The adaptation and utility of the Clinical Global Impression scale for studying treatment outcomes in neurodevelopmental conditions

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ABSTRACT

Background

- The Clinical Global Impression–Improvement (CGI-I) scale is a validated clinician-rated scale widely used in clinical trials of central nervous system conditions
  - Its structure supports reliable and valid adaptation to many different conditions
  - It is especially well suited for neurodevelopmental conditions with heterogeneous clinical presentations between individuals and across individuals' lifespans
- Clinical Global Impression (CGI) scales (referring to both CGI-I and the Clinical Global Impression–Severity (CGI-S) scale) allow an expert rater to assign weight to symptoms based on functional impact and clinical meaningfulness
- CGI avoids presuppositions about clinical effects of specific investigational treatments

Objective

- To review literature that describes the adaptation and utility of CGI, including CGI-I and CGI-S, in selected neurodevelopmental disorders

Methods

- Literature review on the use of CGI in autism spectrum disorder (ASD), Angelman syndrome (AS), Fragile X syndrome (FXS), Prader-Willi syndrome (PWS), and Rett syndrome

Results

- A total of 430 clinical trials were identified that used CGI in the study of neurodevelopmental disorders
  - The vast majority of trials were in patients with ASD or attention-deficit/hyperactivity disorder (ADHD)
  - Twenty-eight trials were in patients with FXS, PWS, Rett syndrome, or AS; among these, 4 studies adapted scales to the unique presentations of the specific disorder

Conclusions

- Findings support the potential of CGI to be adapted for neurodevelopmental conditions for which no condition-specific symptom rating scales are available

BACKGROUND: CGI Adaptations for Specific Diseases and Syndromes

Original CGI

- The original CGI (Table 1)[1] was used in early psychiatry trials, mainly for schizophrenia, depression, anxiety, and bipolar disorders as a supplement to disease-specific rating scales[2]

Need for Disease-/Syndrome-specific Adaptations of CGI

- The reliability of CGI scales has benefited from ratings based on a uniform set of disease parameters using disease-specific scales
- Disease-specific adaptations of CGI have been proposed with the objective of improving reliability and validity in bipolar disorder,[3] schizophrenia,[2,4] depression,[4] and Alzheimer's disease[5]
- These adapted versions of CGI have not been widely adopted, in large measure because good reliability is already achieved in the hands of a clinical expert in the disease under study and rater training[2]
- The greatest advantage of disease-specific adaptations of CGI is realized in:
  1. Conditions with dramatic phenotypic heterogeneity
  2. Rare disorders lacking validated disease-specific symptom rating scales
- In this poster, we summarize how CGI scales have been used in clinical trials of neurodevelopmental disorders to assess clinically meaningful treatment effects

Table 1. Original CGI Guidelines[1]

Severity of illness:	Global improvement:
Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?	Rate total improvement whether or not in your judgment it is due entirely to drug treatment. Compared to the patient's condition at admission to the project, how much has he or she changed?
1 = normal, not at all ill	**1** = very much improved
2 = borderline mentally ill	**2** = much improved
3 = mildly ill	**3** = minimally improved
4 = moderately ill	**4** = no change
5 = markedly ill	**5** = minimally worse
6 = severely ill	**6** = much worse
7 = among the most extremely ill patients	**7** = very much worse

Adapted from Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Rockville, MD: National Institute of Mental Health; 1976.

1. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Rockville, MD: National Institute of Mental Health; 1976; 2. Busner J, Targum SD. *Psychiatry (Edgemont).* 2007;4(7):28–37; 3. Spearing MK et al. *Psychiatry Res.* 1997;73(3):159–171; 4. Haro JM et al. *Acta Psychiatr Scand Suppl.* 2003(416):16–23; 5. Kadouri A et al. *Int Psychogeriatr.* 1996;8(2):277–288; discussion 288–290.

OBJECTIVE AND METHODS: CGI Adaptation Literature Review

Objective

- The objective was to examine ways in which CGI has been applied and adapted in various contexts

Methods

- The following steps were taken:
  1. A PubMed search was conducted using the search terms [(Clinical Global Impression) AND (Neurodevelopment)], which yielded 692 citations, 430 of which were clinical trials, mostly in patients with ASD or ADHD
  2. Specific rare disease searches were conducted using the term pair [(Clinical Global Impression) and (Fragile X syndrome)] and with (Prader-Willi syndrome), (Rett syndrome), or (Angelman syndrome) substituted for the latter term
  3. A search of ClinicalTrials.gov using the above disease terms and “Clinical Global Impression Scale” was conducted
  4. Abstracts of all studies found were examined to identify those relevant to this review
- The combined rare disease searches yielded 9 treatment studies for FXS, 7 each for PWS and Rett syndrome, and 4 for AS

