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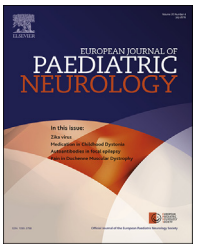

Review article

Management of epilepsy associated with tuberous sclerosis complex: Updated clinical recommendations

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ABSTRACT

Patients with tuberous sclerosis complex (TSC) are at very high risk for developing epilepsy, and the majority experience seizure onset during the first year of life. Early targeted interventions increase the probability of seizure-freedom and may protect neurodevelopment. In 2012, clinical recommendations for the management of epilepsy in patients with TSC were published by a panel of European experts. Since that time novel

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studies, reports, and expert opinions in preclinical and clinical TSC-related sciences prompted the need for updated recommendations, including epileptogenesis in TSC, the potential role of predictive biomarkers, the possible benefits of presymptomatic diagnosis and preventive treatment, and new treatment options including mTOR inhibitors. A reconvened panel reviewed the current literature to answer specific questions and five panelists discussed the findings, followed by a general discussion during which all issues were debated to achieve consensus regarding recommendations. A draft manuscript based on these discussions and recommendations was then circulated several times among the panelists, who added their own comments. All the panelists/authors agreed with the final manuscript, which was then submitted for publication. The panel concluded that the need for early diagnosis of TSC-associated seizures is now established, electroencephalographic monitoring has good predictive value for epilepsy before seizure onset in TSC, and, until conclusive data from the EPISTOP trial are available, administration of vigabatrin may be considered in children with subclinical epileptiform EEG discharges. The panel also supported the role of adjunctive everolimus for TSC-associated drug-refractory seizures and emphasized the necessity of early surgical evaluation.

Contents

1. Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by the occurrence of multiple hamartomas in different organs, mainly in the central nervous system. In TSC, mutations of *TSC1* or *TSC2* cause suppression of mTOR inhibition producing excessive activation of the mTOR signaling pathway and several abnormalities in cell cycle regulation and control.[1] Epilepsy is the most prevalent and clinically challenging manifestation of TSC, affecting approximately 85% of patients; infantile spasms are often followed by other seizure types, leading to refractory epilepsy in up to 75% of cases.[2] Patients with tuberous sclerosis can present with almost any seizure type including tonic, atonic or tonic-clonic seizures, with about two-thirds having refractory focal-onset epilepsy; focal seizures and epileptic spasms are the most prevalent.[3] Seizure onset in the majority of TSC patients occurs before 2 years of age[3,4] and during the first year of life in 62.5–73% of cases.[3,5] Among patients with infantile spasms, 75.4% in one retrospective series developed refractory epilepsy compared with 39.8% without a history of infantile spasms ($P < 0.0001$).[3]

Patients with TSC also are at high risk for neurodevelopmental disorders, described as tuberous sclerosis-

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associated neuropsychiatric disorders (TAND),[6] which are strongly related to refractory epilepsy and infantile seizures[7–9] as well as early seizure onset (Fig. 1).[10,11] Specifically, patients TSC and early onset of seizures — especially infantile spasms — experience greater impairment in intellectual development than those without seizures[10] and the early appearance of seizures usually results in severe forms of intellectual disability.[11]

The goal of epilepsy treatment in tuberous sclerosis is to prevent or control seizures as soon as possible after TSC diagnosis, which may improve cognitive neurodevelopment and will enhance quality of life. Cusmai et al. retrospectively evaluated the long-term outcomes of 44 infants with TSC presenting with seizures in the first 12 months who were treated with vigabatrin and were followed for at least 3.5 years.[12] At the final evaluation, 55% of patients were still having seizures, 80% had intellectual disability, and 30% had autism. Importantly, early treatment (<1 week) with vigabatrin after seizure onset was accompanied by improved seizure control compared with later treatment (>3 weeks; $P < 0.01$). Jóźwiak et al. reported two groups of patients with recently diagnosed TSC; one group (n = 31) received standard antiepileptic therapy following the onset of seizures and the other group was treated preventively before seizure onset (n = 14).[13] At 24 months of age, intellectual disability was significantly more frequent and severe in the standard treatment group compared with the preventive group (48% vs. 14%, $P = 0.031$; mean IQ score 68.7 vs. 92.3, $P < 0.05$).

