DR KENNETH ALEXIS MYERS (Orcid ID : 0000-0001-7831-4593)
PROFESSOR INGRID EILEEN SCHEFFER (Orcid ID : 0000-0002-2311-2174)

Article type : Original Article

[1 original article; 1 figure; 3 tables]

Stiripentol efficacy and safety in Dravet syndrome: a 12-year observational study

KENNETH A MYERS[1]
PAUL LIGHTFOOT[1]
SHEKHAR G PATIL[2]
J HELEN CROSS[3]
INGRID E SCHEFFER[1]

1 Epilepsy Research Centre, Department of Medicine, The University of Melbourne, Austin Health, Heidelberg, Victoria, Australia. **2** Apollo Paediatric Centre, Apollo Hospital, Navi Mumbai, India. **3** UCL Institute of Child Health & Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK.

Correspondence to Ingrid Scheffer, Epilepsy Research Centre, Level 2, Melbourne Brain Centre Austin Health, 245 Burgundy St, Heidelberg, VIC 3084 Australia. E-mail: scheffer@unimelb.edu.au

PUBLICATION DATA

Accepted for publication XXth Month 2018

Published online XXth Month 2018

AIM To assess long-term safety and efficacy of stiripentol as an antiepileptic medication for people with Dravet syndrome.

METHOD A prospective, observational open label study (2003–2015) of the efficacy and long-term safety of stiripentol in patients with Dravet syndrome and ongoing seizures. Frequency of generalized tonic-clonic seizures, focal seizures, status epilepticus, and adverse events were recorded.

RESULTS Forty-one patients started stiripentol, with median age at enrolment 5 years 7 months (range 11mo–22y) and median duration of treatment 37 months (range 2mo–141mo). Twenty out of 41 patients had greater than or equal to 50% long-term reduction in frequency of generalized tonic-clonic seizures. Frequency of focal seizures was decreased by greater than or equal to 50% in 11 out of 23 patients over the long-term. Frequency of status epilepticus was decreased by 50% or more in 11 out of 26 patients.

The most common adverse events were anorexia, weight loss, sedation, and behavioural changes. One patient had worsening of absence and myoclonic seizures. Another developed recurrent pancreatitis on concurrent valproate.

INTERPRETATION Stiripentol improves long-term seizure frequency in approximately 50% of patients with Dravet syndrome, when used as part of unrestricted polytherapy. Long-term use appears safe. In more than 40% of patients, episodes of status epilepticus markedly decrease after stiripentol initiation.

[First page footer]

(c) Mac Keith Press 2018

DOI: 10.1111/dmcn.xxxxx

[Left page footer]

Developmental Medicine & Child Neurology 2018: XX: 000–000

What this paper adds

- Frequency of status epilepticus is reduced in 40% of patients with Dravet syndrome after stiripentol initiation.
- Stiripentol is effective for generalized tonic-clonic and focal seizures.
- Stiripentol can be safely used with a range of antiepileptic drugs.

[main text]

Dravet syndrome is an infantile-onset developmental and epileptic encephalopathy characterized by febrile seizures beginning around 6 months, commonly including hemiclonic status epilepticus. Other seizure types develop later, including afebrile generalized tonic-clonic, focal impaired awareness, absence, and myoclonic seizures. Although development is initially normal, regression or plateau occurs, usually between 12 months and 24 months of age.[1] More than 80% of patients with Dravet syndrome have *SCN1A* mutations, almost all of which occur de novo.[2]

Individuals with Dravet syndrome often have monthly, or sometimes daily, seizures and frequent episodes of status epilepticus, often provoked by hyperthermia. Epilepsy is almost always refractory to medical therapy, with most patients having ongoing seizures despite two or three concurrent antiepileptic drugs. The medication with the best evidence for positive therapeutic effect is stiripentol.[3] This drug is thought to reduce seizure frequency by directly modulating GABA-A receptors[4]; however, stiripentol has also been shown to increase plasma concentrations of other co-administered antiepileptic drugs, including clobazam.[5]

We studied the longitudinal efficacy and safety of open label stiripentol in a cohort of patients with Dravet syndrome with regard to seizure frequency, episodes of status epilepticus, and adverse events.

