AMERICAN AUTISM SOCIETY

July 2023 Newsletter

Table of Contents

Prologue :

Ole Ivar Lovaas, Phd Psychologist

Developer of discrete trial Training

Chapters:

1. Rett Syndrome

2. The first and only FDA- approved pharmaceutical for the treatment of Rett Syndrome

Prologue :

Ole Ivar Løvaas (8 May 1927 – 2 August 2010)[1][2] was a Norwegian-American clinical psychologist and professor at the University of California, Los Angeles. He is most well known for his research on what is now called applied behavior analysis (ABA) to teach autistic children through prompts, modeling, and positive reinforcement. The therapy is also noted for its use of aversives (punishment) to reduce undesired behavior, however these are now used less commonly than in the past.

Lovaas founded the Lovaas Institute and co-founded the Autism Society of America. He is also considered a pioneer of ABA due to his development of discrete trial training and controversial early intensive behavioral intervention for autistic children.

His work influenced how autism is treated, and Lovaas received widespread acclaim and several awards during his lifetime.[3] More recently, his approach has been criticized as a violent form of autistic conversion therapy.[4]

Early in his career, Lovaas worked at the Pinel foundation, which focused on Freudian psychoanalysis.[5] After earning his PhD, he took a position at the University of Washington's Child Development Institute, where he first learned of behavior analysis. Lovaas began teaching at UCLA in 1961 in the Department of Psychology, where he performed research on children with autism spectrum disorder at the school's Neuropsychiatric Institute.[7] He started an early intervention clinic at UCLA called the UCLA Young Autism Project, which provided intensive intervention inside the children's homes. He was named professor emeritus in 1994. Lovaas also established the Lovaas Institute for Early Intervention (LIFE) that provides interventions based on his research.[5][8]

Lovaas taught now prominent behaviorists, such as Robert Koegel, Laura Schreibman, Tristram Smith, Doreen Granpeesheh, John McEachin, Ron Leaf, Jacquie Wynn, and thousands of UCLA students who took his "Behavior Modification" course during his 50 years of teaching. He also co-founded what is today the Autism Society of America (ASA), published hundreds of research articles and several books, and received many accolades for his research. Due to this research, a number of school districts have adopted his programs. His work influenced how autism is treated.[8][9][10][11]

Research

Autism intervention[edit]

Early research[edit]

Lovaas established the Young Autism Project clinic at UCLA in 1962, where he began his research, authored training manuals, and recorded tapes of him and his graduate students implementing errorless learning—based on operant conditioning and what was then referred to as behavior modification—to instruct autistic children. He later coined the term "discrete trial training" to describe the procedure, which was used to teach listener responding, eye contact, fine and gross motor imitation, receptive and expressive language, academic, and a variety of other skills. In an errorless discrete trial, the child sits at a table across from the therapist who provides an instruction (i.e., "do this", "look at me", "point to", etc.), followed by a prompt, then the child's response, and a stimulus reinforcer. The prompts are later discontinued once the child demonstrates proficiency. During this time, Lovaas and colleagues also employed physical aversives (punishment), such as electric shocks and slaps, to decrease aggressive and self-injurious behavior, as well as verbal reprimands if the child answered incorrectly or engaged in self-stimulatory behavior.[1][10][12]

1987 study

In 1987, Lovaas published a study[13] which demonstrated that, following forty hours a week of treatment, 9 of the 19 autistic children developed typical spoken language, increased IQs by 30 points on average, and were placed in regular classrooms. A 1993 follow-up study[14] found that 8 maintained their gains and were "indistinguishable from their typically developing peers", scoring in the normal range of social and emotional functioning. His studies were limited because Lovaas did not randomize the participants or treatment groups. This produced a quasi-experiment in which he was able to control the assignment of children to treatment groups. His manipulation of the study in this way may have been responsible for the observed effects. The true efficacy of his method cannot be determined since his studies cannot be repeated for ethical reasons.[15][16][17] A 1998 study subsequently recommended that EIBI programs be regarded with skepticism.[17] In 1999, the United States Surgeon General said, "Thirty years of research has demonstrated the efficacy of applied behavioral methods in reducing inappropriate behavior and in increasing communication, learning, and appropriate social behavior", and he also endorsed the 1987 study.[18]

