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REVIEW ARTICLE

Update on Drug Management of Refractory Epilepsy in Tuberous Sclerosis Complex

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Abstract
Tuberous sclerosis complex (TSC) is a genetic neurocutaneous disorder with epilepsy as a common and early presenting symptom. The neurological phenotype, however, is variable and unpredictable. Early and refractory seizures, infantile spasms in particular, are associated with a poor neurological outcome. Preliminary data suggests early and aggressive seizure control may mitigate the detrimental neurodevelopmental effects of epilepsy. For infantile spasms, vigabatrin is the first line of treatment, and steroids and classic antiepileptic drugs (AEDs) are suitable for second line. Based on retrospective data, vigabatrin should be considered for other indications, especially in infants with focal seizures, as this may prevent infantile spasms, but also in children and adults with epileptic spasms and tonic seizures. Otherwise, for most seizure types, treatment is similar to that for patients without TSC, including the use of novel AEDs, although limited data are available. Three major developments are changing the field of epilepsy management in TSC. First, final recommendations on preventive treatment with vigabatrin will result from two multicenter trials in the US (PREVeNT, clinicaltrials.gov #NCT02849457) and Europe (EPISTOP, clinicaltrials.gov #NCT02098759). Second, treatment with everolimus, an inhibitor of the mechanistic target of rapamycin (mTOR), reduced seizures when compared to placebo. Further, mTOR inhibitors may have an overall disease-modifying effect. Third, the role of cannabidiol in the treatment of refractory seizures in TSC is yet to be established. With treatment recommendations in TSC, we keep an eye on the prize for the broader field of pediatric epilepsy: the lessons learned from TSC are likely applicable to other epileptic encephalopathies.

1 Introduction

Tuberous sclerosis complex (TSC) is a rare neurocutaneous genetic disorder, with a prevalence of one in 6000 to 10,000 [1, 2]. Pathogenic alterations in the *TSC1* or *TSC2* genes cause upregulation of the mechanistic target of rapamycin (mTOR) pathway, responsible for protein synthesis, cell growth, differentiation, synaptic plasticity, proliferation, and migration. This is associated with the formation of benign hamartomas in the heart (cardiac rhabdomyomas), retina, kidneys (renal angiomyolipomas), and other organs, including the liver and lungs. In the brain, abnormalities in cellular proliferation, differentiation, and migration lead to congenital malformations which include tubers, subendymal nodules, subependymal giant cell astrocytomas, and white matter radial migration lines. Beyond the macroscopically evident lesions on neuroimaging, more subtle abnormalities in white matter connectivity and myelination, in axonal guidance, and in dendritic pruning indicate the brain pathology is ubiquitous rather than multifocal [3].

Diagnosis is based on clinical criteria (Table 1), and can be confirmed in approximately 85% of patients by genetic testing [4].

Here, we will give an overview of the current advancements in timing and indications of optimal epilepsy treatment.

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Key Points

While data from large randomized trials are lacking, early and aggressive treatment of seizures in tuberous sclerosis complex (TSC) is already recommended by expert panels based on observational studies and small retrospective studies. A randomized placebo-controlled, multicenter clinical trial of epilepsy prevention in TSC is currently underway.

Vigabatrin is first-line treatment for infantile spasms. In Europe, but not in the United States, expert consensus recommendations indicate vigabatrin as a first-line drug for all seizures in children under the age of 1 year. It should also be considered for a variety of seizure types in older children and adults.

Conventional drug choices for other seizure types generally follow those of other epilepsies.

Everolimus has antiepileptic effects and acts as a potential disease-modifying drug in TSC.

A randomized, placebo-controlled, multicenter clinical trial for cannabidiol in TSC has been completed, and results are expected soon.

2 Epilepsy in Tuberous Sclerosis Complex (TSC)

Epilepsy is the most common neurological symptom in TSC,and up to 85% of all TSC patients develop seizures in their lifetime [5, 6], often with an onset in infancy and with multiple seizure types. In this review, we use infantile spasms (IS) when referring to articles that specifically reported on spasms in the infantile age range, and epileptic spasms (ES) when studies reported on all spasms in children (which includes IS).

Globally, seizures are often still the presenting symptoms, but in an increasing number of cases, especially selected cohorts from TSC centers of excellence, the diagnosis is known before the onset of seizures, even prenatally. In a prospective, multicenter, observational study of 130 children with TSC, seizures started before time of diagnosis in only 15% of infants, but 73% developed epilepsy within the first year of life. Ultimately, in this cohort, 57% of patients developed ES, with a peak onset between 3 and 9 months [7].

