Audit of use of stiripentol in adults with Dravet syndrome

S. Balestrini\textsuperscript{1,2,3} | S. M. Sisodiya\textsuperscript{1,2}

\textsuperscript{1}Department of Clinical and Experimental Epilepsy, NIHR University College London Hospitals Biomedical Research Centre, UCL Institute of Neurology, London, UK
\textsuperscript{2}Epilepsy Society, Chalfont-St-Peter, Buckinghamshire, UK
\textsuperscript{3}Neuroscience Department, Polytechnic University of Marche, Ancona, Italy

Correspondence
S. M. Sisodiya, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, UK.
Email: s.sisodiya@ucl.ac.uk

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Objectives: There are very few data available in the literature on the use of stiripentol in adults with Dravet syndrome (DS). DS cases are increasingly recognized in adulthood, and more children with DS now survive to adulthood. The aim of the study was to document the effectiveness and tolerability of stiripentol in adults with DS.

Material and methods: We conducted an observational clinical audit in the epilepsy service of the National Hospital for Neurology and Neurosurgery, London (UK).

Results: We included 13 adult subjects with DS (eight females, five males). The responder (defined as more than 50% reduction in all seizure types) rate was 3/13 (23%) at 36 months. The following other outcomes were reported: seizure exacerbation (3/13, 23%), no change (3/13, 23%), less than 50% reduction in seizures (2/13, 15%), more than 50% reduction in generalized tonic-clonic seizures but no other seizure types (1/13, 8%), undefined response (1/13, 8%). The retention rate was 62% after 1 year and 31% after 5 years. Adverse effects were reported in 7/13 (54%): the most frequent were anorexia, weight loss, unsteadiness and tiredness. Withdrawal due to adverse effects occurred in 3/13 (23%).

Conclusions: Compared with previous studies on children with DS, our results show a lower responder rate and a similar tolerability profile. Stiripentol can be effective with a good tolerability profile. Our audit is small, but supports the use of stiripentol in adults with DS when first-line treatments are ineffective or not tolerated, in keeping with published guidelines.

KEYWORDS
antiepileptic drugs, epilepsy, seizures, stiripentol

1 INTRODUCTION

Dravet syndrome (DS) is a severe genetic epileptic encephalopathy with onset in infancy, often associated with drug-resistant epilepsy, developmental slowing, cognitive impairment, occurrence of status epilepticus and elevated risk of early mortality.\textsuperscript{1-3} In most cases, the cause is a mutation in the voltage-gated sodium channel type I alpha subunit gene, SCN1A.\textsuperscript{4} The main challenges include seizure control, prevention of status epilepticus and optimizing development of cognitive function, where possible. The adult phenotype has been described in a number of previous studies.\textsuperscript{2,5-8} Adjustment of treatment may be associated with improved seizure control, cognition and quality of life, even into later adult life.\textsuperscript{2,6} Sodium channel blockers, for example, carbamazepine, oxcarbazepine and phenytoin, should usually be avoided as they can aggravate both seizures and interictal EEG.\textsuperscript{9} Lamotrigine can also cause seizure exacerbation,\textsuperscript{10} although has been reported to be beneficial in some cases.\textsuperscript{11} Effective treatment strategies include valproic acid, clobazam, topiramate, levetiracetam, fenfluramine and bromides,\textsuperscript{12-14} or dietary therapies (ketogenic or modified Atkins diet).\textsuperscript{15} There are ongoing studies on the use of cannabidiol in children with DS.\textsuperscript{16} Stiripentol was licensed under the European Medicine Agency Orphan Drug scheme in 2001 and is the only treatment for which a randomized, placebo-controlled trial has been performed in children with DS, showing that significantly more children with DS on stiripentol adjunctive therapy were seizure-free, or experienced at
least a 50% reduction in seizure frequency, compared with placebo. Very few data are available about the use of stiripentol in adults, with reports for fewer than fifteen DS cases older than 18 years.\textsuperscript{18–21} and twelve healthy adult volunteers.\textsuperscript{22} We conducted a clinical audit to document the effectiveness and tolerability of stiripentol in adults with DS.

2 | MATERIAL AND METHODS

This project was reviewed and registered as an observational clinical audit at the National Hospital for Neurology and Neurosurgery, London (UK). Ethics committee approval is not required for an audit, as clinical audit by definition does not involve intervention beyond usual clinical management.\textsuperscript{23}

We included all adults (>18 years) with DS attending the epilepsy service with previous or current treatment with stiripentol, from January 2001 to July 2015. DS was defined according to the following clinical criteria: seizure onset in the first year of life, with prior normal psychomotor development, intractable epileptic seizures triggered by infections and increased temperature, with no evidence of structural-metabolic aetiology.\textsuperscript{1} Cases were identified by reviewing all known DS cases from clinical registers, reviewing all requests for SCN1A mutation testing by the hospital clinical genetics service and local hospital pharmacy prescriptions of stiripentol. Demographic and clinical information were gathered.

