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Research Paper

Stiripentol for Drug-Resistant Epilepsy Treatment in Tuberous Sclerosis Complex

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ABSTRACT

Background: Drug-resistant epilepsy (DRE) is common in tuberous sclerosis complex (TSC). The role of stiripentol (STP) in seizure treatment in this population is not well understood. This study evaluates the efficacy and tolerability of STP in patients with TSC with DRE.
Methods: We performed a retrospective review of patients with TSC with DRE. Seizure frequencies at 1 month before (baseline) and 1, 3, 6, and 12 months after STP initiation were collected.
Results: Of the 1492 patients, 13 received STP and the number of patients with ≥50% seizure reduction at 1, 3, 6, and 12 months was 6/13 (46.2%), 4/13 (30.8%), 8/13 (61.5%), and 6/13 (46.2%), respectively. Six patients (46.2%) had favorable outcomes with persistent seizure reduction through 12 months. Their mean (±S.D.) percentage of seizure reduction at 1, 3, 6, and 12 months was 68.1 (±22.0), 71.3 (±23.2), 75.7 (±23.5), and 75.7 (±23.5), respectively. One patient had worsening seizures throughout the STP course. Three patients did not have seizure reduction until after 6 months, and 2 had initial seizure reduction before worsening. Younger age (P value <0.001), early STP treatment (P value <0.001), higher doses (P value = 0.004), and higher baseline seizure frequency (P value = 0.01) were associated with favorable outcomes. Side effects were seen in 85% of our cohort.
Conclusions: About 46% of the patients had favorable outcomes. Younger age, early STP treatment, higher doses, and higher baseline seizure frequency were significantly associated with favorable outcomes.

Introduction

Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant disorder estimated to affect about 2 million people worldwide.[1] The condition is caused by inactivating mutations in TSC1 or TSC2. About 70% to 80% of patients with TSC have epilepsy, and their seizures are often refractory to antiseizure medications.[2]

Stiripentol has a unique structure and several antiseizure mechanisms. First, it enhances GABAergic neurotransmission by selectively modulating GABAA receptor subunits, and the effect is most substantial at the α3 subunit, which is highly expressed in the developing brain.[3,4] This subunit selectivity may explain the greater efficacy of STP in childhood-onset epilepsies compared to adults. For this reason, we hypothesize that STP can benefit patients with TSC who commonly develop early-onset epilepsy, and the efficacy is higher in younger patients. Furthermore, STP may be efficacious in benzodiazepine-resistant patients by enhancing the activity of δ-containing GABAA receptors, which are insensitive to the benzodiazepine class of antiseizure medications.[5] Moreover, STP also exhibits an anticonvulsant effect by inhibiting lactate dehydrogenase, leading to neuronal hyperpolarization.[3,6,7] Studies in rodent models have shown the neuroprotective effects of STP by reducing cell injury in the hippocampal CA1 region.[8-10] In addition, the pharmacokinetic effects of STP resulting in increased serum levels of other antiseizure medications contribute to enhanced seizure control.

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The FDA (Food and Drug Administration) approved stiripentol (STP) for treating seizures associated with Dravet syndrome in 2018. Evidence of STP efficacy is most robust for Dravet syndrome but limited in TSC. Its benefits in reduction of seizure frequency and duration, frequency of status epilepticus, rescue medication use, and the number of emergency room visits were notable in patients with Dravet syndrome.[11-13] Limited data suggest that STP may have an additional role in treating status epilepticus, malignant migrating partial seizures in infancy, super-refractory status epilepticus, and intractable focal epilepsy.[14-18]

Only a few studies have reviewed the role of STP in seizure treatment, specifically in patients with TSC. Therefore, its use in this population remains poorly understood. This study aims to assess the efficacy and tolerability of the adjunctive use of STP in patients with TSC with drug-resistant epilepsy (DRE). Moreover, we evaluated factors affecting the treatment outcomes.

Methodology

A retrospective review of patients with TSC at Cincinnati Children's Hospital Medical Center, USA, identified all patients treated with STP from January 2011 until July 2021. This study was approved by the local IRB. DRE was defined as the failure of adequate trials of two tolerated and appropriately chosen and used antiseizure medications to achieve sustained seizure freedom.[19] Seizure frequency was reviewed 1 month before STP initiation (considered the baseline) and 1, 3, 6, and 12 months post-STP initiation. When a seizure frequency was unavailable at any of these specific time points, we used a seizure frequency from the closest time within a two-week window before or after the date. When there was unclear documentation of seizure frequency, we used available information from telephone calls and clinic visits to resolve the discrepancies. A mean was calculated when seizure frequency was documented in range. Seizure frequency was based on the parental report at clinic visits and telephone calls and comprised all seizure types.