Literature reviews

According to a 2007 review study in *Pediatrics*, "The effectiveness of [EIBI] in [autism spectrum disorder] has been well-documented through 5 decades of research by using single-subject methodology and in controlled studies... in university and community settings." It further stated, "Children who receive early intensive behavioral treatment have been shown to make substantial, sustained gains in IQ, language, academic performance, and adaptive behavior as well as some measures of social behavior, and their outcomes have been significantly better than those of children in control groups." However, the study also recommended to later generalize the child's skills with more naturalistic ABA-based procedures, such as incidental teaching and pivotal response treatment, so their progress is maintained.[19]

Another review in 2008 described DTT as a "'well-established' psychosocial intervention for improving the intellectual performance of young children with autism spectrum disorders..."[20] In 2011, it was found that the intervention is effective for some, but "the literature is limited by methodological concerns" due to there being small sample sizes and very few studies that used random assignment,[21] and a 2018 Cochrane review subsequently indicated low-quality evidence to support this method.[7] Nonetheless, a meta-analysis in the same journal database concludes how some recent research is beginning to suggest that because of the heterology of ASD, there is a wide range of different learning styles and that it is the children with receptive language delays who acquire spoken language from Lovaas' treatment.[22]

Aversives[edit]

Lovaas is credited with popularizing the use of aversives in behavior modification, as shown in a *Life* magazine photo spread in 1965.[33]

He later admitted that they were only temporarily effective and punishments became less effective over time.[34] Eventually, Lovaas abandoned these tactics, telling CBS in a 1994 interview, "These people are so used to pain that they can adapt to almost any kind of aversive you give them."[35]

Bibliography

- *The Autistic Child: Language Development Through Behavior Modification*, 1977
- *Teaching Developmentally Disabled Children: The Me Book*, 1981
- *Teaching Individuals With Developmental Delays: Basic Intervention Techniques*, 2003

References

1. ^ Jump up to:[a] [b] [c] *Larsson, Eric V; Wright, Scott (2011). "O. Ivar Lovaas (1927–2010)". The Behavior Analyst. **34** (1): 111–114. doi:10.1007/BF03392239. PMC 3089401.*
2. ^ Jump up to:[a] [b] *Fox, Margalit (August 2010). "O. Ivar Lovaas, pioneer in developing therapies for autism, dies at 83". The New York Times. Retrieved 18 June 2018.*
3. ^ Jump up to:[a] [b] SCCAP Award Winners: Division 53, (Retrieved 29 May 2018)
4. **^** *Pyne, Jake (17 November 2020). ""Building a Person": Legal and Clinical Personhood for Autistic and Trans Children in Ontario". Canadian Journal of Law and Society / La Revue Canadienne Droit et Société. **35** (2): 341–365 – via CambridgeCore.*
5. ^ Jump up to:[a] [b] [c] [d] [e] Eikeseth, Özerk, Özerk, Vea. Ole Ivar Lovaas – His life, merits, and legacy., *International Journal of Elementary Education,* Dec. 2016
6. ^ Jump up to:[a] [b] *"Ole Ivar Lovaas dies at 83; UCLA psychology professor pioneered autism treatment". Los Angeles Times. 6 August 2010. Retrieved 7 October 2019.*
7. ^ Jump up to:[a] [b] *Reichow B, Hume K, Barton EE, Boyd BA (May 2018). "Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD)". The Cochrane Database of Systematic Reviews. **5** (10): CD009260. doi:10.1002/14651858.CD009260.pub3. PMC 6494600. PMID 29742275.*
8. ^ Jump up to:[a] [b] *Smith, Tristram; Eikeseth, Svein (March 2011). "O. Ivar lovaas: pioneer of applied behavior analysis and intervention for children with autism". Journal of Autism and Developmental Disorders. **41** (3): 375–378. doi:10.1007/s10803-010-1162-0. ISSN 1573-3432. PMID 21153872. S2CID 207159059.*
9. **^** *Larsson EV, Wright S (2011). "O. Ivar Lovaas (1927–2010)". The Behavior Analyst. **34** (1): 111–114. doi:10.1007/BF03392239. PMC 3089401.*
10. ^ Jump up to:[a] [b] *Smith, T.; Eikeseth, S. (2011). "O. Ivar Lovaas: Pioneer of applied behavior analysis and intervention for children with autism". J Autism Dev Disord. **41** (3): 375–378. doi:10.1007/s10803-010-1162-0. PMID 21153872. S2CID 207159059.*
11. **^** *Leaf, Ronald; McEachin, John; Taubman, Mitchell (2008). Sense and nonsense in the behavioral treatment of autism: It has to be said. New York: DRL. pp. 13–35. ISBN 978-0-975-58599-3.*
12. **^** *Bowman RA, Baker JP (March 2014). "Screams, slaps, and love: The strange birth of applied behavior analysis". Pediatrics. **133** (3): 364–366. doi:10.1542/peds.2013-2583. PMID 24534411. S2CID 28137037.*

