

## Zonisamide in Parkinson's Disease: An Evidence-Based Review of its Impact on Clinical Outcomes

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**Abstract:** Zonisamide is a benzoisoxazole derivate with a multimodal mechanism of action that is widely available as antiepileptic drug. Serendipitously discovered to exert beneficial effects on motor symptoms of Parkinson's disease (PD), zonisamide has been approved exclusively in Japan for the adjunctive treatment of Parkinsonian symptoms after the positive results of three controlled clinical trials. The current review gives a resumé of the main findings of clinical trials and casuistic reports of the effects of zonisamide in PD with special emphasis on possible mechanisms of action and adverse effects. Summarized, at that time, the use of zonisamide in PD is still investigational; further studies are warranted to confirm the preliminary promising findings and to better define effects, indications and tolerability of zonisamide in PD.

**Keywords:** Parkinson's disease, zonisamide, mechanism of action, clinical outcomes, adverse reactions

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## Introduction

Zonisamide is a benzisoxazole derivative<sup>1</sup> that has been approved worldwide for the treatment of epileptic seizures.<sup>2-4</sup> In 2000, the accidental observation of an amelioration of motor symptoms of Parkinson's disease (PD) in a patient treated with zonisamide for coexisting epileptic seizures<sup>5,6</sup> provoked rising interest in the potentials of zonisamide for the treatment of PD. Subsequently, several clinical trials were able to demonstrate beneficial effects on the cardinal motor symptoms in patients with advanced PD leading to the approval of zonisamide as an antiparkinsonian drug in 2009 in Japan.

## Pharmacokinetics and Drug Interactions

Zonisamide is rapidly and almost completely absorbed from the gastrointestinal tract with a maximum concentration achieved after 2 to 5 hours and an "area under the curve" (AUC) increasing proportionally to the administered dose.<sup>7,8</sup> Food intake has shown to reduce the rate but not the extent of its absorption, with the time to peak concentration extending up to about 6 hours.<sup>7-9</sup> The dose-plasma concentration relationship is linear,<sup>10</sup> and there is low to moderate protein binding at concentrations of 1 to 7 µg/mL.<sup>9</sup> However, zonisamide has a high binding affinity for red blood cells and accumulates within these cells.<sup>8</sup> This characteristic results in a nonlinear dose-erythrocyte concentration relationship, which however contributes only minimally to its pharmacokinetics at therapeutically relevant concentrations.<sup>9,11</sup> The elimination half-life of zonisamide is independent of dose and has been reported to be about 60 hours. Due to its long half-life, zonisamide may take up to 2 weeks to reach serum steady-state concentrations.<sup>11</sup> Therefore, zonisamide is suitable for once- or twice-daily dosing.<sup>12</sup>

According to <sup>14</sup>C studies, zonisamide easily penetrates lipid membranes and the blood brain barrier and has been found to be evenly distributed throughout the entire body with higher concentrations in liver, kidney and adrenal gland than in plasma. It reaches the central nervous system through a lipid-mediated transport mechanism.<sup>13</sup> Based upon rat brain distribution models, high concentrations of zonisamide could be detected in cerebral cortex and midbrain with no measurable accumulation of zonisamide within the central nervous system.<sup>14</sup>

Zonisamide is mainly metabolized by hepatic CYP3A4 inactivation pathway enzymes, which accounts for 50% of ZNS elimination and results in subsequent conjugation to a glucuronide metabolite.<sup>15</sup> Acetylation of zonisamide accounts for a further 20% inactivation and around 15% to 30% of the parent drug is excreted unchanged in the urine.<sup>8</sup> Zonisamide has no relevant inducing or inhibiting effect any hepatic cytochrome P450 (CYP450) isoenzyme and does not significantly modify the steady-state plasma levels of commonly administered antiepileptic drugs (AEDs), oral contraceptives or any other class of therapeutic agents investigated to date.<sup>7</sup> However, zonisamide clearance increases up to about 50% when administered in combination with other AEDs that are known to induce CYP3A4, such as phenobarbital, carbamazepine or phenytoin. This aspect has also been taken into account with the combination of zonisamide and herbal pharmaceuticals that can induce CYP3A4, eg, ginkgo.<sup>16</sup> Valproic acid, which is an enzymatic inhibitor, may marginally elevate ZNS levels.<sup>17</sup> Due to the very mild carbonic anhydrase inhibitory effect of zonisamide, there is at least the theoretic possibility of interactions with metformine (with an enhanced risk of lactic acidosis), flecainide, memantine and other drugs with an urine pH dependent mechanism of excretion. Hypothetically, one has also to be aware of possible interactions between selective serotonin reuptake inhibitors/SSRIs and zonisamide because of its weak monoamine oxidase B (MAO-B) inhibitory capacity which could promote the risk for malignant serotonin syndrome, however, there are no such reported drug interactions up to date.