For treatment efficacy assessment, first, we evaluated seizure responder rate and defined seizure response as a $\geq$50% seizure reduction compared with baseline. Furthermore, we assessed the sustainability of the response by classifying the seizure control outcomes into 2 categories. A favorable outcome was defined as sustained reduced seizure frequency from 1-month through 12-month follow-up. An unfavorable outcome was defined as nonpersistent seizure reduction during the follow-up, seizure reduction that starts after 6 months of STP initiation, or worsening in seizure frequency. We collected information on age, gender, age at seizure onset, age at STP initiation, duration of epilepsy before STP treatment, STP therapy duration, dose, side effects, concomitant and prior antiseizure medications, mammalian target of rapamycin (mTOR) inhibitor use, and other treatments for seizures, as well as seizure types. When the medical record did not clearly state seizure types, we classified them using the seizure description documented in the chart. For drop seizures, we attempted to clarify the actual seizure type (such as myoclonic, brief tonic, and atonic seizure) as much as the available information allowed. When we could not provide further classification, they remained categorized as drop seizures.

Statistical methods

We reported descriptive statistics as absolute numbers with percentages, median with 25th and 75th percentiles (interquartile range [IQR]), or means ± standard deviations (±S.D.). We calculated the percentage change in seizure frequency compared with baseline for each patient at the specified follow-up time points. Next, we compared the variables' mean (±S.D.) between the favorable versus unfavorable outcome groups using the Student *t* test. The Wilcoxon rank-sum was also examined, and it agreed with the *t* test. The Spearman correlation analysis was used to evaluate the correlation between variables and seizure control outcomes. The Pearson analysis was examined, and it agreed with the Spearman analysis; therefore we only presented the Spearman analysis results. Moreover, we used univariable logistic regression to study the effect of continuous-type variables on outcomes. Last, we used Fisher exact test to analyze the independence of nominal variables and outcomes.

Results

Participants

Of the 1492 patients with TSC identified, 13 (10 males) aged 3.8 to 40 years (median 15.2, IQR, 6.7 to 22.0) received STP. Among the patients who had genetic testing, TSC1 and TSC2 gene mutations were identified in 2 and 9 patients, respectively. Two families declined genetic testing. The median age of seizure onset was 3 months, and the baseline seizure frequency/month was 75 (IQR 30.3 to 303.0), combining all seizure types.

Stiripentol was started after a median of 13.5 years (IQR 5.0 to 20.3) following seizure onset, and the median treatment duration was 12.8 months (IQR 9.6 to 16.4) at the time of this study. The median STP dose was 21.1 mg/kg/day (IQR 12.8 to 34.1) and 750 mg/day (range 500 to 2250 mg/day; Table 1).

The median numbers of concurrent and past antiseizure medications were 3 and 8, respectively. Three patients took valproate, and none were on clobazam or oxcarbazepine at the time of STP therapy. Six patients were on everolimus, 4 on sirolimus, and 2 had used and discontinued both. We did not collect the levels of antiseizure medication or mTOR inhibitor as they were not systematically measured as part of the clinical care routine. None of the patients was on dietary therapy at the time of STP treatment, although 4 (30.7%) had unsuccessful trials of a ketogenic diet in the past. Five patients (38.5%) had a vagus nerve stimulator (VNS), and the placement was 6 to 7 years before STP treatment, except for one whose VNS placement occurred 1 month before STP started (patient 6). Six patients (46.2%) had undergone resective epilepsy surgery 5 to 10 years before STP. However, three patients underwent resective epilepsy surgery while on STP (patients 4, 9, and 11; Tables 1 and 2).

Seven patients were diagnosed with infantile spasms at an early age, and three had a history of status epilepticus. Most patients (9 of 13, 69.2%) had more than one current seizure semiology. Eleven patients (84.6%) had focal seizures with impaired awareness, 1 (7.7%) had focal seizures without awareness impairment, 7 (53.8%) had generalized tonic-clonic seizures, 2 (15.4%) had generalized tonic seizures, 3 (23.1%) had drop seizures, and 3 (23.1%) reported mycolic seizures. Four patients (30.8%) reported a single seizure semiology: 2 had focal seizures with impaired awareness and 2 had drop seizures (Table 2).

