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ORIGINAL ARTICLE

The state of pediatric tuberous sclerosis complex epilepsy care: Results from a national survey

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Abstract

Objective: Epilepsy associated with tuberous sclerosis complex (TSC) can be challenging to treat and is associated with significant disease burden. Our objective was to better understand the state of epilepsy care of TSC amongst pediatric neurologists in Canada, identify gaps in care and determine whether access to a dedicated TSC clinic has an impact on epilepsy management.

Methods: A survey was developed after a literature review and discussion amongst two pediatric epileptologists and one nurse practitioner with expertise in TSC about the state of epilepsy care of TSC patients in Canada. Canadian pediatric neurologists were asked to participate in sharing their experiences via an anonymous web-based survey through the Canadian League Against Epilepsy (CLAE) and the Canadian Neurological Sciences Federation (CNSF).

Results: Fifty-seven responses were received. Access to a dedicated TSC clinic was reported by 25% (n = 14). Sixty percent (n = 34) reported performing serial EEG monitoring in infants with TSC and 57% (n = 33) started prophylactic antiseizure therapy when EEG abnormalities were detected, regardless of whether there was access to a TSC clinic ($P = .06$ and $P = .29$, respectively). While 52% (n = 29) did not feel comfortable prescribing mTORi for epilepsy, 65% (n = 36) indicated they would consider it with additional training. Epilepsy surgery was offered in 93% (n = 13) of centers with a dedicated TSC clinic but only 45% of centers without a TSC clinic (n = 19) ($P = .002$).

Significance: Our findings demonstrate the variability in neurological care of pediatric patients with TSC as it pertains to epilepsy management. There is a need for the establishment of epilepsy practice guidelines and a national network to support clinical practice, research, and education.

KEYWORDS

emerging therapies, epilepsy, multidisciplinary care, surveillance EEG, Tuberous sclerosis complex (TSC)

1 | INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic condition characterized by the presence of hamartomas in different organs.[1,2] It is estimated to occur in 1 in 6000 live births.[1] TSC is primarily caused by pathogenic variants in the *TSC1* and *TSC2* genes, causing upregulation of the mammalian target of rapamycin (mTOR) pathway, leading to proliferation and growth of benign tumors in multiple organ systems.[3] Clinical phenotypes of TSC can vary from mild to severe.[4,5] In addition, many of the manifestations of TSC are age-dependent, and may present early (i.e., heart, skin) or later in life (i.e., lungs, eyes).[6] The neurological manifestations of TSC, which include epilepsy, neurodevelopmental disorders, and TSC-associated neuropsychiatric disorders (TAND) are associated with the greatest disease burden and often begin early in life, which is a critical period in neurodevelopment.[6,7] Epilepsy affects 80%-90% of individuals with TSC and in 79% of cases, epilepsy develops within the first two years of life.[8,9] More than 60% of individuals with TSC have medically refractory epilepsy, which remains a major treatment challenge despite advancements in therapies.[10]

The management of epilepsy and neurological care in TSC requires knowledge and familiarity with emerging therapies.[10] Newer medications such as Mammalian target of rapamycin inhibitor (mTORi) have growing therapeutic indications that can cross disciplines (i.e., nephrology and neurology). Everolimus is recommended as a treatment option for subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas (AMLs),[11] and is being increasingly used for the management of medically refractory epilepsy.[12] Epilepsy surgery, neurostimulation, deep brain stimulation, and cannabidiol (CBD) are also now treatment options for epilepsy associated with TSC.[7] Further, newer therapeutic approaches such as preventative vigabatrin therapy in infants and serial electroencephalogram (EEG) monitoring[13] highlight the importance of early diagnosis of TSC and the need for multidisciplinary collaboration and protocol development, which may alter the course of neurodevelopmental outcomes.[14–16]