Clinical recommendations for the management of epilepsy in patients with TSC were published in 2012.[14] Since that time, novel studies, reports and expert opinions in preclinical and clinical TSC-related sciences prompted the need for updated recommendations including the potential role of predictive biomarkers, the possible benefits of presymptomatic diagnosis and preventive treatment, and new treatment options including mTOR inhibitors. Accordingly, a consensus meeting was convened in September 2017 to review what had been reported and what had changed in the management of TSC-associated epilepsy since publication of the 2012 clinical recommendations.[14] The overall goal of the meeting was to revise and update the clinical recommendations for management of TSC-associated epilepsy. A panel of 15 experts from 11 European countries (Appendix) reviewed the recent literature to answer specific questions, and five experts presented the findings, followed by a general discussion during which all issues were independently reviewed and debated to achieve consensus regarding recommendations. A draft manuscript based on these discussions and recommendations was then circulated several times among the panelists, who added their own comments. All the panelists/authors agreed with the final manuscript, which was then submitted for publication.

The panel addressed epileptogenesis and the need for early diagnosis of TSC-associated seizures, particularly to assess the predictive value of early electroencephalographic (EEG) monitoring for epilepsy in TSC. The panel also considered the potential benefit of vigabatrin in children with subclinical epileptiform EEG discharges as well as other AEDs and the role of adjunctive everolimus for refractory TSC-associated seizures. In addition, the panel discussed epilepsy surgery, the ketogenic diet, and vagus nerve stimulation, particularly in cases of refractory TSC-associated seizures.

This review summarizes the issues discussed at the consensus meeting and provides updated clinical recommendations for currently available therapeutic options for TSC-associated epilepsy.

2. Epilepsy in TSC: review of new findings

2.1. *Epileptogenesis*

"Epileptogenesis" originally referred to the time between an initial insult and the appearance of the first unprovoked

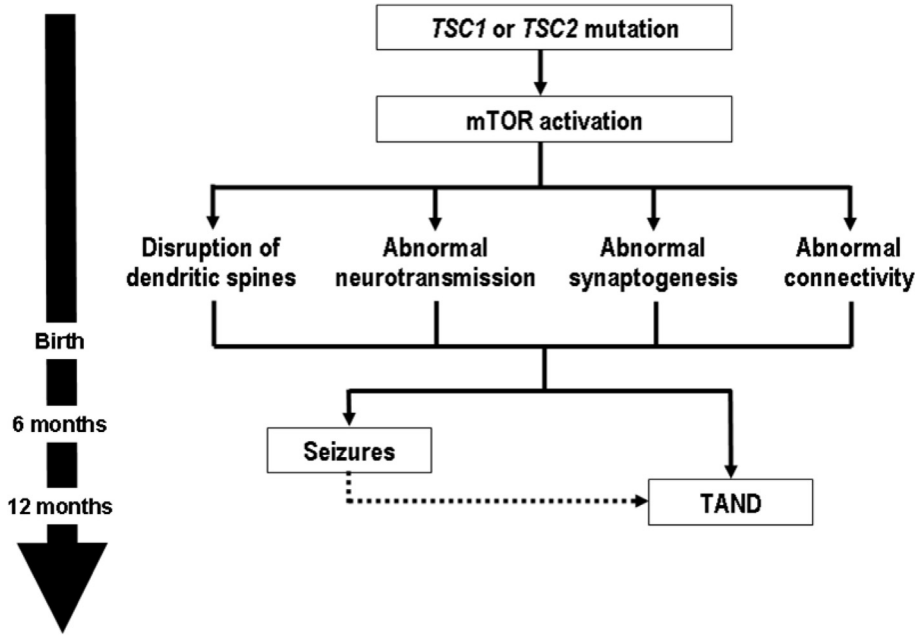

Fig. 1 – TSC-associated seizures and TAND.

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seizure (also called the seizure-free latent period). However, mounting experimental evidence indicated that the cellular or network processes leading to seizures can progress even after an epilepsy diagnosis and may contribute to the progression of seizures.[15–18] Thus, according to this updated definition, epileptogenesis is a chronic process that can be triggered by genetic or acquired factors and includes both the development of epilepsy as well as its progression throughout life after the diagnosis is established.[16,18,19] This evolution of the concept of epileptogenesis resulted in an extended and more challenging "therapeutic window of intervention," with the introduction of the term disease (or syndrome) modification in epilepsy, including both anti-epileptogenesis and potential comorbidity modification.[16–18] Epileptogenesis can be a much more rapid process than previously thought, particularly in epilepsies such as TSC-associated early-onset seizures in which the structural etiology has a well-defined genetic basis. Experimental studies show that as a consequence of the TSC genes mutation, mTOR overactivation determines a substrate for the early appearance of refractory seizures and the encephalopathic process.[20] Studying epileptogenesis in TSC is now possible by clinical and parental observation of asymptomatic infants, with increasing rates of prenatal diagnosis.