Retention and responder rate

Every patient continued STP at 1 and 3 months of treatment. However, only 11 (84.6%) and 8 patients (61.5%) remained on STP at 6 and 12 months, respectively. Of the 13 patients included, the number of patients with $\geq$50% seizure reduction at 1, 3, 6, and 12 months after STP initiation was 6 (46.2%), 4 (30.8%), 8 (61.5%), and 6 (46.2%), respectively (Fig 1).

TABLE 1.
Demographic and Clinical Information

Variable	Number
Male (%)	10 (76.9%)
Baseline median seizure frequency/month (IQR)	75 (30.0-303.0)
Median age (IQR)	15.2 years (6.7-22.0)
Median age at seizure onset (IQR)	3 months (3-4)
Median age at STP initiation (IQR)	13.7 years (5.4-20.5)
Median epilepsy duration before STP initiation (IQR)	13.5 years (5.0-20.3)
Median duration of STP therapy (IQR)	12.8 months (9.6-16.4)
Median dose of STP (IQR)	21.1 mg/kg/day (12.8- 34.1)
Median number of concurrent antiseizure medications (IQR)*	3 (2-3)
Median number of antiseizure medications before STP (IQR)*	8 (6-9)
Number of patients with concurrent valproic acid use	3
Number of patients with concurrent clobazam use	0
Number of patients with concurrent oxcarbazepine use	0
Number of patients treated with mTOR inhibitor	10 (6 EVE, 4 SIR)
Number of patients treated with dietary therapy	4 (30.7%)
Number of patients with a vagus nerve stimulator	5 (38.5%)
Number of patients received resective epilepsy surgery	6 (46.2%)

Abbreviations:
EVE = Everolimus
IQR = Interquartile range
mTOR = Mammalian target of rapamycin
SIR = Sirolimus
STP = Stiripentol
* Excluding mTOR inhibitor.

Short- and long-term efficacy

The percentages of seizure frequency change during 1 to 12 months of STP therapy compared with baseline are presented in Fig 2. Six patients (46.2%) had favorable outcomes with persistent seizure reduction from 1 through 12 months. Their mean (±S.D.) percentage of seizure reduction at 1, 3, 6, and 12 months was 68.1 (±22.0), 71.3 (±23.2), 75.7 (±23.5), and 75.7 (±23.5), respectively. Furthermore, 2 patients (patients 4 and 9) in this group whose seizure reduction began within a month after STP initiation and maintained throughout the follow-up later underwent resective epilepsy surgery and became seizure free after the surgery. In addition, patient 6 received VNS placement 1 month before STP initiation and had a favorable outcome during this study.

Seven patients had unfavorable outcomes. One patient (patient 13) reported worsening seizure frequency throughout the STP treatment course. Three patients did not have seizure reduction until after 6 months of STP (patients 3, 7, 10, and 11), and one of them underwent resective epilepsy surgery 5 months into STP treatment. Two patients had initial seizure reduction before returning to baseline or worsened (patients 2 and 8).

Comparison of variables between favorable and unfavorable outcome groups

Patients with favorable outcomes were significantly younger than those with unfavorable outcomes. The mean age difference was −17.24 ± 6.89 years (P value = 0.001); they were younger at the time of STP initiation (mean difference −17.36 ± 6.98, P value = 0.001) and had shorter duration of epilepsy before STP treatment (mean difference −17.26 ± 7.02 years, P value = 0.001). In addition, they received higher dose of STP (mean difference 20.19 ± 9.96 mg/kg/day, P value = 0.005) and remained on STP for longer duration (mean difference 7.05 ± 5.02 months, P value = 0.026). Furthermore, patients with favorable outcomes also had higher baseline seizure frequency per month (mean difference 212.57 ± 149.40, P value = 0.043; Table 3). We did not find any significant differences in seizure type, status epilepticus or infantile spasms history, VNS, dietary therapy, or respective epilepsy surgery between the two outcome groups.