RESULTS: Select Neurodevelopmental Disorders Findings

- None of the ASD studies found in this literature review made reference to disease-specific adaptations to CGI scales
- Instead, CGI was used in the manner originally conceived, for which ratings are rendered only after other disease-specific symptom rating scales have been completed
- CGI and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)[1] were the most commonly used scales, including an ASD adaptation of the Children's Y-BOCS (CY-BOCS) called CY-BOCS-Pervasive Developmental Disorders[2,3]
- CGI was specifically recommended for ASD intervention trials by Aman and colleagues with the provision that training would be required to ensure reliability and validity[4]
- Arnold and colleagues recommended anchoring CGI with a rating of 3 (mildly ill) as the baseline score for all study participants and considering higher scores to reflect significant maladaptive behaviors associated with ASD[5]
- Bearss and colleagues asked parents/guardians at baseline to identify and describe in detail the child's 2 most pressing problems, including duration and intensity of episodes, and effect on family[6]
  - Following a review of these narratives, subsequent ratings were based on documented changes on these dimensions
  - Other clinical rating scales were also used in this study and were considered in rating CGI

1. Goodman WK et al. *Arch Gen Psychiatry.* 1989;46(11):1012-1016; 2. Scahill L et al. *J Am Acad Child Adolesc Psychiatry.* 1997;36(6):844-852; 3. Scahill L et al. *J Am Acad Child Adolesc Psychiatry.* 2006;45(9):1114-1123; 4. Aman MG et al. *CNS Spectr.* 2004;9(1):36-47; 5. Arnold LE et al. *J Autism Dev Disord.* 2000;30(2):99-111; 6. Bearss K et al. *JAMA.* 2015;313(15):1524-1533.

RESULTS: Clinical Trials Using CGI in Fragile X Syndrome

- Seven published trial reports and 4 registered trials used CGI as an assessment for patients with FXS, resulting in 9 trials (Table 2)
- Most of these trials used additional disease-specific scales, including the Aberrant Behavior Checklist-Community (ABC-C), which was specifically modified for the FXS population (ABC-C_{FXS})[1]
- Only 1 study used CGI-I as the primary outcome,[2] and 2 used it as a co-primary outcome[3,4]
- One study used disease-specific adaptations to CGI, wherein a systematic analysis of clinician narratives was performed from a phase 2 trial of mavoglurant in adolescents with FXS[5]
  - Narratives were coded under blinded conditions based upon disease-specific CGI dimensions and anchors created for this purpose
  - Analysis of the re-coded narratives failed to detect any treatment effects

Table 2. Clinical Trials Using CGI in FXS

Publication(s)/Source	Treatment/Study registry identifier	CGI primary or secondary?	CGI followed disease-specific scales?*	CGI adaptation specified?
Heussler et al. 2019[6]	Transdermal cannabidiol/ ACTRN12617000150347	Secondary	Yes*	No
Ligsay et al. 2017[2]	Ganaxolone/ NCT01725152	Primary	Yes*	No
Berry-Kravis et al. 2017[7]	Arbaclofen/ NCT01282268 NCT01325220	Key secondary	Yes*	No
Bailey et al. 2016[5] Berry-Kravis et al. 2016[8]	Mavoglurant/ NCT01357239	Secondary	Yes*	Yes
Veenstra-VanderWeele et al. 2017[9]	Arbaclofen/ NCT01288716	Secondary	No†	No
Greiss Hess et al. 2016[3]	Sertraline/ NCT01474746	Co-primary	No†	No
Leigh et al. 2013[4]	Minocycline/ NCT01053156	Co-primary	Yes*	No
Paribello et al. 2010[10]	Minocycline/ NCT00858689	Secondary	Yes*	No
Youssef et al. 2018[11]	Basimglurant/ NCT01517698	Secondary	Yes*	No
Unpublished, ongoing/ Ovid Pharma	Gaboxadol (OV101)/ NCT03697161	Secondary	Yes*	No

*Aberrant Behavior Checklist modified for FXS (ABC-C_{FX}).
†Used numerous other scales including for ASD; none designed for/validated in FXS.
CGI, Clinical Global Impression.