13. ^ Lovaas, O. Ivar (1987). "Behavioral treatment and normal educational and intellectual functioning in young autistic children". Journal of Consulting and Clinical Psychology. **55** (1): 3–9. doi:10.1037/0022-006x.55.1.3. ISSN 1939-2117. PMID 3571656.
14. ^ Lovaas, O. Ivar; Smith, Tristram (1988), "Intensive Behavioral Treatment for Young Autistic Children", Advances in Clinical Child Psychology, Boston, MA: Springer US, pp. 285–324, doi:10.1007/978-1-4613-9829-5_8, ISBN 978-1-4613-9831-8, retrieved 18 November 2020
15. ^ Boyd, R. D. (June 1998). "Sex as a possible source of group inequivalence in Lovaas (1987)". Journal of Autism and Developmental Disorders. **28** (3): 211–215. doi:10.1023/a:1026065321080. ISSN 0162-3257. PMID 9656132. S2CID 40178588.
16. ^ Schopler, E.; Short, A.; Mesibov, G. (February 1989). "Relation of behavioral treatment to "normal functioning": comment on Lovaas". Journal of Consulting and Clinical Psychology. **57** (1): 162–164. doi:10.1037/0022-006x.57.1.162. ISSN 0022-006X. PMID 2925968.
17. ^ Jump up to:[a] [b] Gresham, F. M.; MacMillan, D. L. (February 1998). "Early intervention project: Can its claims be substantiated and its effects replicated?". Journal of Autism and Developmental Disorders. **28** (1): 5–13. doi:10.1023/a:1026002717402. ISSN 0162-3257. PMID 9546297. S2CID 7219819.
18. ^ Center for Homeland Defense and Security (1999). "Mental health: A report of the surgeon general". National Institute of Environmental Health Sciences, Substance Abuse and Mental Health Services Administration, Department of Health and Human Services: 164. Retrieved 28 August 2020.
19. ^ Myers SM, Johnson CP (November 2007). "Management of children with autism spectrum disorders". Pediatrics. **120** (5): 1162–1182. doi:10.1542/peds.2007-2362. PMID 17967921.
20. ^ Rogers SJ, Vismara LA (January 2008). "Evidence-based comprehensive treatments for early autism". Journal of Clinical Child and Adolescent Psychology. **37** (1): 8–38. doi:10.1080/15374410701817808. PMC 2943764. PMID 18444052.
21. ^ Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-VanderWeele J (May 2011). "A systematic review of early intensive intervention for autism spectrum disorders". Pediatrics. **127** (5): 1303–1311. doi:10.1542/peds.2011-0426. PMID 21464190. S2CID 10553507.
22. ^ Brignell A, Chenausky KV, Song H, Zhu J, Suo C, Morgan AT (November 2018). "Communication interventions for autism spectrum disorder in minimally verbal children". Cochrane Database of Systematic Reviews. **2018** (11): CD01234PMC. doi:10.1002/14651858.CD012324.pub2. PMC 6516977. PMID 30395694.
23. ^ Jump up to:[a] [b] Rekers, George A.; Lovaas, O. Ivar (1974). "Behavioral treatment of deviant sex-role behaviors in a male child". Journal of Applied Behavior Analysis. **7** (2): 173–190. doi:10.1901/jaba.1974.7-173. PMC 1311956. PMID 4436165.
24. ^ Rekers, George A.; Lovaas, O. Ivar; Low, Benson (June 1974). "The behavioral treatment of a "transsexual" preadolescent boy". Journal of Abnormal Child Psychology. **2** (2): 99–116. doi:10.1007/BF00919093. PMID 4430820. S2CID 23599014.
25. ^ Rekers, George A.; Bentler, Peter M.; Rosen, Alexander C.; Lovaas, O. Ivar (Spring 1977). "Child gender disturbances: A clinical rationale for intervention". Psychotherapy: Theory, Research & Practice. **14** (1): 2–11. doi:10.1037/h0087487.
26. ^ Rekers, George A.; Rosen, Alexander C.; Lovaas, O. Ivar; Bentler, Peter M. (February 1978). "Sex-role stereotypy and professional intervention for childhood gender disturbance". Professional Psychology. **9** (1): 127–136. doi:10.1037/0735-7028.9.1.127.
27. ^ Bronstein, Scott; Joseph, Jessi (7 June 2011). "Therapy to change 'feminine' boy created a troubled man, family says". CNN. Retrieved 9 June 2011.
28. ^ Szalavitz, Maia (8 June 2011). "The 'sissy boy' experiment: Why gender-related cases call for scientists' humility". Time. Retrieved 9 June 2011.
29. ^ Warren Throckmorton (9 June 2011). "Experts and homosexuality: Don't try this at home". HuffPost. Retrieved 9 June 2011.
30. ^ Jump up to:[a] [b] "Expression of Concern". Journal of Applied Behavior Analysis. **53** (4): 1837. September 2020. doi:10.1002/jaba.781. PMID 33084123.
31. ^ IshYoBoy.com. "Dr. Ole Ivar Lovaas | Pioneer of Applied Behavior Analysis (ABA)". The Lovaas Center. Retrieved 18 June 2018.
32. ^ "Applied behavior analysis (ABA)". Therapist Neurodiversity Collective. Retrieved 20 August 2020.
33. ^ "Screams, Slaps, and Love: A Surprising, Shocking Treatment Helps Far-Gone Mental Cripples". Life. 7 May 1965. Retrieved 24 October 2020.