Correlation of variables and seizure outcomes

We found that age, age of STP initiation, and duration of epilepsy before STP treatment significantly correlated with treatment outcomes (r_s 0.87, P value <0.001). In addition, STP dose by mg/kg/day ($r_s = -0.74$, P value = 0.004), STP treatment duration ($r_s = -0.66$, P value = 0.01), and baseline seizure frequency significantly correlated with treatment outcomes ($r_s = -0.68$, P value = 0.01; Table 4). Age of seizure onset, the total daily dose of STP (mg/day), and the number of concurrent and past antiseizure medications did not statistically correlate with the outcomes.

Predictive factors of seizure control outcomes

Individual univariable logistic regression models were conducted where the probability of a favorable outcome was the dichotomous response. These results showed that STP dose (mg/kg/day) was the only statistically significant factor associated with a favorable outcome (odds ratio, 1.21; P value = 0.05; 95% CI, 1, 1.45; Table 5). For each 1-mg/kg/day increment of STP dose, the odds of a favorable outcome increased by 21%.

Effects of comedication

We did not find any statistically significant correlation between comedication and seizure outcomes. None of the patients took clobazam or carbamazepine with STP. Three patients took valproate with STP, two had initial seizure reduction before returning to baseline, and one did not have seizure reduction until after 6 months of treatment. There was also no significant correlation between the response patterns and cenobamate, sirolimus, or everolimus.

Side effects

All but 2 patients reported side effects while taking STP. Aggression and agitation were the most common and reported in 8 patients (61.5%), followed by poor sleep (4 patients, 30.8%), drowsiness (3 patients, 23.1%), tremor (2 patients, 15.4%), increased appetite (1 patient, 7.7%), decreased appetite (1 patient, 7.7%), and flat affect (1 patient, 7.7%). Despite improvement in seizure control, the aggression was severe and resulted in STP discontinuation in 3 patients (patients 7, 9, and 11; Table 2).

Discussion

This study describes the efficacy and tolerability of STP for treating DRE in patients with TSC. The percentage of patients with ≥50% seizure reduction at 1, 3, 6, and 12 months after STP initiation was 46.2%, 30.8%, 61.5%, and 46.2%, respectively. Our study's short-term responder rate is comparable to a previous study reporting 5 of 12 (41.7%) patients with TSC with seizure reduction at 3 months of STP treatment.[18] Unfortunately, the study did not provide long-term outcomes for their patients with TSC. However, our rate is lower when compared with Dravet syndrome population. Chiron et al. showed a 71% responder rate in a 2 month prospective

TABLE 2.
Detailed Patient Data

ID	Favorable Outcome	Age (Years)	Age of Seizure Onset (Months)	Epilepsy Duration Before STP (Years)	Duration of STP Therapy (Months)	STP Dose (mg/kg/day)	Concurrent ASM*	TSC Gene Mutation	Seizure Semiology	KD	VNS	Epilepsy Surgery	Side Effects
P01	N	40.0	3	38.5	8.6†	9.5	CBD, CBM, ZNM, SIR	TSC2	FIA, M	N	N	N	Agitation, drowsiness, poor sleep, increased appetite
P02	Y	14.9	4	13.3	14.4	27.8	CBD, CBM, TPM, SIR	TSC2	D, IS, SE	N	N	Y (left ATLAH and left occipital corticectomy)	Drowsiness
P03	N	15.2	3	13.5	3.7	15.6	BRV, CBD, CBM, LTG, EVE	TSC2	FIA, GTC, IS	N	Y	Y (left frontal lobectomy)	None
P04	Y	4.3	1	2.9	16.2†	21.1	BRV, CLB, PNT, VGB, SIR	TSC2	FIA, D, IS, SE	N	N	Y (right frontal tuber resection and subsequent laser ablation)	Aggression, poor sleep
P05	Y	5.5	2	3.6	21.5†	48.4	CBD, TPM, EVE	TSC1	FIA, GTC, M, IS	Y	N	N	Aggression, poor sleep
P06	Y	8.2	3	6.4	19.9†	30.4	CBM, GPN, RFM	TSC2	FIA, IS	Y	Y	Y (left central tuber resection)	None
P07	N	31.8	3	30.1	9.6	12.8	CBM, VPA, SIR	TSC2	FIA, GTC, GT	N	N	N	Aggression
P08	N	22.0	3	20.3	12.6	9.4	CBD, CBM, LZP, VPA, EVE	TSC2	D	Y	Y	N	Agitation, drowsiness, tremor, decreased appetite
P09	Y	3.8	10	1.5	12.8†	46.0	AZM, LCS	TSC1	FIA, GTC	N	N	Y (right perirolandic tuber resection)	Aggression
P10	N	23.6	16	21.5	9.6†	17.5	CBD, CBM, ECP, EVE	Declined testing	FIA, GTC	N	Y	N	Flat affect, tremor
P11	N	18.9	4	17.1	3.2	6.1	TPM, VPA	Declined testing	FA, FIA, GTC, SE, IS	N	N	Y (left medial parietal tuber laser ablation)	Agitation, aggression
P12	Y	6.7	4	5.0	16.4†	37.5	CBD, EVE	TSC2	FIA, M, IS	N	N	N	Agitation
P13	N	20.0	4	17.9	21.4†	34.1	CBM, LCS, EVE	TSC2	FIA, GTC, GT	Y	Y	N	Poor sleep