The following variables were included in the analysis: age, gender, age at clinical diagnosis, age at genetic testing, SCN1A mutation details, seizure types, history of status epilepticus, antiepileptic drugs (AEDs) tried before the introduction of stiripentol, age at introduction of stiripentol, interval between genetic diagnosis and introduction of stiripentol, AEDs initially used with stiripentol, mean monthly seizure frequency before the introduction of stiripentol and while on stiripentol treatment, maximum dose of stiripentol, adverse effects during treatment with stiripentol, and total duration of exposure to stiripentol. Seizure exacerbation was defined as an increase of more than 25% in seizure frequency compared with seizure frequency before the introduction of stiripentol.

Statistical analysis was performed using Stata/IC V.11.1 (Stata, TX, USA). Descriptive statistics (mean, minimum, maximum, standard deviation, and median—when appropriate) were used.

3 | RESULTS

We identified 32 adult cases with DS in our service. Thirteen adults with DS and previous or current treatment with stiripentol were identified and comprised eight females and five males. DS was diagnosed on the basis of clinical findings, at a mean age of 24 (SD 11, range 2–41). Genetic analysis was undertaken at a mean age of 27 (SD 9, range 12–43). SCN1A mutation or rearrangements were found in 12 of the 13 patients included. All cases had multiple seizure types. Eight patients (62%) had a history of status epilepticus prior to the introduction of stiripentol. In five cases (29%), stiripentol was introduced in adolescence and continued into adulthood. The mean age at introduction of stiripentol was 26 years (SD 12, range 12–47). In four subjects, it was introduced seven to ten years (median 7.5) before the genetic analysis. In the other nine cases, it was introduced a few months to 6 years (median 1 year), after positive genetic testing for SCN1A mutation. At the time of stiripentol introduction, the mean number of AEDs already tried was 9 (range 3–15), and it was used with one to four concurrent AEDs. None of the cases was ever on monotherapy with stiripentol. Details of SCN1A mutations, seizure types, AED history and age at introduction of stiripentol are shown in Table 1.

3.1 | Effectiveness

The frequency of seizures (of any type) at the time of stiripentol introduction varied from daily to weekly. The daily dose varied from 250 mg to 3000 mg with a mean maximum daily dose of 1604 mg. Over an average time of exposure to stiripentol of 42 months (range 3–139), more than 50% reduction in frequency of all seizure types was reported in three cases (23%). The other outcomes were: less than 50% reduction in frequency of all seizure types in two cases (15%), no change in seizure frequency in three cases (23%), more than 50% reduction in frequency of generalized tonic-clonic seizures (GTCs) but no change in frequency of other seizure types in one case (8%), seizure exacerbation in three cases (23%) and undefined response in one case (8%). One case had initially more than 50% reduction in frequency of GTCs, from weekly to monthly GTCs with a 45 day period without any GTCs, and became then free of GTCs for about 12 months, followed by GTCs recurrence precipitated by intense physical exercise. Before introduction of stiripentol, eight patients (62%) had had from one to multiple episodes of status epilepticus. Of these cases, four had no further episodes of status after the introduction of stiripentol until the latest follow-up, over an average time of 43 months (range 3–139) on stiripentol.

Withdrawal due to lack of efficacy occurred in four cases (31%). In seven cases (54%), treatment was still ongoing at the time of the audit (July 2015), after they had been on stiripentol for an average time of 62 months (range 10–139). The following medication changes were undertaken in these seven cases during the course of treatment with stiripentol: in two clobazam was introduced; in one carbamazepine was withdrawn and clobazam introduced; in one phenytoin was withdrawn; in one sodium valproate was introduced; in one topiramate was withdrawn, sodium valproate, levetiracetam, zonisamide and perampanel were introduced sequentially (zonisamide was soon withdrawn due to lack of effectiveness) and a vagus nerve stimulator was recently inserted; one did not have any changes to concurrent AEDs. Five cases (39%) were on clobazam and 10 cases (77%) were on sodium valproate, as concurrent treatment when stiripentol was initiated. In three cases, (23%) clobazam and in one case (8%) sodium valproate were introduced later on.
during the course of treatment with stiripentol. Overall, at some point eight cases (62%) had concurrent treatment with clobazam and 11 cases (85%) with sodium valproate. A summary of stiripentol effectiveness in the audited cohort is reported in Table 2.