2.2. *Neurodevelopment*

Knowledge of the cellular and molecular changes occurring in the TSC brain guides the recognition of the neurobiological mechanisms underlying epilepsy and the seemingly related cognitive and behavioral comorbidities that accompany TSC. These neurobiological mechanisms offer novel targets and potential new approaches to anti-epileptogenic treatment, including preventive therapy, as well as the potential for new biomarkers that may facilitate the diagnosis of epilepsy before the onset of clinical seizures.

2.3. *Biomarkers*

Since not all patients with TSC have seizures, it would be useful to have a biomarker that could predict those patients destined to develop epilepsy and thus identify those TSC patients most appropriate for preventive antiepileptogenic therapy. Several papers report the use of EEG findings to facilitate recognition of infants with TSC who are at risk for clinical seizures.[21,22] A clinical study is being conducted currently to determine whether an EEG during infancy is a reliable biomarker to identify which TSC patients will develop infantile spasms/epilepsy in the near future and therefore are appropriate candidates for an AED trial (ClinicalTrials.gov Identifier NCT01767779).[23] Wu et al. found that all infants with TSC and epileptiform discharges who were enrolled in a prospective observational study subsequently developed epilepsy (100% positive predictive value).[22] However, the use of EEG as a reliable biomarker of future epilepsy has not yet been validated rigorously. Although EEG findings cannot yet be considered as a real biological marker, it has good predictive value in identifying children at higher risk of evolution toward epilepsy and detecting patients with subclinical seizures.

2.4. *Presymptomatic assessment and preventive treatment*

Most commonly, the diagnosis of TSC is made after the onset of epilepsy,[24] although prenatal or early postnatal diagnosis is made in increasing numbers of patients. The possibility of diagnosing TSC prenatally as well as early diagnosis postnatally based on clinical signs, brain magnetic resonance imaging (MRI), echocardiography and genetic testing permit presymptomatic assessment of seizure susceptibility with EEG surveillance of neonates and infants with TSC. This may prove very important since TSC infants who are diagnosed and treated before the onset of seizures have less severe epilepsy and better neurodevelopmental outcomes.[25] Treatment of infants with ictal epileptiform EEG activity and no clinical seizures has been advised by previous European recommendations.[14] Since that time, regular follow-up EEG studies have been introduced in many European and non-European countries.[25,26] Interestingly, in some open-label case series preventive treatment has been found to reduce the severity of TSC-associated seizures and preclude or reduce the severity of subsequent neurodevelopmental disorders.[13,14] In addition, it has been proposed that starting treatment with vigabatrin at an early age, at or prior to the presentation of clinical seizures, may improve the long-term outcome of epilepsy and neurodevelopment in patients with TSC.[12,13,27] However, the early diagnosis of TSC is still a challenge in the majority of cases as diagnostic workup often begins after seizure onset.[28] Although vigabatrin is now considered as first-line treatment of TSC-associated seizures in the first year of life,[29,30] its preventive use needs confirmation from additional clinical trial data from EPISTOP (ClinicalTrials.gov Identifier NCT02098759)[31] and PREVeNT (ClinicalTrials.gov Identifier NCT02849457).[32]

The primary objective of EPISTOP is to examine the biomarkers of epileptogenesis in infants with TSC and compare the effects of standard antiepileptic treatment before or after clinical seizure onset.[31] The estimated completion date is October 2018. Preliminary results in infants enrolled prior to seizure onset and on no anti-epileptic drugs found motor development was the first to be impaired with anomalies already detected at 6 months, and a clear deviation from the normal neurodevelopmental trajectory was evident from 12 months.[33] The primary objective of PREVeNT is to determine the cognitive and developmental impact of vigabatrin in infants with TSC who have not developed seizures and to evaluate the preventive effect of early treatment with vigabatrin.[32] The estimated primary completion date is May 2020; preliminary results are not yet available.

2.5. *Current treatment options*

Current treatment options for epilepsy in patients with TSC are summarized in Table 1.

2.5.1. *Antiepileptic drugs*

- At this time, vigabatrin is still recommended as the first-line monotherapy for TSC-associated infantile spasms and/or focal seizures in the first year of life.[14] In a study published in 2015, vigabatrin was shown to be the most

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Table 1 – Treatment options in the management of epilepsy in patients with TSC.