Abbreviations:
ASM = Antiseizure medication
ATLAH = Amygdalohippocampectomy
AZM = Acetazolamide
BRV = Brivaracetam
CBD = Cannabidiol
CBM = Cenobamate
CLB = Clobazam
D = Drop seizure
ECP = Eslicarbazepine
EVE = Everolimus
FA = Focal seizure without impaired awareness
FIA = Focal seizure with impaired awareness
GPN = Gabapentin
GT = Generalized tonic seizure
GTC = Generalized tonic-clonic seizure
IS = History of infantile spasm
KD = Ketogenic diet
LCS = Lacosamide
LTG = Lamotrigine
LZP = Lorazepam
M = Myoclonic seizure
mTOR = Mammalian target of rapamycin
N = No
PNT = Phenytoin
RFM = Rufinamide
SE = History of status epilepticus
SIR = Sirolimus
STP = Stiripentol
TPM = Topiramate
TSC = Tuberous sclerosis complex
VGB = Vigabatrin
VNS = Vagus nerve stimulator
VPA = Valproate
Y = Yes
ZNM = Zonisamide
* Including mTOR inhibitor.
† Continuing on STP at the time of this study.

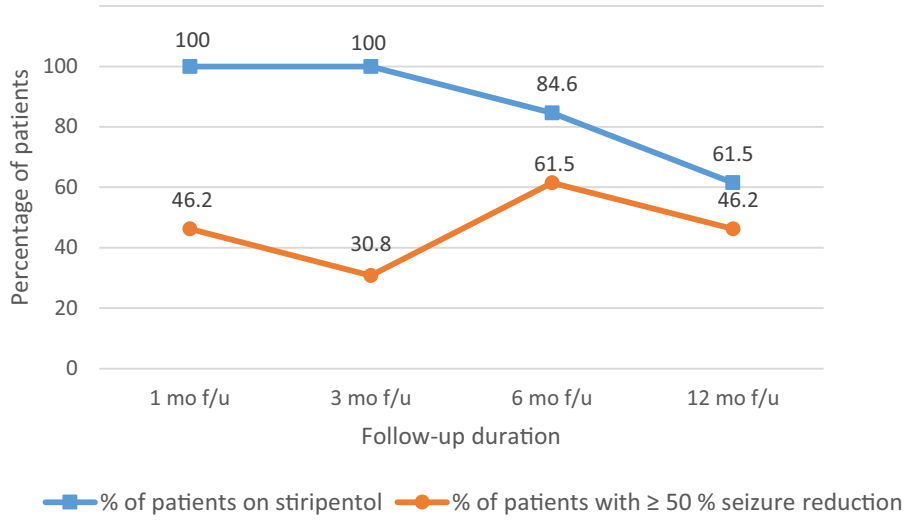

FIGURE 1. Retention and responder rates. All patients continued stiripentol at 1 and 3 months after stiripentol initiation. At 6 and 12 months, 84.6% and 61.5% of the patients remained on the treatment, respectively. The percentage of patients with ≥50% seizure reduction at 1, 3, 6, and 12 months after stiripentol initiation was 46.2%, 30.8%, 61.5%, and 46.2%, respectively. The color version of this figure is available in the online edition.