1. Sansone SM et al. 2012 Jul;42(7):1377-92; 2. Ligsay A et al. *J Neurodev Disord.* 2017;9(1):26; 3. Greiss Hess L et al. *J Dev Behav Pediatr.* 2016;37(8):619-628; 4. Leigh MJ et al. *J Dev Behav Pediatr.* 2013;34(3):147-155; 5. Bailey DB Jr et al. *J Neurodev Disord.* 2016;8:1; 6. Heussler H et al. *J Neurodev Disord.* 2019;11(1):16; 7. Berry-Kravis E et al. *J Neurodev Disord.* 2017;9:3; 8. Berry-Kravis E et al. *Sci Transl Med.* 2016;8(321):321ra325; 9. Veenstra-VanderWeele J et al. *Neuropsychopharmacology.* 2017;42(7):1390-1398; 10. Paribello C et al. *BMC Neurol.* 2010;10:91; 11. Youssef EA et al. *Neuropsychopharmacology.* 2018;43(3):503-512.

RESULTS: Clinical Trials Using CGI in Prader-Willi Syndrome

- Overall, PWS literature found CGI to be an optimal tool for capturing severity and change in the context of treatment for a heterogeneous phenotype (Table 3)
- No studies described disease-specific adaptations, though Tauber and colleagues (2017) employed a uniquely anchored CGI for use in infants with PWS in a clinical trial of oxytocin focusing on behaviors and social skills before and during feeding[1]
- Dykens and colleagues (2018) included CGI-I among several secondary endpoints in a study of carbetocin in which a disease-specific rating scale, the PWS Questionnaire-Responsiveness total score, was the primary endpoint[2]
- Two studies used CGI as a primary outcome measure: a published study of topiramate for eating behaviors in PWS[3] and a trial of hippotherapy (ClinicalTrials.gov identifier NCT03858023)
- Two studies (ClinicalTrials.gov identifiers NCT03858023 and NCT03649477) used or are using disease-specific rating scales and symptom-specific questionnaires to inform their CGI ratings[3]
- CGI was used in a study by Avrahamy and colleagues (2015) to successfully validate a disease-specific questionnaire for assessing behavior in PWS patients[4]

Table 3. Clinical Trials Using CGI in PWS

Publication(s)/Source	Treatment/Study registry identifier	CGI primary or secondary?	CGI followed disease-specific scales?*	CGI adaptation specified?
Consoli et al. 2019[3]	Topiramate/ NCT02810483	Primary	Yes*	No
Dykens et al. 2007[2]	Carbetocin (IN)/ NCT01968187	Secondary	No†	No
Miller et al. 2017[5]	Oxytocin/ NCT02013258	Secondary	No†	No
Durst et al. 2000[6]	Risperidone	Exploratory	No†	No
Unpublished, ongoing/ University of Toulouse	Oxytocin/ NCT03114371	Secondary	No†	Unknown
Unpublished ongoing/ J.Y. Kwon, Samsung Medical Center	Hippotherapy/ NCT03858023	Primary	Yes*	Unknown
Unpublished, on hold due to COVID/Levo Therapeutics	Carbetocin (LV101)/ NCT03649477	Secondary	Yes‡	Unknown

*Hyperphagia in PWS Questionnaire-Responsiveness (HPWSQ-R) total score.
†Used other scales, but none specifically developed/validated for PWS.
‡PWS Anxiety and Distress Questionnaire (PADQ).
CGI, Clinical Global Impression.

1. Tauber M et al. *Pediatrics.* 2017;139(2); 2. Dykens EM et al. *Obesity (Silver Spring).* 2007;15(7):1816-1826; 3. Consoli A et al. *Transl Psychiatry.* 2019;9(1):274; 4. Avrahamy H et al. *Compr Psychiatry.* 2015;58:189-197; 5. Miller JL et al. *Am J Med Genet A.* 2017;173(5):1243-1250; 6. Durst R et al. *Acta Psychiatr Scand.* 2000;102(6):461-465.

RESULTS: Clinical Trials Using CGI in Rett Syndrome

- Three published studies used CGI as a trial endpoint in Rett syndrome (Table 4)[1-3]
- The first validated disease-specific adaptation to CGI for a neurodevelopmental disorder came from Neul and colleagues (2015), who created disease-specific anchors for CGI-S using the Rett Clinical Severity Scale as a guide[3]
- Similar methods were used to adapt CGI-I by anchoring change on the basis of duration, onset, and durability of change, as well as in the context of change across the symptom domains observed in Rett syndrome
- This disease-specific adaptation of CGI has become accepted as standard for use in clinical trials in Rett syndrome,[1,2] and 4 ongoing trials on ClinicalTrials.gov that are using this adapted CGI as a co-primary endpoint were identified