## Zonisamide: Mechanism of Action in Epilepsy

The exact mechanism of zonisamide as an anticonvulsive drug is still not completely understood, but seems to involve multiple mechanisms of action including neuronal sodium channels, T-type voltage dependent calcium channels, and synaptic transmission.<sup>18</sup> Concerning sodium channels, zonisamide has been shown to concentration-dependently modulate the steady-state inactivation behavior and reduction of repetitive firing.<sup>19</sup> Furthermore, in cell cultural models, zonisamide has been found to reduce currents of low-threshold calcium channels.<sup>20,21</sup> In contrast to numerous other anticonvulsant agents, zonisamide



seems to have no direct effects on modifying GABA-A receptor function, but may inhibit glutamatergic synaptic transmission by reducing the presynaptic release of glutamate.<sup>22</sup> Zonisamide is also a weak inhibitor of carbonic anhydrase, although, since it is 100 to 200 times less potent than acetazolamide,<sup>23</sup> this effect obviously does not contribute to the anticonvulsant action of the drug.<sup>24</sup>

## Zonisamide: Mechanism of Action in PD

The antiparkinsonian effect of zonisamide appears to be mediated through various mechanisms including influences on dopaminergic and serotonergic neurotransmission, monoamine oxidase and opioid receptors.

Concerning the dopaminergic system, zonisamide seems to have a biphasic effect since administration of low doses of zonisamide led to an increase of intra- and extracellular dopamine (DA) levels whereas higher doses induced a reduction of DA turnover in the rat striatum.<sup>25</sup> This effect has been attributed to an induction of tyrosine hydroxylase mRNA and protein concentrations inducing an increase of DA synthesis<sup>6</sup> and seems to be related to the inhibition of T-type calcium channels in the striatum and substantia nigra neurons.<sup>26,27</sup>

As to zonisamide effects on the degradation enzymes of dopamine, it was reported that zonisamide weakly inhibited MAO-B activity. IC<sub>50</sub> (half maximal inhibitory concentration) values using liver microsomal fractions were reported to be rather high (600 μM), whereas the IC<sub>50</sub> using striatal membrane fractions was 28 μM in rats and 10 μM in monkeys.<sup>6,25</sup> Although data from human testing systems are not available, one might speculate that the MAO-B inhibitory activity of zonisamide within the central nervous system is higher than in the periphery accounting at least partially for its dopaminergic effects. No effect of zonisamide was reported on catechol-o-methyltransferase (COMT).<sup>28</sup> Moreover, zonisamide has been found to have no affinity to any of the DA receptor subtypes.<sup>6</sup>

Data concerning the serotonergic system are less consistent with one report that therapeutic doses of zonisamide are able to enhance serotonin and its metabolites whereas suprathreshold doses rather have a converse effect.<sup>29</sup> However, these findings

could not be reproduced by another investigation.<sup>6</sup> Furthermore, zonisamide has been found to increase acetylcholine release and metabolism without affecting cholinesterase activity,<sup>29</sup> but has no affinity for glutamate or adenosine receptors of the rat brain.<sup>6</sup>

Additionally, it has been assumed that zonisamide exerts its antiparkinsonian effects by a suppression of neurotransmission in the indirect striatopallidal pathway mediated through the δ-opioid receptor, since striatal perfusion of zonisamide has been found to differentially influence extracellular neurotransmitter levels in the basal ganglia independent from dopamine concentrations. However, this mechanism of action could be inhibited by a blockade of the δ-opioid receptor.<sup>30</sup>

