

## BRIEF COMMUNICATION

# Does long-term phenytoin have a place in Dravet syndrome?

George A. Zographos<sup>1</sup> , Sophie J. Russ-Hall<sup>1</sup>  & Ingrid E. Scheffer<sup>1,2,3</sup> <sup>1</sup>Epilepsy Research Centre, Department of Medicine, University of Melbourne, Austin Health, Melbourne, Australia<sup>2</sup>Florey Institute of Neuroscience and Mental Health, Melbourne, Australia<sup>3</sup>Murdoch Children's Research Institute and Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia

## Correspondence

Ingrid Scheffer, Epilepsy Research Centre, University of Melbourne, Level 2, Melbourne Brain Centre, 245 Burgundy St, Heidelberg, Victoria 3084, Australia. Tel: 03 9035 7344; Fax: 03 9496 2291; E-mail: scheffer@unimelb.edu.au

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## Abstract

Anti-seizure medications that block sodium channels are generally considered contraindicated in Dravet syndrome. There is, however, considerable debate about the sodium-channel blocker phenytoin, which is often used for status epilepticus, a frequent feature of Dravet syndrome. We describe four patients with Dravet syndrome in whom long-term phenytoin therapy reduced seizure frequency and duration. In two patients, phenytoin produced prolonged periods without status epilepticus for the first time. Attempting to wean phenytoin in all patients after 1 to 20 years of use resulted in seizure exacerbation. Reintroducing phenytoin improved seizure control, suggesting phenytoin is beneficial in some patients with Dravet syndrome.

## Introduction

Dravet syndrome (OMIM# 607208) is the prototypic developmental and epileptic encephalopathy (DEE).<sup>1,2</sup> The classical phenotype presents with prolonged febrile tonic-clonic seizures in the first 19 months of life.<sup>3</sup> The median duration of the first seizure is 15 min, with around one-third of patients presenting with status epilepticus (seizure lasting  $\geq 30$  min). Other seizure types include hemiclonic, focal impaired awareness, myoclonic, and absence seizures. Development in Dravet syndrome is usually normal in the first year of life, with slowing or regression observed after 1 year of age.<sup>3</sup>

Over 90% of patients with Dravet syndrome have loss-of-function pathogenic variants in *SCN1A*, which usually arise *de novo*.<sup>3,4</sup> *SCN1A* encodes the  $\alpha 1$  subunit of the voltage-gated sodium-channel Nav1.1, which plays a key role in inhibitory GABAergic interneurons. The  $\alpha 1$  subunit constitutes the Na<sup>+</sup> channel pore and is the target of sodium-channel blocking (SCB) medications.<sup>5</sup> The spectrum of *SCN1A* epilepsy syndromes is broad and extends beyond Dravet syndrome, to profound impairment in early infantile *SCN1A*-DEE to mild phenotypes of genetic epilepsy of febrile seizures plus (GEFS+).<sup>3,6,7</sup>

Dravet syndrome is associated with loss-of-function *SCN1A* pathogenic variants which are truncation in about 40% of patients and missense in about 40% of cases.<sup>5</sup> The nature and location of these variants determines their functional effect with some missense variants causing gain-of-function and early infantile *SCN1A*-DEE.<sup>5,6,8</sup> The functional impact influences whether SCB anti-seizure medications (ASMs) may be effective or contraindicated. However, a nuanced understanding of the modes of action of different SCB ASMs suggests that a blanket contraindication of these drugs is not appropriate in loss-of-function diseases, such as Dravet syndrome.<sup>5,9,10</sup>

Phenytoin is a SCB ASM, commonly used for tonic-clonic seizures, focal seizures, and status epilepticus. It acts by stabilizing the inactive state of the Nav1.1 channel, blocking sodium conductance and prolonging recovery from inactivation.<sup>5</sup> Emergency use of phenytoin is well established for treating status epilepticus,<sup>11</sup> which occurs in >90% of patients with Dravet syndrome.<sup>3</sup> However, phenytoin use in Dravet syndrome for status epilepticus remains controversial due to concerns of potential seizure exacerbation.<sup>10,12</sup>

We report four patients with *SCN1A*-Dravet syndrome, where long-term phenytoin was beneficial, and weaning after several years resulted in increased seizure frequency and duration.