In 2012, the International TSC Consensus Conference established recommendations for the surveillance and management of TSC, and these guidelines were updated in 2021.[17] A multidisciplinary care approach was recommended[13,14] and roadmaps for the implementation of successful[17,18] multidisciplinary care have been previously established[19] However, implementation of such guidelines can be challenging and resource intensive for many practitioners.[20] Coordinated care delivery in TSC has been the focus of a few publications[20,21] and patient advocacy groups to date, however, and it is unclear how access to multidisciplinary care may influence the epilepsy management of TSC.[22]

Key Points

- The epilepsy care of pediatric patients with TSC remains variable, despite treatment advances.
- Surveillance EEG and preventative ASM treatments in infants with TSC have been adopted by many clinicians, although 40% are not following this practice.
- mTORi for the management of TSC-associated epilepsy remains underutilized; educational intervention may help increase the comfort of prescribing them.
- Epilepsy surgery is more commonly utilized when there is access to a local TSC clinic.
- Major barriers to TSC care include a lack of knowledge of new therapies, limited resources, and access to multidisciplinary clinics.
- There is a need for the establishment of TSC-specific epilepsy practice guidelines and a national network to support clinical practice, research, and education.

Given the challenges of caring for individuals with TSC and the significant burden that neurological manifestations and particularly epilepsy can have[23–25]; our objective was to better understand the state of TSC epilepsy care amongst pediatric neurologists in Canada as a quality improvement initiative. A key to creating recommendations and implementing change is to first identify the state of care delivery, identify resource needs, access to therapies, and the knowledge required to implement such therapies. Thus, our aims were to: (a) identify patterns of epilepsy care as they relate to current guidelines and treatment advancements, (b) identify barriers and gaps in care, and (c) determine whether epilepsy care differs when there is access to a local multidisciplinary TSC clinic. Finally, we also sought to determine factors that contribute to the preparedness of providers when considering emerging therapies for the management of TSC-associated epilepsy.

2 | METHODS

A survey was developed after a review of the literature and discussion amongst two pediatric epileptologists and one pediatric nurse practitioner with expertise in the management of TSC. Pediatric Neurologists and allied healthcare

professionals across Canada were invited to participate in a web-based survey. A link to the anonymous survey was distributed through the Canadian League Against Epilepsy (CLAE), Canadian Pediatric Epilepsy Network (CPEN) and the Canadian Neurological Sciences Federation (CNSF). Participation was voluntary. Data were gathered over a three-month time frame (during the spring of 2021) and two separate reminders were sent to engage and encourage participation. The survey completion time was between 5 and 10 minutes. This study was considered a quality improvement project and thus formal ethics board approval was waived.

The survey was divided into four sections. The first portion of the survey gathered demographic information such as participants' practice settings and years of training. The second section asked questions regarding TSC practices such as access to a dedicated TSC clinic, number of TSC patients followed, genetic testing practices, access to a transition clinic, and familiarity with the 2012 International TSC Consensus Guidelines (Table 1). The third section of the survey focused on emerging epilepsy therapies in epilepsy care such as pre-emptive serial EEG monitoring and treatment with antiseizure medications (ASMs) in individuals with newly diagnosed TSC and the use of mTORi for different indications in TSC (i.e., epilepsy, SEGAs). The survey concluded by asking a free-text question about general barriers to treating individuals with TSC. A copy of the survey can be found in Supplementary Material S1.

All analyses were carried out using the Stata statistical programming version 15.1 for Mac. Descriptive statistics were calculated using mean and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. Binary logistic regression models were used to assess factors in a practitioner's preparedness to consider emerging therapies in TSC-associated epilepsy (considered as either preventative treatment for infantile spasms/epilepsy or the use of mTORi for treatment of epilepsy). The Fisher's exact value was used to report the management of TSC-associated epilepsy in those with and without access to a TSC clinic. $P < .05$ was used to determine statistical significance. Responses to qualitative questions were reviewed and categorized into major themes by the authors.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3 | RESULTS

