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Improving Treatment Trial Outcomes for Rett Syndrome: the development of Rett-specific anchors for the Clinical Global Impression Scale

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Author contributions

JN and DG provided the clinical and conceptual framework for development of the clinical anchors, collected data and participated in cross-study calibration of the measure. AP, TF, AB, TD collected data and participated in cross-study calibration of the measure. BS collected data and completed calibration scoring on the measure. EA developed the calibration procedures for the measure. JH and MS developed the idea of a Rett-syndrome-specific version of the Clinical Global Impression scales and contributed to the development of the clinical anchors. NJ contributed to the writing of the manuscript and to the development of the clinical anchors and development of the calibration procedures for the measure. JN, DG, AP, TF, EA, MS, NJ, JH all provided critical review of and made contributions to the writing of the manuscript.

Declaration of conflicting interests

JN receives research funding from the NIH/NICHD, International Rett Syndrome Foundation, and the Rett Syndrome Research Trust, participated in the Neuren NNZ 2566 clinical trial and serves on the advisory board for the International Rett Syndrome Foundation and the International FoxG1 Foundation. DG receives research funding from NIH/NICHD, International Rett Syndrome Foundation, participated in the Neuren NNZ 2566 clinical trial and serves on the advisory board for International Rett Syndrome Foundation. AP receives research funding from the NIH/NICHD, participated in the Neuren NNZ 2566 clinical trial and serves on the advisory board for International Rett Syndrome Foundation. TF participated in the Neuren NNZ 2566 clinical trial. AB participated in the Neuren NNZ 2566 clinical trial, and is a professional advisor for the International Rett Syndrome Foundation. BS participated in the Neuren NNZ-2566 clinical trial. TD participated in the Neuren NNZ-2566 clinical trial. EA receives research funding from Sanofi-Aventis Canada and SynapDX and has received consultation fees from Roche and Novartis. NJ and JH are executives of Neuren Pharmaceuticals. MS receives consulting fees from Neuren Pharmaceuticals.

Ethical approval

The study was approved by the Institutional Review Board of the three participating centers at Baylor College of Medicine and Affiliated Hospitals, University of Alabama at Birmingham (Institution # W130719007; WIRB Study Number 1141068), and Gillette Children's Specialty Healthcare (IRB Number 1312M46322). Informed consent was obtained from parents or legal guardians for all participants.

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Abstract

Rett syndrome is a genetically based neurodevelopmental disorder. While the clinical consequences of Rett syndrome are profound and life-long, currently no approved drug treatments are available specifically targeted to Rett symptoms. High quality outcome measures, specific to the core symptoms of a disorder are a critical component to well-designed clinical trials for individuals with neurodevelopmental disorders. The Clinical Global Impression Scale is a measure of global clinical change with strong face validity that has been widely used as an outcome measure in clinical trials of central nervous system disorders. Despite its favorable assay sensitivity in clinical trials, as a global measure, the Clinical Global Impression Scale is not specific to the signs and symptoms of the disorder under study. Development of key anchors for the scale, specific to the disorder being assessed, holds promise for enhancing the validity and reliability of the measure for disorders such as Rett syndrome.

Keywords

Rett syndrome; *MECP2*; Clinical trials; outcome measures; Clinical Global Impression Scales

Introduction

Rett Syndrome is a genetically based neurodevelopmental disorder usually caused by mutations in the gene *Methyl-CpG-binding Protein 2* (*MECP2*). The disorder occurs almost exclusively in females with current incidence rates of 1 in 10,000[1]. Young girls with Rett syndrome have apparently normal early development with an onset of regression between 6 to 18 months old including developmental arrest, loss of spoken communication, purposeful hand use, and motor skills[2]. Affected individuals also have loss or impairment of ambulation and the development of characteristic stereotyped repetitive hand movements. Additional clinical features common in Rett syndrome include a variety of autonomic and physiological abnormalities such as disordered breathing with hyperventilation and apnea[3], abnormal heart rate variability[4], and vasomotor disturbances. Scoliosis is common[5] and most individuals are considered to have severe intellectual disability[6]. Individuals with Rett syndrome also have high rates (60-79 percent) of seizures[7,8] and abnormal EEGs with epileptiform abnormalities[9]. Though sudden unexpected death occurs more frequently than in the general

population[10], survival into adulthood is expected with a significant number of individuals with Rett syndrome reaching the ages of 30-60 years[11].