In addition to these effects, zonisamide has been discovered to provide neuroprotection in cerebral ischemia and epilepsy by acting as scavenger of hydroxyl radicals and nitric oxide and therefore protecting neurons from oxidative stress.<sup>31,32</sup> Related to PD, DA quinone formation (which induces dopaminergic neuron specific oxidative stress and therefore might play a role in the pathogenesis and progression of neurodegeneration in PD) can be prevented by zonisamide.<sup>33</sup> Furthermore, zonisamide has been shown to prevent MPTP-induced dopaminergic neurodegeneration when administered before MPTP application probably mediated by its MAO-B-inhibiting potentials.<sup>34</sup>

## Zonisamide: Clinical Effects in PD

In 2001, there was a first report case report about possible beneficial effects of zonisamide on motor function in PD deriving from the observation of a Parkinsonian patient who received zonisamide for the treatment of epileptic seizures. Zonisamide administered in a daily dose of 300 mg per day not only led to seizure control but also induced an amelioration of motor symptoms of PD.<sup>5</sup> A subsequently initiated open clinical trial with n = nine PD patients with an average Hoehn&Yahr score of 3.78 (range 2 to 5) in the OFF state who were on stable but uncontrolled dopaminergic medication was able to reproduce this first observation. Participants were additionally treated with zonisamide (average daily dose: 122.22 mg, range 50 to 200 mg), and after a period of 12 weeks, there was a significant reduction of Unified Parkinson's Disease Rating Scale/UPDRS II score



(activities of daily living) in the ON and OFF state, a reduction of UPDRS III (motor score) in the ON state and a significant prolongation of ON time in patients with motor fluctuations (7 out of 9). Adverse effects noted were a dry mouth ( $n = 1$ ) and the exaggeration of dyskinesias ( $n = 4$ ) which were attenuated by a reduction of the levodopa dosage (however, no quantitative data are provided).<sup>5</sup>

These first encouraging findings led to the initiation of a 23-center, randomized, placebo-controlled, double blind study performed throughout Japan. PD patients with a mean age of 62.9 years (SD 8.0) and a mean disease duration of 10.0 years (SD 5.7) were randomly allocated in four groups receiving either 50 mg/d zonisamide ( $n = 29$ ), 100 mg/d zonisamide ( $n = 32$ ), 200 mg/d zonisamide ( $n = 23$ ) or placebo ( $n = 31$ ). Concomitant antiparkinsonian medication as levodopa and dopamine agonists were maintained in stable dosages at least 4 weeks before the begin of the study and until the follow-up examination after 10 weeks with the exception that levodopa could be reduced for the control of exaggerated dyskinesias or psychosis. As a main result, zonisamide showed a significant reduction of UPDRS III scores, especially in the low dose zonisamide group, ranging from a decrease of 9.7 ( $\pm 10.0$ ) pts in the 50 mg/d group over 7.9 ( $\pm 6.4$ ) pts in the 100 mg/d group to 6.7 ( $\pm 8.4$ ) pts in the 200 mg/d group whereas the placebo group showed a decrease of 3.5 ( $\pm 9.8$ ) pts. Responder rates of the UPDRS III were reported to be 60.7% (50 mg/d), 51.9% (100 mg/d) and 65.2% (200 mg/d) as compared to 30.0% in the placebo group with a frequency of adverse events in the middle and low dose group equal to the placebo group. Summarized, the authors concluded that a small dose of zonisamide as add on therapy induced a significant amelioration of motor symptoms in PD.<sup>35</sup>