Treatment	Limitations
Antiepileptic Drugs	
• Vigabatrin – Recommended as first-line monotherapy in TSC related spasms or focal seizures in children <1 year of age – Initiating treatment at an early age, at or prior to the clinical onset of seizures, may improve long-term outcome of epilepsy and neurodevelopment – May be initiated presymptomatically in the presence of focal spikes • Other AEDs – ACTH is effective for TSC-related infantile spasms and is used as second-line therapy • AED combination therapy – Appropriate when first line therapy has failed	• Retinal toxicity • Currently no clinical trials supporting the use of vigabatrin to prevent seizures based on serial EEG monitoring • Careful selection for maximal synergy and minimal unfavorable reactions/ toxicity
mTOR inhibitors: everolimus	
• Seizures and seizure frequency significantly reduced in an open-label, phase I/II clinical trial of patients with treatment-refractory TSC-associated epilepsy • Significantly greater proportion of patients with ≥50% reduction in seizure frequency and median percentage reduction in seizure frequency with low- and high-exposure everolimus vs. placebo with good tolerability in core phase of double-blind randomized EXIST-3 trial • Extension phase of EXIST-3 demonstrated sustained efficacy in those patients who continued to take the drug • Approved in December 2016 by EMA for adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalization, are associated with TSC • Introduction of everolimus as add-on therapy should be considered if TSC-associated seizures are refractory to two AEDs	• Potential drug interactions • Limited experience in some European centers • Seizures may recur when discontinued
Surgery	
• Currently underutilized in TSC-associated refractory seizures • Should be preceded by a comprehensive presurgical evaluation • Early presurgical evaluation immediately recommended after failure of two AEDs • Early surgery significantly increases probability that patients will be seizure-free • Resection beyond tuber margins associated with greater probability of seizure freedom • Multifocal and bilateral lesions do not preclude presurgical assessment or subsequent resective surgery	• Seizures persist in one third of TSC patients
Ketogenic diet	
• Should be considered in early infancy and early childhood if surgery is not an option • Consider for patients who are not surgical candidates, who have failed surgery, or with multifocal seizure onset • Use instead of other AEDs after vigabatrin failure remains controversial • Decreased mTOR activation in animal models may provide biological basis for MOA in TSC-associated seizures	• Compliance a problem in children past infancy • Half of patients in one study eventually required epilepsy surgery for persistent seizures or seizure relapse • Growth of SEGA may be observed
Vagus nerve stimulation	
• May be a first option when ketogenic diet is not acceptable or may be used in combination with ketogenic diet • Limited data indicate many patients experience reduction of seizure frequency	• Almost no patients become seizure-free
Cannabinoids: cannabidiol	
• Clinical trial results pending	• Limited experience in Europe • Mechanism of seizure inhibition remains unclear • Mainly anecdotal reports

effective AED when prescribed as the initial treatment of TSC-associated seizures in children.[34] In this study of 71 patients from a single center over a 26-year period, however, only 30% (21 of 71) achieved a remission longer than 24 months despite many treatments.

- The problem of vigabatrin-associated visual field constriction has not been resolved since the last recommendations were published in 2012. There are multiple studies indicating a high incidence of visual field constriction demonstrated by perimetry or ocular computed tomography; in particular, visual field defects were found in 34% of the cohort of 35 children in a recent multicenter international study.[35] The rate of visual field defects increased from 9 to 63% as the duration of treatment with vigabatrin increased. However, the risk of clinically obvious visual field constriction seems to be very low among children with brief exposure.[36]
- Although infantile spasms are reported in 30–60% of patients with TSC,[37] focal seizures are the most frequent seizure type by presentation; 50–60% of TSC patients develop multiple seizure types, including focal seizures with intact or impaired awareness, which may evolve to

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bilateral tonic or clonic seizures. ACTH (natural or synthetic) or prednisolone has been shown to be effective for TSC-related infantile spasms and is used as second-line therapy; GABAergic AEDs other than vigabatrin such as topiramate, carbamazepine and oxcarbazepine are also used as second-line therapy for focal seizures,[34] to increase the GABA inhibitory neurotransmitter level in the peri-tuberal area.