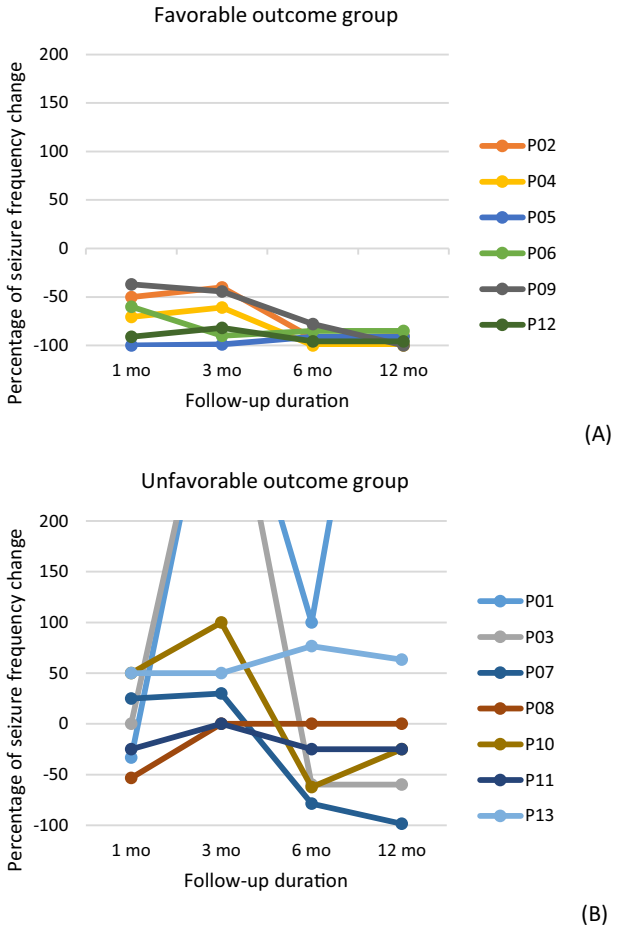

FIGURE 2. Percentage of seizure frequency change of each patient during stiripentol therapy. (A) Six patients (46.2%) had favorable outcomes with persistent seizure reduction from 1 through 12 months. Their mean (±S.D.) percentage of seizure reduction at 1, 3, 6, and 12 months was 68.1 (±22.0), 71.3 (±23.2), 75.7 (±23.5), and 75.7 (±23.5), respectively. (B) Seven patients had unfavorable outcomes characterized as nonpersistent seizure reduction, seizure reduction that starts after 6 months of stiripentol initiation, or worsening in seizure frequency. The color version of this figure is available in the online edition.

double-blind control study in 21 patients with Dravet syndrome compared with 20 controls.[11] A retrospective study in Dravet syndrome showed overall seizure reduction in 33% to 80% of patients across different groups of antiseizure medication combinations, including STP.[13] Furthermore, a study in a heterogeneous group of children with epilepsy reported long-term efficacy of 75% in their cohort.[18] We believe there are several contributing factors to the lower responder rates in our study compared with others, as discussed later.

Furthermore, we assessed the sustainability of the seizure control and classified a sustained seizure reduction from 1 through 12 months of STP treatment as a favorable outcome. Six patients (46.2%) had a favorable outcome, and their mean (±S.D.) percentage of seizure reduction at 1, 3, 6, and 12 months was 68.1 (±22.0), 71.3 (±23.2), 75.7 (±23.5), and 75.7 (±23.5), respectively. Although STP efficacy studies commonly reported percentages of responders, there is limited evidence of the long-term rate of seizure reduction. For short-term outcome comparison, the percentage of seizure reduction in our cohort is comparable to the 69% reported at 2 months of STP treatment in patients with Dravet syndrome.[11] Besides, we described 2 patients (15.4%) with seizure reduction from the beginning who eventually became seizure free after resective epilepsy surgery. Previous studies reported a seizure freedom rate of 10% and 43% in studies in children with epilepsy and patients with Dravet syndrome, respectively.[11,18] The studies did not provide data on concomitant surgical treatments during STP treatment. Moreover, we observed initial seizure reduction with subsequent efficacy loss in 2 patients (15.4%) and worsening seizures from the beginning of STP treatment in 1 patient (7.7%). Comparable rates were reported in a large heterogeneous cohort of childhood epilepsy and a Dravet syndrome-specific cohort.[13,18]