Currently no pharmacological treatments are approved specifically for the signs and symptoms of Rett syndrome. A treatment that could limit the symptom burden of Rett Syndrome would be an important therapeutic advance. High-quality outcome measures are a requisite component of well-designed clinical trials in subjects with Rett syndrome. We describe the development of novel anchors specific to Rett signs and symptoms for the Clinical Global Impression Scales (Severity and Improvement). This effort was part of a clinical trial involving adolescent and adult females with Rett syndrome, which is the first industry-sponsored, multi-site clinical trial in this clinical population.

The Clinical Global Impression Scale (CGI)[12] is a measure of global clinical change with strong face validity. It has been widely used as an outcome measure in central nervous system clinical trials, including trials in neurodevelopmental disorders such as autism and Fragile X syndrome[13, 14]. The Clinical Global Impression Scale is a 7-point Likert rating scale that reflects expert clinical judgment. It includes independent *severity of illness* (CGI-S) and *improvement* (CGI-I) scales.

Despite its favorable assay sensitivity in clinical trial settings involving a number of different neuropsychiatric disorders, a disadvantage of the Clinical Global Impression Scale has been its lack of focus on the specific signs and symptoms of the disorder under study (or consideration)[15]. This has diminished its utility as a primary outcome measure in clinical trials. In other developmental disorders such as Fragile X syndrome and Autism Spectrum Disorders, the scoring rubric used to ensure consistency across clinical experts in a given study has been tied to relevant “anchors” specific to the signs and symptoms of the disorder. The complete set of anchors can be found in the supplementary material in Tables S1 and S2. Scores of 1 and 2 for improvement are often used in clinical trials to define treatment “responders”, especially in trials involving episodic disorders (e.g. major depressive disorder). In the current study, the full range of improvement scores (1, 2 or 3) were used to determine improvement. Our aim was to develop clinical anchors for the Clinical Global Impression Scales that would be specific to the signs and symptoms of Rett syndrome.

Methods and Results

The CGI was administered as part of a double-blind, placebo controlled Phase 2 study of NNZ-2566 in adolescent and adult females between the ages of 16-45 years with Rett syndrome. NNZ-2566 is an analog of the terminal tripeptide of Insulin-like Growth Factor-1 (IGF-1). In the brain, IGF-1 contributes to the growth of brain cells and synapses and plays an important role in repairing damaged cells[16]. The terminal tripeptide, glypromate or GPE, is cleaved from the main molecule and acts on brain cells by itself in a different manner than the full IGF-1 molecule[16, 17, 18]. NNZ-2566 is a modified synthetic version of GPE that is orally available and crosses the blood-brain barrier[19, 20].

Baseline characteristics of the participating subjects are outlined in Table 1. Participants all had a clinical diagnosis of typical Rett syndrome and a confirmed, pathogenic *MECP2*

mutation. Participants were required to have a Clinical Global Impression severity score of 4 or higher at screening, and a score between 10 and 36 on the Rett Clinical Severity Scale[21], a thirteen item clinician measure of severity. See the Clinicaltrials.gov listing (NCT01703533) for the complete inclusion/exclusion criteria and full list of outcome measures.

For the Clinical Global Impression Severity scale, a classification grid of symptom severity was created using scores from the Rett Clinical Severity Scale as a guide. The Clinical Severity Scale has been used to evaluate over 1000 Rett syndrome children and adults enrolled in the NIH sponsored Natural History of Rare Diseases Project for Rett syndrome[11] and in studies looking at genotype/phenotype correlations[21,22] and epilepsy in Rett syndrome[7]. This thirteen item measure provides a clinician rating of core symptoms of Rett syndrome on a Likert scale of either 0-4 or 0-5 with a maximum total score of 58. This first step provided an anchoring of the Clinical Global Impression severity ratings against an established clinical rating scale specific to Rett syndrome with excellent face validity and extensive longitudinal use. This is shown in Table 2.

