Clinical Management of Rett Syndrome in the Real World: A Physician Survey

Jeffrey L. Neul,[1] Damian M. May,[2] Ambika Satija,[3] Wendy Y. Cheng,[3] Neema Lema,[4] Andra Boca,[3] Patrick Lefebvre,[5] Jesús Eric Piña-Garza[6]

[1]Vanderbilt University Medical Center, Nashville, TN, USA; [2]Acadia Pharmaceuticals Inc., San Diego, CA, USA; [3]Analysis Group, Inc., Boston, MA, USA; [4]Analysis Group, Inc., Menlo Park, CA, USA; [5]Analysis Group, Inc., Montréal, Canada; [6]Centennial Children's Hospital, Nashville, TN, USA

BACKGROUND

- Rett syndrome (RTT) is a severe neurodevelopmental disorder predominantly affecting girls, characterized by multisystem comorbidities[1]
- There are no approved therapies targeting the underlying cause of RTT; thus, all available treatment strategies are aimed at managing symptoms,[2,3] making the treatment approach highly heterogeneous and individually tailored, with a lack of a clear consensus on how to define success in treating RTT[1]
  - This can result in considerable burden, both on the health system and on individuals with RTT and their caregivers
- The literature on current treatment goals and real-world clinical management strategies in RTT from physicians' perspectives is limited in the United States
- To address this, the present study gauged the perspectives of physicians with experience managing RTT (ie, RTT-treating physicians), with the aim of describing physician decision-making regarding diagnosis, treatment goals, and therapeutic strategies to better understand RTT clinical management in the United States

METHODS

Study Design

- This study employed a mixed-methods research approach that involved the sequential use of qualitative and quantitative methods; the former was used to help inform the design of the latter
- During the qualitative phase, in-depth individual interviews were conducted with 5 RTT-treating physicians to gain a broad understanding of RTT clinical management and to extract key themes
- In the quantitative phase, data from the interviews guided the development of a cross-sectional survey through which RTT-treating physicians reported on diagnostic methods, treatment goals, and management strategies among individuals with RTT under their care

Study Population

- To be eligible for this study, physicians were required to meet all of the following criteria: (1) practicing neurologist or pediatrician in the United States, (2) experienced with treating ≥2 individuals with RTT at any time, (3) treated ≥1 individual with RTT in the past 2 years, and (4) willing to provide informed consent to participate in the study
- Given that RTT is predominantly diagnosed among females, physicians who had seen an unexpected number (ie, ≥2) and distribution (ie, ≥20%) of male individuals with RTT were excluded

Statistical Analysis

- During the qualitative phase, transcripts from the in-depth interviews were reviewed to identify and describe major themes; these were used to guide the development of the quantitative survey
- The quantitative survey collected information on physician characteristics, experience managing individuals with RTT, treatment goals, and real-world management strategies
- Results were summarized using descriptive statistics, overall and stratified by specialty of RTT-treating physicians, specifically, pediatricians (including developmental pediatricians) and neurologists (including pediatric neurologists, neurologists who were also geneticists, and neurologists who were also RTT specialists)

RESULTS

Study Population

- After applying all eligibility criteria, 100 RTT-treating physicians completed the survey in the quantitative phase, including 51 neurologists and 49 pediatricians

Physician Characteristics (Table 1)

- Surveyed physicians had spent a mean of 19.3 years in their specialty following residency
- A substantial proportion of neurologists worked in academic/university medical centers (43.1%), whereas the majority of pediatricians belonged to private practices (67.3%)

Table 1. Physician characteristics[a,b]

	All physicians (N = 100)	Neurologists (N = 51)	Pediatricians (N = 49)
Medical specialty[c]			
Pediatrics[d]	47 (47.0)	1 (2.0)	46 (93.9)
Neurology	31 (31.0)	31 (60.8)	0
Pediatric neurology	25 (25.0)	25 (49.0)	0
Years in specialty (following residency)	19.3 ± 9.0	17.1 ± 8.4	21.6 ± 9.2
Type of institution			
Private practice	48 (48.0)	15 (29.4)	33 (67.3)
Academic/university medical center	29 (29.0)	22 (43.1)	7 (14.3)
Community-based hospital	12 (12.0)	9 (17.6)	3 (6.1)
Community clinic	9 (9.0)	5 (9.8)	4 (8.2)
Geographic region			
South	32 (32.0)	15 (29.4)	17 (34.7)
Northeast	29 (29.0)	12 (23.5)	17 (34.7)
West	20 (20.0)	11 (21.6)	9 (18.4)
Midwest	19 (19.0)	13 (25.5)	6 (12.2)