Responses were received from 57 healthcare practitioners across Canada. Ninety-one percent (51/56) of the participants were physicians, while the remainder was composed of trainees (i.e., neurology residents/fellows), nurses, and nurse practitioners. Most respondents (82%, 47/57) practiced in an academic setting (Table 1). The distribution of respondents from across Canada is depicted in Figure 1. Most participants were pediatric providers (82%, 47/57) with an equal mix of pediatric neurologists and epileptologists (42% and 39%, respectively). Thirty-five percent of respondents were in practice for less than 5 years (35%, 20/57), 21% were in practice between 5 and 10 years (12/57), 21% were in practice between 11 and 20 years (12/57), and 23% were in practice >20 years (13/57). Thus, there was a larger representation in our cohort of respondents who were within 5 years of starting their practice (Table 1). Two-thirds of the respondents (69%, 38/55) indicated that they followed up to 10 patients with TSC in their practice. While only 10% (5/55) followed greater than 100 individuals with TSC. Access to a pediatric-specific TSC clinic was reported by 25% (14/57) of the respondents. Most of the respondents were familiar with and were implementing the recommendations from the 2012 International TSC Conference Consensus Guidelines in their clinical practice (49/57, 89%). Centers with a higher number of TSC patients were more likely to have a dedicated TSC clinic ($P < .001$). mTORi was only considered by one-quarter of the participants for the management of epilepsy (15/57, 26%). Most respondents did not feel comfortable prescribing mTORi for the treatment of TSC-associated epilepsy (29/56, 52%) (Table 2). Administration of mTORi for other indications (SEGA, AML) was often led by pediatric neuro-oncologists and pediatric nephrologists (Table 2).

Our survey inquired about existing and emerging practices in the management of TSC-associated epilepsy; Table 3 compares such practices amongst those who did and did not have access to a TSC clinic. While screening EEG and preventative ASM treatment in infants was considered by nearly 60% of participants, employing such novel practices was not influenced by access to a TSC clinic ($P = .06$ and $P = .29$, respectively). Variable practices were reported with respect to the frequency of EEG screening in infants with a new diagnosis of TSC as depicted in Table 3, and most participants repeated EEGs every 1-2 months in the first 1-2 years of life ($P = .42$). A similar number of respondents, regardless of access to a TSC clinic reported using vigabatrin as a preventive ASM in infants with an abnormal screening EEG ($P = .92$). Other ASMs that were reported as preventative were topiramate (n = 2), clobazam (n = 1), phenobarbital (n = 1), valproate (n = 1), levetiracetam (n = 1) and oxcarbazepine (n = 1). Epilepsy surgery was offered in 93% of centers with a dedicated TSC clinic but only in 45% of centers without a TSC clinic ($P = .002$). Consideration of initiating mTORi for the purpose of

TABLE 1 Demographic characteristics of respondents and overall TSC practice and access to TSC clinics

Questions (N = number of responses)	Responses	N (%)
Job description (N = 56)	Physician	51 (91%)
	Nurse (includes advanced nurse practitioner)	3 (6%)
	Trainees (i.e., residents, fellows)	2 (3%)
Specialty (N = 57)	Pediatric epilepsy	22 (39%)
	Pediatric neurology	24 (42%)
	Adult neurology	6 (11%)
	Other	5 (9%)
Primary area of practice (N = 57)	Private/community practice	10 (17%)
	Academic/university setting	47 (82%)
Years in practice (N = 57)	<5 years	20 (35%)
	5-10 years	12 (21%)
	11-20 years	12 (21%)
	>20 years	13 (23%)
No. of TSC patients seen per year (N = 55)	0-10 patients	38 (69%)
	10-30 patients	7 (13%)
	30-50 patients	1 (2%)
	50-100 patients	4 (7%)
	>100 patients	5 (9%)
Access to dedicated TSC clinic (N = 57)	Yes	14 (25%)
	No	43 (75%)
Access to adult TSC clinic (N = 55)	Yes	22 (40%)
	No	33 (60%)
Does access to TSC clinic enhance care delivery (N = 16)	Yes	15 (93%)
	No	1 (6%)
Routine genetic testing in TSC (N = 57)	Yes	36 (62%)
	No	10 (18%)
	When clinical diagnosis is in doubt	11 (20%)
Implementing 2012 International TSC guidelines (N = 57)	Yes	49 (86%)
	No	8 (14%)

Abbreviations: ASM, antiseizure medication; CBD, cannabidiol; DBS, deep brain stimulation; No, number; VNS, vagus nerve stimulation.

treating epilepsy was not influenced by the absence or presence of a TSC clinic ($P = .43$).