Early and refractory seizures, particularly IS, are associated with a poor neurodevelopmental outcome. In a retrospective study at the Mayo Clinic, 90% of 264 patients ultimately developed seizures. Of those who developed seizures before age 1 year, only 8% had a normal intelligence, and the rate of intellectual disability was 61% in those who had IS [9]. In a similar retrospective TSC study, profound intellectual disability was reported in 68% of children with IS [8]. Several other studies have consistently reported that IS are a major predictor for intellectual disability, and IS in TSC may carry a worse neurodevelopmental prognosis than in children with IS or TSC alone [9]. More recently, a prospective, multicenter, observational study of 130 children with TSC demonstrated strong associations between age of onset of epilepsy, the presence of (refractory) epilepsy, and poor neurodevelopmental outcome, using serial neuropsychological evaluations [10].

While the association between early and refractory epilepsy and adverse neurological outcome has been firmly established, this co-occurrence may reflect an overall more severe neurological phenotype rather than a causal relation between epilepsy and neurodevelopment. Genotype and measures of neurological disease burden (e.g., quantification of tuber load or diffusion imaging metrics of white matter) correlate with both epilepsy and neurocognitive phenotypes [11, 12]. Below, we discuss the timing of treatment, referring to studies that provide preliminary evidence that early epilepsy treatment may mitigate a detrimental effect seizures have on development. Thus, in current practice, the treatment of epilepsy in TSC aims to control seizures and optimize neurodevelopment. In future practice, prevention of seizures rather than control may be desirable.

2.1 Timing of Treatment and Outcome

Several reports have suggested that early and aggressive treatment is associated with an improved neurodevelopmental outcome and a lower rate of refractory epilepsy and, conversely, that delayed treatment is associated with an adverse neurological outcome [13–15]. These findings are limited by small study sample sizes, retrospective designs, and comparison to historical controls. Moreover, these studies do not sufficiently correct for important confounders like genotype and measures of disease burden (tuber load, white matter DTI measures) which are strongly associated with neurological outcome [11].

Despite these limitations, it is, however, the standard of care to treat as early as possible and aim for complete seizure control if feasible. Parental education is recommended for early recognition of IS and focal seizures, and in Europe, frequent serial electroencephalographic (EEG) monitoring is becoming the standard of care [16]. The retrospective data and cumulative clinical experience at specialized TSC centers has been sufficiently compelling to prompt trials of epilepsy prevention.

Jozwiak et al. reported in a single-center, open-label study that treatment of patients with epileptiform discharges

Table 1 Updated diagnostic criteria for TSC 2012 [4]

A. Genetic diagnostic criteria
The identification of either a *TSC1* or *TSC2* pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (http://www.lovd.nl/TSC1, http://www.lovd/TSC2, and Hoogeveen-Westerveld et al., 2012 and 2013). Other *TSC1* or *TSC2* variants whose effect on function is less certain do not meet these criteria and are not sufficient to make a definite diagnosis of TSC. Note that 10–25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC or have any effect on the use of clinical diagnostic criteria to diagnose TSC
B. Clinical diagnostic criteria
Major features
1. Hypomelanotic macules (≥ 3, at least 5-mm diameter)
2. Angiofibromas (≥ 3) or fibrous cephalic plaque
3. Ungual fibromas (≥ 2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias[a]
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)[b]
11. Angiomyolipomas (≥ 2)[b]
Minor features
1. "Confetti" skin lesions
2. Dental enamel pits (> 3)
3. Intraoral fibromas (≥ 2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas
Definite diagnosis: 2 major features or 1 major feature with ≥ 2 minor features
Possible diagnosis: Either 1 major feature or ≥ 2 minor features

TSC tuberous sclerosis complex

[a]Includes tubers and cerebral white matter radial migration lines

[b]A combination of the two major clinical features LAM and angiomyolipomas without other features does not meet criteria for a definite diagnosis

on EEG prior to seizure onset was associated with a lower rate of refractory epilepsy and improved neurodevelopmental outcome. This study enrolled 14 infants with an early diagnosis of TSC, who underwent surveillance EEG every 6 weeks from time of TSC diagnosis. Vigabatrin was started upon detection of epileptiform abnormalities in the EEG. Comparison was made to a historic group ($n = 31$) who received treatment only after onset of clinical seizures (spasms, focal seizures)—at the time still considered the standard of care. Outcome measures included neurodevelopment at 24 months (Psyche-Catell test) and seizure freedom [17].