METHOD

This prospective, open label observational study examined the long-term efficacy and safety of stiripentol in people with Dravet syndrome. All patients had a clinical diagnosis of Dravet

syndrome and were followed at a paediatric epilepsy clinic in Australia or the United Kingdom. Between 2003 and 2015, patients who had ongoing seizures were offered treatment with stiripentol. Dosage was gradually titrated up to 67mg/kg/day or a maximum of 4g per day, depending on seizure control and development of adverse events. If patients were concurrently taking clobazam or sodium valproate, the doses of these medications were kept below 0.5mg/kg/day and 30mg/kg/day respectively, whenever possible.

Participants were reviewed in clinic within 3 months of stiripentol initiation to assess initial therapeutic effect and ask about adverse events. Patients were reviewed regularly thereafter while on stiripentol therapy. Throughout the period of observation, frequency of focal seizures, generalized tonic-clonic seizures, status epilepticus, and adverse events were recorded. Screening blood work, including complete blood count and liver enzymes, was collected at least once during the first month of therapy and repeated every 6 months per recommended guidelines.[6] Data was added and accrued at consecutive clinic and ward visits.

For this study, the clinical data was reviewed based on each patient's most recent clinic visit. Percentage improvement in frequency of seizure types and status epilepticus was determined based on seizure diaries. In order to capture only those patients with ongoing frequent episodes of status epilepticus, we only included patients in the status epilepticus analysis if they had experienced at least one episode of status in the 3 months before stiripentol initiation. Patients were defined as responders if they had greater than or equal to 50% improvement in seizure frequency for a defined seizure type or status epilepticus.

The study was approved by the Human Research Ethics Committee of Austin Health (Project No. H2007/02961), and informed written consent was obtained from all Australian patients or their guardians. The United Kingdom data was collected in anonymized form as an audit, registered with the Great Ormond Street Hospital Research and Development Office.

RESULTS

Forty-one patients took stiripentol during the study period 2003 to 2015 (demographic data in Table I). All patients received at least two other antiepileptic medications during the study period. The most commonly co-administered agents were clobazam and valproate; however, 10 other antiepileptic medications were used during the study period (Table II).

Data regarding frequency of seizures and status epilepticus at 3 months and most recent follow-up are summarized in Table III. Adverse events are also documented. All but two of the 41 patients were still taking stiripentol at the 3-month timepoint (Fig. 1). The first patient who discontinued developed streptococcus-induced toxic shock syndrome 2.5 months after starting the medication; stiripentol was held during the severe illness and was not restarted after recovery as she became seizure-free. The toxic shock syndrome was not thought to be related to stiripentol. The second patient had a good clinical response to stiripentol for 1 month but seizures returned and the medication was discontinued 1 month later; he then suffered sudden unexplained death in epilepsy just before the 3-month point.

Median duration of treatment was 37 months (interquartile range 13.5mo–66mo, absolute range 2mo–141mo) with 29 out of 41 patients still on therapy at the time of most recent follow-up (Fig. 1). Of the remaining 12 patients, ten discontinued stiripentol because of adverse events and/or lack of efficacy after median treatment duration 7 months (interquartile range 3mo–12mo, absolute range 2mo–81mo). Three patients died, two with sudden unexplained death in epilepsy (patients #12 and #14 in Cooper et al.),[7] and another from cerebral oedema after convulsive status epilepticus (patient #3 in Myers et al.[8] and #13 in Cooper et al.).[7] This includes the patient mentioned in the previous paragraph, who died weeks after discontinuing stiripentol but was still considered to be involved in the study.

With respect to generalized tonic-clonic seizures, 23 out of 41 patients were responders with greater than or equal to 50% reduction in seizure frequency at 3 months. At the point of final data collection, 12 of these 23 patients remained responders, and an additional eight were now classified as responders, resulting in 20 out of 41 being long-term responders. One patient was seizure-free and a second had been seizure-free for 18 months before suffering status epilepticus and subsequent fatal cerebral oedema (previously mentioned).