[a]Data are presented as n (%) or mean ± SD; [b]"Other" and "unknown" response options as well as response options selected by ≤5 respondents have not been shown; [c]Physicians were able to select multiple specialties; [d]1 physician indicated being a neurologist, pediatric neurologist, and pediatrician--that physician was categorized as a neurologist

SD, standard deviation

Physicians' Experiences Managing Individuals With RTT (Table 2, Figure 1)

- Neurologists had treated more individuals with RTT than pediatricians throughout their careers (23.5 vs 6.8 individuals), as well as in the past 2 years (10.8 vs 2.5 individuals)
- A higher proportion of neurologists expressed being "somewhat comfortable" or "very comfortable" managing RTT compared with pediatricians (78.5% vs 44.9%)
- Almost all physicians (93.0%) had experience diagnosing RTT
  - Most neurologists (50.0%) tended to use a combination of evaluating symptoms, genetic testing, and the 2010 consensus diagnostic criteria for diagnosing RTT
  - Pediatricians were more likely to use a combination of evaluating symptoms and genetic testing (56.8%)
- Most physicians (87.1%) considered an alternative diagnosis when evaluating RTT-like symptoms
  - Autism spectrum disorder (86.4%), nonspecific developmental delay (60.5%), and Angelman syndrome (54.3%) were the most common differential diagnoses considered

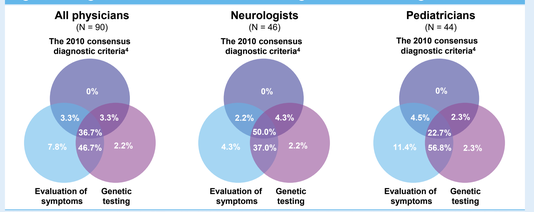
Table 2. Physicians' experiences managing individuals with RTT[a,b]

	All physicians (N = 100)	Neurologists (N = 51)	Pediatricians (N = 49)
Number of individuals with RTT treated throughout career	15.3 ± 23.7	23.5 ± 30.3	6.8 ± 7.4
Number treated in the past 2 years	6.7 ± 11.7	10.8 ± 15.3	2.5 ± 2.4
Proportion of individuals that the physician newly diagnosed with RTT[c]	42.6 ± 29.6	44.5 ± 30.1	40.6 ± 29.3
Proportion of individuals for whom the physician confirmed RTT diagnosis[d]	39.6 ± 29.0	34.8 ± 26.8	44.5 ± 30.6
Most recent encounter treating an individual with RTT, months ago	5.7 ± 6.4	4.3 ± 5.4	7.3 ± 7.0
Longest duration of providing care for an individual with RTT, years	7.0 ± 5.5	7.8 ± 6.0	6.2 ± 4.9
Comfort level managing individuals with RTT			
1—Not comfortable	1 (1.0)	0	1 (2.0)
2—Somewhat not comfortable	8 (8.0)	3 (5.9)	5 (10.2)
3—Neither comfortable nor not comfortable	29 (29.0)	8 (15.7)	21 (42.9)
4—Somewhat comfortable	44 (44.0)	24 (47.1)	20 (40.8)
5—Very comfortable	18 (18.0)	16 (31.4)	2 (4.1)
Number of physicians with experience diagnosing RTT[e]	**(n = 93)**	**(n = 48)**	**(n = 45)**
Most recent RTT diagnosis, either newly assigned or confirmed, years ago	2.0 ± 2.3	1.0 ± 1.0	3.1 ± 2.7
Criteria/tests used to assign/confirm diagnosis			
Evaluation of individual's symptoms	85 (91.4)	43 (89.6)	42 (93.3)
Genetic testing	80 (86.0)	43 (89.6)	37 (82.2)
The 2010 consensus diagnostic criteria[4]	39 (41.9)	26 (54.2)	13 (28.9)
The 2002 consensus diagnostic criteria[5]	10 (10.8)	4 (8.3)	6 (13.3)
Other diagnostic tools (eg, imaging, lab values)	28 (30.1)	16 (33.3)	12 (26.7)
Typically assign RTT classification (classic/variant)			
No	50 (53.8)	23 (47.9)	27 (60.0)
Yes	32 (34.4)	23 (47.9)	9 (20.0)
Unknown/not sure	11 (11.8)	2 (4.2)	9 (20.0)
Typically consider alternative diagnoses	81 (87.1)	42 (87.5)	39 (86.7)
Top 5 alternative diagnoses most typically considered	**(n = 81)**	**(n = 42)**	**(n = 39)**
Autism spectrum disorder	70 (86.4)	34 (81.0)	36 (92.3)
Nonspecific developmental delay	49 (60.5)	22 (52.4)	27 (69.2)
Angelman syndrome	44 (54.3)	25 (59.5)	19 (48.7)
Cerebral palsy	36 (44.4)	18 (42.9)	18 (46.2)
CDKL5 mutation	28 (34.6)	23 (54.8)	5 (12.8)