## Patients and Methods

Of 238 individuals with *SCN1A*-Dravet syndrome, 42 patients had received phenytoin. We reviewed phenotypic data to identify individuals who had long-term phenytoin treatment. Patients who had only received phenytoin acutely for termination of prolonged seizures or status epilepticus were excluded. We reviewed the clinical records of four patients who had received long-term phenytoin.

The Austin Health Human Research Ethics Committee approved the study. Written informed consent was obtained from patients, parents, or legal guardians if they were minors or had intellectual disability. Clinical data were de-identified.

## Results

We identified four patients with *SCN1A*-Dravet syndrome who had received long-term phenytoin, including three male adolescents, aged 17–18 years, and one man aged 28 years. All four patients were commenced on phenytoin in addition to two ASMs and had previously tried 4–7 ASMs (Table 1).

Seizure frequency reduced in all four patients at the time of commencing phenytoin: 30% in patient 1, 60% in patient 3, and 10% in patient 4 (Figure. 1). Patient 3 was seizure-free for 4 weeks after commencing phenytoin, previously having had 2–3 seizures per week for 2 years. While the exact seizure frequency before phenytoin in patient 2 was not recorded, he had almost 4 years without status epilepticus after starting phenytoin, having previously had three status-related hospital admissions per month. Introducing phenytoin did not exacerbate seizures in any patient, nor did it trigger onset of new seizure types.

Patients were on phenytoin between 1 and 20 years. On weaning long-term phenytoin, the patients had a 2- to 14-fold increase in seizure frequency and duration, which required the phenytoin dose to be increased. Only patient 1 weaned phenytoin completely on the first attempt but nocturnal seizures and status epilepticus increased. Patient 3's parents elected to wean phenytoin and he developed myoclonus. With the re-introduction of phenytoin, there was sustained improvement in seizure frequency and duration in all four patients with a median follow-up period of 4 years.

All patients showed improved alertness after recommencing phenytoin, with patient 3 becoming more interactive and less unsteady. Phenytoin had no effect on the cognitive level, with the degree of intellectual disability being stable in each patient (moderate in patient 1, severe in patients 2–4).

## Discussion

As a sodium-channel blocking drug, phenytoin has been traditionally regarded as contraindicated in Dravet syndrome, with limited data to support this contention.<sup>13</sup> However, phenytoin continues to be cautiously prescribed acutely for status epilepticus.<sup>3</sup> We describe four patients with Dravet syndrome who achieved their best levels of seizure control while on phenytoin with amelioration of episodes of status epilepticus. When phenytoin was reduced, there was a marked increase in seizure frequency and duration.

On dissecting the literature, there is limited evidence to support the avoidance of phenytoin in Dravet syndrome. Many papers advising against phenytoin reference the Guerrini et al. paper focusing on seizure exacerbation with lamotrigine.<sup>9</sup> In Guerrini's 1998 study of 21 patients, only one was on phenytoin and there was no comment regarding its efficacy. This study predates the identification of *SCN1A* pathogenic variants as the cause of Dravet syndrome in most individuals. The 2011 study by Catarino et al. reports mixed responses to phenytoin in the three of 22 patients who received phenytoin.<sup>13</sup> One had seizure exacerbation, one had seizure improvement, and one had improved control of GTCS and exacerbation of myoclonic seizures. Other small series do not show clear responses to phenytoin, although it is noteworthy that choreoathetosis was observed in three patients aged 8–21 years when the dose of phenytoin was increased.<sup>14</sup>

Variable efficacy within SCB ASMs in Dravet syndrome emphasizes that we cannot adopt a whole-of-class approach to prescribing these drugs. Current consensus advises against use of carbamazepine and oxcarbazepine in Dravet syndrome.<sup>10,13</sup> Carbamazepine has threefold lower affinity for depolarized channels than phenytoin but binds to them at a fivefold faster rate, demonstrating different sodium-channel blocking mechanisms.<sup>5</sup>