Of the 20 patients with focal seizures, 11 had greater than or equal to 50% seizure frequency reduction at 3 months. Four of these failed to maintain long-term control, but four more came under late control, such that 11 out of 20 were classified as long-term responders.

Of the 27 patients with status epilepticus in the 3 months before commencing stiripentol (age at initiation of stiripentol: 0.9y–22.3y), 11 had greater than or equal to 50% reduction in frequency of status epilepticus. Of these, nine had at least 90% reduction in status events, with seven having no further status epilepticus after initiation of stiripentol.

With respect to adverse events, 30 out of 41 patients had reported adverse events after starting stiripentol (Table III). The most common were anorexia, weight loss, drowsiness, sedation, and behavioural changes. One patient reported transient worsening of absence seizures and myoclonus with dose increases, but stayed on the medication because of a beneficial effect on generalized tonic-clonic seizures. One patient developed hypoalbuminemia with limb oedema at 22 years of age (8 years after starting stiripentol) because of a protein-losing enteropathy of unknown cause (endoscopy and intestinal biopsies were normal).

One patient developed recurrent pancreatitis, having at least 10 episodes over a 2-year period. The episodes involved abdominal pain and vomiting, with serum lipase rising as high as 7000 units per litre and returning to normal between attacks. The patient had been taking valproate since the age of 8 months but did not have the first episode of pancreatitis until 3 years of age, 2 months after initiation of stiripentol. Valproate levels were therapeutic throughout the period of recurrent pancreatitis (542–677μmol/L; reference range 350–700). A magnetic resonance cholangiopancreatography scan was normal and there was no other apparent cause for the recurrent pancreatitis. Stiripentol was first weaned; however, the patient had an additional episode of pancreatitis. Stiripentol was then restarted, and valproate weaned, after which there were no further episodes of pancreatitis, implicating valproate in its causation.

DISCUSSION

The best evidence for the use of stiripentol in Dravet syndrome comes from two randomized controlled European trials, which included a total of 41 patients in one study and 11 in the other who received stiripentol.[9,10] These studies used a relatively short double-blind treatment period of 2 months (though Chiron et al. had a median open label follow-up period of 25mo),[9] and employed stiripentol as add-on medication to patients already on valproate and clobazam (no other concomitant medications were allowed). This triple therapy protocol was also employed in retrospective open label and cross-sectional European studies.[11,12] The only long-term prospective open label trial in which stiripentol was used for up to 56 weeks also allowed concomitant bromide in addition to the required valproate and clobazam.[13] The only data on stiripentol efficacy when not used in combination with valproate and clobazam comes from a retrospective multicentre survey conducted in the United States, where stiripentol is not currently approved and must be obtained through special access.[14] We present an open label, prospective,

long-term study of stiripentol safety and efficacy in 41 patients with Dravet syndrome. Stiripentol was added in an unrestricted manner to the patients' baseline antiepileptic medications, reflecting routine clinical practice.

Stiripentol maintained a greater than or equal to 50% reduction in generalized tonic-clonic and focal seizures in 49% and 55% of patients long-term respectively. Our responder rates are less than the short-term responder rates reported of 67% to 71%,[15,10,9] but similar to the long-term responder rate of 54% reported by Inoue and Ohtsuka,[13] reflecting the honeymoon period often seen in refractory epilepsies. In Wirrell et al.'s retrospective USA study,[14] they defined the change in seizure frequency differently, reporting 68 out of 103 (66%) of patients having 'mild or marked reduction' in seizure frequency overall, with variable periods of follow-up. Our responder rate would not have captured patients with a mild reduction in seizure frequency.