The preemptive treatment group had lower rates of intellectual disability than the standard care group (48% vs 14%) and better epilepsy outcomes than the standard of care group. Fewer patients in the preventative treatment group developed epilepsy (43% vs 71%), and they were older at the time of their first seizure (5.5 months vs 5 months) and less often had ongoing seizures at 24 months (17% vs 91%). A recent report of follow-up of these same patients provides some preliminary evidence for ongoing benefits of preemptive treatment for epilepsy control and cognitive outcome beyond the age of 24 months [18].

The North-American Tuberous Sclerosis Autism Centers of Excellence Research Network (TACERN) performed a large, prospective, multicenter, observational study of EEG and imaging markers of autism in 160 children with TSC. In a sub-study of 40 children, surveillance EEGs were performed at 1.5, 3, 4.5, 6, 9, 12, 18, and 24 months of age. Preliminary analysis of the data from 28 children showed epileptiform EEG abnormalities in young patients without clinical seizures to be 100% predictive of the subsequent

development of epilepsy within 2.8 ± 3.4 months. There were five false negatives, possibly reflecting a relatively long interval between surveillance EEGs [19]. The final results of the sub-study showed that 17 of 38 children (45%) had epileptiform activity detected on EEG before onset of clinical seizures (sensitivity 85%, positive predictive value 77%) (Wu et al., *Epilepsia* 2019). One other study of the same cohort found increased neural connectivity in the EEG precedes ES in infants with TSC, but whether connectivity can be used as a biomarker for impending spasms in TSC has not been established yet [20].

The European Long-term, Prospective Study Evaluating Clinical and Molecular Biomarkers of Epileptogenesis in a Genetic Model of Epilepsy-Tuberous Sclerosis Complex (EPISTOP, clinicaltrials.gov #NCT02098759) is a multicenter prospective study that combined the identification of EEG, imaging, and molecular biomarkers of the neurological phenotype with a randomized controlled clinical trial. In this randomized controlled trial, patients were allocated to either preventive or conventional treatment. Preventive treatment with vigabatrin was defined as treatment given when interictal epileptiform activity was found on EEG prior to clinical or electrographic seizures. Conventional treatment with vigabatrin was defined as treatment after the onset of either clinical or electrographic seizures. Enrolled subjects had serial video EEG recordings and clinical assessments every 4 weeks. Neuropsychological assessments were performed every 6 months. The outcome measures of the trial are the time from birth to the first clinical seizure and the proportion of seizure-free patients, patients with refractory seizures, and patients with normalized EEG, as well as neurodevelopmental outcome, recognized as the results in a battery of neuropsychological tests performed at the age of 24 months. The EPISTOP project ended in 2018, and results were presented at the 2019 International Tuberous Sclerosis Complex Research Conference in Toronto, Canada. The data had not been published at the time of this article going to press. Of note, not all centers were allowed to randomize, so there was a proportion of the 101 enrolled patients who were considered to be in the "observational study"; they were assigned to the preventative or conventional treatment arm according to the local TSC center's current practice. From the EPISTOP website's press release, we cite, "The results of the EPISTOP research showed that young patients treated preventively are now mostly free of epileptic seizures. For half of the children it was possible to discontinue the treatment, and 80% has a development within the normal range." [http://www.epistop.eu/images/EPISTOP_press_release.pdf].

Finally, in the USA, the Preventing Epilepsy Using Vigabatrin In Infants With Tuberous Sclerosis Complex (PREVeNT, clinicaltrials.gov #NCT02849457) trial is currently actively enrolling patients. In this study, infants with TSC but without seizures undergo monthly surveillance EEG, which is interpreted centrally by two off-site clinical neurophysiologists blinded to patient data and clinical care. Once epileptiform activity is detected,infants are randomized to vigabatrin or placebo. The primary outcome includes measures of cognition and neurodevelopment (e.g., Bayley Scales of Infant and Toddler Development and Vineland II scores) and various epilepsy severity metrics. The study is expected to complete enrollment by the end of 2019, and is currently adding study sites to increase geographic availability in the USA and Canada [21].

