

# Caregiver insight on the core domains in Angelman syndrome

Mathews Adera<sup>1</sup>, Aaron Tansy<sup>1</sup>, Alex Kolevzon<sup>2</sup>

<sup>1</sup>Ovid Therapeutics Inc., New York, NY, USA; <sup>2</sup>Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

## Disclosures

Drs. Adera and Tansy are full-time employees and stakeholders of Ovid Therapeutics Inc.

Dr. Kolevzon has consulted for Ovid Therapeutics, Acadia, Takeda, and SEMA4, and has received research support from Amn Pharma.

## INTRODUCTION

### Background

- Angelman syndrome (AS) is a rare, genetic, neurodevelopmental condition characterized by heterogeneous symptomatology, including behavior-related abnormalities, motor and communication impairment, and sleep disturbances<sup>1</sup>
- Currently available treatments address only symptoms without the ability to target AS-specific pathophysiology<sup>2</sup>
- Heterogeneity of symptomatology in AS poses a challenge to the selection of relevant measurements of efficacy for therapeutic clinical trials
- Thorough appreciation of the aspects of AS that are most salient and challenging for patients and their caregivers is essential to successful development and evaluation of new treatments
- One group discussion and 6 individual interviews with caregiver-parents of pediatric and adult patients with AS aged 2–28 years were conducted to gather information on challenges of care

### Study Objective

- **Primary:** to identify the most salient and challenging features of AS for caregiver-parents within 5 specific domains—communication, behavior, anxiety behavior, motor, and sleep—and to define meaningful change as viewed by these family members

## OBJECTIVE AND METHODS

### Study Participants

- Twelve caregiver-parents of pediatric and adult patients with AS (10 mothers and 2 fathers)
  - Six respondents participated in a 3-hour group interview (Chicago, IL)
  - Six respondents participated in 70-minute in-person individual interviews (1 in Chicago, IL; 5 in Boston, MA)
  - Children of caregiver-parents ranged in age from 2 to 28 years and demonstrated varying levels of cognitive and behavioral functioning as reported by their caregiver-parents

### Study Design

- Caregiver-parents were interviewed in person during a 3-hour group interview or 70-minute individual interview (**Table 1**)
- In a Card Sort Activity session, caregiver-parents responded to 5 prespecified clinical domains of AS: communication, behaviors, anxiety behaviors, motor, and sleep
  - Caregiver-parents gave impressions of domains and ranked them from most challenging to least challenging
  - Within domains, caregiver-parents described areas they were most concerned about and would most like to see improvement in
- Qualitative assessment of the interview transcripts determined how caregiver-parents define each domain, which domains they found most challenging regarding care, and how they would define meaningful progress within the domains (**Tables 2–5**)

**Table 1: Group and Individual Interview Flow**

Section	Group*	Individual
Introduction	5 minutes	5 minutes
Getting to Know You (as Caregivers)	30 minutes	10 minutes
Angelman Syndrome Lexicon/Comprehension	30 minutes	10 minutes
Unpacking Clinical Features	25 minutes	25 minutes <sup>†</sup>
Card Sort Activity	50 minutes	
The Treatment Landscape/The Future	15 minutes	10 minutes
Vignette Testing	10 minutes	10 minutes

\*The group interview also included 5- and 10-minute breaks.

<sup>†</sup>The Card Sort Activity was part of the Unpacking Clinical Features section for individual interviews.

