**Trazodone: A New Antiepileptic Drug for Dravet Syndrome?**

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**Abstract**

Dravet syndrome (DS) is associated with severely refractory seizures. Recent studies suggest possible antiepileptic effects of serotonergic drugs. We report the case of a 25-year-old woman with DS-related epilepsy (SCN1A mutation), with daily seizures since childhood, associated with developmental delay. Several antiepileptic drug regimens were tested, without clear benefit. Over the years, she maintained a pattern of diurnal and nocturnal seizures, with a nocturnal predominance averaging two tonic–clonic seizures per night, with periods of seizure clusters. On routine electroencephalography (EEG), frequent, subtle myoclonic seizures during sleep were detected. A seizure-free period or significant reduction in seizure frequency was never attained. Trazodone was started due to insomnia. This led to a remarkable as well as long-standing clinical and neurophysiological improvement: less than one reported tonic–clonic seizure per month during the next 18 months, reduction in interictal epileptiform activity (170/h vs. 30/h of sleep), myoclonic seizures (90/h vs. 0.7/h of sleep), and tonic–clonic seizures (2/night to 0) on video-EEG. Serotonergic pathway modulation effects on DS-related epilepsy were observed in animal studies, in addition to small case series using lorcaserin and fenfluramine. To the best of our knowledge, no clinical data exist showing that trazodone may be an efficacious agent in patients with DS. Despite limitation of an isolated case with possible chance factors, our data, given the striking effect, provide this clinical evidence for the first time, and may have important clinical implications in patients with DS, reinforcing the need for further research on this subject.

**Keywords**

► Dravet syndrome
► serotonergic pathways
► trazodone

**Introduction**

Dravet syndrome (DS), previously known as severe myoclonic epilepsy in infancy, is an epileptic encephalopathy that normally presents in the first year of life, with febrile and prolonged seizures.¹⁻³ It affects 1 in 20,000 to 40,000 people.² Usually, there is normal development before seizure onset.³ Seizures may be of several types, including tonic-clonic, myoclonic, absence, hemiclonic, and focal seizures.²⁻³ Besides fever, seizures may also be provoked by photo-stimulation.¹² In addition to epilepsy, DS is associated with developmental delay, behavioral disorders, and an elevated risk of sudden death.² Epilepsy is characteristically refractory to antiepileptic drugs.¹⁻³ Genetic mutations are the main cause of DS,² with a mutation in the voltage-gated sodium channel 1α gene (SCN1A) being present in up to 85% of DS patients.³ Other mutations have also been established as possible causes of DS²; approximately 20% do not carry an
SCN1A mutation. Most are de novo mutations, but cases of inheritance and parental mosaicism have been reported. A recent study by Griffin et al proposed that serotonin pathway modulation may play an important role in DS patients’ treatment. Through animal studies with mutated SCN1A zebrafish, they demonstrated that clemizole binds to serotonin receptors, suppressing epileptic activity in this animal model. They have further suggested that its antiepileptic activity could be mimicked by other compounds acting on serotonin pathways, such as trazodone and lorcaserin. Furthermore, they treated five patients with DS with lorcaserin, a clinically approved serotonin receptor agonist, having observed promising results regarding reduction in seizure frequency and/or severity.