One of the most frightening issues for families facing Dravet syndrome is the risk of status epilepticus which can be fatal.[8] The incidence of status epilepticus in this cohort was clearly decreased in 41% of those for whom we could reasonably assess a change as they had experienced status epilepticus in the 3 months before stiripentol initiation. Unfortunately, changes in the frequency of status epilepticus are difficult to assess, even with long-term studies, since the frequency varies considerably in and between patients with Dravet syndrome. There is, however, a growing body of evidence supporting the efficacy of stiripentol in status epilepticus.[14,11] Experimental evidence for this has been shown in vitro with the demonstration that stiripentol has ongoing GABA-A modulation during prolonged seizures when the modulatory effects of diazepam are no longer present.[16]

Anorexia and weight loss were the most common adverse events with stiripentol, occurring in 49% of patients. Somnolence and sedation were the second most frequent group, occurring in 34% of individuals, and may be partially related to potentiation of concurrently administered clobazam or valproate. Although rare, recurrent pancreatitis can be associated with stiripentol therapy when added to valproate, thus clinicians should consider this previously undescribed adverse event and adjust management accordingly if it occurs by weaning valproate if possible.

We note that our methodology allowed for adjustments of other antiepileptic medications during the period of stiripentol treatment. Such adjustments could have affected both seizure

control and occurrence of adverse events, a point which should be considered when evaluating our data.

In summary, this study demonstrates that stiripentol is an effective antiepileptic medication in Dravet syndrome, when used as part of unrestricted polytherapy. Roughly half of patients can be expected to have at least 50% reduction in frequency of both generalized tonic-clonic and focal seizures long term. Most notable was that some patients have a dramatic improvement in frequency of status epilepticus, so we advocate earlier institution of stiripentol in an infant or child experiencing frequent episodes of life-threatening status epilepticus.

ACKNOWLEDGEMENTS

This study was supported by funding from an Australian National Health and Medical Research Council (NHMRC) Program Grants (628952, 1091593). IES has a NHMRC Practitioner Fellowship (1104831). KAM holds a Taking Flight Award from Citizens United for Research in Epilepsy (CURE; grant number 439534). JHC is supported by the National Institute for Health and Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London and is a NIHR Senior Investigator. None of the funders had any role in study design, data collection, data analysis, manuscript preparation, or publication decisions. The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

REFERENCES

1. Dravet C. The core Dravet syndrome phenotype. *Epilepsia* 2011; **52**(Suppl. 2): 3–9.

2. De Jonghe P. Molecular genetics of Dravet syndrome. *Dev Med Child Neurol* 2011; **53**(Suppl. 2): 7–10.

3. Brigo F, Storti M. Antiepileptic drugs for the treatment of severe myoclonic epilepsy in infancy. *Cochrane Database Syst Rev* 2013; **11**: CD010483.

4. Quilichini PP, Chiron C, Ben-Ari Y, Gozlan H. Stiripentol, a putative antiepileptic drug, enhances the duration of opening of GABA-A receptor channels. *Epilepsia* 2006; **47**: 704–16.

5. Chiron C. Stiripentol. *Expert Opin Investig Drugs* 2005; **14**: 905–11.

6. Lexicomp Online, Pediatric & Neonatal Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc.; (accessed 27 November 2017).

