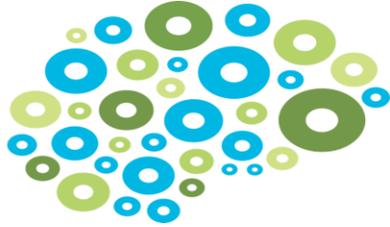


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Clinical Global Impression Scale – Severity (CGI-S)

Considerations for Alto Neuroscience
ALTO-100-201 Clinical Trial



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Clinical Global Impression Scale for Major Depressive Disorder



Clinical Global Impression Scale – Severity use in the ALTO-100-201 Clinical Trial

- The Clinical Global Impressions-Severity is a single-item, 7-point scale designed to assess global impression of severity rather than rating individual depressive symptoms
- The CGI-S requires the clinician to rate the severity of a study participant's illness from a global perspective, relative to the clinician's experience with individuals who have MDD

Several studies have evaluated the association between change on the MADRS and a 1-point change on the CGI-S and report a range of results

- A 1-point reduction in CGI-S score translated into an 8–9-point change in MADRS total score, in a study evaluating the relationship of MADRS and CGI-S scales in patients with MDD¹
- Another study concluded that based on a 1-point improvement in the CGI-S anchor, a 10-point improvement on the MADRS is an appropriate meaningful change threshold for within-patient change²

¹Leucht S, Fennema H, Engel RR, Kaspers-Janssen M, Lepping P, Szegedi A. What does the MADRS mean? Equipercntile linking with the CGI using a company database of mirtazapine studies. *J Affect Disord.* 2017;**210**:287–293. doi: 10.1016/j.jad.2016.12.041

²Hudgens S, Floden L, Blackowicz M, et al. Meaningful change in depression symptoms assessed with the Patient Health Questionnaire (PHQ-9) and Montgomery-Asberg Depression Rating Scale (MADRS) among patients with treatment resistant depression in two, randomized, double-blind, active-controlled trials of esketamine nasal spray combined with a new oral antidepressant. *J Affect Disord.* 2021;**281**:767–775.



	Double Blind (DB) Treatment Period					Open Label (OL) Treatment Period				Follow-up Period
Visit Name	Day 1 DB Baseline	Week 1	Week 2	Week 4	Week 6 DB EOT	Week 7	Week 8	Week 10	Week 13 OL EOT	Safety FUV
Visit Number	3	4	5	6	7	8	9	10	11	12
Visit Window		±3 days	±3 days	±4 days	±5 days	±3 days	±4 days	±5 days	-5 days	±3 days
CGI-S	X		X	X	X		X	X	X	X

- The CGI-S will not be assessed at Screening
- The CGI-S will be assessed at Baseline, Week 2, Week 4, Week 6, Week 8, Week 10, Week 13, and Safety Follow-up period
- As a best practice, the CGI-S should be done at the end of the Visit after you have gathered all information on the study participant
- Overall global impression of depression severity will be assessed after ALTO-100 administration in the Double-Blind Treatment Period, the Open Label Treatment Period and the Follow-up Period

Timeframe under consideration

- The CGI-S is always assessed based on the participant's severity of symptoms within the past week



CGI-S for Major Depressive Disorder: “Considering your total clinical experience with this particular population, what level of severity is the study participant’s major depressive disorder (MDD) at this time?”

All the CGI-S assessments are rated on the following seven-point scale:

- 1 – Normal, not at all affected
- 2 – Borderline affected
- 3 – Mildly affected
- 4 – Moderately affected
- 5 – Markedly affected
- 6 – Severely affected
- 7 – Extremely affected

This rating is based upon observed and reported symptoms, behavior, and function **in the past week (i.e., seven days)**



CGI-S

Sources of Information for Scoring



When scoring **the overall severity** of major depressive disorder with the CGI-S, consider overall severity of symptoms **AND** interference with functioning

The CGI-S is designed to make use of all information available. Thus, a clinical interview with the patient should be combined with any other information available for the time period under consideration from such sources as medical chart notes, family members, other assessments completed in the study (e.g., MADRS), etc.