[a]Data are presented as n (%) or mean ± SD; [b]"Other" and "unknown" response options as well as response options selected by ≤5 respondents have not been shown; [c]A new diagnosis refers to an initial diagnosis of RTT for an individual not previously diagnosed with RTT; [d]A confirmed diagnosis refers to a physician verifying an RTT diagnosis previously assigned by another physician; [e]The subsequent questions were only surveyed among physicians who had diagnosed or confirmed a diagnosis for ≥1 individual with RTT

RTT, Rett syndrome; SD, standard deviation

Figure 1. Diagnostic Criteria/Tests Used to Assign/Confirm RTT Diagnosis[a]



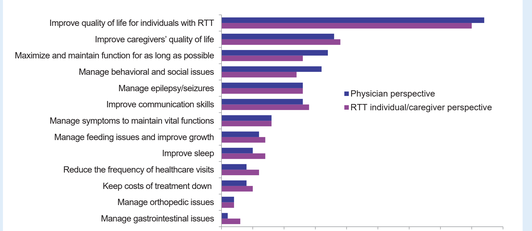
[a]90/93 physicians with experience diagnosing RTT used the 2010 diagnostic criteria, symptom evaluation, and genetic testing, alone or in combination, for RTT diagnoses. Other diagnostic strategies used by physicians to diagnose RTT included diagnostic tools such as imaging, other diagnostic guidelines, and consultation with/referral to other specialists (data not shown)

RTT, Rett syndrome

Treatment Goals (Figure 2)

- From both the physicians' and the RTT individuals'/caregivers' perspectives, improving the quality of life of individuals with RTT was the most important goal, followed by improving the caregivers' quality of life
- Other important treatment goals included maximizing and maintaining function for as long as possible, managing behavioral/social issues, managing epilepsy/seizures, and improving communication skills

Figure 2. Mean Rank for RTT Treatment Goals From the Perspectives of Physicians and Individuals With RTT/Caregivers[a]



[a]Physicians provided a rank to these treatment goals by importance. Each physician ranked ≤5 goals from 1 to 5, with 5 being the most important goal and 1 being the fifth most important goal. Treatment goals not ranked were given a score of 0

RTT, Rett syndrome

Real-world Management Strategies (Table 3, Table 4)

- The top 5 symptoms physicians most commonly managed were behavioral issues (67.0%), epilepsy/seizures (63.0%), feeding issues (33.0%), constipation (30.0%), and loss of communication skills (29.0%)
- Treatment strategies were symptom-specific. Pharmacological strategies (eg, antiepileptic drugs) were commonly used to treat behavioral issues and epilepsy; however, feeding issues, constipation, and loss of communication skills were mainly treated using nonpharmacological approaches (eg, occupational therapy and dietary recommendations)
- For all symptoms, referral to appropriate specialists was common
- The majority of physicians (60.0%) used clinical practice guidelines to monitor the progress of individuals with RTT
- Apart from symptom control, the main factors considered when recommending treatments were age of the individual (80.0%), disease stage (76.0%), and preference of the individual with RTT/family (71.0%)
- The lack of disease-modifying therapies and reliance on symptom-specific management was identified as an unmet need by a large proportion of physicians (36.8%)