We found several factors supporting our hypotheses of the differential outcomes in our population. First, we believe that the seizure control effect of STP is age dependent. We found that patients with favorable outcomes were significantly younger than those without and had a mean age of STP initiation of 5.78 (±4.16) years, whereas those with unfavorable outcomes had a mean age of 23.14 (±8.66) years (P value = 0.001). We also showed that patient's age and age of STP initiation significantly correlated with treatment outcomes (P value <0.001). Compared with studies with higher responder rates, our cohort started STP at an older median age (13.7

TABLE 3.
The Comparison of Variables' Means ± S.D. Between the Favorable Versus Unfavorable Outcome Groups

Variable	Favorable Outcome Group		Unfavorable Outcome Group		Difference Between Groups		*t* Test
	Mean	S.D.	Mean	S.D.	Mean	S.D.	*P* Value
Age (years)	7.25	4.07	24.49	8.55	−17.24	6.89	0.001*
Age of seizure onset (months)	4	3.16	5.14	4.81	−1.14	4.14	0.619
Age of STP initiation (years)	5.78	4.16	23.14	8.66	−17.36	6.98	0.001*
Duration of epilepsy before STP treatment (years)	5.44	4.21	22.71	8.69	−17.26	7.02	0.001*
STP treatment duration (months)	16.87	3.28	9.82	6.1	7.05	5.02	0.026*
STP total daily dose (mg/day)	916.67	376.39	1142.86	556.35	−226.19	482.93	0.404
STP dose (mg/kg/day)	35.19	10.72	15	9.29	20.19	9.96	0.005*
Baseline seizure frequency (per month)	286	190.79	73.43	102.90	212.57	149.40	0.043*
Number of concurrent ASM	2.50	1.05	2.86	0.90	−0.36	0.97	0.528
Number of past ASM	6.83	3.31	9.43	2.99	−2.60	3.14	0.171

Abbreviations:
ASM = Antiseizure medication
STP = Stiripentol
* *P* value <0.05 was considered statistically significant. Patients with favorable outcomes were significantly younger, had shorter epilepsy duration before STP treatment, were younger at the time of STP initiation, had higher baseline seizure frequency, received a higher dose of STP (mg/kg/day), and stayed on treatment longer, compared with those with unfavorable outcomes.

versus 6 to 9 years).[11,13,18] Stiripentol has the most significant impact on GABAA receptors containing an α3 subunit, which is highly expressed in young brains. mRNA for the α3 subunit has a high level in most brain regions of the embryonic and newborn mammals.[3] As the brain matures, α3 subunit expression becomes more limited. The preferential expression of α3 subunit in young children and the selectivity of STP on this subunit explain the higher efficacy of STP in younger children.

Second, we also found a significantly shorter duration of epilepsy before STP treatment (5.44 ± 4.21) in patients with favorable outcomes compared with those without (22.71 ± 8.69). This finding aligns with the relationship between age and outcomes, as outlined above. Cortical hyperexcitability results from prolonged or recurrent seizures that cause irreversible synaptic plasticity and aberrant growth of excitatory neurons. And longer epilepsy duration potentiates cortical hyperexcitability.[20-23] Therefore, we believe that longer epilepsy duration is associated with unfavorable treatment outcome. This hypothesis is supported by our finding of a significant correlation between the duration of epilepsy before STP treatment and seizure outcomes (*P* value <0.001).

TABLE 4.
Spearman Correlation Analysis of the Relationship Between Variables and Seizure Control Outcome in Patients With Tuberous Sclerosis Complex Treated With Stiripentol

Variables	Correlation Coefficient	*P* Value
Age	0.87	<0.001*
Age of seizure onset	0.13	0.67
Age of STP initiation	0.87	<0.001*
Duration of epilepsy before STP treatment	0.87	<0.001*
STP treatment duration	−0.66	0.01*
STP dose (mg/kg/day)	−0.74	0.004*
STP total daily dose	0.26	0.39
Baseline seizure frequency	−0.68	0.01*
Number of concurrent ASM	0.17	0.57
Number of past ASM	0.42	0.16

Abbreviations:
ASM = Antiseizure medication
STP = Stiripentol
Age, age of STP initiation, duration of epilepsy before STP treatment, STP dose (mg/kg/day), STP treatment duration, and baseline seizure frequency significantly correlated with treatment outcomes.
* *P* value <0.05 was considered statistically significant. Age, age of STP initiation, duration of epilepsy before STP treatment, STP dose (mg/kg/day), STP treatment duration, and baseline seizure frequency significantly correlated with treatment outcomes.