34. ^ *Gonnerman, Jennifer. "The school of shock". Mother Jones. Retrieved 16 August 2020.*
35. ^ *"Eye to Eye". TV Guide. Retrie*

Chapter 1

Overview

Rett syndrome is a rare genetic neurological and developmental disorder that affects the way the brain develops. This disorder causes a progressive loss of motor skills and language. Rett syndrome primarily affects females.

Most babies with Rett syndrome seem to develop as expected for the first six months of life. These babies then lose skills they previously had — such as the ability to crawl, walk, communicate or use their hands.

Over time, children with Rett syndrome have increasing problems with the use of muscles that control movement, coordination and communication. Rett syndrome can also cause seizures and intellectual disabilities. Unusual hand movements, such as repetitive rubbing or clapping, replace purposeful hand use.

Although there's no cure for Rett syndrome, potential treatments are being studied. Current treatment focuses on improving movement and communication, treating seizures, and providing care and support for children and adults with Rett syndrome and their families.

Symptoms

Babies with Rett syndrome usually are born after an uncomplicated pregnancy and delivery. Most infants with Rett syndrome seem to grow and behave as expected for the first six months. After that, signs and symptoms start to appear.

The most pronounced changes generally occur at 12 to 18 months of age, over a period of weeks or months. Symptoms and their severity vary greatly from child to child.

The main signs and symptoms include:

- **Slowed growth.** Brain growth slows after birth. Smaller than usual head size (microcephaly) is sometimes the first sign that a child has Rett syndrome. As children get older, there is delayed growth in other parts of the body.
- **Loss of movement and coordination abilities.** The first signs often include reduced hand control and a decreasing ability to crawl or walk. At first, this loss of abilities occurs rapidly, and then it continues more gradually. Eventually muscles become weak or stiff, with unusual movement and positioning.
- **Loss of communication abilities.** Children with Rett syndrome typically begin to lose the ability to speak, to make eye contact and to communicate in other ways. They may become disinterested in other people, toys and their surroundings. Some children have rapid changes, such as a sudden loss of language. Over time, children may gradually regain eye contact and develop nonverbal communication skills.
- **Unusual hand movements.** Children with Rett syndrome usually develop repetitive, purposeless hand movements, which differ from child to child. Hand movements may include hand-wringing, squeezing, clapping, tapping or rubbing.