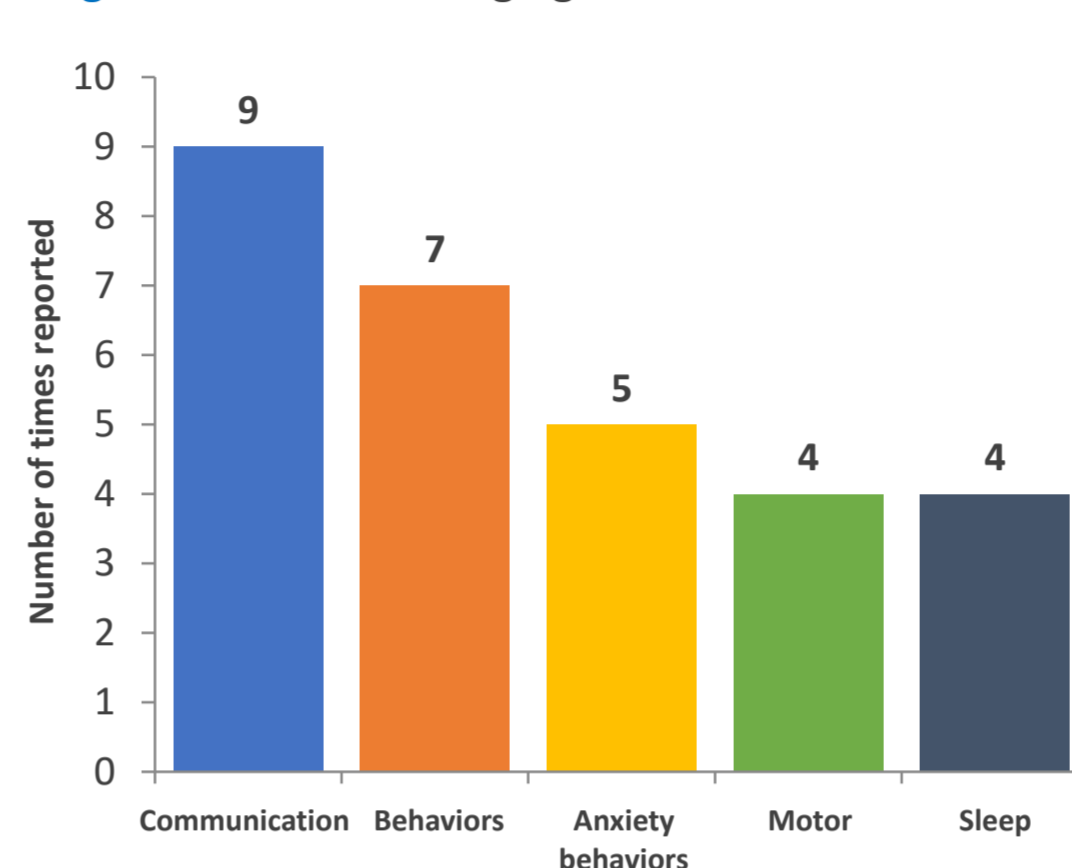
**ACKNOWLEDGMENTS:** We would like to thank all caregivers and their families for their participation in this research. Writing and editorial support, funded by Ovid Therapeutics Inc. (New York, NY, USA), was provided by Gian Greenberg, PhD, and Anne Cooper, MA, of Ashfield Healthcare Communications (Middletown, CT, USA).

Presented at The Virtual Joint 16th International Child Neurology Congress (ICNC) & 49th Annual Meeting Child Neurology Society (CNS) Meeting

### Caregiver-Parent Domain Rankings

- While caregiver-parents described domains as interconnected, trends in their attitudes toward individual domains were observed (**Figure 1**)
  - Caregiver-parents ranked communication as the most challenging domain of AS, followed by behaviors and anxiety behaviors
  - Responses regarding motor and sleep were varied, with some caregiver-parents viewing these domains as less impactful and others viewing them as highly challenging
  - While caregiver-parents described domains as interconnected, trends in their attitudes toward individual domains were observed (**Figure 1**)

**Figure 1: Most Challenging Domains**



### Domains in Depth – Communication

- Caregiver-parents reported the following about patients' communication (**Table 2**)
  - Inability to convey needs and wants, particularly the inability to express physical or emotional pain
  - Inability to communicate effectively was emotionally laborious, and caregiver-parents worried that they were insufficiently tending to patients' needs
  - Frustration and anxiety-fueled behaviors in patients when they were unable to express and ultimately fulfill their needs
- Caregiver-parents desired improved ability for expressive communication for patients, preferably through speech or augmentative and alternative communication (AAC) devices