Furthermore, we believe that STP efficacy is dose-dependent. The median STP dose in our study was 21 mg/kg/day, which was lower than that of other studies (40 to 50 mg/kg/day).[11,13,18,24] Patients with favorable outcomes received a significantly higher dose of STP (mg/kg/day) compared with those with unfavorable treatment results (35.19 [±10.72] versus 15 [±9.29] mg/kg/day, *P* value = 0.005). The correlation between STP dose and seizure outcomes was significant (*P* value 0.004). Individual univariable logistic regression strengthened this hypothesis by showing that for every 1-mg/kg/dose increment in STP dose, the odds of a favorable outcome increased by 21% (*P* value 0.047).

We observed significantly higher baseline seizure frequencies in patients with better outcomes (*P* = 0.043). The patients in this study had a baseline median seizure frequency/month of 75 (IQR 30.0 to 303.0), including all seizure types. Therefore, one might speculate that patients in the upper quartile group who had as high as 10 seizures per day on average may have had seizures of lesser physical impact (e.g., myoclonic and absence seizures) rather than focal with secondary generalization. However, the statistical analysis showed no significant correlation between seizure type and treatment outcomes.

Moreover, STP inhibits a variety of hepatic cytochrome P450 enzymes, with high activity in human CYP1A2, CYP3A4, and CYP2C19. As a result, it can increase the concentration of some medications, including clobazam, carbamazepine, and an mTOR inhibitor (sirolimus). However, our analysis did not show a significant association between comedications and treatment outcomes.[4,5,11,13,18]

Neurobehavioral and gastrointestinal side effects were common with STP and seen in 85% of our cohort. The most common side effects were aggression/agitation, poor sleep, and drowsiness. Three patients (23%) discontinued STP due to behavioral side effects. A prospective study reported moderate side effects in 100% of their patients. Another study reported only 48% of patients with side effects, and 4% discontinued STP due to side effects.[11,18]

This study has limitations. Owing to a retrospective study design with small sample size, we could not adequately evaluate the impact of concurrent antiseizure medication adjustments or surgical interventions on the outcomes and side effects. In addition, parental reports of seizures have critical importance. The distinction between seizure types in the medical record is not always clear. Besides, seizure frequency is affected by recall bias, and some seizure types are inherently challenging to count by the patient's caretaker.

TABLE 5.
Individual Univariable Logistic Regression of Variables and Outcomes

Variables	OR	*P* Value	95% CI		AUC	95% CI	
Age	0.01	0.66	<0.001	>999.99	1.00	1.00	1
Age of seizure onset	0.92	0.60	0.67	1.26	0.57	0.22	0.92
Duration of epilepsy before STP treatment	0.08	0.86	<0.001	>999.99	1.00	1.00	1
Age of STP initiation	0.16	0.80	<0.001	>999.99	1.00	1.00	1
Baseline seizure frequency	1.01	0.06	1.00	1.02	0.89	0.72	1
STP treatment duration	1.36	0.07	0.98	1.88	0.88	0.64	1
STP total daily dose	1.00	0.40	1.00	1.00	0.64	0.33	0.95
STP dose (mg/kg/day)	1.21	0.047*	1.00	1.45	0.93	0.78	1
Number of concurrent ASM	0.64	0.49	0.18	2.24	0.60	0.28	0.92
Number of past ASM	0.74	0.17	0.48	1.14	0.74	0.45	1

Abbreviations:
AUC = Area under the receiver operating characteristic curve
ASM = Antiseizure medication
CI = Confidence interval
STP = Stiripentol
* *P* value <0.05 was considered statistically significant. The individual univariable logistic regression analysis of variables and outcomes showed that STP dose (mg/kg/day) was significantly associated with a favorable outcome.

In conclusion, this study describes the favorable efficacy of STP as an adjunctive treatment in patients with TSC with DRE. We showed that younger age, early STP treatment, higher doses of STP (mg/kg/day), and higher baseline seizure frequency were associated with favorable outcomes. However, we believe prospective studies with adequate statistical power to investigate the role of STP in seizure treatment in this population will further elucidate its application in this population. In addition, studies addressing STP impact on the frequency of rescue medications, status epilepticus, and emergency room visits as an outcome will benefit the generalizability and application of the knowledge in clinical practice.

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