Poster #7

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Expert Consensus on Real-world Use of Trofinetide for Rett Syndrome: a Delphi Study

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BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterized by core symptoms of loss of purposeful hand skills and verbal communication, gait abnormalities, and hand stereotypies[1,2]
- Trofinetide is the first and only FDA-approved treatment for RTT in adults and pediatric patients aged ≥2 years[3]
- Clinical trial data demonstrate trofinetide led to sustained improvements in RTT core symptoms, as measured by caregivers and clinicians[4-6]
- Real-world evidence supports these findings, with caregivers reporting meaningful improvements in nonverbal communication, alertness, social engagement, and overall quality of life[7]
- A Delphi method was initiated to establish best practices for trofinetide from US RTT experts practicing at an International RTT Syndrome Foundation (IRSF)-designated Center of Excellence (COE)

OBJECTIVE

- To establish consensus on trofinetide use in RTT across key domains of clinical practice

METHODS

- A modified Delphi method convened a virtual steering committee of five US RTT experts, defined as individuals practicing at one of the 21 US COEs
- The steering committee generated 72 consensus statements across 6 key domains:

A. Trofinetide as a first-line treatment for RTT

B. Pre-trofinetide assessments and counseling

C. Initiating trofinetide

D. Assessing trofinetide benefits

E. Assessing and managing trofinetide tolerability

F. Discontinuing or pausing trofinetide

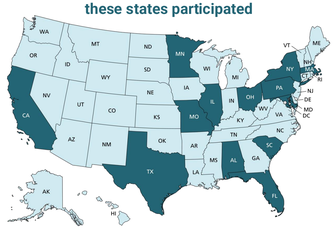
- An electronic survey containing these statements was developed and distributed to all US RTT experts with experience prescribing trofinetide as Round 1
- Respondents rated their level of agreement with each statement using a four-point Likert scale
- Results were analyzed to determine level of agreement for each statement and need for revision and retesting
- The panel developed an additional 10 statements for re-testing, which was again sent to all US RTT experts as Round 2 and followed the same process as Round 1
- The consensus threshold was set *a priori* at ≥75% agreement (i.e., strongly agree and tend to agree)

RESULTS

Figures. RTT Expert Delphi Participation by (A) State; (B) Proportion of US RTT COEs; and (C) Proportion of US RTT Experts

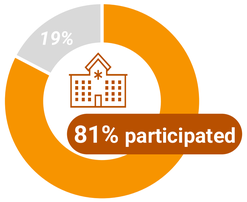
A

At least 1 RTT expert in these states participated



B

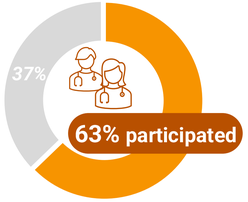
Four in five RTT COEs participated



17 of 21 US RTT COEs were represented across the 25 responses received in each round

C

Nearly two thirds of RTT experts participated



27 of 43 US RTT experts participated with a representative mix of MDs, DOs, and NPs spanning <5 to 20+ years in their RTT-related practice

Table 1. Consensus Agreement for Key Statements After 2 Survey Rounds *(all numbers rounded to the nearest whole number)*