A subsequent randomized multi-center placebo-controlled double-blind study conducted by the same group in Japan was able to confirm that zonisamide was effective and well tolerated as an adjunct treatment in PD patients.<sup>36</sup> In this study, 279 PD patients who were on different, but stable regimen of dopaminergic medication, including PD patients with motor fluctuations, completed the study protocol. Patients were randomized into the treatment groups of 25 mg/d, 50 mg/, or 100 mg/d zonisamide or placebo. To reduce placebo effects, baseline examinations were

conducted after a 2-week period of placebo treatment, followed by a 12-week “verum” treatment period and a further 2-week dose-reduction period. Clinical assessment including UPDRS and Hoehn&Yahr staging was performed in the ON state every 2 weeks with the change of UPDRS III at the final assessment point as primary end point. Secondary endpoints included a change from baseline in total daily OFF time as determined from patients diaries, and a change from baseline in UPDRS I, II and IV scores and Hoehn&Yahr score. UPDRS III scores significantly improved in all treatment groups as compared to the placebo group (reduction of UPDRS III: 25 mg/d:  $6.3 \pm 0.8$ ; 50 mg/d:  $5.8 \pm 0.8$ ; 100 mg/d:  $4.6 \pm 0.8$ ; placebo:  $2.0 \pm 0.8$ ). The proportions of responders, defined as patients with a  $\geq 30\%$  reduction of UPDRS III scores, were 35.1% (25 mg/d), 38.8% (50 mg/d), 31.7% (100 mg/d) and 22.0% (placebo). The degree of change for the primary endpoint was similar in the 25 mg/d and 50 mg/d groups, and these were higher than in the 100 mg/d group and significantly greater than for placebo. Mean reduction of OFF time (hours) ranged from 0.22 (25 mg/d) over 1.30 (50 mg/d) to 1.63 (100 mg/d) as compared to 0.20 (placebo), but there were no significant changes for UPDRS I, II and IV and Hoehn&Yahr stage. The incidence of reported adverse events was similar in the 25 mg/d group (70.9%), the 50 mg/d group (72.9%) and the placebo group (65.1%), but was significantly higher in the 100 mg/d group (79.5%), with a predominance of somnolence (10.9%), apathy (8.5%), decrease of body weight (6.9%) and constipation (6.5%).

A third trial based upon a comparable study protocol was able to generally confirm these data by enrolling 185 patients with advanced PD (average Hoehn&Yahr stage of 2.7 (ON) and 3.5 (OFF)) receiving placebo, 25 mg/d or 50 mg/d zonisamide. The changes in the UPDRS III were reported as follows: placebo group  $-2.9 \pm 0.9$ ; 25 mg/d group  $-5.9 \pm 0.9$ ; 50 mg/d group  $-5.5 \pm 0.9$ . The proportion of responders of UPDRS III was 27.0% (placebo), 41.0% (25 mg/d) and 45.8% (50 mg/d) respectively.<sup>37</sup>

Performed by the same investigators, this study was followed by an open label administration of zonisamide (25–100 mg/d) as adjunctive medication in 92 PD patients (average Hoehn&Yahr stage 2.4 (ON) and 3.3 (OFF)) to survey long-term efficacy and tolerability. Of the 92 patients initially enrolled in the



study, 62 patients completed the 52 weeks of study duration with a mean zonisamide dose of 48.4 mg/d. The authors reported a significant improvement of UPDRS II, III and IV, which were even more pronounced after 52 weeks than after 28 weeks, however, without reporting the UPDRS raw data. Main adverse events were somnolence (10.9%), apathy (10.9%), appetite loss (9.8%), depression (8.7%), dyskinesias (7.6%) and hallucinations (7.6%), without an increase of adverse events over time.<sup>38</sup> Similar results of long term efficacy of zonisamide were reported in 12 patients with PD which showed a significant worsening of UPDRS III (average increase of 5.5 pts) one month after withdrawal of zonisamide which had been administered for a period of more than one year.<sup>39,40</sup>

Although adverse events of zonisamide were rather infrequent and fully reversible when administered in relatively low dosages for the treatment of PD, the possibility of side effects in this patient population has to be kept in mind. Patients have to be clinically monitored for the new occurrence of somnolence and apathy (which might be caused by a general CNS depressant effect of zonisamide) or an exaggeration of dyskinesias and hallucinations which could be induced by the dopaminergic effects of zonisamide.