Other signs and symptoms can include:

- **Unusual eye movements.** Children with Rett syndrome tend to have unusual eye movements, such as intense staring, blinking, crossed eyes or closing one eye at a time.
- **Breathing problems.** These include breath holding, rapid breathing (hyperventilation), forcefully blowing out air or saliva, and swallowing air. These problems tend to occur during waking hours. Other breathing disturbances such as shallow breathing or short periods of stopping breathing (apnea) can occur during sleep.
- **Irritability and crying.** Children with Rett syndrome may become increasingly agitated and irritable as they get older. Periods of crying or screaming may begin suddenly, for no apparent reason, and last for hours. Some children may experience fears and anxiety.
- **Other unusual behaviors.** These may include, for example, sudden, odd facial expressions and long bouts of laughter, hand licking, and grasping of hair or clothing.
- **Intellectual disabilities.** Loss of skills may be connected to losing the ability to think, understand and learn.
- **Seizures.** Most people who have Rett syndrome experience seizures at some time during their lives. Multiple seizure types may occur and are associated with changes on an electroencephalogram (EEG).

- **Sideways curvature of the spine (scoliosis).** Scoliosis is common with Rett syndrome. It typically begins between 8 and 11 years of age and progresses with age. Surgery may be required if the curvature is severe.
- **Irregular heartbeat.** This is a life-threatening problem for many children and adults with Rett syndrome and can result in sudden death.
- **Sleep disturbances.** Problems with sleep patterns can include irregular sleep times, falling asleep during the day and being awake at night, or waking in the night with crying or screaming.
- **Other symptoms.** A variety of other symptoms can occur, such as a decreased response to pain; small hands and feet that are usually cold; problems with chewing and swallowing; problems with bowel function; and teeth grinding.

Stages of Rett syndrome

Rett syndrome is commonly divided into four stages:

- **Stage 1: Early onset.** Signs and symptoms are subtle and easily overlooked during the first stage, which starts between 6 and 18 months of age. Stage 1 can last for a few months or a year. Babies in this stage may show less eye contact and start to lose interest in toys. They may also have delays in sitting or crawling.
- **Stage 2: Rapid deterioration.** Starting between 1 and 4 years of age, children lose the ability to perform skills they previously had. This loss can be rapid or more gradual, occurring over weeks or months. Symptoms of Rett syndrome occur, such as slowed head growth, abnormal hand movements, hyperventilating, screaming or crying for no apparent reason, problems with movement and coordination, and a loss of social interaction and communication.
- **Stage 3: Plateau.** The third stage usually begins between the ages of 2 and 10 years, and it can last for many years. Although problems with movement continue, behavior may slightly improve, with less crying and irritability, and there may be some improvement in hand use and communication. Seizures may begin in this stage and generally don't occur before the age of 2.
- **Stage 4: Late motor deterioration.** This stage usually begins after the age of 10 and can last for years or decades. It's marked by reduced mobility, muscle weakness, joint contractures and scoliosis. Understanding, communication and hand skills generally remain stable or improve slightly, and seizures may occur less often.

When to see a doctor

Signs and symptoms of Rett syndrome can be subtle in the early stages. See your child's health care provider right away if you begin to notice physical problems or

changes in behavior after what appears to be typical development. Problems or changes may include:

- Slowed growth of your child's head or other parts of the body
- Decreased coordination or mobility
- Repetitive hand movements
- Decreasing eye contact or loss of interest in usual play
- Delayed language development or loss of previous language abilities
- Any clear loss of previously gained milestones or skills

Request an appointment

Causes

Rett syndrome is a rare genetic disorder. Classic Rett syndrome, as well as several variants (atypical Rett syndrome) with milder or more-severe symptoms, occur based on several specific genetic changes (mutations).

The genetic changes that cause Rett syndrome occur randomly, usually in the MECP2 gene. Very few cases of this genetic disorder are inherited. The genetic changes appear to result in problems with the protein production critical for brain development. However, the exact cause is not fully understood and is still being studied.

Rett syndrome in males

Because males have a different chromosome combination from females, males who have the genetic changes that cause Rett syndrome are affected in devastating ways. Most of them die before birth or in early infancy.

A very small number of males have a different genetic change that results in a less destructive form of Rett syndrome. Similar to females with Rett syndrome, these males are likely to live to adulthood, but they're still at risk of a number of intellectual and developmental problems.

Risk factors

Rett syndrome is rare. The genetic changes known to cause the disease are random, and no risk factors have been identified. In a very small number of cases, inherited

factors — for instance, having close family members with Rett syndrome — may play a role.