2.2 Corticosteroids and Vigabatrin

2.2.1 Infantile Spasms

In past trials studying the efficacy of corticosteroids in IS, often only small numbers of children with TSC were included, limiting generalizability [22]. In a small, prospective, randomized, multicenter, cross-over study of treatment of IS associated with TSC specifically, 11 patients first started on vigabatrin all became seizure free, compared to five of 11 patients started on oral hydrocortisone. During the cross-over, 63% of the hydrocortisone treatment group was switched to vigabatrin, and all became seizure free, with a mean time to maximum effect of 3.5 days [23].

In patients with TSC and IS refractory to vigabatrin, though, add-on corticosteroids are recommended [16, 24]. Side effects of steroid use in TSC are no different than in the general population, with the most common being irritability, hypertension, weight gain, and immunosuppression—limiting long-term tolerability [22].

For IS from causes other than TSC, the ICISS study demonstrated that combination therapy of vigabatrin and corticosteroids has superior efficacy over corticosteroids alone, and is standard of care in some centers in Europe (but not the USA). Patients with TSC were excluded in this study, and combination therapy has not been studied in TSC specifically [25, 26].

In TSC, the consistent response rate to vigabatrin, up to 95% across studies, is clearly higher than that of corticosteroids [14, 23, 27–33], and the potential higher yield of combination therapy is therefore currently not being investigated. For now, vigabatrin alone is recommended as first-line treatment for IS in TSC, both in Europe and in the USA. As shown in Table 2, however, these studies are mostly small or retrospective, and vigabatrin versus high-dose corticosteroids has not been prospectively compared in a properly powered clinical trial for TSC specifically. Such a trial may not be desirable given the good efficacy of vigabatrin as per the TSC experts' collective clinical experience, nor be feasible given the generic availability of these drugs.

The main concern with regard to the use of vigabatrin is the associated visual field loss, due to irreversible retinal toxicity. This adverse event is estimated to occur in approximately 15% of children, which has led to the recommendation that visual field testing be performed at baseline and frequently thereafter. In the USA, the practice is to test every 3 months during treatment, but there is no compelling evidence to support such frequent testing. For TSC, many experts recommend once or twice a year testing, unless there are additional concerns that warrant more frequent assessment [34]. Although there are reports of visual field loss detected as early as at 3 months of vigabatrin use, it seems the prevalence of this side effect increases with higher dose and longer duration of use, suggesting the effect is cumulative [35]. It is questionable whether minor changes in peripheral visual fields have clinical relevance; several studies showed discrepancies between rate of visual field loss detected by perimetry and the number of patients with actual clinical symptoms [34, 36].

Using low doses of vigabatrin to avoid cumulative retinal toxicity, however, may also carry risks. In a prospective, multicenter study of 50 children with IS and TSC who responded to vigabatrin, each increment of 50 mg/kg/day in dosage of vigabatrin was associated with a decreased risk of IS relapse [37].

Vigabatrin is associated with reversible cytotoxic edema, evident on structural magnetic resonance imaging (MRI) as T2w hyperintensities in the brainstem, cerebellar dentate nuclei, thalamus, and globus pallidus. This distribution may reflect selective vulnerability of these structures to vigabatrin from regional variations in γ-aminobutyric acid (GABA) metabolism [38, 39].

2.2.2 Vigabatrin for Other Seizure Types in TSC

Regardless of a diagnosis of TSC, in the USA, vigabatrin is Food and Drug Administration (FDA) approved for the adjunct treatment of refractory complex partial seizures in adults. Variability exists in current practice. In Europe, expert consensus recommends vigabatrin as a first-line treatment for all seizures in infants [16]. In the USA, it was not a first choice for focal seizures as per the last expert consensus meeting in 2012 [24]. Unfortunately, for TSC specifically, there is only retrospective data available about the efficacy of vigabatrin for seizure types other than IS.

In a retrospective study of 49 children and adults with TSC, 25% became seizure free or had a > 90% seizure reduction and an additional 6% had an 50–90% reduction of seizures [40], when vigabatrin was added to their regimens.

In a retrospective cohort studying treatment and epilepsy outcome in 71 children with TSC, vigabatrin was more effective than other antiepileptic drugs (AEDs) when prescribed as the first treatment [41].

Efficacy seems particularly high when this treatment is used for tonic seizures and ES. In a small retrospective study of 21 children with TSC and tonic seizures or ES outside of the infantile age range, 50% became seizure free, and the response rate was 80% to treatment with vigabatrin. In this study, the discontinuation of vigabatrin after a mean of 16 months did not lead to seizure relapse, and therefore vigabatrin was considered as a potentially temporary treatment, akin to its use in IS [42]. Other studies have reported similar success rates with vigabatrin for ES and various other types of spasms in children with TSC [43, 44].