### Zonisamide: Effects on Tremor

The experimental framework for understanding the mechanisms of action of zonisamide on tremor has been based upon the finding that T-type voltage dependent calcium channels are associated with the generation of pathological firing patterns in animal models of tremor.<sup>41–43</sup> Consequently, one might expect some tremor suppressive effect of zonisamide linked to its calcium channel antagonism.

Actually, there are reports of a specific anti-tremor effect of zonisamide which seems to be not only restricted to the typical Parkinsonian rest tremor, but also positively influences different types of non-Parkinsonian tremor. Concerning tremor in PD, a preliminary open study including 9 patients with residual Parkinsonian tremor non responsive to dopaminergic medication reported a reduced tremor severity after add-on administration of an average dose of 100 mg/d zonisamide.<sup>44</sup> Additionally, several case reports and small studies were able to demonstrate some effectiveness of zonisamide in suppressing tremor in PD.<sup>45,46</sup>

Moreover, according to several clinical observations, zonisamide has been suggested to have beneficial effects on non-Parkinsonian tremor such as Holmes tremor after subarachnoidal haemorrhage or isolated head tremor.<sup>47,48</sup> Furthermore, there are encouraging preliminary studies demonstrating some effectiveness of zonisamide in an average dose of 200 mg/d in suppressing essential tremor.<sup>49–53</sup> In one cross-over investigation, the anti-tremor effect of zonisamide was found to be similar to arotinolo,<sup>49</sup> however, one double-blind study consisting of 20 individuals with essential tremor was not able to confirm a significant tremor reduction capacity of 200 mg/d zonisamide when compared to placebo.<sup>53</sup> Summarized, according to the latest report of the Quality Standards subcommittee of the American Academy of Neurology, zonisamide has not been estimated to be verifiably effective for the treatment of essential tremor.<sup>54</sup>

### Zonisamide: Possible Indications for the Treatment of Non-Motor Symptoms of PD?

In a recent open label study in a group of 15 patients with PD suffering from impulse control disorders (ICD) under dopaminergic medication, zonisamide was administered as an add on medication and was titrated up to 200 mg/d (150 mg/d in one patient). ICD symptoms were rated based upon Clinical Global Impression (according to an analogue scale from 0 to 10) and the Barratt Impulsiveness Scale and were found to be significantly reduced under zonisamide. UPDRS III showed only a marginal reduction (from 25.8 to 24.9 pts).<sup>55</sup> Another open label study on non-Parkinsonian patients suffering from binge eating disorder (BED) was able to demonstrate some superiority of a combination of cognitive behavioral therapy and zonisamide administration (maximum dose of 100 mg/d) over cognitive behavioral therapy alone.<sup>56</sup> As a possible mechanism of action, the authors assumed that zonisamide was able to act on the central hunger and satiety mechanisms, reducing the urge to binge. However, one might alternatively hypothesize that zonisamide exerts more complex effects inducing a stabilization of the dopaminergic tone of the intrinsic “reward” system which could be an interesting approach for the therapy of drug-induced ICDs in PD patients.



Anxiety and depression are frequently reported non-motor symptoms of PD and have an enormous impact on patients' quality of life.<sup>57</sup> In this respect, zonisamide might be a useful therapeutic for PD patients with mood disorders since zonisamide in an average dose of  $160 \pm 70$  mg/d has shown to effectively augment response to anxiolytic medication at least in non-Parkinsonian patients with refractory anxiety.<sup>58</sup> However, since patients with PD often are particularly vulnerable to psychotropic side effects, dopaminergic adverse effects of zonisamide, especially the propagation of hallucinations, have to be carefully monitored.

### Zonisamide: Adverse Events

Zonisamide is widely used in the treatment of epilepsy and is considered to be well tolerated. The most frequently observed adverse effect of zonisamide were sedation and dizziness, occurring in about 15% of patients.<sup>59,60</sup> Furthermore, cognitive disturbance as language disruption, mental slowing and difficulties concentrating (resembling the profile of cognitive impairment induced by topiramate) have been reported<sup>59,61,62</sup> as well as sporadic psychiatric side effects as agitation and irritability depression, aggressive behaviour and psychosis.<sup>61-67</sup>

Related to the treatment of PD, even in the relatively low doses used in these patients, there were adverse events as sedation, apathy, body weight loss and constipation (as mentioned above). Although these side effects were reported to be rather infrequent and fully reversible after discontinuation of the medication, they can be of relevance especially in Parkinsonian patients since gastrointestinal symptoms, somnolence and apathy are typical non-motor symptoms of PD itself (often aggravated by the routine antiparkinsonian medication).