No.	Key statements	Agree	Disagree
Domain A: Trofinetide as a first-line treatment for Rett syndrome (RTT)			
1	Trofinetide is the first FDA-approved treatment to demonstrate improvement in several core symptoms of RTT, in contrast to other therapies which primarily target one symptom of RTT	88%	12%
2	Trofinetide should be part of standard of care for RTT individuals at least 2 years of age, as indicated	88%	12%
4	The side effects of trofinetide can be successfully managed in most cases	96%	4%
7	Trofinetide can be given at any time throughout the patient's lifetime as indicated	100%	0%
8	Trofinetide may improve patient's attention and (non-verbal and verbal) communication within a month of initiation	92%	8%
9	Trofinetide may improve patient's (fine and gross) motor skills, hand use, hyperventilation, altered breathing patterns, bruxism, sleep patterns, anxiety and irritability, as early as three months after initiation	84%	16%
Domain B: Pre-trofinetide assessments and counseling			
14	Functional status (daily living activities, communication and motor function) should ideally be documented prior to initiating trofinetide, to help assess any improvements while on trofinetide	92%	8%
22	Counsel patients and/or caregivers that improvements may be subtle, incremental, and variable depending on the patient	100%	0%
23	Counsel patients and/or caregivers that the results of treatment may appear in different symptom domains based on the individual patient	100%	0%
24	Counsel patients and/or caregivers that potential side effects may occur (diarrhea and vomiting) and guidance for managing them	100%	0%
27	Encourage patients to start, or restart, supportive therapies (e.g., physical therapy, occupational therapy, speech therapy) to maximize the benefits of trofinetide after initiation	100%	0%
Domain C: Initiating trofinetide			
29	A dose titration schedule should be created prior to initiation, with flexibility to adapt as needed based on tolerability	100%	0%
32	Particularly if there are tolerability concerns (e.g., GI comorbidities), most physicians initiate trofinetide at either 5-10 mL (1,000-2,000 mg) BID or 25-50% of the recommended weight-banded dose BID and titrate thereafter; however, the starting dose should be individualized, taking into account factors such as the ability to consume liquids	84%	16%
35	For patients unable to tolerate titration of 5-10 mL (1,000-2,000 mg) per dose every 1-2 weeks, slower titrations should be considered	92%	8%
36	Most patients achieve their full recommended weight-banded dose, but those who do not may still achieve significant benefits from trofinetide treatment on a lower dose	88%	12%
Domain D: Assessment of trofinetide benefits			
41	Patients should receive trofinetide for six months after titrating to their weight-banded, or highest tolerable, dose to properly assess the efficacy of the treatment	96%	4%
43	Documentation of improvements on trofinetide should be mainly based on caregiver and/or clinician observations, rather than the exclusive use of CGI-I or RSBQ assessments, as not all improvements can be captured by these assessments	96%	4%
Domain E: Assessing and managing trofinetide tolerability			
46	Reducing a patient's trofinetide dose to a level at which side effects can be managed, or pausing and restarting on a lower dose with the intention to increase as tolerated, is preferable to stopping the dose entirely	100%	0%
51	Fibrous foods such as bananas, peanut butter, avocado or fiber bars may be used to manage diarrhea	96%	4%
52	For those receiving nutrition through gastrostomy, consider switching to an alternative brand of formula or a blenderized diet to improve digestive tolerance and manage diarrhea	76%	24%
54	Imodium may be considered short-term (i.e., a few days) to manage severe diarrhea, but only if other options are unsuitable or ineffective, and should be discontinued as soon as clinically appropriate	80%	20%
56	Despite trofinetide's risk of diarrhea, maintaining adequate hydration and routinely monitoring bowel activity are important to prevent or minimize development or redevelopment of constipation as their body adjusts to trofinetide	100%	0%
65	Based on limited data, trofinetide is generally accepted as "seizure neutral"	100%	0%
Domain F: Discontinuing or pausing trofinetide			
69	Pausing the dose is an option if a patient is traveling, hospitalized, or experiencing acute, severe side effects	100%	0%
71	Trofinetide can be safely discontinued without tapering	94%	4%
72	Stopping trofinetide may lead to the loss of improvements acquired during treatment, although further observation and research is required	88%	12%

In both rounds of survey, completed questionnaires were received from 25 respondents. Following Round 1, 10 statements failed to meet the 75% consensus threshold. These were reviewed by the steering group, amended, and reissued in Round 2. At the end of Round 2, consensus threshold was achieved for all remaining statements.

Based on the final statement set the following recommendations have been developed:

1. **Enlist trofinetide as part of standard of care for eligible patients with RTT**
2. **Conduct baseline functional assessments and provide education on potential improvements and side effects**
3. **Initiate trofinetide early, monitor broadly for improvements, and personalize care**
4. **Start trofinetide at a low dose, titrate slow, and tailor the dose to patient needs**
5. **Customize administration strategies to fit each patient's unique need**
6. **Allow adequate time, at least 6 months, to fully assess trofinetide benefits**
7. **Manage side effects with dose adjustments, pauses, & other interventions prior to discontinuation**

CONCLUSIONS

This Delphi consensus recommends trofinetide as part of RTT standard of care and supports a flexible, patient-centered approach to individualized dosing and titration, real-world benefit assessment, and side effect management

These recommendations aim to guide best practice across care settings and improve patient and caregiver outcomes

DISCLOSURES

All authors served as consultants to Acadia during this Delphi consensus project. Financial compensation was provided for their steering committee activities. Triducive was commissioned by Acadia to facilitate the Delphi process and analyze responses.

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