2.3 Conventional Antiepileptic Drugs

In Europe, a recent expert consensus statement recommended that conventional AEDs are considered in children under 2 years of age as second-line therapy, only after vigabatrin monotherapy has failed [16]. In the USA, no such treatment guideline exists, and vigabatrin is limited to being the drug of choice for IS associated with TSC [24].

The efficacy of most AEDs has been studied retrospectively in single centers or has been reported in case series only. These studies and case reports are summarized in Table 2 [41, 45–49]. Although valproic acid, topiramate, and oxcarbazepine are often used as first-line AEDs in TSC, there are no data on their disease-specific efficacy.

2.4 Disease-Modifying Drugs

Recently a new approach to treatment has emerged with the use of drugs which modify the mTOR pathway. This class is referred to as mTOR inhibitors, and includes everolimus and sirolimus [50]. Everolimus was first FDA-approved for the treatment of subependymal giant cell astrocytoma and renal angiomyolipoma associated with TSC [51, 52]. During one of these trials, a decrease in seizures was observed; however, the seizure frequency at baseline in the everolimus group and the placebo group were too disparate to draw a firm conclusion [52]. Given this promise, everolimus was studied as an adjunct and targeted therapy for refractory focal seizures associated with TSC in a large, randomized, placebo-controlled, double-blind trial (A Placebo-controlled Study of Efficacy and Safety of 2 Trough-ranges of Everolimus as Adjunctive Therapy in Patients With Tuberous Sclerosis Complex (TSC) and Refractory Focal-onset Seizures (EXIST-3); clinicaltrials.gov #NCT01713946) in patients with TSC aged 2–65 years (in Europe 1–65 years). The overall response rate (defined as > 50% seizure reduction from baseline) in the high-exposure add-on everolimus treatment arm was 40.0%, compared to 15.1% in the placebo arm, and the median seizure reduction was 39.6% versus 14.9% [53]. A post-hoc analysis was performed on the 299 included children [54], and the response rate in the subgroup < 6 years of

Table 2 Overview of epilepsy drug studies in TSC

Author and study design	Medication	*N*[a]	Seizure type(s)	Age start treatment (years)	Response rate (50% reduction)	Seizure freedom (90% reduction)	Adverse events
Overwater 2015, retrospective	Carbamazepine	29	–	–	67%	–	–
Jennesson 2013, retrospective	Clobazam	23	ES, FS	0.3–24	69%	19%	Sedation, behavioral disorders
Mishal 2015, case report	Felbamate	1	AB, GA	7	100%	100%	Aplastic anemia, hepatotoxicity
Geffrey 2015, retrospective	Lacosamide	27	FS	1–18	48%	17%	Aggression, worsening of the seizures
Collins 2006, retrospective	Levetiracetam	20	FS, GTC, M	2–19	40%	–	Behavioral disorders
Franz 2001, retrospective	Lamotrigine	57	FS, IS	0.4–35	63%	42%	Rash
Curatolo 2018, randomized controlled trial	Everolimus	299	FS	2–18	48%	–	Infections, leukopenia, elevated levels of cholesterol
Overwater 2016, randomized controlled trial	Sirolimus	23	–	2–10	Not statically significant	Not statically significant	Infections, leukopenia, elevated levels of cholesterol
Samueli 2016, prospective	Everolimus	15	FS, GTC, GA	1–18	80%	58%	Infections, leukopenia, elevated levels of cholesterol
Krueger 2016, prospective	Everolimus	20	FS, GTC	2–21	60%	–	Infections, leukopenia, elevated levels of cholesterol
Jozwiak 2011, open-label study	Vigabatrin, preventative	45	Electrographic, IS, FS	0.20–2.25	Less refractory seizures and better cognitive outcome		Vigabatrin-associated visual field loss
Chiron 1997, randomized controlled cross-over trial	Vigabatrin Hydrocortisone	22	IS	0.2–1.25	100% –	100% 45%	Vigabatrin-associated visual field loss Increased blood pressure and body weight, infections, irritability
Aicardi 1996, retrospective	Vigabatrin	28	IS	–	–	27%	Increased blood pressure and body weight, infections, irritability
Yum 2012, retrospective	Vigabatrin	31	IS, FS	–		IS 89% FS 46%	Increased blood pressure and body weight, infections, irritability
Bombardieri 2010, retrospective	Vigabatrin	10	IS, FS	0.2–0.92	–	IS 80% FS 40%	Increased blood pressure and body weight, infections, irritability
Camposano 2008, retrospective	Vigabatrin	42	IS	–	76%	–	Increased blood pressure and body weight, infections, irritability
Greinier 2012, retrospective	Vigabatrin	100	IS, FS	0.1–29.2	–	33%	Increased blood pressure and body weight, infections, irritability