Furthermore, there are some casuistic reports of the occurrence of psychotic symptoms under zonisamide especially in young patients with epileptic seizures<sup>63,64</sup> and the induction of manic episodes by zonisamide.<sup>65-67</sup> Although there were no psychotic adverse events documented due to zonisamide in PD so far, this possibility should be taken into account, the more so, as psychosis in general is a common complication in patients with advanced PD.

Restless legs syndrome (RLS) has sporadically been reported to occur under treatment with

zonisamide.<sup>68,69</sup> Since RLS has been reported to be associated in PD in more than 20% of patients,<sup>70</sup> a possible worsening of RLS complaints should be borne in mind under zonisamide medication in PD.

Besides these side effects on neurological or psychiatric function, idiosyncratic reactions as cutaneous manifestation of hypersensitivity have been observed which can range from mild urticarioid/maculopapular eruptions to potentially life-threatening reactions.<sup>71</sup> The incidence of non-serious skin rashes leading to discontinuation of zonisamide in individual patients ranged from 1.4% in the US and Europe to 2% in Japan. Non-serious skin rashes seem to occur with a slightly greater frequency in patients on zonisamide monotherapy (7% to 9%) than on polytherapy (5%).<sup>72</sup> Furthermore, zonisamide has been associated with kidney stones, weight loss and oligohydrosis. The mechanism of these adverse effects has been attributed to the weak inhibition of carbonic anhydrase activity caused by this drug.<sup>73,74</sup> The risk of developing renal stones during zonisamide treatment seems to be low but increases at higher doses and with longer treatment duration.<sup>75</sup> In Western epilepsy trials, mean weight loss was about 1.5 kg (no subjects had more than 5 kg weight decrease), did not appear to be progressive and stabilized over a time.<sup>2,73</sup> Oligohydrosis, characterized as a reduction in sweat secretion, is often caused by zonisamide treatment, but only in particular circumstances (hot temperature, high physical activity), this effect may have clinical consequences in predisposed subjects.<sup>76,77</sup>

### Conclusion

According to the available data, zonisamide in a dose of 25–50 mg/d seems to be a promising add-on medication in patients with advanced PD leading to significant and enduring amelioration of motor symptoms. The positive results of clinical trials have been lead to the approval of zonisamide as an antiparkinsonian drug in 2009 in Japan exclusively. However, international multi-center studies to reproduce these findings are still missing. Although zonisamide has been considered as well-tolerated drug with good safety profile, the possibility of adverse events as somnolence and apathy, gastrointestinal symptoms and psychiatric effects have to be taken into



account in the individual PD patient. Furthermore, zonisamide might have particular potentials in the treatment of tremor and non-motor symptoms such as ICD, depression and anxiety in PD. Zonisamide has been shown to exert multiple mechanisms of action including effects on the central dopaminergic metabolism and on different ion channels as well, however, the antiparkinsonian mechanism of action is still not fully understood.

Summarized, zonisamide seems to be an interesting, but still investigational drug for the treatment of PD. Further placebo-controlled double-blind multicenter studies with participants with different genetical background and in different stages of PD are warranted to gather a better insight into mechanisms of action and treatment effects of zonisamide in PD. Besides, such investigations are required for the evaluation not only of the clinical outcomes, but of the economical aspects as well. The daily costs of an adjunctive treatment with zonisamide in Europe are about 1.5 to 2.0€ which seems to be justifiable if add-on treatment will reproducibly show a verifiable benefit for patients with PD.

### Author Contributions

Analysed the data: SS. Wrote the manuscript and developed the structure and arguments for the paper: SS. The author reviewed and approved of the final manuscript.

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