Table 3. Common real-world management strategies for the top 5 symptoms managed by RTT-treating physicians[a,b]

	All physicians (N = 100)	Neurologists (N = 51)	Pediatricians (N = 49)
Behavioral issues[c]	**(n = 67)**	**(n = 35)**	**(n = 32)**
Antiseizure/antiepileptic medications[d]	42 (62.7)	23 (65.7)	19 (59.4)
Antianxiety medications[e]	41 (61.2)	24 (68.6)	17 (53.1)
Referral to behavioral therapist/psychologist/ psychiatrist	41 (61.2)	19 (54.3)	22 (68.8)
Medications that work on the serotonin system[f]	28 (41.8)	18 (51.4)	10 (31.3)
Management by social worker	13 (19.4)	8 (22.9)	5 (15.6)
Epilepsy/seizures	**(n = 63)**	**(n = 44)**	**(n = 19)**
Antiseizure/antiepileptic medications[d]	56 (88.9)	41 (93.2)	15 (78.9)
Antianxiety medications[e]	31 (49.2)	25 (56.8)	6 (31.6)
Ketogenic diet	25 (39.7)	22 (50.0)	3 (15.8)
Referral to epileptologist/neurologist	22 (34.9)	9 (20.5)	13 (68.4)
Vagus nerve stimulation	20 (31.7)	19 (43.2)	1 (5.3)
Feeding issues[g]	**(n = 33)**	**(n = 6)**	**(n = 27)**
Occupational therapy	20 (60.6)	2 (33.3)	18 (66.7)
Speech therapy	20 (60.6)	2 (33.3)	18 (66.7)
Supplements[h]	19 (57.6)	2 (33.3)	17 (63.0)
Referral to nutritionist	17 (51.5)	4 (66.7)	13 (48.1)
Gastrostomy tube	13 (39.4)	3 (50.0)	10 (37.0)
Referral to dietician	13 (39.4)	5 (83.3)	8 (29.6)
Constipation	**(n = 30)**	**(n = 7)**	**(n = 23)**
Dietary recommendations/guidance[i]	24 (80.0)	3 (42.9)	21 (91.3)
Referral to dietician	22 (73.3)	4 (57.1)	18 (78.3)
Laxatives[j]	19 (63.3)	3 (42.9)	16 (69.6)
Referral to nutritionist	11 (36.7)	2 (28.6)	9 (39.1)
Enemas	9 (30.0)	1 (14.3)	8 (34.8)
Referral to gastroenterologist	9 (30.0)	4 (57.1)	5 (21.7)
Suppositories	6 (20.0)	0	6 (26.1)
Loss of communication skills	**(n = 29)**	**(n = 12)**	**(n = 17)**
Speech therapy	19 (65.5)	6 (50.0)	13 (76.5)
Occupational therapy	17 (58.6)	6 (50.0)	11 (64.7)
Referral to behavioral therapist/psychologist/ psychiatrist	16 (55.2)	6 (50.0)	10 (58.8)
AAC devices[k]	14 (48.3)	7 (58.3)	7 (41.2)
Speech-generating devices	11 (37.9)	4 (33.3)	7 (41.2)

[a]Data are presented as n (%); [b]"Other" and "unknown" response options as well as response options selected by ≤5 respondents have not been shown; [c]Eg, anxiety, hysteria, irritability; [d]Eg, carbamazepine, divalproex, lamotrigine, levetiracetam, perampanel, phenobarbital, pregabalin, sodium valproate, topiramate, zonisamide, valproate; [e]Eg, benzodiazepine, clobazam, clonazepam, diazepam, diphenhydramine, hydroxyzine; [f]Eg, selective serotonin reuptake inhibitors; [g]Eg, chewing/swallowing dysfunction; [h]Eg, levocarnitine, PediaSure; [i]Eg, fiber, hydration; [j]Eg, bisacodyl, docusate, magnesium citrate, magnesium hydroxide, polycarbophil, polyethylene glycol, psyllium, senna glycoside; [k]Eg, communication board, picture exchange communication systems, Tobii Dynavox device

AAC, augmentative and alternative communication; RTT, Rett syndrome

Study Limitations

- The quantitative phase of this study was subject to common limitations of surveys, including differences between participants' interpretations of the survey questions
- The study relied on the physicians' experiences treating individuals with RTT when reporting data, which could be subject to recall error
- Although this study surveyed 100 physicians from a range of backgrounds (including pediatricians and neurologists), the results of the survey may not be generalizable to physicians outside of the sample studied