7. Cooper MS, McIntosh A, Crompton DE, et al. Mortality in Dravet syndrome. *Epilepsy Res* 2016; **128**: 43–7.
8. Myers KA, McMahon JM, Mandelstam SA, et al. Fatal cerebral edema with status epilepticus in children with Dravet syndrome: report of 5 cases. *Pediatrics* 2017; **139**: e20161933.
9. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet* 2000; **356**: 1638–42.
10. Guerrini R, Tonnelier S, d'Athis P, Rey E, Vincent J, Pons G. Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial. *Epilepsia* 2002; **43**: 155.
11. Thanh TN, Chiron C, Dellatolas G, et al. [Long-term efficacy and tolerance of stiripentol in severe myoclonic epilepsy of infancy (Dravet's syndrome)] (Article in French). *Arch Pediatr* 2002; **9**: 1120–7.
12. De Liso P, Chemaly N, Laschet J, et al. Patients with Dravet syndrome in the era of stiripentol: a French cohort cross-sectional study. *Epilepsy Res* 2016; **125**: 42–6.
13. Inoue Y, Ohtsuka Y; STP-1 Study Group. Long-term safety and efficacy of stiripentol for the treatment of Dravet syndrome: a multicenter, open-label study in Japan. *Epilepsy Res* 2015; **113**: 90–7.
14. Wirrell EC, Laux L, Franz DN, et al. Stiripentol in Dravet syndrome: results of a retrospective U.S. study. *Epilepsia* 2013; **54**: 1595–604.
15. Inoue Y, Ohtsuka Y; STP-1 Study Group. Effectiveness of add-on stiripentol to clobazam and valproate in Japanese patients with Dravet syndrome: additional supportive evidence. *Epilepsy Res* 2014; **108**: 725–31.
16. Grosenbaugh DK, Mott DD. Stiripentol is anticonvulsant by potentiating GABAergic transmission in a model of benzodiazepine-refractory status epilepticus. *Neuropharmacology* 2013; **67**: 136–43.

Figure 1: Outcomes of patients initiated on stiripentol treatment. [a]One patient discontinued stiripentol approximately 2 months after initiation and suffered sudden unexplained death in epilepsy before the 3-month timepoint. STP, stiripentol.

Table I: Characteristics of patients

Variable	
Male (%)	23/41 (56)
Median age at stiripentol initiation (interquartile range; absolute range)	5y 7mo (4y–9y 7mo; 8mo–22y)
SCN1A mutation present (%)	39/41 (95)
Median duration of stiripentol therapy (interquartile range; absolute range)	37mo (13.5mo–66mo; 2mo–141mo)
Mean number of co-administered antiepileptic drugs during stiripentol therapy (range)	2.8 (2–5)

Table II: Medications received in conjunction with stiripentol

Medication	**Number of patients receiving (%)**
Clobazam	33 (80)
Valproate	29 (71)
Topiramate	25 (61)
Levetiracetam	7 (17)
Clonazepam	6 (15)
Ethosuximide	3 (7)
Lamotrigine	3 (7)
Phenobarbital	2 (5)