**Table 2: Meaningful Change: Communication Domain**

Symptom	What improvement looks like to caregiver-parents
Making sentence/full thought	• Caregiver-parents wish their children had the ability to string together complete thoughts on AAC devices, allowing them to explicitly state their needs and wants (eg, hunger, gastrointestinal problems) and circumvent frustrations that come from an inability to do so
Deciding between options	• Caregiver-parents often find themselves playing a guessing game of what patients want, especially at mealtime. Patients are presented with options, but sometimes are unable to communicate their preference, causing frustration
Recognizing options on AAC device	• Many caregiver-parents view AAC devices as a gateway for their child to communicate. First steps in AAC use are the ability to recognize and act on visual cues on such devices
Consistent yes/no	• Several caregiver-parents notice inconsistencies in how patients answer yes/no questions—shaking their head when they mean yes and nodding when they mean no. Answering such questions in a consistent way would open up new communication paths

### Domains in Depth – Behavior

- Behavior and anxiety were recognized by caregiver-parents as overlapping areas within the same domain, and results for these 2 domains are grouped together within the Behavior section
- Caregiver-parents reported the following about patients' behavior (**Table 3**):
  - Uncertainty about tantrums, yelling, and aggressive outbursts, causing anxiety in caregiver-parents
    - Caregiver-parents avoid trips and public outings for fear of embarrassment and harm to their children or others
  - Challenges understanding causal relationship between situation and behavior
    - Set routines may circumvent anxiety-inducing situations and unexpected outbursts
  - Standardized routines may limit caregiver-parents by preventing visits from guests, trips to new places, and “spur-of-the-moment” outings

**Table 3: Meaningful Change: Behavior Domain**

Symptom	What improvement looks like to caregiver-parents
Ability to handle changes in routine	• Caregiver-parents often feel trapped in routines in the attempt to preemptively quell patients' anxiety. Patients' ability to handle new situations would relieve worries and open doors to new activities and social situations
Ability to handle overstimulation	• Caregiver-parents are often wary of overstimulating environments (eg, a party, social gathering, a crowded restaurant). The ability to handle such places would expand where caregiver-parents and their families could go
Decreased aggression	• Caregiver-parents notice that patients tend to lash out, especially when they do not get their way; they wish their children would react with less aggression and physicality (eg, hitting, rolling on the ground, pushing)
Decreased morning irritability	• Caregiver-parents note that patients tend to be irritable during the morning routine (eg, being uncooperative in getting dressed, pushing back when brushing teeth). Reduced conflict to start the day would improve their own emotional well-being
Fewer attention-seeking behaviors	• Caregiver-parents feel that some patients' behaviors are to get attention; these behaviors (eg, yelling, hitting/patting) are disruptive

## RESULTS

### Domains in Depth – Motor

- Caregiver-parents reported the following about patients' motor skills (**Table 4**)
  - Impaired fine and gross motor skills inhibit patients' potential independence
    - Patients may be unable to walk or perform everyday tasks, such as dressing and feeding themselves autonomously
  - Impaired fine motor functioning is a salient inhibitor to improvement in communication with caregiver-parents
    - Use of AAC devices requires the ability to point and press small buttons
  - Gross motor skills create both opportunities and difficulties for caregiver-parents and patients
    - Patients' ability to walk independently is a positive development, but there are concerns that patients may wander and get lost
    - Caregiver-parents are insecure about patients' balance and concerned about falls if patients are unsupervised

### Domains in Depth – Sleep

- Caregiver-parents reported the following about patients' sleep (**Table 5**):
  - Late-night disruptions have a negative impact on the family's quality of life
    - Caregiver-parents and other family members are often woken up when patients seek attention and/or cause a commotion late at night
  - Impact of impaired sleep on patients' own behavior varied
    - Some caregiver-parents saw little relationship between hours of sleep obtained and behavior, while others related decreased sleep with increased irritability, aggressive behaviors, and attention problems
  - Tools to help patients fall and stay asleep include sleep supplements, secure beds, sleep monitors, and 1:1 personal supervision/bonding activities, such as reading and/or lying in bed with patients at bedtime, using a tablet/watching TV, or doing puzzles during late-night awakenings
  - Improvement in sleep domain can be defined by patients consistently sleeping through the night and not awakening other family members when they do wake up during the night