Binary logistic regression was designed to evaluate the relationship between potential predictors (academic affiliation, local pediatric TSC clinic, subspeciality, years in practice, and being an epilepsy surgery center) and response variable (emerging therapies in TSC-associated epilepsy, defined as consideration of either preventative treatment in infants with TSC and abnormal EEG or use of mTORi for management of epilepsy) (Table 4). Of the potential predictors that were tested in this model, the highest odds of implementing emerging therapies were in those participants who had a dedicated pediatric TSC clinic (OR 4.08, $P = .08$), were pediatric epileptologists (OR 4.07, $P = .06$) and were adhering to 2012 International TSC Guidelines (OR 4.04, $P = .07$).

Additional qualitative data collected as part of this survey were analyzed to better understand barriers influencing the management of TSC patients as summarized in Figure 2. Most participants identified the absence of expertise and familiarity with new treatments as an important barrier (41%, n = 24). Lack of resources for screening and managing TAND (33%, n = 19) and lack of access to multidisciplinary care (21%, n = 12) were also identified as gaps by providers. Sixty-five percent (36/57) of the participants agreed that with more support and education, they would feel more confident in using mTORi for various manifestations of TSC including treating seizures (Table 1).

FIGURE 1 Geographic distribution of the participants nationally (N = 57)