- Currently there are no clinical trials supporting the use of vigabatrin to prevent seizures based on serial EEG monitoring, and other AEDs may be as effective, especially for focal seizures.
- AED combination therapy is appropriate when vigabatrin monotherapy has failed, although careful AED selection is required based in part on seizure type (e.g., GABAergics for infantile spasms), and evidence of better efficacy than other AED classes has not been confirmed.[38]
- Presently there is limited evidence in Europe supporting the use of cannabidiol as AEDs for TSC-associated seizures, and the mechanism of seizure inhibition by cannabidiol, a non-psychoactive component of the cannabis plant, remains unclear.[39] In a dose-ranging study of cannabidiol titrated up to 50 mg/kg in 56 patients with drug-resistant epilepsy, a sub-analysis of 18 patients with TSC showed a 50% reduction in seizure frequency at 12-month follow-up in 50% of patients.[40] Anecdotal reports, including reports by parents who have administered tetrahydrocannabinol or cannabidiol to their children with TSC-associated seizures, indicate variable efficacy. A recently published online survey of TSC patients and their parents found a reduction of seizures in 7 of 10 who were treated with medicinal cannabis/cannabidiol.[41] A randomized controlled trial of cannabidiol for seizures in TSC (ClinicalTrials.gov Identifier NCT02544763)[42] and an open-label extension of that study (ClinicalTrials.gov Identifier NCT02544750)[43] are presently underway.

2.5.2. *mTOR inhibitors*

- mTOR inhibitors such as sirolimus (rapamycin) and everolimus inhibit mTOR signaling events by reducing the phosphorylation of downstream mTOR effectors, which are responsible for the translation of mRNA-encoding proteins that are necessary for cell cycle regulation, cell size control and growth, angiogenesis and glycolytic activity.[44] Several animal and human studies have demonstrated that mTOR activation can result in increased neuroexcitability and seizures, and, accordingly, mTOR inhibitors have been studied as anti-seizure therapy.[45] Sirolimus and everolimus have similar molecular mechanisms but distinct clinical profiles[46]; everolimus has been studied more extensively in TSC-associated seizures (Table 2).[47–52] The effect of everolimus on mTOR signaling currently is being measured in a study of patients with TSC who will be undergoing brain surgery (ClinicalTrials.gov Identifier NCT02451698).[53]
- The EXIST-3 trial showed that adjunctive everolimus produced a sustained reduction in TSC-associated treatment-refractory seizures over time in a significant proportion of children aged 2 years and older; the reduction in seizures was both time- and exposure-dependant.[51] Side effects were common and overlapped with previous data but led to treatment discontinuation in less than 5% of the everolimus low/high exposure groups. As a result of the EXIST-3 trial, everolimus was approved in December 2016 by the European Medicines Agency for "adjunctive treatment of patients aged 2 years and older whose refractory focal-onset seizures, with or without evolution to bilateral tonic-clonic seizures, are associated with tuberous sclerosis complex."[54] In clinical practice however, refractory TSC-associated seizures typically begin much earlier than 2 years of age, and additional research into earlier introduction of everolimus is warranted to address this need,

Table 2 – Clinical studies of mTOR inhibitors in TSC-associated seizures.

Study	Results
Open-label cross-over study of add-on efficacy of sirolimus titrated to 5–10 ng/mL in 23 children with TSC and intractable epilepsy randomized to treatment immediately or after 6 months.[49] Primary endpoint was change in seizure frequency during the sixth month of sirolimus treatment.	Sirolimus resulted in 41% reduction of seizure frequency compared with standard-care period ($P = 0.11$); 14 children who reached sirolimus target trough levels in the sixth sirolimus month showed seizure frequency decrease of 61% ($P = 0.06$).[49]
Effect of everolimus on seizure control assessed in 23 patients with TSC-associated treatment-refractory epilepsy in an open-label, phase I/II clinical trial.[47]	Seizures were reduced significantly by 73% ($P < 0.001$) in 17 of 20 evaluable patients, and seizure frequency also was reduced significantly during 23-hour EEG monitoring ($P = 0.007$).[47] At 4-year follow-up, quality of life improved by an average of 14%.[48]
Open-label prospective study of everolimus efficacy and safety in 15 children and adolescents with TSC-associated seizures.[50]	At final observation, 80% of patients were responders, 58% of whom were seizure free.[50] Overall reduction in seizure frequency was 60% for focal seizures, 80% for generalized tonic-clonic seizures, and 87% for drop attacks.
Phase III randomized, double-blind, placebo-controlled trial (EXIST-3) of 366 mainly pediatric patients with severe TSC-associated treatment-resistant seizures who were randomized in the core phase to placebo (n = 119), low-exposure everolimus (n = 117), or high-exposure everolimus (n = 130).[51] Primary endpoints were proportion of patients achieving ≥50% reduction in seizure frequency and median percentage reduction in seizure frequency.	Proportion of patients achieving ≥50% reduction in seizure frequency was 15.1% with placebo compared with 28.2% for low-exposure everolimus ($P = 0.0077$ vs. placebo) and 40.0% for high-exposure everolimus ($P < 0.0001$ vs. placebo).[51] Median percentage reduction in seizure frequency was 14.9% with placebo vs. 29.3% with low-exposure everolimus ($P = 0.0028$ vs. placebo) and 39.6% with high-exposure everolimus ($P < 0.0001$ vs. placebo). Extension phase demonstrated sustained efficacy of everolimus.[52]