Case Report

In our epilepsy consultation, in a tertiary care hospital in Lisbon, we have a clinical case that both meets and reinforces such findings. It concerns a 25-year-old woman, with refractory epilepsy and developmental delay since 5 months of age. She had a genetic test in 2016 that confirmed an SCN1A gene mutation, nonsense variant R222X (OMIM 607208), having established both a clinical and genetic DS diagnoses. As an infant, she had frequent febrile seizures, with various seizures types (tonic-clonic, myoclonic, and focal seizures). Her developmental milestones were delayed (e.g., started walking autonomously by the age of 6 years). She began consultations with a neuropsychiatrician before 1 year of age. Over the years, she had maintained a pattern of both diurnal and nocturnal seizures, with a clear nocturnal predominance averaging two per night, with periods of seizure clusters (up to four seizures, following each other). The seizure frequency was aggravated by menses. She was medicated with several antiepileptic drugs since childhood, including valproic acid, levetiracetam, rufinamide, clonazepam, lamotrigine, zonisamide, and stiripentol, never having attained a seizure-free period or a significant reduction in seizure frequency. Exact drug combinations during childhood are unknown. The only improvement that followed zonisamide introduction was a strict occurrence of daily nocturnal seizures. She had a normal magnetic resonance imaging (MRI) of the brain from 2013. Seizures were documented on electroencephalographic (EEG) and polysomnographic (PSG) studies: frequent and bilateral frontal paroxysmal activity, with sharp waves and polyspike patterns, mostly during sleep, associated with subtle eye opening, upward eye deviation, and eyelid myoclonus. The frequency of this type of seizures detected on a routine EEG was around 90/h of sleep. An overnight ambulatory PSG documented two seizures, with bilateral involuntary movements similar to the usual seizures reported by the patient’s mother. Interictal generalized paroxysms occurred on average at a rate of 170/h (averaging the results of the routine EEG and two ambulatory PSGs performed). This epileptiform activity was present in all throughout the sleep stages including N2, slow wave sleep, and rapid eye movement (REM) sleep at similar rates (-160/h; 130/h and 100/h, respectively). There was also no clear circadian effect, despite slightly higher activity in middle and final periods of the night (-130/h and 150/h, respectively) compared with the first sleep cycle (-60/h).

In June 2017, the patient’s mother mentioned worsening of her sleep pattern with significant insomnia. Trazodone was introduced (225 mg/day), and at this time, the patient was on rufinamide 1,600 mg/day, zonisamide 300 mg/day, and clonazepam 6 mg/day. By September 2017, a noteworthy improvement of seizure frequency was registered, with only four nocturnal seizures in 4 months, a pattern clearly distinct from any other achieved with antiepileptic drugs since the patient’s childhood. A new EEG and video-PSG study was conducted, which showed a considerable improvement of interictal epileptiform activity (averaging 30/h of sleep), only two brief eyelid myoclonic seizures (averaging 0.7/h of sleep), and no documentation of generalized tonic-clonic seizures (Fig. 1B). Furthermore, the patient’s mother stated that her sleep pattern had quite improved, currently maintaining a regular period of 7 to 8 hours of nonfragmented sleep throughout the night, which did not happen before. The PSG confirmed an improvement in the amount of slow wave sleep (7–28% of total sleep time) comparing to the PSG performed before trazodone introduction. Nevertheless, the overall sleep macrostructure was otherwise quite similar.

Discussion

The first suggestion supporting serotonin modulation effectiveness in epileptic seizures is found in the 1980s decade, by Aicardi and Gastaut who published three cases of patients with intractable self-induced photosensitive seizures that responded to fenfluramine, a serotonin release agent. Since then, many other papers suggesting fenfluramine effectiveness have been published (reviewed by Ceulemans et al). Sourbron et al also presented findings suggesting that serotonergic modulation may be an effective therapeutic intervention for DS through a zebrafish model. Ceulemans et al showed that fenfluramine was effective as add-on treatment in a group of 12 DS patients, having published a prospective study of the original cohort (including 10 original patients), with general good fenfluramine tolerability, and seizure control. To the best of our knowledge, no clinical data have been published showing that trazodone may be an efficacious antiepileptic drug in DS patients. Our data provide this clinical evidence for the first time.