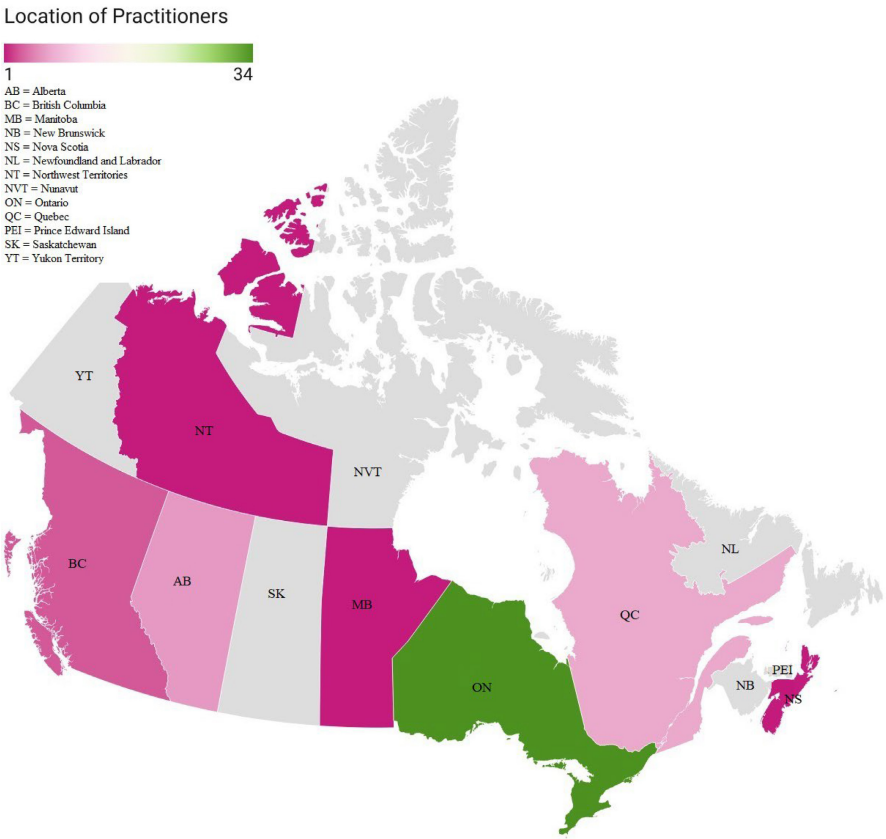

TABLE 2 Reported patterns of mTORi use in TSC

Discipline primarily involved for the use of mTORi for treatment of SEGAs (N = 55)	Pediatric Neuro-Oncologist	22 (40%)
	Pediatric Neurologist	16 (29%)
	Other: Adult Nephrologist, Adult Neuro-Oncologist, Adult Epileptologist	3 (5%)
	Not identified	14 (25%)
Discipline primarily involved for the use of mTORi for treatment of AMLs (N = 50)	Pediatric Nephrologist	21 (42%)
	Pediatric Neurologist	3 (6%)
	Pediatric Neuro-Oncologist	2 (4%)
	Other: Adult Epileptologists, Nephrologist, Urologist	5 (10%)
	Not identified	19 (33%)
Consideration of mTORi to primarily treat intractable seizures (N = 57)	Yes	15 (26%)
	No	38 (67%)
	Not identified	4 (7%)
Comfortable prescribing mTORi to treat seizures in TSC (N = 56)	Yes	26 (46%)
	No	29 (52%)
	Not identified	1 (2%)
Additional training/support would allow increased use of mTORi for treating the various manifestations of TSC including seizures (N = 55)	Yes	36 (65%)
	No	2 (4%)
	Not applicable, already feel comfortable	17 (31%)

Abbreviations: AML, angiomyolipoma; mTORi, mammalian target of rapamycin inhibitor; SEGA, subependymal giant cell astrocytoma.

TABLE 3 Management of TSC-associated epilepsy compared by participant access to TSC clinic

Variables, N = total responses	Access to TSC clinic (N = 14) N (%)	No access to TSC clinic (N = 43) N (%)	*P*-value[a]
Screening EEGs in newly diagnosed TSC infants (N = 48)	11 (78%)	23 (53%)	.08
Frequency of EEG screening (N = 35)			
Every 1-2 months in the first 1-2 years	4 (44%)	13 (50%)	.63
Every 3-6 months in the first 1-2 years of life	3 (33%)	8 (31%)	
Once at diagnosis of TSC	0 (0%)	1 (4%)	
Every 6-8 weeks in first year if referred prior to seizure onset	1 (11%)	0 (0%)	
Only if clinically indicated, i.e., concerns for seizures	1 (11%)	4 (15%)	
Use of presymptomatic ASM in those with an abnormal EEG in the absence of clinical seizures (N = 33)	10 (71.5%)	23 (53.5%)	.46
Choice of ASM as first line treatment for prevention (N = 26)			
Vigabatrin	6 (86%)	16 (84%)	.73
Other ASM	1 (14%)	3 (16%)	
Duration of ASM treatment for prevention (N = 20)			
<6 months	0 (0%)	1 (7%)	.47
6-12 months	4 (80%)	6 (40%)	
>12 months	1 (20%)	8 (53%)	
Working at a center that offers epilepsy surgery to patients with TSC (N = 57)	13 (93%)	19 (45%)	.002
Consideration of mTORi to primarily treat intractable seizures (N = 15)	4 (28%)	11 (25%)	.35

Abbreviations: ASM, antiseizure medication; EEG, electroencephalogram.

[a]Fisher's exact test.

TABLE 4 Logistic regression results looking at factors that contribute to consideration of newer emerging therapies in managing TSC-associated epilepsy

Predictor	Odds Ratio	Lower CI (95%)	Upper CI (95%)	*P*-value
Practice set up (academic vs community)	2.2	0.57	9.2	.24
Pediatric TSC clinic	4.08	0.81	20.6	.08
Specialty (ref: pediatric neurology)				
Pediatric epilepsy	4.07	0.92	17.9	.06
Adult neurology	0.64	0.10	3.9	.60
Other	0.16	0.015	1.7	.12
Years in practice (ref: <5 years)				
5-10 years	0.64	0.14	2.8	.57
11-20 years	0.75	0.17	3.2	.70
>20 years	2.9	0.51	17.2	.22
Following 2012 International TSC guidelines	4.04	0.84	19.3	.07
Epilepsy surgery center	2.3	0.73	7.2	.15

