Measuring Remission and Response using CDRS-R and MADRS: An Analysis in Adolescents with MDD and Imminent Risk for Suicide

Denia Cai Shi[1,2*], Li Chen[1], Colette Kosik-Gonzalez[1], Abi Bangerter[1], Dong Jing Fu[1]

[1]Johnson and Johnson Innovative Medicine, Titusville, NJ;
[2]Drexel University College of Medicine, Philadelphia, PA

Presenting Author

INTRODUCTION

- Major depressive disorder (MDD) is one of the most common mental disorders in children and adolescents[1,2].
- The Children's Depression Rating Scale, Revised (CDRS-R), is used widely as the primary efficacy endpoint in clinical trials in children and adolescents with MDD[3].
- With the development of rapidly acting antidepressants (RAADs), it is important to evaluate CDRS-R as a measure for rapid onset of antidepressant effects in this population.
- The Montgomery-Asberg Depression Rating Scale (MADRS) has been validated for use to assess RAADs in adults with MDD[4] and was used as the primary endpoint in esketamine studies to assess the rapid reduction in depressive symptoms in adults with MDD who were at imminent risk for suicide.
- The CDRS-R and the MADRS were co-administered in a recent double-blind, randomized, psychoactive placebo-controlled (oral midazolam) trial of intranasal esketamine, in adolescents with MDD who were at imminent risk for suicide; the CDRS-R at Day 2 (24 hours post first dose) was used as the primary endpoint.
- It is of methodological and clinical interest to examine the correspondence of these scales in the adolescent population (12 to 17 years of age). To our knowledge, there is only one analysis that compares the properties of the MADRS and CDRS-R scales in children between 8 and 11 years of age[5].

OBJECTIVES

- To examine the correspondence between the CDRS-R and MADRS scales in measuring response and remission in adolescents with MDD who were at imminent risk for suicide.
- To report on the correlation between change from mean baseline total scores in CDRS-R and MADRS.
- To evaluate CDRS-R as a measure for rapid onset of antidepressant effects.

METHODS

Study Design

- The data presented here were from a phase 2b, double-blind, randomized, psychoactive placebo-controlled (oral midazolam) trial of intranasal esketamine, plus standard of care, in adolescents ages 12 to 17 years with MDD who were assessed to be at imminent risk for suicide (N = 145).
- During the double-blind treatment phase of 25 days, participants received the double-dummy study intervention 2 times per week for 4 weeks.
- The MADRS and CDRS-R assessments were conducted at various time points, including baseline (pre-first dose), 4 hours post-first dose, 24 hours post-first dose (Day 2), pre-dose for each dosing session, and 4 hours post-final dose (Day 25).
- MADRS and CDRS-R were administered simultaneously via an integrated assessment approach[a], wherein items measuring similar concepts in the MADRS and the CDRS-R were asked concurrently.

[a]Developed by Drs. M. Opler, A. Zygmunt, B. Rothman, G. Zalsman, T. Carmody & C. Canuso for use in pediatric clinical trials with support from Janssen Research & Development (JRD).

Instruments

Children's Depression Rating Scale, Revised (CDRS-R)

- CDRS-R is a clinician-rated instrument for the assessment of severity of depression, originally designed for children ages 6 to 12 years. It is based on the Hamilton Depression Rating Scale[6] and it consists of 17 items with a total score ranging from 17-113.
- At the Day 2 assessment, the impaired schoolwork item was not assessed; the item score was carried forward from the Day 1 pre-dose assessment to calculate the total score.
- At the Day 25 (4H) assessment, items of sleep disturbance, impaired schoolwork, and difficulty having fun were not assessed; these item scores were carried forward from the Day 25 pre-dose assessment to calculate the total score.

Montgomery-Asberg Depression Rating Scale (MADRS)

- The MADRS is a clinician assessment that consists of 10 items that measure the severity of mood disorders in adults and its scores range from 0-60[7].
- At the Day 25 (4H) assessment (4 hours after the last dose of study medication), the sleep item was not assessed; the item score was carried forward from the Day 25 pre-dose assessment to calculate the total score.

Statistical Analysis

- This analysis examined the agreement between the CDRS-R and MADRS at 2-time points: on Day 2 and Day 25 (4H).
- Responder criteria for both CDRS-R and MADRS was an improvement (reduction) in total scores of ≥50%.
- Remission criteria, based on previous clinical trials, was a total score of ≤28 for the CDRS-R[8–11], and a total score of ≤12 for the MADRS[12–14].
- The total number and percentage of responders and remitters in each scale were calculated. The overall Pearson correlation coefficient (PCC) and 95% confidence interval between CDRS-R and MADRS total scores during the double-blinded phase were also included.
- The agreement between the CDRS-R and MADRS was calculated as follows:
  - % Responders agreement = (Number that met both CDRS-R and MADRS criteria ÷ Sum that met either CDRS-R or MADRS criteria) × 100
  - % Remitters agreement = (Number that met both CDRS-R and MADRS criteria ÷ Sum that met either CDRS-R or MADRS criteria) × 100

NEUROPSYCHIATRY

RESULTS

Demographics and Baseline Characteristics

TABLE 1: Demographics and clinical characteristics

	Total
Age, years	
N	145
Mean (SD)	14.9 (1.45)
Median	15
Range	(12; 17)
12 to 14	60 (41.4%)
15 to 17	85 (58.6%)
Sex	
N	145
Female	113 (77.9%)
Male	32 (22.1%)
Mean Baseline Total Score	
CDRS-R	76.3
MADRS	38.8

CDRS-R, Children's Depression Rating Scale-Revised; MADRS, Montgomery-Asberg Depression Rating Scale; SD, standard deviation.