Table 2 (continued)

Author and study design	Medication	N[a]	Seizure type(s)	Age start treatment (years)	Response rate (50% reduction)	Seizure freedom (90% reduction)	Adverse events
Pellock 2016, retrospective	Vigabatrin	670	IS	–	88%		Increased blood pressure and body weight, infections, irritability
Elterman 2001, randomized controlled trial	Vigabatrin	25	IS	–	–	92%	Increased blood pressure and body weight, infections, irritability
Friedman 2013, retrospective	Vigabatrin	49	FS	0.2–33	31%	25%	Increased blood pressure and body weight, infections, irritability
Hsieh 2013, retrospective	Vigabatrin	10	ES	3–35	–	50%	Increased blood pressure and body weight, infections, irritability
Jackson 2017, retrospective	Vigabatrin	103	ES, FS, GTC, M, T, GA, AB	0–11	–	39%	Increased blood pressure and body weight, infections, irritability
Van der Poest Clement 2018, retrospective	Vigabatrin	21	ES, T	1.1–18.3	81%	67%	Increased blood pressure and body weight, infections, irritability
Hess 2016, retrospective	Cannabidiol	18	FS, T, GTC, ES, AB	2–31	50%	–	Drowsiness, ataxia,diarrhea

AB absences, *ES* epileptic spasms, *FS* focal seizure, *GA* generalized atonic, *GTC* generalized tonic clonic, *IS* infantile spasms, *M* myoclonic, *T* tonic, *TSC* tuberous sclerosis complex

[a]Corrected for pediatric population and specific medication

age was as high as 60%, compared to a 30% rate in the older subgroup. An exposure dose-dependent effect was found as well. Low exposure (target serum level 3–7 ng/mL) versus high exposure (target serum level 9–15 ng/mL) resulted in a 30.3% versus 59.5% response rate, respectively, in the younger group. In the older age subgroup, this difference was not evident (27% vs 30.3%, respectively). Finally, there was an increase in the number of responders with longer use, suggesting a benefit from a long treatment trial in patients [53]. Seizure freedom was achieved in 0.8% in the placebo group, 5.1% in the low-exposure everolimus group and 3.8% in the high-exposure group. Data from the 2-year open-label extension phase suggest long-term seizure reduction and the safety profile are comparable with the results from the core phase of the EXIST-3 trial [55].

A placebo-controlled, open-label, cross-over trial from the Netherlands reported no benefit from adjunct use of sirolimus in the treatment of refractory partial seizures associated with TSC in 22 children aged 1.8–10.9 years [56]. The study was likely negative due to underpowering, change of concomitant AEDs in eight children, and low trough serum levels. The target sirolimus levels were set at 5–10 ng/mL, but the group mean was 3.7 ng/mL (range 0.9–8.0).

Two smaller studies of mTOR inhibitors for epilepsy in children with TSC have been published. In a single-center, open-label study of 15 children with refractory epilepsy, 80% were considered responders (> 50% decrease of seizure frequency) and 58% became seizure free [57]. Similarly, the open-label extension phase of a prospective, open-label, phase I/II clinical trial of 18 patients (median age 8.0 years, range 2.0–21.3 years) with everolimus trough levels of 7.4–10.8 ng/mL at 48 months reported a large and sustained effect on focal-onset seizures (83% reduction of median frequency) and on generalized seizures (41% reduction) [58]. Such open-label extension phase data are more suitable for demonstrating safety,however, than sustained efficacy as, by design, such extensions include only those patients already proven to benefit from the drug and who have stayed on it.

In summary, there are several lines of evidence suggesting the highest efficacy of mTOR inhibitors occurs in the treatment of younger patients, with higher trough levels, and with sustained use.