Since the Clinical Global impression scale is designed to be a *global* clinical assessment and not simply duplicate what can be determined by ratings of specific signs and symptoms, the next step was to develop the symptoms in the grid into narrative anchors that would provide a description of progressive levels of impairment in core signs and symptoms. In addition, general instructions provide a framework for applying the anchors in consideration of both number and severity of symptoms in the global classification. In applying the anchors to real life cases, the signs and symptoms should be considered as a whole. An individual does not necessarily need to be impaired to the same degree across all signs/symptoms. The severity score ratings are shown in Table 3. The full set of anchors is shown in Table S1 in the supplementary materials.

Separate anchors were developed for Clinical Global Impressions Scale-Improvement. The severity scale anchors provide a detailed description of the specific signs and symptoms that may be encountered at each level of severity. Since the Improvement Scale is focused on determining change in symptoms from baseline, these anchors were developed to provide a framework for considering the following factors related to symptom severity in order to determine the global change score: duration, onset, durability of change, and the context of sign/symptom change across the symptom domains. The Clinical Global Impression-Improvement anchors provide examples of sign/symptoms, and for scores representing important thresholds for treatment response, information on factors to differentiate between the scores is provided. The improvement scale scoring is shown in Table 3. The full set of anchors is shown in Table S2 in the Supplementary Materials.

To ensure consistency in the application of the anchors, clinician raters participated in periodic calibration sessions in which they co-rated sample Rett syndrome vignettes. Following best practice for the administration of the Clinical Global Impression scales, scores within a 1 point difference were considered reliable. Scores within a 2 or more point difference or at a 1 point difference at a critical threshold score (e.g. 2 versus 3 or 3 versus 4), were discussed and a consensus decision was made on the interpretation of the anchors,

so rescores were normed within an acceptable difference. Scoring of a sample vignette is also shown in Table 3.

Discussion

This rating scheme developed for the Clinical Global Impression Scales captures clinically relevant gradations in severity and improvement of Rett-related signs and symptoms, offering the prospect of more consistent and relevant administration across research sites and studies. This report describes the early development of this novel format for the Clinical Global Impression Scales in the context of a clinical trial involving adolescent and adult females with Rett syndrome. Future analyses will examine the psychometric properties of this Rett-specific version of the Clinical Global Impression scales in the context of this clinical trial. Further formal validation analyses will be conducted to confirm its construct and content validity, and demonstrate reliability of rater calibration across studies.

The Clinical Global Impression assessment is a widely used outcome measure in clinical trials of central nervous system disorders that has been demonstrated to be sensitive to treatment change. Having Rett-specific anchors for this measure would provide not only a valid measure of global treatment change, but co-validation of this popular change measure with other Rett measures can accelerate the development of a battery of outcome measures valid for use in clinical trials of Rett syndrome.

Advances in the understanding of the underlying pathophysiology of neurodevelopmental disorders (NDD) is rapidly leading to the development of new ideas for therapeutics and the implementation of clinical trials. Excitingly, there is growing evidence of a degree of molecular and pathway convergence of various NDD, such as common alterations in mTOR signaling in Tuberous Sclerosis and other NDD that provides for application of common therapeutics to different disorders[23]. That said, the specific clinical features within these disorders are distinct, and it is unlikely that a generic outcome measure can be uniformly applied across multiple disorders. One solution is to utilize the methodology outlined here to develop disease specific anchors and scoring systems for the CGI. This will provide the ability to capitalize on disease specific features while allowing for cross-disease comparisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline Characteristics of Study Participants*

	N	Mean	Median	SD
Age	53	25.5	24.3	7.2
CSS Total Score	53	24	23	6.6
CGI-S	53	5.02	5.00	0.84
4-Moderately Ill	18			
5-Markedly Ill	16			
6-Severely Ill	19			
MECP2 Genotype	53			
Proximal	35			
Distal	18			