Lamotrigine, also a SCB ASM, was originally thought to worsen seizures in Dravet syndrome,<sup>9</sup> which has led to the avoidance and withdrawal of lamotrigine use. We reported efficacy of long-term use of lamotrigine in three Dravet patients, aged 10–28 years.<sup>15</sup> It is unclear whether age could impact on the efficacy of phenytoin and lamotrigine, noting the older age of the patients in our lamotrigine study and the adolescents (17–18 years) and adult (28 years) reported here. Why it would be more efficacious in older individuals is unclear.

The intriguing question is why long-term use of phenytoin was beneficial in these four patients with Dravet syndrome, noting that it is only rarely trialed in patients with *SCN1A* haploinsufficiency. There was no clear correlation between the location of the pathogenic variants in

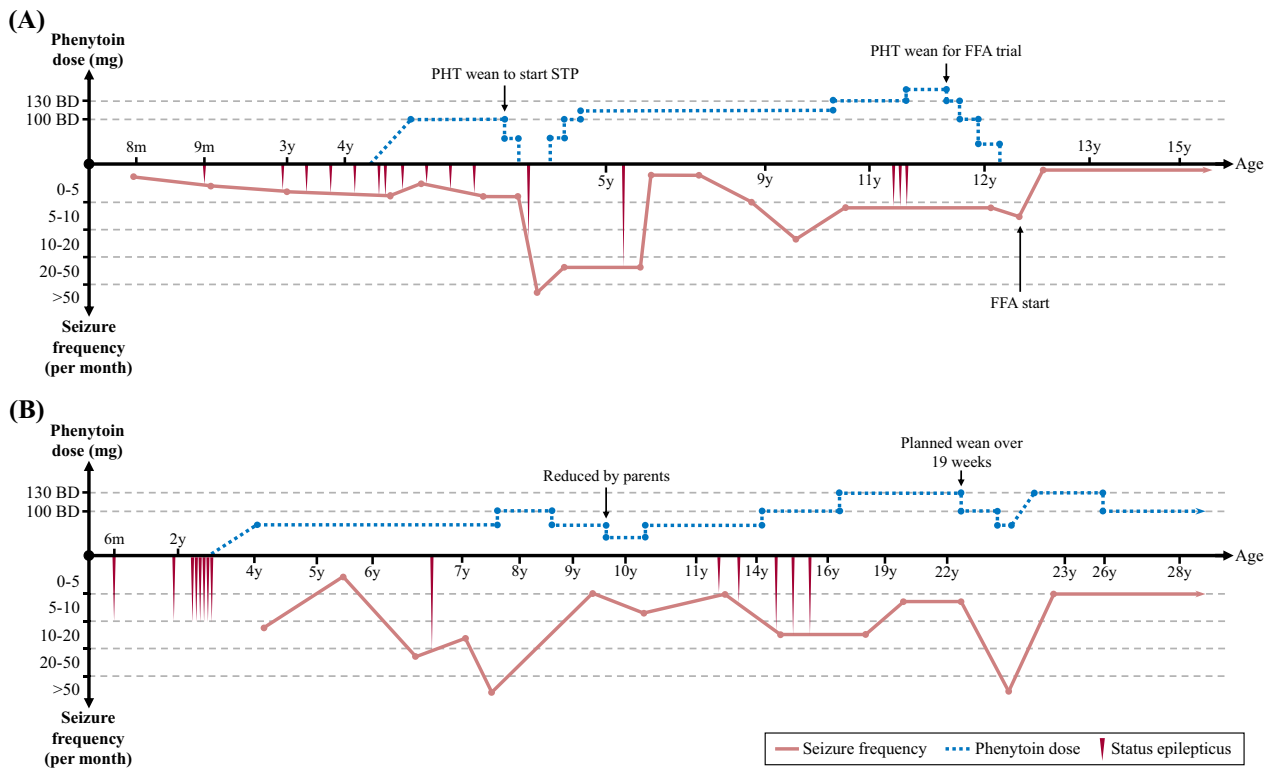
**Table 1.** Clinical features of patients with Dravet syndrome and effects of phenytoin treatment.