4 | DISCUSSION

Our study aimed to explore the state of epilepsy care of pediatric patients with TSC nationally and determine factors that contribute to the preparedness of providers when considering emerging therapies for the management of TSC-associated epilepsy. We also examined whether access to a local TSC clinic influenced decision-making and explored barriers faced by practitioners who treat patients with TSC. Previous survey-based studies have examined the

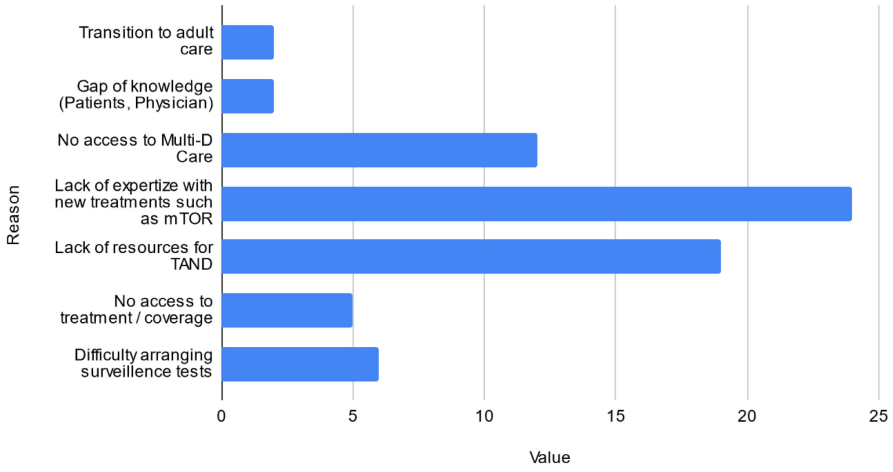

FIGURE 2 Main barriers identified by participants in management of patients with TSC. Legend: Barriers identified to managing patients with TSC, showing the barriers identified and the raw count (number of participants) who identified these as barriers

approach to the preventative treatment of epilepsy in infants with TSC, as well as patterns of ASM use in individuals with TSC, although to our knowledge have not explored clinicians' level of preparedness and comfort with prescribing newer therapies.[26,27] Although none of the factors in our survey achieved statistical significance, being an epileptologist, familiarity with the 2012 International TSC Consensus Guidelines, and affiliation with a TSC clinic resulted in the highest odds when considering emerging therapies such as mTORi and preventive ASM treatment. Interestingly, practice settings (academic versus community practice) and years of practice had lower odds of incorporating emerging therapies for the management of epilepsy.

The use of surveillance EEG and preventative ASM treatment with vigabatrin has been the subject of several studies over the last decade and more recently the results of the EPISTOP trial were published.[28–30] The findings from the EPISTOP study demonstrated that preventative vigabatrin treatment in infants with TSC reduces the frequency of infantile spasms, clinical seizures, and medically refractory epilepsy at 24 months.[13,31] Although, the risk of developmental delay and autism spectrum disorder was not statistically different between the groups. Despite the results of the EPISTOP trial and others,[16,32–34] we found that the practice of surveillance EEG monitoring and preventative ASM use in infants with TSC was highly variable across the country. Only 60% of the respondents endorsed performing screening EEGs in infants with TSC and this practice was more common when affiliated with a local TSC clinic (78% versus 53%). The frequency of EEG monitoring was also variable in our study, although the new 2021 TSC Consensus Guidelines (published after our survey was distributed) recommend obtaining a routine EEG in infants with TSC every 6 weeks up to the age of 12 months and every 3 months up to the age of 24 months.[17] A recent survey examining preventative epilepsy treatment in 23 countries similarly found that 70% of clinicians perform regular EEG screening in infants with TSC. More than half (57%) of the respondents in our cohort endorsed the use of preventive ASM treatment for infants with abnormal EEGs and TSC, which was slightly more than what clinicians endorsed from the 23-country survey (51.7%). Starting preventive ASM was more common when there was access to a local TSC clinic in our study (71% vs 53%), although this was not statistically significant ($P = .46$). Vigabatrin was the preferred ASM used for preventative treatment in our study, similar to the 23-country study.[26]

