [86]. ZNS was dosed either 30 minutes before and 4 hours after or 15 minutes before and

4 hours after the occlusion of the middle cerebral artery [86]. This data suggests ZNS might have a potential therapeutic role in the treatment of ischemic stroke and forms the foundation for further studies.

Psychiatric Disorders

Bipolar Disorders

Bipolar disorder (BD) is characterized by periods of mania and depression interspersed with periods of normal mood. ZNS might be an effective adjunct treatment for bipolar depression because of its structural similarity with serotonin and pharmacological action similar to carbamazepine [24, 87-89]. ZNS has been shown to facilitate both dopaminergic and serotonergic neurotransmission [16-18].

Anand *et al.* in an open-label study demonstrated that most of the bipolar depressive patients who completed 8 weeks of ZNS therapy had improvement on the Hamilton Rating Scale for Depression (HAM-D) and Clinical Global Impression Scale (CGI-I) [90]. The starting dose of ZNS was daily 100mg, gradually increased to 300mg over 4 weeks. There was no significant effect on the Young Mania Rating Scale (YMRS) in this study. McElroy *et al.* in an open label study showed ZNS as a beneficial adjunct therapy on mood and body weight in bipolar patients [91]. Another study by Kanba *et al.* showed its efficacy in mania in bipolar patients [92]. Fifteen of 21 patients with bipolar and schizoaffective mania showed improvement on CGI with adjunct ZNS therapy [92]. Baldassano *et al.* did a retrospective chart review of 12 patients showing that on ZNS (236+/-68 mg) mean CGI-S scores improved from 4.54 at baseline to 3.42 at week 6 [89]. However, this change was not statistically significant. In this study 6 patients were considered responders to ZNS. Four patients discontinued ZNS therapy, two because of sedation and two because of poor response.

Conversely, negative effects of newer AEDs on mood are being studied [93]. Mood disorders may occur in approximately 7% of patients taking high dose ZNS [93]. Monotherapy and slow titration of ZNS can decrease the incidence of these mood disorders [93].

Overall, the results of these studies suggest that ZNS may be used as a potential adjunctive treatment for some patients with bipolar depression. However, randomized and double blind studies need to be done to better determine the thymoleptic properties of ZNS.

Binge-Eating Disorder

Binge-eating disorder commonly occurs with obesity and is characterized by recurrent episodes of overeating without any compensatory weight loss behavior. ZNS is associated with weight loss and has potential role in this disorder. In an open trial McElroy *et al.* showed that ZNS was effective in reducing the frequency and severity of illness in this disorder [94]. Eight out of fifteen subjects completed the 12 weeks of treatment in this trial. A highly significant decrease in binge-eating episode frequency, binge day frequency, body mass index, weight, CGI-S, Obsessive-Compulsive Scale Modified for Binge Eating (YBOCS-BE) total score, Three Factor Eating Questionnaire (TFEQ) hunger and disinhibition score was noticed in this study. Wang *et al.* assessed the effectiveness and tolerability of adjunctive ZNS in the treatment of obesity in euthymic BD patients [95]. Their study showed that adjunctive ZNS is effective and well tolerated, but had higher rates of mood problems in obese BD patients [95]. Further promising data is emerging about its role in obesity and binge-eating disorder.

Gadde *et al.* in their preliminary trial showed that ZNS and hypo-caloric diet in the short term resulted in more weight loss than placebo and hypocaloric diet in the treatment of obesity [96].

55 patients with a mean body mass index of 36 were enrolled in this randomized controlled study. Patients were randomly assigned to receive ZNS (n=30) or placebo(n=30). All participants were treated with hypocaloric diet (500 kcal/d). Compliance was self-reported. Incremental doses of ZNS were given starting 100mg/d orally, and gradually increased to 400mg/d. ZNS group lost more body weight than the placebo group (mean [SE], 5.9 [0.8] kg [6.0% loss] *vs* 0.9 [0.4] kg [1.0% loss]; $t = 5.5$; $P<.001$) during the 16-week period. However, the current data is not sufficient to support the regular use of ZNS in these disorders. The potential worsening of underlying psychiatric conditions should always be considered in these patients before starting them on ZNS.

Anxiety Disorders

Anxiety disorders are one of the most prevalent psychiatric disorders in the general population [98]. ZNS may be used as an adjunct therapy with other anxiolytic medications in patients with refractory anxiety [97]. Kinrys *et al.* investigated its efficacy and tolerability in a small open label study. 60% response rate after augmentation with ZNS was observed in this study [97]. Most of the patients tolerated it very well without any significant side effects. Further prospective and controlled studies need to be done to confirm the findings of this study and it is not possible to draw any inference from this limited data about the use of ZNS in patients with anxiety and related disorders.

SUMMARY

Besides its main indication in partial seizure disorders, ZNS has a potential role in other neuropsychiatric disorders. However, results of most of these studies need to be interpreted with caution because of different limiting factors including study design; e.g. open label, and small sample size. The most common side effects found in these studies were sedation and mood changes with increased incidence directly related to dose. Rare side effects include nephrolithiasis Stevens-Johnson syndrome, toxic epidermal necrosis, agranulocytosis, and aplastic anemia. In pediatric populations, oligohidrosis and hyperthermia have been reported. According to the Physicians Desk Reference 2006, ZNS has several mechanisms: (1) blocks sodium channels and decreases voltage dependent, transient inward currents (T-type calcium currents), (2) stabilizes neuronal membranes and suppresses neuronal hypersynchronization, (3) allosteric binding to the GABA/benzodiazipine receptor ionophore complex, which does not produce changes in chloride flux, (4) suppresses synaptically driven electrical activity without affecting post synaptic GABA or glutamate responses, neuronal or glial

uptake of GABA, and (5) facilitates DOPAminergic and serotonergic neurotransmission.

The above mentioned mechanisms of ZNS forms the foundation for its apparent neurological beneficence pattern. Currently, ZNS is indicated for adult partial seizures but in the future, other indications might be within the scope of ZNS. At the present, some evidence exists for its use as an add-on therapy in pediatric seizures, Parkinsonism, and neuropathic pain, but these are off label indications and not approved by FDA. Animal studies in rat stroke models have shown neuroprotective effects for pre and post ischemic stroke however there remains a need to investigate its role in other cerebrovascular conditions including hemorrhagic stroke and sub-arachnoid hemorrhage. Finally, the psychiatric front could benefit from ZNS therapy in patients with binge-eating, bipolar and anxiety disorders. Larger prospective and double-blinded studies are warranted to confirm the efficacy and tolerability of ZNS in these neuropsychiatric conditions.

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