Patient no./sex/age	1/Male/17 <sup>a</sup>	2/Male/28 <sup>b</sup>	3/Male/18 <sup>c</sup>	4/Male/18 <sup>d</sup>
<i>SCN1A</i> pathogenic variant	c.4446_4447dupCA p.Ile1483ThrfsX2 <i>de novo</i>	c.4547C>A p.Ser1516X <i>de novo</i>	c.3939delA p.Lys1313AsnfsX6 <i>de novo</i>	c.2624C>A p.Thr875Lys Not present in mother, father unavailable
Age of seizure onset	8 m	6 m	5 m	9 m
Age of developmental regression or plateau	12 m	5y	7y	18 m
Level of ID	Moderate	Severe	Severe	Severe
Age when phenytoin first introduced and reason	4y - unknown	2y9m - SE	3y11m - uncontrolled SZ	8y1m - uncontrolled SZ
Maximum dose of phenytoin	130 mg mane 160 mg nocte	130 mg BD	50 mg mane 75 mg nocte	100 mg BD
Seizure type/frequency prior to phenytoin (duration)	TCS 1-2/m (3 min) FIAS 2/m (1-2 min)	GTCS FIAS Myoclonus	GTCS 1-2/w (3-4 min) Absence 2/w (2 secs)	TCS 8/m (1-2 min) Absence Myoclonus
Concomitant ASMs when phenytoin commenced	CLB 10 mg nocte VPA 400 mg BD	CZP 0.25 mg BD VPA 150 mg mane, 200 mg nocte	CLB 2.5 mg mane, 5 mg nocte VPA 200 mg BD	VPA 200 mg BD ZNS 25 mg BD
Effects of phenytoin	↓ TCS 1-2/m (<2 min) ↓ FIAS 1/m (1 min)	↓TCS 3/w (<1 min) ↓FIAS 1/w (3 min) ↓Myoclonus 1/d	↓ GTCS 0-1/w (1-2 min) ↓ Absence 1/w (1 sec) ↑interaction / balance 4 w SZ free after commencing phenytoin (previously 2-3 SZ/w)	↓TCS 7/m
Other ASMs tried ( <b>bold</b> : begun after phenytoin commenced)	CLB, <b>CZP, DZP, FFA, KD, LEV, LTG, STP, TPM, VPA, ZNS</b>	CBZ, CLB, CZP, <b>DZP, KD, LTG, STP, TPM, VGB, VPA</b>	<b>CBZ, CLB, CZP, LEV, PB, STP, TPM, VPA</b>	<b>CBZ, CBZ, CLB, LEV, LTG, OCBZ, PER, STP, TAK-935, VPA, ZNS</b>
Onset of new seizure types with phenytoin	No	No	No	No
Duration of phenytoin before wean	1y	20y	1y	5y
Effect of weaning phenytoin	↑ GTCS frequency 1-4/d (3-6 min) ↑ Nocturnal SZ	↑ TCS frequency (from 1/w to 4/night) ↑Myoclonus ↓Level of function	↑ GTCS 4/w ↑ Absence 2-3/d (<5 secs) New myoclonus	↑SZ frequency > 10/m
Duration of phenytoin continuation after reconstitution	7y	5y (ongoing)	4 m	3y
Overall effect of phenytoin	Reduced seizures 6y SE free after restarting PHT (previously 3 SE events/y)	Reduced seizures 4y SE free after commencing PHT (previously 3 SE events/m)	Reduced seizures More alert Improved development 4 w SZ free after commencing PHT (previously 2-3 SZ/w)	Reduced seizures