Complications

Complications of Rett syndrome include:

- Sleep problems that cause significant sleep disruption to the person with Rett syndrome and family members.
- Difficulty eating, leading to poor nutrition and delayed growth.
- Bowel and bladder problems, such as constipation, gastroesophageal reflux disease (GERD), bowel or urinary incontinence, and gallbladder disease.
- Pain that may accompany problems such as gastrointestinal issues or bone fractures.
- Muscle, bone and joint problems.
- Anxiety and problem behavior that may hinder social functioning.
- Needing lifelong care and assistance with activities of daily living.
- Shortened life span. Although most people with Rett syndrome live into adulthood, they may not live as long as the average person because of heart problems and other health complications.

Prevention

There's no known way to prevent Rett syndrome. In most cases, the genetic changes that cause the disorder occur spontaneously. Even so, if you have a child or other family member with Rett syndrome, you may want to ask your health care provider about genetic testing and genetic counseling.

By Mayo Clinic Staff

Request an appointment

May 03, 2022

Life Expectancy

Unfortunately, Rett Syndrome occurrences diminish the life range of persons affected. Most male patients will die within infancy years, and girls will be forced to live with uncontrolled movements that can result in convulsion/seizures. The life expectancy is undetermined, as both sudden death occurrences and regular death occurrences are tied with Rett. Generally, if a person with Rett does live past childhood, they will require aid for the rest of their life, dealing with regular movements like walking and going to the bathroom.

References:

1. Rett syndrome fact sheet. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Rett-Syndrome-Fact-Sheet. Accessed Jan. 10, 2022.

2. Rett syndrome. Merck Manual Professional Version. https://www.merckmanuals.com/professional/pediatrics/learning-and-developmental-disorders/rett-syndrome?query=rett%20syndrome. Accessed Jan. 10, 2022.

3. Rett syndrome. Eunice Kennedy Shriver National Institute of Child Health and Human Development. https://www.nichd.nih.gov/health/topics/factsheets/rett. Accessed Jan. 10, 2022.

4. Adam MP, et al., eds. MECP2 disorders. In: GeneReviews. University of Washington, Seattle; 1993-2022. https://www.ncbi.nlm.nih.gov/books/NBK1116/. Accessed Jan. 10, 2022.

5. Banerjee A, et al. Towards a better diagnosis and treatment of Rett syndrome: A model synaptic disorder. Brain. 2019; doi:10.1093/brain/awy323.

6. Gold WA, et al. Rett syndrome: A genetic update and clinical review focusing on comorbidities. ACS Chemical Neuroscience. 2018; doi:10.1021/acschemneuro.7b00346.

7. Ivy AS, et al. Rett syndrome: A timely review from recognition to current clinical approaches and clinical study updates. Seminars in Pediatric Neurology. 2021; doi:10.1016/j.spen.2021.100881.

8. Fu C, et al. Consensus guidelines on managing Rett syndrome across the lifespan. BMJ Paediatrics Open. 2020; doi:10.1136/bmjpo-2020-000717.

9. Rett syndrome: For families. International Rett Syndrome Foundation. https://www.rettsyndrome.org/for-families/. Accessed Jan. 10, 2022.

10. Cutsforth-Gregory JK (expert opinion). Mayo Clinic. Jan. 18, 2022.

Chapter 2

DAYBUE™ (trofinetide) | Rett Syndrome | Acadia Pharmaceuticals

https://daybue.com

The first and only FDA- approved pharmaceutical for the treatment of Rett Syndrome.

Indication: DAYBUE is a prescription medicine used to treat Rett syndrome in adults and children 2 years of age and older. It is not known if DAYBUE is safe and effective in children under 2 years of age.

Important Safety Information What are the possible side effects of DAYBUE? • Diarrhea: Diarrhea is a common side effect of DAYBUE that can sometimes be severe. Diarrhea may cause you to lose too much water from your body (dehydration). Before starting treatment with DAYBUE, stop taking laxatives. Tell your healthcare provider if you have diarrhea while taking DAYBUE. Your healthcare provider may ask you to increase the amount you drink or take antidiarrheal medicine as needed

Rett syndrome: A complex genetic disorder with a range of symptoms—but limited treatment options. Rett syndrome is a rare neurodevelopmental disorder that can cause lifelong complications. Your child's experience with Rett syndrome is unique to them—the symptoms can affect every individual in different ways, at different times, and at different stages of the disorder. As varied as these symptoms can be, your child can also experience regressions and unexpected setbacks throughout their life. This may leave you and your family continually seeking new solutions to the ongoing changes in your child. Along with a variation in symptoms, the ability to think and understand may also vary among children. Many children with Rett syndrome are cognitively aware but are unable to effectively act on their desire to communicate. This may leave them feeling frustrated and misunderstood

MECP2 is thought to control how many genes work, including those important for brain development. In Rett syndrome, mutations in MECP2 can disrupt the activity of these genes and are thought to lead to the symptoms of Rett syndrome.

