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

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BACKGROUND

Original CGI

The original CGI (Table 1) was used in early psychiatry trials, mainly for schizophrenia, depression, anxiety, and bipolar disorders as a supplement to disease-specific rating scales1

Table 1: Original CGI Guidelines

<table>
<thead>
<tr>
<th>Severity of Illness:</th>
<th>Global Improvement:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, not ill</td>
<td>1 Very much improved</td>
</tr>
<tr>
<td>Moderately ill</td>
<td>2 Much improved</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>3 Minimally improved</td>
</tr>
<tr>
<td>Severe</td>
<td>4 No change</td>
</tr>
<tr>
<td>Extreme</td>
<td>5 Minimally worse</td>
</tr>
<tr>
<td>Extremely ill</td>
<td>6 Much worse</td>
</tr>
</tbody>
</table>

Need for Disease-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, schizophrenia, depression, and Alzheimer's disease.
- 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 in rating training.
- The greatest advantage of disease-specific adaptations of CGI is realized in:
  1. Conditions with dramatic phenotypic heterogeneity.
  2. Rare disorder tracking validated disease-specific symptom ratings.

In this poster, we summarize how CGI scales have been used in the objective of improving reliability and validity in bipolar disorder, schizophrenia, depression, and Alzheimer's disease2

OBJECTIVE AND METHODS

Objective

The objective was to identify and examine ways in which CGI has been applied and adapted in various clinical study settings.

Methods

- The following steps were taken:
  1. A PubMed search was conducted using the search terms “Clinical Global Impression” AND (Neurodevelopmental disorder), which yielded 623 citations, of which 408 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 (Clinical Global Impression) and (Rett syndrome) and (Clinical Global Impression) and (Autism Spectrum Disorder) to identify studies with specific adaptations to CGI scales.
  3. 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

1. No studies included the CGI in their evaluation of disease-specific adaptations to CGI scales.
2. 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.
3. CGI and the Yale-Brown Obsessive Compulsive Scale (CY-BOCS) were the most commonly used scales, including an ASD adaptation of the CY-BOCS, which was specifically recommended for ASD interventions by Aman and colleagues with the provision that training would be required to ensure reliability and validity.
4. Arnold and colleagues asked parents/guardians at baseline to identify and describe in detail the child’s 2 most pressing problems, including and limits of episodes of intensity, and effect on behavior.

Table 2: Clinical Trials Using CGI in FXS

Clinical Trials Using CGI in Rett Syndrome

- The first identified disease-specific adaptation to CGI for a neurodevelopmental disorder came from Neuf and colleagues (2017), who used CGI in the Rett Clinical Severity Scale as a guide.
- Similar adaptations were used to adapt CGI for assessing change in the symptom domain observed in Rett syndrome.

Conclusions

- CGI is a valid measure for assessing change in the symptom domain observed in Rett syndrome.
- CGI ratings were identified as primary outcomes in a phase 3 study of gaboxadol in children and adolescent with AS (NEPTUNE, ClinicalTrials.gov identifier NCT04106557).
- CGI-AS is currently the primary outcome in a phase 3 study of gaboxadol in children and adolescent with ASD (NEPTUNE, ClinicalTrials.gov identifier NCT04106557).

CONCLUSIONS

- CGI has been widely adopted over the past decade and extremely well-documented 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 assessment of all studies included in this review to determine those relevant to the review.
- CGI was used in a study by Anwyl and colleagues (2018) to successfully identify a disease-specific secondary outcome for assessing behavior in PWS patients.

Table 3: Clinical Trials Using CGI in PWS

Table 4: Clinical Trials Using CGI in Rett Syndrome

Table 5: Clinical Trials Using CGI in AS

Table 6: Clinical Trials Using CGI in FXS

Table 7: Clinical Trials Using CGI in Rett Syndrome

Note: All tables are generated based on the provided information and are subject to change due to the dynamic nature of the research field.