<sup>a</sup>Patient 48 in Li et al.<sup>3</sup> <sup>b</sup>Patient 2 in Li et al.<sup>3</sup> <sup>b</sup>Patient 19 in Rodda et al.<sup>19</sup> <sup>b</sup>Patient AusE in Singh et al.<sup>20</sup> <sup>b</sup>Patient 52 in Wallace et al.<sup>21</sup> <sup>c</sup>Patient 43 in Li et al.<sup>3</sup> <sup>c</sup>Patient 2 in Rodda et al.<sup>19</sup> <sup>d</sup>Patient 81 in Li et al.<sup>3</sup> ASM, anti-seizure medication; BD, twice a day; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; d, day; DZP, diazepam; FFA, fenfluramine; FIAS, focal impaired awareness seizure; GTCS, generalized tonic-clonic seizure; ID, intellectual disability; KD, ketogenic diet; LEV, levetiracetam; LTG, lamotrigine; min, minutes; m, month; nocte, at night; PB, phenobarbitone; PER, perampanel; PHT, phenytoin; SCB, sodium-channel blocker; SE, status epilepticus; secs, seconds; STP, stiripentol; SZ, seizure; TCS, tonic-clonic seizure; TPM, topiramate; VGB, vigabatrin; VPA, sodium valproate; w, week; y, year; ZNS, zonisamide.

*SCN1A* and the efficacy of phenytoin. It is likely that genetic background also influences ASM efficacy, such as drug metabolism.<sup>16</sup> Tate et al. found that *SCN1A* intronic

polymorphisms were associated with higher maximal doses of phenytoin and therefore affected therapeutic value and dosing. Polymorphisms affecting the 5' splice



**Figure 1.** Phenytoin dose plotted against seizure frequency for patient 1 (A) and patient 2 (B), with episodes of status epilepticus shown as downgoing red spikes. For patient 2, the seizure frequency line starts after 4 years, as previous habitual seizure frequency was not documented. BD, twice a day; FFA, fenfluramine; PHT, phenytoin; STP, stiripentol; y, year.

site which increase alternate *SCN1A* transcripts with increased sensitivity to phenytoin have been identified.<sup>17</sup>

Optimization of ASMs in Dravet syndrome may improve cognitive function and quality of life.<sup>13</sup> Phenytoin was noted to improve alertness in one of our patients at initiation. In addition, two patients went into status epilepticus with a reduction of phenytoin dose, resulting in a life-threatening complication. Much debate exists around whether phenytoin should be used for status epilepticus in patients with Dravet syndrome, with some reports showing efficacy.<sup>18</sup> Clinical trials exploring the use of phenytoin in Dravet syndrome are required to establish whether phenytoin has a place in the treatment of this disease, both acutely and over the long-term. A complex interplay between the *SCN1A* pathogenic variant, ASMs and their metabolism, and the patient's genetic background, contribute to the variable efficacy of phenytoin in patients with Dravet syndrome.

## Author Contributions

Data acquisition was completed by G. Zographos, S. Russ-Hall, I. Scheffer. Drafting and manuscript revision was completed by G. Zographos, S. Russ-Hall, I. Scheffer.

Study supervision and co-ordination was completed by S. Russ-Hall, I. Scheffer. Study conceptualization and design was completed by I. Scheffer.

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## Conflict of Interest

Ingrid Scheffer has served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, Rogcon, Takeda Pharmaceuticals, UCB, Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, Liva Nova and Eisai; has received funding for travel from UCB, Biocodex,

GlaxoSmithKline, Biomarin and Eisai; has served as an investigator for Anavex Life Sciences, Cerecin Inc, Cerevel Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc, Epygenyx, ES-Therapeutics, GW Pharma, Marinus, Neuren Pharmaceuticals, Neurocrine BioSciences, Ovid Therapeutics, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceutical, Zogenix and Zynerba; and has consulted for Atheneum Partners, Care Beyond Diagnosis, Epilepsy Consortium, Ovid Therapeutics, UCB and Zynerba Pharmaceuticals; and is a Non-Executive Director of Bellberry Ltd and a Director of the Australian Academy of Health and Medical Sciences and the Australian Council of Learned Academies Limited. She may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has a patent for *SCN1A* testing held by Bionomics Inc and licenced to various diagnostic companies; has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy (BFIE) [PRRT2] 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012-009). The remaining authors do not have any disclosures.

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