DAYBUE was studied in a 12-week clinical trial of 187 female patients aged 5 to 20 years old

Caregivers and doctors evaluated signs and symptoms of Rett syndrome in the clinical trial with DAYBUE. While not all symptoms are listed here, these are examples of the types of symptoms that were evaluated: Read on to learn more about how the effectiveness and safety of DAYBUE were studied.

Breathing, Hand movements or stereotypies , Vocalizations and Moods

Patients in LAVENDER all had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria, and a documented mutation in the MECP2 gene. And, to reflect how unique Rett syndrome is for each person, patients in both groups of the study had a range of symptoms and disease severity.

How was DAYBUE studied? The effectiveness and safety of DAYBUE were evaluated in the 12-week **LAVENDER™** clinical trial of 187 females aged 5 to 20 with Rett syndrome.

Changes were assessed in signs and symptoms of Rett syndrome in the **LAVENDER™** trial. Because caregivers possess such a deep knowledge of their child, they contributed directly to the evaluation of the overall effectiveness of DAYBUE. Doctors evaluated if patients improved or got worse, while caregivers looked for changes in the signs and symptoms of Rett syndrome. CAREGIVERS Used the Rett Syndrome Behaviour Questionnaire (RSBQ) to evaluate changes in the signs and symptoms of Rett syndrome DOCTORS Used the Clinical Global Impression Improvement (CGI-I) scale to evaluate if a patient has improved or worsened

During the trial, 93 patients were given DAYBUE, and their results were compared with those of 94 patients who were given a placebo (treatment without any active medication). 187 patients

Following the 12-week **LAVENDER™** clinical trial, eligible patients and their families were given the option to continue treatment with DAYBUE (or start treatment with DAYBUE if they had previously received a placebo) in the **LAVENDER™** study .

The **LILAC™** Study

154 patients enrolled for the 40-week study

Caregivers evaluated changes in a range of symptoms using the Rett Syndrome Behaviour Questionnaire (RSBQ)

What does the RSBQ measure? An instrument used in studies of Rett syndrome, the RSBQ is a measurement scale used by caregivers to evaluate 45 items representing symptoms of Rett syndrome. Caregivers were asked to rate each item as it relates to their child. These are examples of the types of symptoms that caregivers evaluated

Breathing Hand Movements or Stereotypies Repetitive Behaviors Night Time Behaviors

Vocalizations Facial Expressions Eye Gaze Mood

What could At 12 weeks, caregivers observed: improvements look like? After caregivers completed the RSBQ, the scores of the 45 items were added up to create the RSBQ total score. The maximum possible score was 90. To determine how symptoms were impacted by treatment, researchers looked at how much the average RSBQ total score changed for all patients in the clinical trial at 12 weeks of treatment

The patients receiving DAYBUE saw almost 3x greater decrease in average RSBQ total score from the start of the trial when compared with placebo. A lower score meant signs and symptoms of Rett syndrome were less severe

Before starting treatment, the average RSBQ total score for the DAYBUE group was 43.7. For the placebo group, the average RSBQ total score before treatment was 44.5. *Results varied between patients in the clinical trial. Individual results may vary with DAYBUE. -8 -6 -4 -2 0 -4.9 DAYBUE The difference between the 2 groups was -3.2 Average Decrease From Start of the Trial* -1.7 Placebo.

The most common side effects of DAYBUE were diarrhea and vomiting. Other side effects include fever, seizure, anxiety, decreased appetite, tiredness, and the common cold. These are not all the possible side effects of DAYBUE. Tell your healthcare provider if you have any side effects that bother you or do not go away.

Call Acadia Connect®: 1-844-737-2223 Monday-Friday 8 am-8 pm ET or visit acadia.com to learn more.

Please read the full Prescribing Information, including Patient Information.

- **The International Rett Syndrome Foundation (IRSF)** has designated Centers of Excellence across the country that offer specialized care for the Rett syndrome community.
- **Locate a center**
- **Child Neurology Society** assists parents in their search for child neurologists, support groups, or other websites that may prove useful in helping them to understand and address the challenges confronting their family.
- **Find a neurologist**

DAYBUE is now available by prescription through your doctor