Consider participant responses on patient reported outcomes and clinician-rated assessments such as the: CHRT-C, CHRT-S12, Q-LES-Q-SF, PHQ-9, MADRS, observations of the participant during the study visit, and participant reports not otherwise captured in a questionnaire of clinical assessment



CGI-S

Scores and Anchor Points



Score and Anchor Point	Definition
1 – Normal, not at all affected	Normal, <u>not at all affected</u>
2 – Borderline affected	Symptoms are few and only <u>intermittently present</u> . There is <u>no interference in functioning</u> or no interference in the participant’s usual and occupational roles
3 – Mildly affected	<u>Few or mild symptoms</u> of illness with <u>effective functioning</u> or <u>very little interference</u> in participant’s usual and occupational roles
4 – Moderately affected	Some <u>prominent symptoms</u> with <u>some interference</u> in the level of daily functioning
5 – Markedly affected	<u>Significant illness</u> symptoms with <u>very substantial interference</u> in the participant’s usual roles
6 – Severely affected	<u>Very marked illness</u> symptoms. Participant is <u>unable to function in most areas</u> of daily activities
7 – Extremely affected	<u>Extreme illness</u> symptoms. Participant is <u>completely incapacitated</u> and requires extra care and supervision

Guy W. Clinical Global Impressions: In ECDEU Assessment Manual for Psychopharmacology. 1976; 218-222. Revised DHEW Pub. (ADM) Rockville, MD: National Institute for Mental Health



Type of Bias	Definition/Possible Effect on CGI Score
Halo Effect	The tendency for a single positive rating on one item on the MADRS or other assessment to cause raters to inflate all other ratings
Central Tendency	Causes some raters to score every question of a scale near the center; a clear example is scoring every item on a 7-point scale as a 4
Recency Bias	The tendency for a recent event to dominate past events within a timeframe; can lead to score overestimation if the participant recently experienced a positive perspective of their symptoms; alternatively, can lead to score underestimation if the participant recently experienced negative effects of their symptoms



- Disease-specific rating scales are composed of individual symptom ratings (items) selected to assess the range of symptoms and signs associated with depression
- Items on disease-specific scales are equally weighted, and the summary scores do not adequately reflect the true condition of the participant or the importance of observed change over time
- The shortcomings of disease-specific rating scales can be largely overcome by balancing the weight and importance of individual PRO items and clinician-rated items with **expert clinical judgment as measured by the CGI**



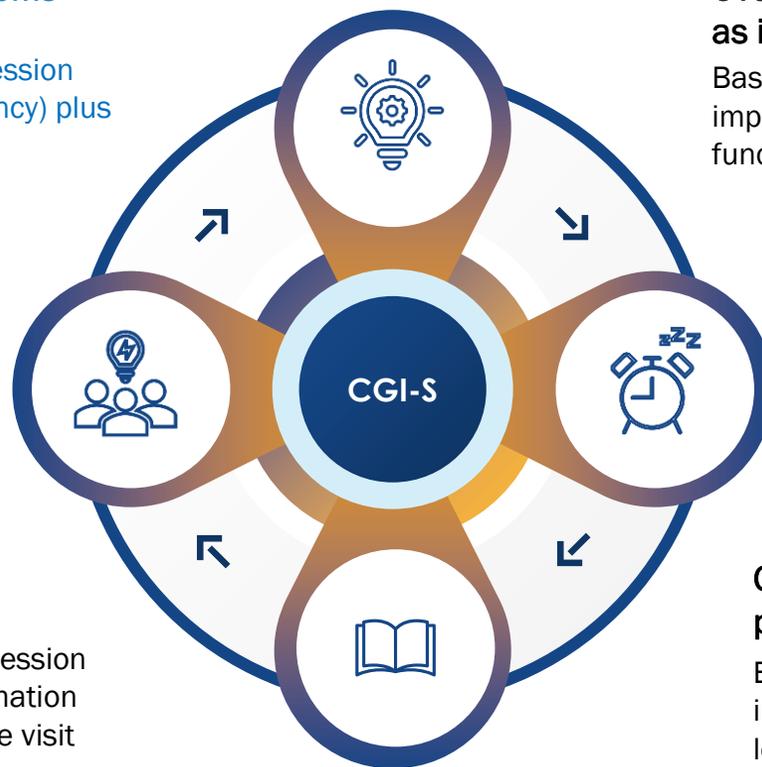


Overall Impression of Symptoms of Depression

Consider the participant's depression symptoms (intensity and frequency) plus degree of impairment