**Table 4: Meaningful Change: Behavior Domain**

Symptom	What improvement looks like to caregiver-parents
Fine motor control	• Caregiver-parents equate fine motor skills with independence, finding them necessary for patients to eat and dress unassisted
Walking confidence/safety	• They also view refined motor skills as being the key to communication, allowing patients to point and use AAC devices
Endurance	• Prior falls and lack of confidence often deter patients from walking, especially over non-flat terrain; patients' increased confidence to use stairs independently would be significant to caregiver-parents
	• Many patients lack endurance to walk in long spurts; improved endurance would allow them to walk down a hallway or through a store uninterrupted

**Table 5: Meaningful Change: Sleep Domain**

Symptom	What improvement looks like to caregiver-parents
Consistently sleeping through the night	• Inconsistent sleep is cyclical, shifting between periods of no night time awakenings and periods of waking up every night
Not waking others up/putting self back to sleep	• Caregiver-parents wish patients were able to consistently sleep through the night, especially getting over the “3 AM hump” (the time when they most often wake up)
	• During night time awakenings, patients need attention or supervision
	• There is a desire for patients to be able to fall back to sleep on their own without disturbing the family

## CONCLUSIONS

### Overarching Caregiver Insights

- The Communication and Behavior Domains presented the greatest challenges for caregiver-parents
- Caregiver-parents learn to manage patients' challenges and embrace their special needs
- Caregiver-parents are wary of medications, particularly those that target mood and aggression, based on a concern that they may alter patients' personality and demeanor
- Caregiver-parents find the episodic nature of their children's challenging behaviors to be one of the most difficult features of AS to manage
  - Treatment that results in more consistent and predictable behavior would allow for more social opportunities and could potentially have a positive impact on caregiver-parents' quality of life

### Implications for Treatment Development

- Medications are generally not considered for treatment, and education is needed to highlight the role of medications in managing specific behaviors
- While caregiver-parents maintain a realistic view on achievable progress, they nonetheless set goals for their children's future
  - Reliable metrics are needed to identify meaningful change in AS and help guide caregiver-parents' expectations
- Ultimately, caregiver-parents wish to spread awareness of AS
  - Caregiver networks recognize the value of disease awareness education and drug development programs

### Unmet Needs and Consequences for Drug Development

- AS represents a high unmet medical need with no approved therapies<sup>2</sup>
- Caregiver experiences provide insight into areas of potentially clinically meaningful impact so that development programs can maximize therapeutic benefit
- Communication and behavior ranked as the most salient and challenging domains for caregiver-parents
  - Caregiver-parents were divided on the impact of motor and sleep domains on daily life, but they reported improvement in fine motor control to be very meaningful in the motor domain, as it may increase independence in patients
- Caregiver-parent insights and their consequences for drug development include the following<sup>1</sup>:
  - Caregiver-parents are unwilling to use medications that risk altering patients' demeanor or personality
  - Caregiver-parents desire consistency in patients' behavior
  - Education is needed to underscore the biological underpinnings of behaviors in AS and highlight the value of treating the pathophysiology
- Caregiver-parents suggested that reliable metrics are required to track progress toward developmental and behavioral goals
  - Evaluation of treatment efficacy is dependent upon having outcome measures that effectively capture disease manifestations that are salient and clinically meaningful to caregivers
  - Rating scales developed specifically for AS, such as the Clinical Global Impressions–Improvement-AS (CGI-I-AS) and Clinical Global Impressions–Severity-AS (CGI-S-AS) scales, are being tested in AS in clinical trials currently underway and hold great promise to advance the field and potential for effective treatments within it<sup>3</sup>

### References:

1. Williams CA, et al. *Am J Med Genet A*. 2006;140(5):413–418.
2. Dagli AI, et al. Angelman Syndrome. In: Adam MP, et al., eds. *GeneReviews*®. University of Washington; 1998. Accessed March 9, 2020. <https://www.ncbi.nlm.nih.gov/books/NBK1144>.
3. Keary C, et al. The pivotal phase 3 NEPTUNE trial investigating gaboxadol in Angelman syndrome: study design. Presented at: American Academy of Neurology Annual Meeting 2020; virtual meeting.