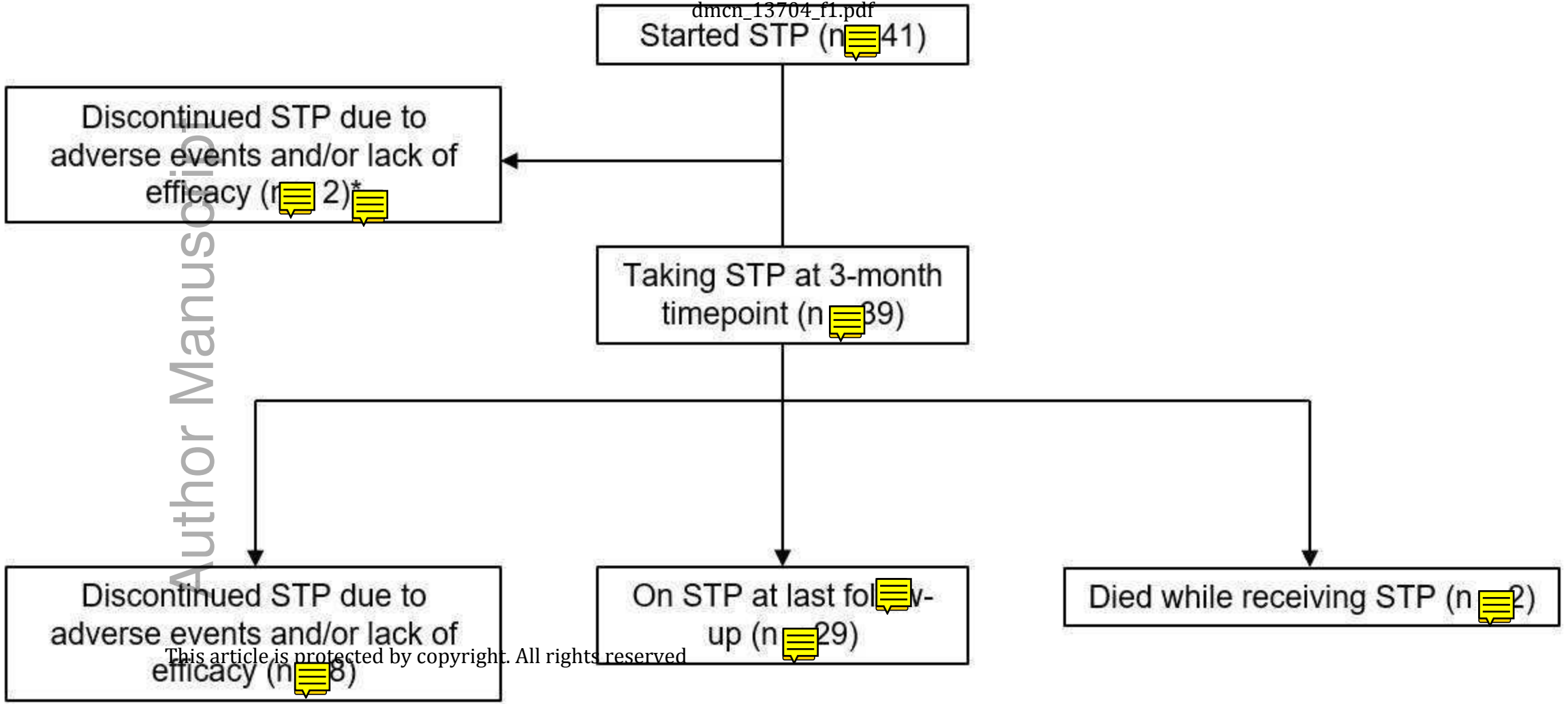
Phenytoin	2 (5)
Acetazolamide	1 (2)
Lacosamide	1 (2)
Piracetam	1 (2)

Table III: Clinical response to stiripentol

Outcome	
3 months – number still taking stiripentol (%)	39/41 (95)
3 months – ≥50% reduction in generalized tonic-clonic seizures (%)	23/41 (56)
3 months – ≥50% reduction in focal seizures (%)	11/20 (55)
Last follow-up – ≥50% reduction in generalized tonic-clonic seizures (%)	20/41 (49)
Last follow-up – ≥50% reduction in focal seizures (%)	11/20 (55)
Last follow-up – ≥50% reduction in status epilepticus (%)	11/27 (41)
AE – Anorexia/weight loss (%)	20 (49)
AE – Drowsiness/sedation (%)	14 (34)
AE – Behavioural change (%)	9 (22)
AE – Neutropenia (%)	5 (12)
AE – Abdominal pain (%)	4 (10)
AE – Insomnia (%)	4 (10)
AE – Ataxia/unsteadiness (%)	3 (7)
AE – Drooling (%)	3 (7)
AE – Tremor/myoclonus (%)	3 (7)
AE – Vomiting (%)	2 (5)
AE – Absence seizure increase (%)	1 (2)
AE – GGT elevation (%)	1 (2)
AE – Hypoalbuminemia and oedema (%)	1 (2)

AE – Nightmares (%)	1 (2)
AE – Recurrent pancreatitis (%)	1 (2)
AE – Streptococcus-induced toxic shock syndrome (%)	1 (2)

AE, adverse event; GGT, gamma-glutamyl transferase.



Author/s:
Myers, KA; Lightfoot, P; Patil, SG; Cross, JH; Scheffer, IE

Title:
Stiripentol efficacy and safety in Dravet syndrome: a 12-year observational study

Date:
2018-06-01

Citation:
Myers, K. A., Lightfoot, P., Patil, S. G., Cross, J. H. & Scheffer, I. E. (2018). Stiripentol efficacy and safety in Dravet syndrome: a 12-year observational study. DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY, 60 (6), pp.574-+. https://doi.org/10.1111/dmcn.13704.