Table 4. Clinical Trials Using CGI in Rett Syndrome

Publication(s)/Source	Treatment/Study registry identifier	CGI primary or secondary?	CGI followed disease-specific scales?*	CGI adaptation specified?
Glaze et al. 2019[1]	Trofinetide/ NCT02715115	Not specified	No*	No
O'Leary et al. 2018[2]	Mecasermin/ NCT01777542	Secondary	Yes†	No
Neul et al. 2015[3]	NNZ-2566/ NCT01703533	Secondary	Yes‡	Yes
Unpublished, ongoing/ GW Research	Cannabidiol/ NCT03848832	Co-primary	Yes†	Unknown
Unpublished, ongoing/ Acadia Pharma	Trofinetide/ NCT04181723	Co-primary	Yes†	Unknown
Unpublished, ongoing/ Anavex Life Sciences	ANAVEX2-73/ NCT03758924 NCT03941444	Co-primary	Yes†	Unknown
Unpublished, ongoing/ Anavex Life Sciences	ANAVEX2-73 in Pediatrics/ NCT04304482	Co-primary	Yes†	Unknown

*Used other scales, but none developed/validated for Rett syndrome.
†Rett Syndrome Behavior Questionnaire (RSBQ).
‡Rett Syndrome Natural History Motor Behavior Assessment (MBA).
CGI, Clinical Global Impression.

1. Glaze DG et al. *Neurology.* 2019;92(16):e1912-e1925; 2. O'Leary HM et al. *Ann Clin Transl Neurol.* 2018;5(3):323-332; 3. Neul JL et al. *J Child Neurol.* 2015;30(13):1743-1748.

RESULTS: Clinical Trials Using CGI in Angelman Syndrome

- No citations were found using planned PubMed search terms for AS
- A broader search was conducted on the term "Angelman syndrome" by specifying all clinical trials, and it yielded 6 studies[1–6]
  - A search of ClinicalTrials.gov yielded 3 additional records
  - Two published studies used CGI as a trial endpoint in AS (Table 5)[5,6]
  - None of the remaining 4 papers used CGI as an endpoint
- Following on the work of Neul et al (2015) in Rett syndrome, disease-specific adaptations of CGI-S and CGI-I, called CGI-S-AS and CGI-I-AS, respectively, have been validated in AS[7]
- CGI-I-AS is currently the primary outcome in a phase 3 study of gaboxadol in children and adolescent with AS (NEPTUNE; ClinicalTrials.gov identifier NCT04106557)

Table 5. Clinical Trials Using CGI in AS

Publication(s)/Source	Treatment/Study registry identifier	CGI primary or secondary?	CGI followed disease-specific scales?*	CGI adaptation specified?
Grieco JC et al.[5]	Minocycline/ NCT01531582	Secondary	No	No
Ruiz-Antoran et al.[6]	Minocycline/ NCT02056665	Secondary	No	No
Unpublished, completed/ Ovid Pharma	Gaboxadol (OV101)/ NCT02996305	First exploratory efficacy measure (safety trial)	No	Yes
Unpublished, ongoing/ Ovid Pharma	Gaboxadol (OV101)/ NCT04106557	Primary	No	Yes

*Used other scales not specific to AS.
CGI, Clinical Global Impression.

1. Tan WH et al. *Am J Med Genet A.* 2018;176(5):1099-1107; 2. Bird LM et al. *Am J Med Genet A.* 2011;155a(12):2956-2963; 3. Peters SU et al. *Am J Med Genet A.* 2010;152a(8):1994-2001;
4. Braam W et al. *J Child Neurol.* 2008;23(6):649-654; 5. Grieco JC et al. *BMC Neurol.* 2014;14:232; 6. Ruiz-Antoran B et al. *Orphanet J Rare Dis.* 2018;13(1):144; 7. Data on file.

CONCLUSIONS

- CGI has been widely adopted over the past decade and become almost ubiquitous as a global rating of severity and change in interventional studies for neurodevelopmental disorders
- For rare diseases that are phenotypically heterogeneous, such as FXS, PWS, Rett, and AS, efforts have focused on improving the reliability and validity of CGI by either employing it together with disease-specific or symptom-specific rating scales or developing disease-specific anchors
- An advantage of CGI over disease-specific symptom rating scales is that CGI anchors establish that minimal improvement is only rated if it is clinically meaningful
  - By definition, CGI ratings can establish meaningfulness of treatment effect
- Disease-specific adaptations of CGI are slowly emerging for rare diseases to improve the sensitivity, reliability, and validity of this tool in clinical trials