Our clinical case supports findings by Griffin et al on the possible role of serotonin modulation in DS patients and gives clinical sustenance to their suggestion that trazodone may be an efficacious agent in these patients. Nevertheless, it has shown to have mixed effects on pharmacodynamics of antiepileptic drugs, with possible pro epileptogenic effects. Lefkowitz et al (1985) published a case of a patient with new-onset seizures 18 days after trazodone initiation for depression; by then, 30 other reports to the manufacturer had been made concerning trazodone-associated seizures. Borowicz et al examined acute and chronic trazodone treatment effects in mice, concluding that it would not be
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A good candidate for antidepressant treatment in epilepsy patients. Trazodone reduced the anticonvulsant effect of phenytoin and carbamazepine (after single and chronic administration), chronic trazodone lowered the brain levels of carbamazepine and phenobarbital, and acute and chronic trazodone increased valproate brain concentration. However, trazodone did not show any effect on the anticonvulsant action of valproate and phenobarbital. Still regarding use of trazodone and seizure risk, Hill et al.11 showed that the highest risk for seizures/epilepsy in the first 5 years of follow-up was, in fact, for trazodone (hazard ratio 5.41), among an increased hazard ratio for all antidepressant drug classes. For this reason, further research, regarding the safety of this intervention, is warranted.

Our patient presented with mainly sleep-related seizures, either very frequent brief eyelid myoclonus or less frequent, albeit daily, generalized tonic-clonic seizures. Paroxysmal interictal epileptiform activity was also very frequent and mainly sleep related. Trazodone works mainly as a sleep-inducing agent.12–14 In insomnia studies, this agent has been shown to have a beneficial pharmacologic profile, usually not presenting with significant adverse effects, improving sleep quality, decreasing wake periods after sleep,12 and increasing the amount of slow wave sleep.13,14 This agent has also been shown to improve sleep microstructure, decreasing non–rapid eye movement (NREM) sleep fragmentation and instability.13 Sleep instability and wake/sleep transitions may function as seizure precipitants.15 Therefore, it is possible

Fig. 1 Video-EEG before (A) versus after introduction of trazodone (B). (A) Thirty-second epoch of the video-EEG showing frequent eyelid myoclonic seizures during sleep (2013), before introduction of trazodone therapy. (B) After trazodone introduction, there was a considerable improvement of interictal epileptiform activity (averaging 30/h of sleep), only two brief eyelid myoclonic seizures (averaging 0.7/h of sleep), and no documentation of generalized tonic-clonic seizures.
that the first thought in mind regarding our patient would be that the decrease in seizure frequency could be related to sleep improvement. However, despite having verified an increase in slow wave sleep after trazodone introduction, no other difference concerning sleep macro- or microstructure was detected. The most striking difference after analyzing all neurophysiologic data from our patient is the noteworthy decrease in interictal epileptiform activity. This leads us to believe that trazodone action in this case was not limited to sleep-related improvement, and was indeed related to a possible antiepileptic mechanism of action, as previously proposed. Another possible explanation might be a chance-related fluctuation in epileptic seizures. However, during the long-lasting follow-up of our patient (18 months), we have never experienced any noteworthy fluctuation on tonic-clonic or myoclonic seizures. The enduring and maintained improvement following trazodone introduction reinforces its antiepileptic effect. For ethical reasons, removal of the drug to confirm seizures' relapse was not attempted.

All these data—both laboratory and clinical evidence—are reason to consider that serotonergic modulation is, indeed, a possible means to control seizures in DS. However, there is a need for individual risk-benefit assessments in all patients. This case may denote important clinical implications in DS patients, with major changes in their treatment paradigm, reinforcing the need of further research on this subject.

**Note**
Informed consent for the publication of this case was obtained from the patient’s mother.

**Authors’ Contributions**

**Linda Azevedo Kauppila:** assisting physician during inpatient admission for prolonged neurophysiological testing; manuscript preparation, revision and review of the literature.

**Isabel Amorim:** content contribution and revision of the manuscript.

**Carla Bentes:** responsible-in-chief of Electroencephalography and Sleep Laboratory, neurophysiologist, content contribution, and revision of the manuscript.

**Ana Rita Peralta:** assisting physician in outpatient epilepsy clinic, neurophysiologist, content contribution, and revision of the manuscript.
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References
9 Lefkowitz D, Kilgo G, Lee S. Seizures and trazodone therapy. Arch Gen Psychiatry 1985;42(5):523
10 Borowicz KK, Gurdziel E, Czuczwar SJ. Trazodone reduces the anticonvulsant action of certain classical antiepileptics in the mouse maximal electroshock model. Pharmacol Rep 2012;64(5):1136–1145