Common side effects in these studies have been pneumonitis (16%), upper respiratory tract infections (32%), and gastro-enteritis (7%). Painful stomatitis (38%), leukopenia and elevated levels of cholesterol have been reported also. In the EXIST-3 trial, a higher prevalence of side effects was evident in the younger high-dose subgroup. Typically, however, the adverse effects were transient and resolved with supportive treatment [54, 57, 59]. A guide was written on how to manage the adverse effects [60].

With regard to safety, a recent retrospective study surveyed multiple centers on the use of everolimus and sirolimus in children under the age of 2 years [59]. Data were collected from the clinical records of 45 children with a mean age of 16.7 ± 7.2 months for everolimus and 11.7 ± 7.8 months for sirolimus. Thirteen children started before the age of 6 months. Treatment was initiated for various indications, including epilepsy (45%), SEGA (39%), rhabdomyomas (7%), and other hamartomas (4%). Mean levels were 6.0 ± 4.8 ng/mL for everolimus and 7.6 ± 6.6 ng/mL for sirolimus. Adverse effects were reported in 78%, but none were disabling or life threatening. The most frequent were the aforementioned infections (20–69%), aphthous ulcers and stomatitis (40%), and elevated cholesterol (14%). Although the study was not designed to determine clinical efficacy, participating clinicians reported an improvement in the primary indication for treatment in 64% of the children.

As parents in the EXIST-I trial reported behavioral improvement, a randomized controlled trial was performed to formally assess potential improvements in neurocognition. The results were negative, likely due to underpowering and the broad range of baseline abilities of subjects enrolled in the trial [61].

TSC can be considered a model disease, as the mTOR pathway is involved in various other malformations of cortical development, including focal cortical dysplasia, and hemimegalencephaly. The efficacy of mTOR inhibition in TSC paves the way for clinical trials of targeted therapy in epilepsies arising from mTOR pathway defects [62].

2.5 Cannabidiol

Cannabidiol (CBD) is a non-psychoactive drug extracted from the cannabis plant. Several large, multicenter, double-blinded, placebo-controlled trials showed efficacy of CBD oil in Lennox Gastaut syndrome (GWPCare3 and 4, $n = 225$ and 171, respectively) and Dravet syndrome (GWPCare1, $n = 120$) [63–66]. One large, open-label trial of oral CBD oil in patients with refractory epilepsy and multiple concomitant AEDs reported a 50% reduction of refractory seizures over 12 weeks in 137 patients, aged 1–30 [67]. The most common adverse events were somnolence (25%), decreased appetite (19%), diarrhea (19%), fatigue (13%), and convulsion (11%). This study included only nine patients with TSC, and disease-specific efficacy data were not reported.

In a sub-study of the expanded access program from the GWPCare4 study, the effect of CBD on refractory seizures in 18 patients with TSC (a mean age of 14 years; range 2–31) has been analyzed [68]. Dosages were started at 5 mg/kg/day and titrated up to 25 mg/kg/day in 15 patients; the three others did not tolerate this dosage. The response rate (defined as a median seizure reduction of 50% or more) after 3 months of treatment was 50%. The efficacy, however, seemed to differ between seizure types. A dramatic decrease was found for ES after 6 months, but multiple other seizure types responded well, too. Efficacy was highest with concurrent clobazam use, and interaction with CBD caused levels of active clobazam metabolites to rise. Based on parental questionnaires, improvements in cognitive and behavioral functioning were also reported, independent from the seizure responsiveness.

For TSC, the first phase of a large, two-phased clinical trial has recently been completed (Double-blind, Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Cannabidiol (GWP42003-P, CBD) as Add-on Therapy in Patients with Tuberous Sclerosis Complex Who Experience Inadequately-controlled Seizures-GWPCare6, clinicaltrials.gov #NCT02544763 and #NCT02544750). The first phase was a double-blind, placebo-controlled trial with a target enrollment of 210 TSC patients, with change in median seizure frequency as the primary outcome over 16 weeks of treatment. The second phase is an open-label extension trial with the incidence of adverse events as the primary outcome over an anticipated 2-year period.