### 3.2 | Tolerability

Adverse effects were not systemically sought as this was not a prospective study, but were reported in seven cases (54%). These were: anorexia (n=4), weight loss (n=4), unsteadiness (n=3), tiredness/somnolence (n=2), nausea (n=1), abdominal pain (n=1), diarrhoea (n=1), myelodysplasia (thrombocytopenia and neutropenia) (n=1), behavioural disturbance (n=1), increased tremor (n=1). In six cases, reduction or withdrawal of one or two concurrent AEDs was reported. Withdrawal of stiripentol due to adverse effects occurred in three cases (23%): one due to anorexia and weight loss together with lack of efficacy, one due to behavioural disturbance and diarrhoea and one due to anorexia, unsteadiness

### Table 1

| Case ID | SCN1A mutations | Type of mutations | Seizure types<sup>a</sup> | AEDs tried before the introduction of stiripentol<sup>b</sup> | Age at introduction of stiripentol (years) |
|---------|-----------------|-------------------|---------------------------|-------------------------------------------------|------------------------------------------|
| 1       | c.4568T>C       | Missense          | Atonic, GTC, myoclonic    | Carbamazepine, clonazepam, ethosuximide, lamotrigine, levetiracetam, nitrazepam, phenobarbitone, phenytoin, piracetam, primidone, topiramate, vigabatrin | 41                                       |
| 2       | c.80G>C; c.3749C>T; c.3706-2A>G | Missense, missense, splice-site | Focal, GTC, tonic | Carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, phenobarbitone, phenytoin, sodium valproate | 15                                       |
| 3       | c.2792G>A       | Missense          | Focal, GTC                | Clobazam, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, zonisamide | 44                                       |
| 4       | c.4369_4372dupCTGT | Premature STOP codon | Focal, GTC, myoclonic | Carbamazepine, clobazam, ethosuximide, oxidazepine, piracetam | 29                                       |
| 5       | c.603-2A>G      | Splice-site       | Focal, sGCT               | Carbamazepine, ethosuximide, lamotrigine, levetiracetam, phenobarbitone, phenytoin, pregabalin, topiramate, vigabatrin | 25                                       |
| 6       | c.429delGT      | Premature STOP codon | Focal, GTC, myoclonic | Carbamazepine, clonazepam, ethosuximide, lamotrigine, piracetam | 14                                       |
| 7       | c.2244G>A       | Premature STOP codon | Focal, GTC, myoclonic | Acetazolamide, carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, lamotrigine, levetiracetam topiramate, vigabatrin | 16                                       |
| 8       | c.4913T>C       | Missense          | Focal, GTC, myoclonic     | Carbamazepine, gabapentin, oxcarbazepine, phenytoin, sodium valproate, topiramate, vigabatrin | 23                                       |
| 9       | c.5639G>A       | Missense          | Atypical absences, focal, myoclonic | Primidone, topiramate | 47                                       |
| 10      | c.2837G>A       | Missense          | GTC, myoclonic            | Clobazam, lamotrigine, levetiracetam, phenytoin | 28                                       |
| 11      | c.2293G>A       | Missense          | Atypical absences, focal, GTC | Acetazolamide, carbamazepine, clonazepam, lamotrigine, nitrazepam, topiramate, vigabatrin, zonisamide | 30                                       |
| 12      | Not detected    | -                 | Absences, atonic, clonic, focal, GTC, myoclonic, tonic | Carbamazepine, gabapentin, lamotrigine, phenytoin, vigabatrin | 12                                       |
| 13      | c.5359G>A       | Missense          | Atonic, clonic, focal, GTC, hemi-clonic, myoclonic, tonic | Carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, phenobarbitone, phenytoin, topiramate | 12                                       |

AED, antiepileptic drugs; GTC, generalized tonic clonic seizures; sGTC, generalized tonic clonic seizure with apparent focal onset.  
<sup>a</sup>Seizure types were clinically determined.  
<sup>b</sup>AEDs are not listed in the temporal order of introduction.
Table 2 Summary of stiripentol effectiveness and tolerability