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particularly in patients for whom add-on AEDs and/or the ketogenic diet with or without surgery have failed.

- In the EXIST-3 trial, the most frequent (≥10%) all-grade adverse events reported with everolimus (low exposure/high exposure) vs. placebo included stomatitis (28.2%/30.8% vs. 3.4%), mouth ulceration (23.9%/21.5% vs. 4.2%), diarrhea (17.1%/21.5% vs. 5.0%), aphthous ulcer (4.3%/14.6% vs. 1.7%), fever (19.7%/13.8% vs. 5.0%), cough (11.1%/10.0% vs. 3.4%) and rash (6.0%/10.0% vs. 2.5%).[51] Long-term treatment with everolimus in this population is safe and well tolerated.[48]
- In an anecdotal case report, it was observed that TSC-associated seizures may recur when everolimus is discontinued.[55]
- mTOR inhibitors such as sirolimus and everolimus have the potential to provide targeted therapy for other TSC-associated disease manifestations such as subependymal giant cell astrocytomas (SEGAs), renal angiomyolipomas (AMLs), skin angiofibromas, pulmonary lymphangioleiomyomatosis and cardiac rhabdomyomas as well as epilepsy.[56] Therefore, the positive effects that mTOR inhibitors have on a wide variety of TSC disease manifestations make this a promising systemic treatment option for this disorder. It should be noted, however, that short-term treatment of impaired neurocognition and behavioral problems with everolimus once daily for 6 months in patients 6–21 years of age with TSC did not significantly improve neurocognitive functioning or behavior.[57]

2.5.3. *Epilepsy surgery*

- Eligibility for resective or disconnective epilepsy surgery is currently not explored in the majority of TSC cases for reasons that include limited access to presurgical investigations and surgical treatment, the presence of multiple tubers, the occurrence of multifocal EEG abnormalities, and country-specific differences, although the literature on surgical outcomes is now quite extensive. A consensus panel on pediatric epilepsy surgery concluded in 2006 that children with epilepsy should be evaluated at a dedicated pediatric epilepsy center, although the recommendation was not specific to children with TSC-associated seizures.[58]
- Identification of the epileptogenic zone remains challenging in TSC and should be addressed in a comprehensive preoperative evaluation based on the objective analysis of multimodal functional and structural imaging techniques.[59]
- Prompt presurgical evaluation is recommended after the failure of two AEDs, even before infantile spasms occur and even with interictal epileptiform activity outside the selected area for resection, or when seizures are highly stereotyped (video-EEG) with a predominant focus or a large dysplastic lesion.[60]
- Noninvasive (scalp) video-EEG recording may be sufficient in cases with concordant clinical, EEG, and MRI findings, but invasive recording may be necessary in cases of multiple epileptogenic zones or to delineate the resected area.[61]
- Depending on the procedure, early surgical intervention can increase the probability of seizure-freedom significantly, even in complex patients, but may also have a palliative use targeting the most devastating seizure type.[61]
- A review of the literature[62–64] concluded that 55–60% of patients become seizure-free postoperatively, but seizures persist generally in approximately 40% of surgically-treated TSC patients. Predictors of seizure recurrence were generalized seizure semiology including tonic seizures, intellectual disability, multifocal EEG abnormalities, and EEG/MRI imaging disconcordance.
- A multicenter study found higher rates of seizure freedom with resection beyond tuber margins among consecutive surgical cases.[65]
- Epilepsy surgery not only successfully controls seizures but may also lead to improvements in quality of life and IQ, especially in patients who remain seizure-free postoperatively.[66]

2.5.4. *Ketogenic diet*

- Studies have identified the ability of the ketogenic diet to decrease mTOR activation in animal models, providing a biological basis for its mechanism of action in TSC-associated seizures.[67]
- The ketogenic diet could be beneficial in refractory TSC-associated seizures. In one small, open-label study, four of 12 of patients with TSC were seizure-free after 3 months on the ketogenic diet.[68] According to the experience of experts, the ketogenic diet should be considered especially in infancy and early childhood, even in combination with vigabatrin.
- In a study of 42 patients with epileptic encephalopathies treated with oral corticosteroids, the addition of a ketogenic diet for at least 6 months allowed 14 patients (10 steroid-dependent and 4 steroid-resistant) to discontinue steroids, the ketogenic diet.[69]
- The ketogenic diet can be initiated at a very young age[68] because there are minimal compliance problems with the use of commercial formulas.