Overall, the results of our study and the 23-country study suggest that although preventative EEG monitoring and ASM treatment have been adopted by a sizable portion of clinicians, this practice has not been adopted by all.[26] Some clinicians in our cohort cited difficulties with arranging surveillance tests and knowledge gaps in prescribing newer therapies as shown in Figure 2. In addition, a lack of familiarity with monitoring practices, discomfort with prescribing ASMs in the absence of seizures (i.e., due to long-term side effects of vigabatrin for example), lack of additional randomized control trial data, and a perceived lack of impact on developmental outcomes could be other reasons for why preventative monitoring/therapies were not used by all respondents.[26,35] However, the pending results of the PREVeNT trial (clinicaltrials.gov identifier NCT02849457) may help provide further evidence of the benefits of preventive EEG monitoring and ASM treatment in infants with TSC. Likewise, the development and implementation of national standard of care guidelines for preventative treatment in infants with TSC may provide the additional support needed for clinicians. At present time, the 2021 TSC Consensus Guidelines do not provide recommendations about starting preventative ASM in infants with TSC and abnormal EEGs.[17]

The use of mTORi for the treatment of medically refractory epilepsy in TSC has been widely studied and mTORi

therapy should be considered as an add-on therapy for individuals with medically refractory epilepsy associated with TSC. However, only 26% of participants in our cohort reported prescribing mTORi for the treatment of epilepsy associated with TSC, despite the majority working in an academic center. In a recent adult cohort, similarly, 30% of adult patients with epilepsy and TSC were treated with mTORi therapy.[26] More than 50% of participants in our cohort did not feel comfortable prescribing mTORi therapy for seizures associated with TSC, for reasons such as lack of knowledge (i.e., regarding dosing and side effects), cost, and insurance/healthcare coverage. The use of mTORi for the treatment of epilepsy was not positively influenced by access to a TSC clinic in our study either. Furthermore, AMLs and SEGAs were most often treated by non-neurologists in our cohort, which may explain why neurologists were uncomfortable prescribing them for epilepsy. Interestingly, with additional training, two-thirds of the cohort indicated that they would use mTORi for the various manifestations of TSC. These findings suggest that educational intervention and additional training for neurologists/healthcare practitioners could increase their comfort with prescribing mTORi. To our knowledge, previous studies have not explored neurologists' comfort with mTORi therapy in TSC. The Project ECHO model has been previously shown to improve primary care providers' knowledge and self-confidence in managing epilepsy, and it is possible that such a model could be created to increase neurologists' comfort with prescribing mTORi in TSC, particularly when there is no access to a specialized clinic.[36] Although, it is important to note that regardless of knowledge and comfort, in some regions, the cost of mTORi may be prohibitive for some patients. The economic costs and the resource utilization requirements of TSC are also significant. Nevertheless, from a patient's perspective, retention rates of mTORi therapy for the various manifestations of TSC have been found to be high, and they are also generally well tolerated. Thus, obtaining more affordable access to mTORi is a critical focus of advocacy for patients with TSC, given their benefits as a disease-modifying therapy.[37,38]

We found that epilepsy surgery was more likely to be offered in our cohort when there was an affiliated TSC clinic. This finding could be secondary to specialized expertise within a dedicated TSC clinic and clinicians being more aware of the role of epilepsy surgery in TSC including both resective surgical approaches and palliative procedures such as corpus callosotomy and vagal nerve stimulation. The benefits of epilepsy surgery have been explored in several studies; although, surgery remains underutilized in patients with TSC and refractory epilepsy and is not always considered as observed in our study.[39–44]