Table 4. Overall management of individuals with RTT[a,b]

	All physicians (N = 100)	Neurologists (N = 51)	Pediatricians (N = 49)
Clinical scales, tests, or guidelines typically used to monitor progress			
Clinical practice guidelines	60 (60.0)	30 (58.8)	30 (61.2)
Rett syndrome clinical severity scale	34 (34.0)	21 (41.2)	13 (26.5)
Rett Syndrome Behaviour Questionnaire	25 (25.0)	14 (27.5)	11 (22.4)
Motor behavior assessment scale	18 (18.0)	12 (23.5)	6 (12.2)
None	17 (17.0)	7 (13.7)	10 (20.4)
Factors considered when recommending treatment for symptom control			
Age of the individual with RTT	80 (80.0)	38 (74.5)	42 (85.7)
Disease stage	76 (76.0)	38 (74.5)	38 (77.6)
Preference of individual with RTT/family	71 (71.0)	33 (64.7)	38 (77.6)
Insurance coverage	58 (58.0)	30 (58.8)	28 (57.1)
Price/cost of treatment for the individual with RTT/family	45 (45.0)	25 (49.0)	20 (40.8)
Frequency and duration of administration of the treatment	44 (44.0)	27 (52.9)	17 (34.7)
Route of administration	38 (38.0)	22 (43.1)	16 (32.7)
Ease of access to healthcare facility (eg, distance to providers)	32 (32.0)	15 (29.4)	17 (34.7)

[a]Data are presented as n (%); [b]"Other" and "unknown" response options as well as response options selected by ≤5 respondents have not been shown

RTT, Rett syndrome

CONCLUSIONS

- The pediatricians in this study had less experience with and were less comfortable diagnosing and treating individuals with RTT than the neurologists; thus, better education and support is needed for pediatricians, as they are among the main care providers for individuals with RTT
- This study demonstrates that RTT is typically managed using symptom-specific strategies, underscoring the need for novel treatments that target multiple symptoms to reduce burden and improve the quality of life of individuals with RTT and their caregivers

REFERENCES

1. Gibelta-Rodriguez J, et al. *Int J Environ Res Public Health*. 2020;17(12):4466.
2. National Institute of Neurological Disorders and Stroke. Rett Syndrome Fact Sheet. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Rett-Syndrome-Fact-Sheet. Accessed April 27, 2021.
3. Sandweiss AJ, et al. *Lancet Neurol*. 2020;19(8):689–698.
4. Neul JL, et al. *Ann Neurol*. 2010;68(6):944–950.
5. Hagberg B, et al. *Eur J Paediatr Neurol*. 2002;6(5):293–297.

ACKNOWLEDGMENTS

This analysis was sponsored by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Editorial assistance was provided by Evidence Scientific Solutions, Inc., and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

JLN has received research funding from the International Rett Syndrome Foundation, the National Institutes of Health, and Rett Syndrome Research Trust; has received personal consultancy fees from Acadia Pharmaceuticals Inc., Analysis Group, Inc., AveXis, GW Pharmaceuticals, Hoffmann-La Roche, Myrtelle, Neurogene Inc., Newron Pharmaceuticals, Signant Health, and Taysha Gene Therapies; serves on the scientific advisory board of Alcyone Lifesciences; is a scientific cofounder of LizarBio Therapeutics; and was a member of a data safety monitoring board for clinical trials conducted by Ovid Therapeutics.
DMM is an employee of Acadia Pharmaceuticals Inc. **AS**, **WYC**, **NL**, **AB**, and **PL** are employees of Analysis Group, Inc., a consultancy that received funding from Acadia Pharmaceuticals Inc. to conduct this study. **JEP-G** is a consultant and speaker for Aquestive Therapeutics, Eisai, Neurelis, SK Life Science, and UCB Pharma, and is a consultant for Analysis Group, Inc.

To receive a copy of this poster, scan QR code via barcode reader application.

By requesting this content, you agree to receive a one-time communication using automated technology. Message and data rates may apply. Links are valid for 30 days after the congress presentation.

ACADIA