2.5.5. *Vagus nerve stimulation*

- Use of vagus nerve stimulation is not specific for TSC, but it can be an option for children older than 2 years with refractory TSC-associated seizures who are not candidates for epilepsy surgery.
- Data are limited but indicate that, while approximately half of the patients with TSC experience a significant reduction of seizure frequency with vagus nerve stimulation, almost none becomes seizure-free.[70–73] In the largest study of vagus nerve stimulation in children with drug-resistant seizures, 5.8% became seizure-free by 6 months and 8.2% by 24 months, but the underlying disorder was not limited to TSC.[74]
- In a cost-utility analysis of competing treatment strategies for drug-resistant epilepsy in children with TSC, vagus nerve stimulator implantation was more expensive and less effective than other management options.[75]

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3. Recommendations, unanswered questions and future research

The need for early diagnosis of TSC-associated seizures is now well established, and early EEG monitoring and the policy of informing and educating parents to recognize seizures as soon as they appear has been adopted in some European countries. However, not all panelists agreed that EEG findings currently represent a biomarker for risk of epilepsy in infants with TSC. According to the experts' opinion, it is still disputable which EEG abnormalities predict the subsequent appearance of epilepsy and when the onset of clinical seizures can be expected based on EEG findings, which could guide therapeutic interventions aimed at subsequent disease modification.

According to experts' opinion and recommendation, vigabatrin should be initiated presymptomatically in the presence of paroxysmal ictal activity, with the preventive dose ranging from 50 to 150 mg/day, although currently there is no consensus regarding dosage. The optimal time to discontinue preventive AEDs in this setting remains to be determined but varies from 6 months to 2 years of age. The experts agreed that the first add-on AED after vigabatrin failure in the first year of life should be ACTH/hormonal therapy (e.g., prednisolone) in cases of infantile spasms with hypsarrhythmia. When infantile spasms are associated with focal/multifocal abnormalities, topiramate should be added. For focal seizures, other AEDs that enhance GABAergic inhibition can be considered. Administration of vigabatrin should be considered in presymptomatic infants or children with TSC and ictal epileptiform EEG discharges but without clinical seizures. Cannabinoids have been studied as AEDs, as yet with inconclusive results.

There is growing but still limited experience in European countries with the use of mTOR inhibitors as adjunctive treatment of TSC-associated drug-refractory seizures. However, in the experts' view, more clinical experience is needed to understand the efficacy of mTOR inhibitors for children less than 2 years of age with TSC-associated epilepsy.

Despite increasing reports with positive results, epilepsy surgery continues to be underutilized. According to the experience of experts, the ketogenic diet should be considered especially in infancy and early childhood, potentially in combination with vigabatrin or ACTH. Whether the ketogenic diet should be used immediately after vigabatrin failure instead of other AEDs is still unclear. Vagus nerve stimulation may be the next option when the ketogenic diet is not tolerated, or it may be used in combination with the ketogenic diet.

Since 2012, however, a number of questions still remain unanswered and new questions have arisen, which can provide insights and guidance for the future direction of research into and clinical studies of TSC-associated seizure prevention and management. These unresolved issues are listed in Table 3. A number of ongoing studies of TSC-associated seizures in addition to those noted above may provide answers to these unresolved issues. These studies include an assessment of potential EEG biomarkers and anti-epileptogenic strategies for epilepsy in TSC, an evaluation of the effects of everolimus on brain mTOR activity in TSC,[76] and new diagnostic and therapeutic methods in TSC-associated epilepsy.[77]