Finally, we identified that most providers across Canada were caring for approximately ten patients with TSC. While TSC patients use a wide array of healthcare services, fewer than a third are accessing healthcare services and treatment at TSC clinics where multidisciplinary care is available. Despite this finding, most clinicians (89%) were adhering to the 2012 International TSC Consensus Guidelines, which were the most current guidelines at the time of our survey. For those that had access to a TSC clinic, the majority agreed that it enhanced care delivery. Currently, more literature regarding the benefits and goals of establishing a multidisciplinary care team in TSC is needed. Although, a recent study in adults with TSC demonstrated global patient satisfaction with a multidisciplinary approach to care, and a three-step approach to developing a multidisciplinary TSC team/clinic has been previously established.[19,21] In addition to limited multidisciplinary care, we also found that access to adult TSC and transition clinics was limited. Lack of knowledge and comfort with newer therapies, difficulty accessing resources, and lack of TAND support were identified as major barriers to the treatment of patients with TSC and require additional advocacy nationally and beyond.

Our study has limitations, including a relatively small sample size, although comparable to the 23-country survey of preventative epilepsy treatment in TSC, as well as representation from only one country.[26] The results of our study may therefore not be generalizable to other countries with different healthcare systems, funding, and resources available. Further, most participants in our cohort were in their first five years of practice and from an academic center, and thus may not be representative of clinicians in other practice settings. Most of our cohort followed a relatively small number of patients with TSC, which may have affected their level of expertise. Moreover, less than half of the cohort had access to a dedicated TSC clinic and because of small numbers, this affected our ability to find differences in care regarding the presence or absence of a dedicated TSC clinic. We also did not conduct a power calculation to estimate the number of participants needed to find meaningful results and this is a significant limitation of our study. Future survey-based studies should conduct power calculations to avoid this. Our survey did not address the state of care delivery for all the multisystemic manifestations of TSC and future surveys can be designed to evaluate this. We did not evaluate the type of support required to allow for current care practices (i.e., surveillance EEG) to be used (i.e., nursing, administrative, funding, etc.). We also did not ask whether participants adhered to the 2021 guidelines as they were not available in print form at the time our survey was distributed. Finally,

another limitation was that not all participants answered each question in the survey and there was missing data.

Future directions of study include: (a) the implementation of the standard of care treatment guidelines for the use of novel neurological therapies in TSC, (b) employing an ECHO framework to increase clinicians' use of novel therapies (i.e., especially for those who do not have access to multidisciplinary care/TSC clinic) and (c) the establishment of a national/regional TSC network. In settings where the creation of multidisciplinary TSC clinics is not feasible given the limited local resources and smaller patient volumes, the creation of regional and national TSC hubs/networks can provide the support smaller centers need. The establishment of a national TSC network can aid in the development of care guidelines by considering regional resources and support the development of additional multidisciplinary clinics and support smaller centers by identifying regional referral hubs, TSC-focused case discussions, and update meetings. Further, it will provide a forum to review current practices and support consistent practice nationwide. Future evaluation of the impact of a national TSC network with defined clinical, educational, and research goals on the care of patients with TSC will be important.

5 | CONCLUSION

In summary, we have demonstrated the current state of TSC epilepsy care nationally, as well as gaps and challenges with care delivery. Overall, we have shown that the epilepsy care of pediatric patients with TSC remains variable, despite recent treatment advances. Although surveillance EEG and preventative ASM treatment have been adopted by many clinicians, there remains a sizable portion who are not yet following these practices despite current evidence. mTORi for the management of TSC-associated epilepsy is rarely considered and it is an emerging therapy that many pediatric neurologists do not feel comfortable prescribing, although would be with additional training. Epilepsy surgery is more commonly considered when there is access to a TSC clinic. Major barriers to TSC care included a lack of knowledge of new therapies, limited resources, and access to multidisciplinary clinics. Overall, there is a need for the establishment of TSC-specific epilepsy standard of care practice guidelines and a country-specific network to support clinical practice, research, and education.

AUTHOR CONTRIBUTIONS

R. Whitney involved in the study design, analysis of data, and drafting and revision of the manuscript. M. Zak involved in the study design, analysis of data, and drafting and revision of the manuscript. D. Haile involved in the analysis of data and revision of the manuscript. M. Nabavi Nouri involved in the study design, analysis of data, and drafting and revision of the manuscript.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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