| Case ID | Concurrent AEDs initially associated with stiripentol | Seizure frequency before the introduction of stiripentol | Maximum dose of stiripentol (mg) | Concomitant AEDs modification with introduction of stiripentol | Seizure frequency while on stiripentol | More than 50% reduction in frequency of GTCs | Reduction of episodes of status epilepticus | Adverse effects | Withdrawal (reason) | Time of exposure to stiripentol until withdrawal or last follow-up (months) |
|---------|------------------------------------------------------|--------------------------------------------------------|---------------------------------|--------------------------------------------------------------|--------------------------------------|---------------------------------|---------------------------------|-----------------|----------------------|-------------------------------------------------|
| 1       | Clobazam, sodium valproate, zonisamide               | 4–17 GTCs per month                                    | 750                             | No                                                          | Exacerbation of seizures (GTCs on a daily basis, increase of myoclonic seizures) and several episodes of status epilepticus | No                                             | No                                             | None            | Yes (lack of efficacy) | 3±                  |
| 2       | Clobazam, topiramate                                 | Daily                                                  | 1750                            | na                                                          | Daily                               | No                                             | na                                             | None            | Yes (lack of efficacy) | 72±                |
| 3       | Carbamazepine, sodium valproate                      | 3–4 GTCs monthly, 2–3 focal seizures daily            | 2000                            | Reduction of sodium valproate (carbamazepine was withdrawn 5 months after introduction of stiripentol) | 1–2 GTCs monthly, 5–8 focal seizures monthly | Yes                                           | na                                             | Unsteadiness and sedation (1000 mg daily), lethargy (1500 mg), loss of appetite and weight (1750) | Ongoing | 48                   |
| 4       | Levetiracetam, sodium valproate                      | 3 GTCs monthly, myoclonic seizures daily              | na                              | Withdrawal of oxcarbazepine                                 | Unchanged                          | no                                           | na                                             | Anorexia and weight loss | Yes (lack of efficacy and adverse effects) | 6±                  |
| 5       | Sodium valproate, zonisamide                         | Weekly, clusters every few weeks                      | 1500                            | Reduction of zonisamide and sodium valproate                | No clusters, reduction in hospitalisations/emergency room visits | Yes                                           | Yes                                           | Weight loss      | Ongoing               | 10                  |
| 6       | Clobazam, sodium valproate                           | Weekly                                                 | 3000                            | na                                                          | Initially 1–2 GTCs per month and 45 days free of GTCs, more recently free of GTCs for about 12 months | Yes (seizure-free)                   | na                                             | Nausea, unsteadiness, abdominal pain, myelodysplasia (thrombocytopenia and neutropenia) | Ongoing, with dose adjustments, haematological review and regular monitoring | 80                  |
| 7       | Sodium valproate                                     | 5–19 seizures per month                               | 750                             | na                                                          | 9–33 seizures per month             | No                                             | No                                             | None            | Yes (lack of efficacy) | 31±                 |
| 8       | Lamotrigine, levetiracetam                           | Weekly                                                 | 2000                            | Withdrawal of carbamazepine                                 | Weekly                             | No                                             | Yes                                           | None            | Ongoing               | 34                  |
| 9       | Sodium valproate                                     | Focal seizures daily                                   | 1000                            | Reduction of sodium valproate                               | Focal seizures daily               | No                                             | na                                             | Increased aggression and diarrhoea | Yes (adverse effects) | 3±                  |
| 10      | Sodium valproate, topiramate                         | 4 seizures per month                                   | 750                             | No                                                          | 11 seizures per month               | No                                             | No                                             | Loss of appetite, unsteadiness and increased tremor | Yes (adverse effects) | 4±                  |

(Continues)
DISCUSSION

In a small cohort, we show that stiripentol can be effective in adults with DS, with a reasonable tolerability profile. The responder rate in our cohort was lower than that from studies in children with DS. Not enough data on adult DS cases treated with stiripentol are available to make adequate comparisons with our findings. We note that some adults have no useful response to stiripentol.

A randomised placebo-controlled trial conducted in children with DS showed 15 of 21 (71%) were responders (seizure-free or experienced at least a 50% reduction in seizure frequency) on stiripentol, whereas there was only one responder of 20 (5%) on placebo (none were seizure-free). The frequency of responders was greater on stiripentol (95% Confidence Interval 52.1–90.7) than on placebo (95% Confidence Interval 0–14.6; \( P < .001 \)). Significantly more DS cases on stiripentol adjunctive therapy experienced drug-related adverse events compared with patients who only had placebo add-on (100% vs 25%; \( P = .0009 \)). The adverse events most frequently observed on stiripentol were drowsiness and loss of appetite, sometimes causing loss of weight. The mean age of the DS cases on stiripentol was 9.4 years (interquartile range 3–16.7).