4. Conclusions

- Investing in education and awareness to promote early recognition of infantile spasms and focal seizures in infants should be encouraged, and early diagnosis and treatment will be facilitated by regular EEG monitoring.
- The need for early and close clinical and video EEG monitoring is widely accepted to identify seizure susceptibility and recognize seizures. EEG has a good predictive value for epilepsy in TSC, and early treatment based on EEG monitoring significantly improves the outcomes of young children with epilepsy.
- Certain EEG patterns can be predictive of subsequent seizure presentation as well as seizure type. For example, multifocal spikes may precipitate hypsarrhythmia, with subsequent clinical infantile spasms. Some studies have shown that EEG abnormalities can predict impending epilepsy in asymptomatic children with TSC, a finding currently being assessed further in the EPISTOP and PREVeNT trials.
- Until results of EPISTOP are available, vigabatrin may be considered in infants and children within 24 months of life if ictal discharges occur in the absence of clinical manifestations. Antiepileptic treatment before the onset of clinical seizures may reduce epilepsy severity and neurodevelopmental disorders in infants with TSC.
- Vigabatrin is accepted as the first choice for infantile spasms and focal seizures, since, if started early, it may prevent the evolution of focal seizures to infantile spasms in the first year of life. Response to vigabatrin therapy

Table 3 – Questions and unresolved issues.

- There is a need to identify infants at high risk for early seizures soon after a presymptomatic diagnosis of TSC.
- There is also a need to identify biomarkers that can provide an early indication of TSC-associated seizure risk.
- It remains to be determined how long an infant with TSC should be treated preventively.
- There is a need to identify early predictive factors for refractoriness to AEDs.
- The optimal first add-on AED after vigabatrin failure in focal seizures remains to be identified.
- There is a need to identify which combination of existing treatment options is most effective in reducing seizure frequency and severity.
- There is a need for studying the efficacy and safety of mTOR inhibitors for refractory epilepsy in children below 2 years of age with TSC.
- A means of identifying specific patient subgroups that are more likely to be mTOR inhibitor responders/non-responders will be helpful clinically.
- It remains to be determined definitively whether mTOR inhibition benefits cognitive and behavioral problems associated with epilepsy in TSC.

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initiated early after onset of focal seizures or infantile spasms is rapid and high, but generally only one third of all patients achieve long-term seizure remission.

- The first add-on AED after vigabatrin failure in the first year of life is ACTH/hormonal therapy in cases of infantile spasms and hypsarrhythmia, and possibly GABAergics such as topiramate for infantile spasms with focal/multifocal EEG abnormalities. AEDs that enhance GABA inhibition, such as topiramate, carbamazepine and oxcarbazepine, can be considered for focal seizures.
- Trials on the use of cannabidiol are underway and definitive recommendations will depend on the results.
- mTOR inhibition should be considered early for seizures refractory to 2 or more appropriate AEDs, particularly when other systemic lesions can benefit from targeted molecular treatment (e.g., renal AMLs, SEGAs).
- The EXIST-3 extension phase analysis demonstrated sustained efficacy of adjunctive everolimus for the treatment of TSC-associated drug-refractory seizures, and greater reduction of seizure frequency has been observed with high everolimus exposure in younger children, with an overall acceptable safety profile.
- Surgery still is underutilized, and prompt presurgical evaluation is recommended after the failure of two AEDs or even earlier in infants with large dysplastic lesions.
- Success of surgery is increased by early intervention and accurate localization of the epileptogenic region, but seizures persist generally in 40% of surgically-treated TSC patients.
- Studies have identified the ability of the ketogenic diet to decrease mTOR activation in animal models, providing a biological basis for its mechanism of action in TSC-associated seizures.
- The ketogenic diet should be considered especially in early infancy and early childhood if surgery is not an option before the age of one year even, in combination with vigabatrin or ACTH, with better compliance in young infants.
- Vagus nerve stimulation can be an option for patients who are not candidates for surgery.

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Conflicts of interest

The author(s) have no relevant disclosures related to this manuscript.

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Appendix. Participants in the European Consensus Meeting, Management of Epilepsy Associated with Tuberous Sclerosis Complex: Updated Clinical Recommendations, September 9, 2017, Rome, Italy.

Chair	
Paolo Curatolo	Italy
Participants (in alphabetic order)	
Eleonora Aronica	The Netherlands
Martha Feucht	Austria
José Carlos Ferreira	Portugal
Christoph Hertzberg	Germany
Anna Jansen	Belgium
Floor Jansen	The Netherlands
Sergiusz Jóźwiak	Poland
Katarzyna Kotulska	Poland
Lieven Lagae	Belgium
Romina Moavero	Italy
Rima Nabbout	France
Finbar O'Callaghan	United Kingdom
Antigone Papavasiliou	Athens, Greece
Michal Tzadok	Israel

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