Pearson Correlation Coefficient

TABLE 2: Pearson correlation coefficient (95% confidence interval) between change from mean baseline in CDRS-R and MADRS total score

Timepoint	PCC (95% confidence interval)
Day 2 (N = 145)	0.88 (0.83; 0.91)
Day 25: 4H (N = 128)	0.76 (0.68; 0.82)

PCC, Pearson correlation coefficient.

CDRS-R and MADRS Agreement

TABLE 3: Total number and percentage of responders and remitters on Day 2 and Day 25 (4H) after treatments

	Day 2 (N = 145)		Day 25: 4H (N = 128)	
Number/ percentage meeting criteria	**Responders**	**Remitters**	**Responders**	**Remitters**
CDRS-R Criteria	78 (54%)	20 (14%)	115 (90%)	67 (52%)
MADRS Criteria	78 (54%)	38 (26%)	111 (87%)	95 (74%)
Both CDRS-R and MADRS Criteria	72 (50%)	20 (14%)	108 (84%)	66 (52%)
Either CDRS-R or MADRS Criteria	84 (58%)	38 (26%)	118 (92%)	96 (75%)
Agreement between CDRS-R and MADRS	86%	53%	92%	69%

CDRS-R, Children's Depression Rating Scale- Revised; MADRS, Montgomery-Asberg Depression Rating Scale.

REFERENCES

1. Bitsko, R. H. *et al.* Mental health surveillance among children—United States, 2013–2019. *MMWR Suppl* 71, 1 (2022); **2.** Mullen, S. Major depressive disorder in children and adolescents. *Mental Health Clinician* 8, 275–283 (2018); **3.** Mayes, T. L., Bernstein, I. H., Haley, C. L., Kennard, B. D. & Emslie, G. J. Psychometric properties of the Children's Depression Rating Scale–Revised in adolescents. *J Child Adolesc Psychopharmacol* 20, 513–516 (2010); **4.** Johnson, K. M. *et al.* Evidence to support Montgomery-Asberg Depression Rating Scale administration every 24 hours to assess rapid onset of treatment response. *J Clin Psychiatry* 77, 21987 (2016); **5.** Jain, S. *et al.* A psychometric evaluation of the CDRS and MADRS in assessing depressive symptoms in children. *J Am Acad Child Adolesc Psychiatry* 46, 1204–1212 (2007); **6.** Poznanski, E. O. & Mokros, H. B. Children's depression rating scale, revised (CDRS-R). (1996); **7.** Quilty, L. C. *et al.* The structure of the Montgomery-Åsberg depression rating scale over the course of treatment for depression. *Int J Methods Psychiatr Res* 22, 175–184 (2013); **8.** Emslie, G. J. *et al.* A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 54, 1031–1037 (1997); **9.** Emslie, G. J. *et al.* Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 41, 1205–1215 (2002); **10.** Cheung, A. H., Emslie, G. J. & Mayes, T. L. Review of the efficacy and safety of antidepressants in youth depression. *Journal of Child Psychology and Psychiatry* 46, 735–754 (2005); **11.** Wagner, K. D. *et al.* A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *American Journal of Psychiatry* 161, 1079–1083 (2004); **12.** Montgomery, S. A. & Möller, H.-J. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? *Int Clin Psychopharmacol* 24, 111–118 (2009); **13.** Thase, M. E., Larsen, K. G. & Kennedy, S. H. Assessing the 'true'effect of active antidepressant therapy v. placebo in major depressive disorder: use of a mixture model. *The British Journal of Psychiatry* 199, 501–507 (2011); **14.** Daly, E. J. *et al.* Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry* 76, 893–903 (2019).

Poster presented at the 20th Annual Scientific Meeting of International Society for CNS Clinical Trials and Methodology (ISCTM) (Washington DC), 21-23 February 2024

DISCUSSION AND CONCLUSION

- In this study, the CDRS-R was able to detect a rapid change in adolescents with moderate to severe MDD who were imminently suicidal at baseline as shown by the 54% of responders on Day 2. There was 86% agreement with MADRS ratings.
- The Pearson correlation coefficient of 0.88 and 0.76 indicated a high correlation between the change from baseline in CDRS-R and MADRS on Day 2 and Day 25 (4H), respectively.
- The results also showed a high level of agreement between CDRS-R and MADRS responders, with 86% on Day 2 and 92% on Day 25 (4H).
- The agreement between the CDSR-R and MADRS remitters was lower: 53% on Day 2 and 69% on Day 25 (4H).
- Our findings of lower agreement were not unexpected. Remission cut-off scores for both the CDRS-R (≤28)[8–11] and the MADRS (≤12)[12–14] were adopted from prior pediatric and adult studies. The conversion of total scores between these scales described in the literature suggests that these remission criteria do not represent the same level of severity[5]. For example, Jain *et al.* calculate a CDRS-R total score of 28 (our trial's total minimum remission score) as converting to an approximate total MADRS score of 5.
- Further research is needed to explore the conversion between the CDRS-R and MADRS scales and better define the cut-off scores for remission in adolescents.

ACKNOWLEDGMENTS:

The authors would like to thank the participants and investigators for their support. Sandeep Chavan (SIRO Clinpharm Pvt. Ltd., India) for providing graphic layout and design support for the development of this poster.

DISCLOSURES:

All authors are employees of Johnson and Johnson Innovative Medicine.