Overall Impression of Functioning as it relates to their MDD

Based on the rater's overall impression of the participant's functional outcomes



Information for Scoring

CGI-S should be completed after conducting a clinical interview

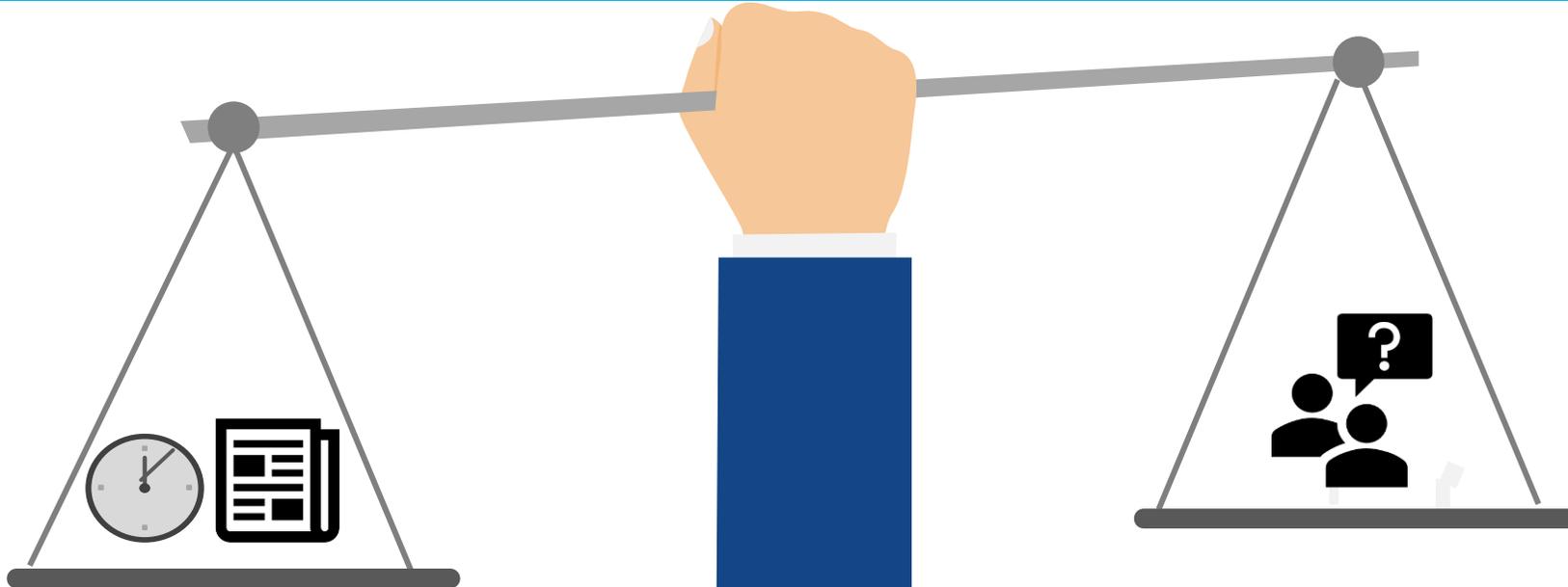
Rating should be based the depression history and should include information observed and reported during the visit

Overall Impression of the participant's level of Distress

Based on the clinician's overall impression of the participant's level of distress reported during the visit



CGI-S Considerations for Scoring



Timeframe

State-dependent:

- CGI-S: Seven days

Information Sources

Chart notes, family, significant others, clinical providers

Questions to Ask

- Frequency of depressive symptoms
- Intensity or severity of symptoms
- Effect of symptoms on functioning in major areas of participant's life (e.g., work, home, school, relationships, activities)



CGI-S Case Study



32-year-old female who presented with symptoms of depression. She lives with her husband of 5 years and their three children. She stopped working two weeks prior to the visit as a result of her depression.

- The participant stated that within the past week she cried daily, felt sad “all the time,” had trouble sleeping at night and was overeating
- Sleep: The participant reported that her sleeping was disturbed in that it frequently took her several hours to fall sleep, and that 2 nights within the past week she only slept about 3 hours. She stated that she spent the time “awake thinking and worrying about everything in her life”
- Family: The participant indicated that she did not think she was a good mom and wife. She also reported that she did not feel that she achieved what her mother wanted for her. She felt this way everyday for the past week
- Functioning: The participant stated that she was not able to take care of her children and husband with their daily activities, she did not participate in any family events, she did not work for the past week and it financially impacting her family, and she expressed unhappiness that she was not the person she wanted to be. The participant was taking no interest or gaining any pleasure of any activities she performed over the past week.
Distress: The participant reported feeling “stressed” about lack of financial resources, long hours spent at home with her children, relationship with her mother, and difficulty in managing her behavior. She also reported that she felt she was 40 lbs. overweight and was not comfortable with her appearance
- Fatigue and loss of energy: The participant reported that she has no energy, no motivation, and was always tired but she can take care of her children “minimally” by cooking and doing minor household chores. Her husband needed to help her with most of the household chores.
- Thought processes: The participant described her thoughts as “jumbled and confused.” She reports that it takes a long time to make a decision, and then she would change her mind.



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4 – Moderately affected	Some prominent symptoms with some interference in the level of daily functioning
5 – Markedly affected	Significant illness symptoms with very substantial interference in the participant’s usual roles
6 – Severely affected	Very marked illness symptoms. Participant is unable to function in most areas of daily activities
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CGI-S

Case Study Score



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Thank you!

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