LETTER TO THE EDITOR

To The Editor

Seizure Control with Add-On Eslicarbazepine in Two Patients with Dravet Syndrome

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Dravet syndrome is an epileptic encephalopathy with a genetic aetiology, in 70%–80% due to mutations in the neuronal voltage-gated sodium channel (VGSC) α-subunit (*SCN1A*) gene.[1,2] It usually presents in the first year of life, with generalised tonic-clonic (GTC) or hemiconvulsive seizures, often triggered by hyperthermia[3]. Intellectual disability usually starts in the second year of life,[2,3] with seizure frequency and duration being important factors in the development of cognitive deterioration.[3] Also, there is an increased risk for sudden unexpected death in these patients.[2] Therefore, it is important to assertively treat and prevent convulsive seizures and *status epilepticus*. Despite new antiseizure medications (ASMs) available in recent years, a high percentage of these patients have a pharmacoresistant epilepsy. First-line treatment includes valproic acid (VPA) and clobazam (CLB), followed by second-line stiripentol (STP) and topiramate (TPM).[4] Some ASMs, like sodium channel blockers, should be avoided[2] due to a paradoxical effect, possibly explained by pharmacodynamic effects in patients with *SCN1A* gene mutations.[4]

Eslicarbazepine acetate (ESL) is a sodium channel blocker ASM that has differences in its mechanism of action,[5] which may lead to a different effectiveness across various syndromes. There is only one published small-case series with two patients reporting the use of ESL in Dravet syndrome.[6] Our aim was to report two patients with a refractory epilepsy due to Dravet syndrome, who became seizure-free after starting ESL.

The first case is a 26-year-old Portuguese man who developed febrile and non-febrile convulsions in his first year of life. He was diagnosed with Dravet syndrome, with a variant in the *GABRB2* gene (c.1181C > G), in a gene panel testing (variants in *SCN1A*, *SCN2A* and *SCN8A* genes were excluded). This is a newly described variant, with new variants within this gene having previously been associated with epileptic encephalopathies. This variant causes the substitution of a serine by a cysteine which, according to prediction algorithms, is probably tolerated. However, it is not present in population databases and has an unknown inheritance pattern, remaining a variant of unknown clinical significance, although we believe it is probably disease-related. In the course of his disease, he was treated with VPA 1600 mg/day, ethosuximide (ETX) 1000 mg/day, levetiracetam (LEV) 1500 mg/day, STP 1000 mg/day and TPM 250 mg/day. Vagus nerve stimulation (VNS) therapy was tried with no improvement. By 23 years of age, having daily GTC seizures, it was decided to try ESL. At that time, he was being treated with VPA 1000 mg/day, LEV 1000 mg/day, STP 1000 mg/day and TPM 200 mg/day. ESL was introduced at a dosage of 200 mg once daily, and in the first week after ESL treatment he became seizure-free. After 6 months of ESL, it was possible to taper off LEV and reduce VPA. At 3 years of follow-up, he is on ESL 200 mg/day, VPA 800 mg/day, TPM 200 mg/day and STP 1000 mg/day, presenting only very rare myoclonic jerks.

The second patient is a 22-year-old Portuguese man who, at 5 months of age, started having febrile and non-febrile seizures. He was diagnosed with Dravet syndrome, with a new variant, likely pathogenic, in the *SCN1A* gene (c.1724delT), in a single-gene testing. This is a frameshift mutation that generates a truncated protein and has been previously described in a patient with a severe infantile multifocal epilepsy. Epilepsy was refractory to all the ASMs regimens tried, including VPA 2000 mg/day, STP 2000 mg/day, LEV 1500 mg/day, rufinamide 400 mg/day, felbamate 1800 mg/day, CLB 30 mg/day, zonisamide 100 mg/day, perampanel 4 mg/day, TPM 200 mg/day, phenobarbital 100 mg/day and ETX 1000 mg/day. Ketogenic diet and VNS implantation were tried, with no improvement. When ESL was introduced by the age of 18 years, he was having an average of 4 to 7 GTC seizures weekly, under treatment with VPA 1600 mg/day, LEV 1500 mg/day and CLB 40 mg/day. ESL was started at a dosage of 200 mg daily. After 1 month, as soon as he increased the dosage to 400 mg of ESL, he achieved complete seizure control and gradually a concomitant improvement in behaviour was observed. One year later, LEV was suspended and VPA dosage was reduced after a hyperammonaemia was documented. He remains seizure-free at 4 years of follow-up with ESL 400 mg/day, VPA 800 mg/day and CLB 30 mg/day. In both patients, ESL was well tolerated with no adverse effects reported.

Both of our adult Dravet patients presented a refractory epilepsy, having frequent GTC seizures among other generalised seizures. Since these types of seizures are life-threatening, it was decided to try ESL as an off-label therapy, resulting in a fast improvement in seizure control. One interesting feature was the improvement under low dosages of ESL. Our patients were controlled with 200 and 400 mg, which was lower than reported in the two previous adult Dravet patients, who were both under 800 mg of ESL.[6] The reason for this therapeutical efficacy with such low dosages is still unclear.

Although all sodium channel blockers are avoided in patients with Dravet syndrome, the slight differences in their mechanism of action may explain our patients favourable outcome. Classically, sodium channel blockers such as CBZ, OXC and phenytoin work by interfering with fast inactivation pathways. However, ESL acts mainly in slow inactivation of the VGSC, therefore reducing the availability of the channel[7], and has a lower affinity to VGSC in their resting state compared with the other ASMs from the same family. Another distinctive property of ESL over CBZ is that it effectively inhibits high- and low-affinity hCa_v 3.2 inward currents.[8] This blockade of calcium currents as a mechanism of action observed in ESL is shared with other ASMs (like VPA, TPM and ETX), which are commonly used in the treatment of generalised epilepsies. One other explanation for the effectiveness and non-aggravation of generalised seizures by ESL is that CBZ potentiates $GABA_A$

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currents, while ESL, in contrast, is devoid of action in GABA receptors.[7]

Pharmacogenomics could also play an important role in the clinical response to ESL. To the best of our knowledge, there is only one previous description on the efficacy of ESL in adult Dravet syndrome patients.[6] The authors reported two patients, with a pathogenic variant in the *SCN1A* gene (point mutations), who also presented a significant decrease in seizure frequency with ESL. It is possible that the presence and characteristics of the *SCN1A* variants may relate to the effectiveness of ESL. However, we have genetically different Dravet syndrome patients (involving VGSC and GABA genes), with an apparent similar response to treatment. Hence, further cases are needed in order to explore this hypothesis.

Despite advances in recent years, we continue to direct our treatments to syndromes rather than to aetiology. This is particularly true in rare diseases such as Dravet syndrome, in which treatment remains mainly empirical. These reports show that ESL can be useful in some adult patients with refractory Dravet syndrome. Although these are encouraging results, evidence on the usage of ESL in Dravet patients is still scarce. Therefore, more data are required to confirm the potential efficacy and safety of ESL in this syndrome.

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Statement of Authorship

All those designated as authors meet all four criteria for authorship according to the guidelines of the International Committee of Medical Journal Editors (ICMJE) and all co-authors have reviewed and approved the contents of the manuscript.

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