The results of the first phase have been presented at the 2019 International Tuberous Sclerosis Complex Research Conference in Toronto, Canada, and at the 2019 Annual Meeting of the American Epilepsy Society in Baltimore, PA, but the data were not published at the time of this article going to press. A press release in May 2019 and AES abstract in December 2019 from the sponsoring company mention that the trial met its primary endpoint, reporting a "reduction in seizure frequency compared to baseline of the Epidiolex 25 mg/kg/day dose group vs. placebo ($p = 0.0009$). Results for both the 25 and 50 mg/kg/day dose groups were similar, with seizure reductions of 48.6% and 47.5% from baseline respectively, vs 26.5% for placebo (50 mg/kg/day vs placebo, $p = 0.0018$). […] The trial randomized 224 patients into three arms, where Epidiolex 25 mg/kg/day ($n = 75$), Epidiolex 50 mg/kg/day ($n = 73$) or placebo ($n = 76$) was added to current anti-epileptic drug (AED) treatment. The median age of trial participants was 11 years (range 1–57). On average, patients were taking three AEDs, having previously tried and discontinued four other AEDs". We have put this text in quotes as it has not been subjected to peer review

yet. Table 3 provides an overview of actively recruiting drug trials for epilepsy in TSC registered at clinicaltrials.gov.

3 Future Directions

Recent developments of drug treatment of epilepsy in TSC are threefold:

First, the development of new biomarkers allows for stratification of patients at high risk for the near-immediate development of seizures. As such, biomarkers are key for the design of preventive treatment trials. The abovementioned EPISTOP trial results are expected soon. In the PREVeNT trial, children with TSC with emerging EEG abnormalities are randomized to vigabatrin or placebo, and first results are expected in 2020 [21]. The EPISTOP and PREVeNT trials differ in design, but will complement each other in answering whether preventive treatment should be implemented as the standard of clinical care in TSC, as opposed to early and aggressive treatment of seizures once they emerge.

Second, evolving insight in the role of the mTOR pathway in epileptogenesis in TSC has prompted a well-designed, large, phase III clinical trial of mTOR inhibitors in TSC, which was clearly positive. The higher efficacy in younger patients with sustained exposure raises the question of whether mTOR inhibitors would be suitable for preventative treatment of impending epilepsy in TSC or in combination with the start of vigabatrin treatment. In rodent models of TSC, mTOR inhibitors have been able to prevent epilepsy [69]; rodents, however, have a different phenotype considering brain lesions. Although available data suggest the feasibility of treatment in patients under age 1 year, before a trial in humans can be conducted, more knowledge about the long-term safety and efficacy of treating young children with mTOR inhibitors is needed [70].

Third, preliminary results from the phase III trial indicate CBD to be effective for the treatment of various seizure types in TSC. However, final results have not been published yet through scientific channels. From earlier open-label, expanded access studies, the possible beneficial effects on behavior and cognition warrant further investigation.

Besides medical treatment, resective epilepsy surgery renders children with TSC seizure free in approximately 60%, and should be considered in all cases of refractory epilepsy [71, 72]. How early in the clinical course surgery should be pursued is a topic of active investigation.

4 Conclusions

Epilepsy is highly prevalent in TSC and refractory in up to two-thirds of cases. Because of the interference with neurodevelopment, early and aggressive treatment is warranted. Vigabatrin is a first-line treatment for TSC-related IS in both Europe and the USA, and is considered a first-line treatment choice for focal seizures in Europe only. Preliminary results of preventative treatment trials are promising, and improved outcomes are seen. There is no good evidence for the efficacy of any other AEDs in TSC, and treatment usually follows that of other epilepsies. mTOR inhibitors have shown efficacy, possibly more so in younger patients, with higher doses and with sustained use. Trial data on CBD are pending.

Table 3 Currently recruiting randomized controlled trials of drugs for epilepsy in TSC registered at clinicaltrials.gov

Group and study design	Medication	Approximate enrollment target	Age	Primary outcome	Results expected
Preventing Epilepsy Using Vigabatrin In Infants With Tuberous Sclerosis Complex (PREVeNT trial) A Randomized, Double-blind, Placebo-controlled, Seizure Prevention Clinical Trial for Infants With TSC	Preventative vigabatrin	80	Until 24 months or first seizure	Cognitive Assessment Scores and Developmental Impact at 24 months	May 2021
A Placebo-controlled Study of Efficacy and Safety of Aspirin as an add-on Treatment in Patients with Tuberous Sclerosis Complex (TSC) and Refractory Seizures (study is in China)	Aspirin	98	6–30 years	Average seizure frequency and response rate	Nov 2020

TSC tuberous sclerosis complex

Compliance with Ethical Standards

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Conflict of interest Dr. Jurriaan Peters is an investigator in the PREVeNT trial, and has consulted for Philips Neuro and GW Pharmaceuticals. Drs. Braun and Jansen are investigators in the EPISTOP trial. Dr. van der Poest Clement has no conflicts of interest to report.

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