*Randomized and completed the study

Table 2

Initial assignment of Rett Clinical Severity Scale scores and symptoms to Clinical Global Impression Scale Severity rating score

CLINICAL DOMAINS	CGI-S: 1 (CSS =0)	CGI-S: 2 (CSS <5)	CGI-S: 3 (CSS 5-10)	CGI-S: 4 (CSS 10-20)	CGI-S: 5 (CSS 20-25)	CGI-S: 6 (CSS 25-35)	CGI-S: 7 (CSS 35-40)
Language/ Communication	Normal	Appropriate. May have unusual features such as perseveration/ echolalia. Reading disability/dyslexia	Phrases-sentences. May have conversations or echolalia	Words (<5) Babbles Makes choices 25-50%	No Words Babbles Makes choices ≤25%	Vocalizations Occasionally screams Makes No Choices or only rarely makes choices	No Words No Vocalizations Screams No Choices
Ambulation	No impairment	Normal, may have slight evidence of dystonia/ataxia/ dyspraxia on careful exam	Walks, able to use stairs/ run. May ride tricycle or climb	Walks Independently, unable to use stairs or run	Walks with Assistance	Stands With Support or independently May walks with support Sits independently or with support	Cannot sit Doesn't Stand or Walk
Hand Use	Completely normal, no impairment	Normal, may have slight fine motor issues	Bilateral Pincer grasp. May use pen to write but has some fine motor issues like tremor	Reaches for objects, raking grasp or unilateral pincer. May use utensils/cup	Reaches No Grasps	Rarely-Occasionally Reaches Out No Grasp	None
Social (Eye Contact)	Normal	Occasional eye gaze avoidance	Appropriate eye contact, >30 sec	Eye Contact <20 secs	Eye Contact <10 secs	Eye Contact, Inconsistent 5 secs	No eye Contact
Autonomic	None	Minimal	No or minimal breathing abnormalities (<5% of times observed) and Warm, pink extremities	Breathing Dysrhythmia <50% No Cyanosis Cool UE & LE Pink	Breathing Dysrhythmia 50% No Cyanosis Cool UE & LE Pink	Breathing Dysrhythmia, 50%-100%, maybe with Cyanosis Cold LE or UE, may be Blue	Breathing Dysrhythmia, Constantly with Cyanosis Cold UE & LE Mottled/Blue
Seizures	None	None or controlled	None, with or without meds	Monthly-Weekly	Weekly	Weekly-Daily	Daily
Attentiveness	Entirely normal	Occasional inattention	Attentive to conversation and follows commands	50-100% of Time	50% of Time	Less than 50% time	0%

CSS: Clinical Severity Scale. CGI-S: Clinical Global Impression Scale-Severity. UE: Upper extremity. LE: Lower extremites

Table 3

Clinical Global Impression Scale Scores and Calibration Vignette

Score	CGI-S:	CGI-I:	Calibration Vignette Example
1	*Normal, not at all ill*	*Very much improved*	**Baseline** Severity: 5 She is a 17yo who can walk independently although she frequently needs assistance with initiation. She vocalizes only and does so infrequently. She does not reach out or hold a bottle. She maintains infrequent eye contact for 10-20 seconds. She uses the iPad for communication by pointing with her nose and consistently makes choices >50%. She breath holds <10% of the time, no hyperventilation. Her extremities are pink and cool without cyanosis. Her seizures are controlled with medications and a vagal nerve stimulator. **Day 14** Severity: 5 Improvement: 3 She comes back today and her caretaker complained of irritability she attributed to GI upset and loose stool and was given several days of pepto bismol and mylanta. Positive changes reported by caretaker included more vocalizations, decreased hand wringing and relaxed arms and legs. She also reported increased stamina with walking and stationary bike. There were no remarkable changes on exam during visit.
2	*Borderline ill*	*Much improved*	
3	*Mildly ill*	*Minimally improved*	
4	*Moderately ill*	*No change*	
5	*Markedly ill*	*Minimally worse*	
6	*Severely ill*	*Much worse*	
7	*Extremely ill*	*Very much worse*	