Inoue et al. performed a retrospective survey in Japan examining the effect of AEDs on clonic seizures or GTCs in DS and then started compassionate use of stiripentol as add-on therapy in an open-label multicenter study. They included 25 DS cases, with an older subgroup with age from 8 to 22 years \( (n=8) \). The study period lasted 6–34 months (mean 14.1). A specified protocol was used, with 2–4-week periods of evaluation (early and late), which were compared with a 4-week baseline period. In the older subgroup, four of eight cases (50%) had more than 50% reduction of GTCs, including one who became seizure-free, in the early period, and five cases (63%) had more than 50% reduction of GTCs in the late period. Duration of seizures was shortened in four cases (50%) in the early period and in two cases (25%) in late period. The frequency of episodes of status epilepticus decreased in one of the eight older cases (13%). Stiripentol was discontinued in two cases (after 89 months) because seizure frequency was unchanged. The adverse effects most often observed were loss of appetite, sleep disturbance, hyperactivity or irritability, and ataxia during the early and intermediate periods. In most cases, these effects disappeared after dose modification of other AEDs/stiripentol, or in the late period.

A further prospective, open-label, multicentre study was conducted in Japan, including 24 DS cases, already on treatment with clobazam and sodium valproate at stable doses for at least 4 weeks (bromide was also allowed as concomitant therapy). This cohort included an older subgroup aged 21–24 years \( (n=8) \). The study consisted of a 4-week baseline, 4-week dose adjustment and 12-week fixed-dose phase. Three of the four older subjects (75%)}
had more than 50% reduction in frequency of clonic seizures or GTCs during the last 4 weeks of the fixed-dose phase vs baseline, including one who became seizure-free. After the 12-week fixed-dose phase, 21 of the initial 24 DS cases entered the 40-week long-term administration phase.21 None of the older cases remained responders in the long-term (one terminated the study due to poor response without entering the long-term phase). Adverse events were reported in all patients enrolled; the most frequent included somnolence, loss of appetite and ataxia, occurring mostly during the dose-adjustment phase and were of mild-to-moderate severity.

Strzelczyk et al.20 retrospectively evaluated health-care utilization over a 2-year period in patients with DS at an outpatient clinic of a German epilepsy centre. Thirteen DS cases were included. Of these, nine (mean age 10.3, range 3–23) were switched to adjunctive treatment with stiripentol and clobazam and experienced more than 25% reduction in seizure frequency between baseline and follow-up phases of 1 year each.

One double-blind placebo-controlled dose ranging study, assessing stiripentol pharmacokinetics, enrolled exclusively adult subjects (22–37 years, mean 29), but these were healthy volunteers.22 This study confirmed the Michaelis-Menten pharmacokinetic profile of stiripentol that was previously described in adult healthy volunteers and people with epilepsy.24,25 Only two adverse effects (one rhinitis and one pharyngitis) were observed, unlikely related to the treatment.

Recently, stiripentol was reported to be effective in treating super-refractory status epilepticus, on the basis of clinical and experimental data.26,27 Three of five adult patients who were treated with stiripentol for super-refractory status epilepticus had resolution of status within 2–4 days after the start of stiripentol.26 A rodent model of established status epilepticus showed effectiveness of stiripentol when seizures had already become resistant to treatment with benzodiazepines, by potentiating GABAergic inhibition. The action of stiripentol seemed independent of the benzodiazepine binding site on the GABAA receptor, with the most common adverse effects. One case had severe haematological adverse effects with myelodysplasia (thrombocytopenia and neutropenia). However, the response to stiripentol was so dramatic as to decrease, whereas focal dyscognitive seizures persist.21

We report seizure exacerbation in three cases (23%). The reason for this is unknown, and this outcome is not described in the stiripentol literature for adult cases and it is rarely reported in children with DS.17–21

Dravet syndrome cases are increasingly recognized in adulthood, and many children with DS survive to adulthood. Better treatment strategies are required. Stiripentol is an allosteric modulator of the GABAA receptor,29 proven to be effective and well-tolerated in children with DS.21–33 There are no data available in the literature on treatment with stiripentol of DS cases older than 24 years. Although this was a small retrospective study with incomplete information for some cases, it is the largest and oldest sample of DS adult cases treated with stiripentol and with the longest follow-up to our knowledge. In some cases, because there were other drug changes made on clinical grounds, we cannot be certain that the entire response observed after stiripentol introduction was due solely to stiripentol: this was an audit, not a prospective clinical trial.

In view of our findings, the effectiveness demonstrated in previous studies17,21 and its reasonable tolerability profile, we suggest stiripentol is worth considering for adults with DS and drug-resistant epilepsy when first-line treatments are ineffective or not tolerated, in keeping with recommendations from National Institute for Health
and Care Excellence guidelines in the UK. Stripentol use may lead to improved seizure control, with reduction of hospitalization costs and subsequent better health-care service utilization, as previously shown. Prospective studies, including well-designed trials in larger cohorts, would seem warranted.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest to disclose.

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