Pediatric Extrapolation in Psychiatry: What Works, What Doesn't, and Why

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Disclosure Statement

This author has no financial disclosures to report.

To maintain confidentiality for sponsors who have submitted new drug applications, regardless of approval status, only summary level information is presented.

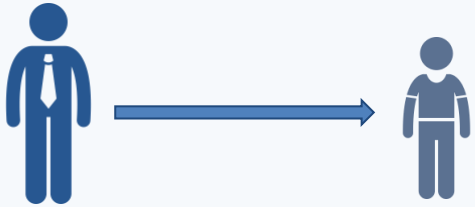
Regulatory Challenges

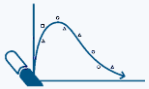
- How can existing data inform future pediatric drug development?
  - When is extrapolation appropriate?
  - What if adult and pediatric trial results differ?

Extrapolation of Antipsychotic Efficacy from Adults to Pediatrics

January 2020 General Advice Letter

Drugs with Similar MoA
Extrapolation of Efficacy

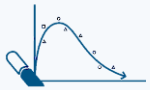




Pharmacokinetic Study

Open-label Safety Study

Drugs with New MoA
Inclusion of Pediatrics in Adult Registration Trials



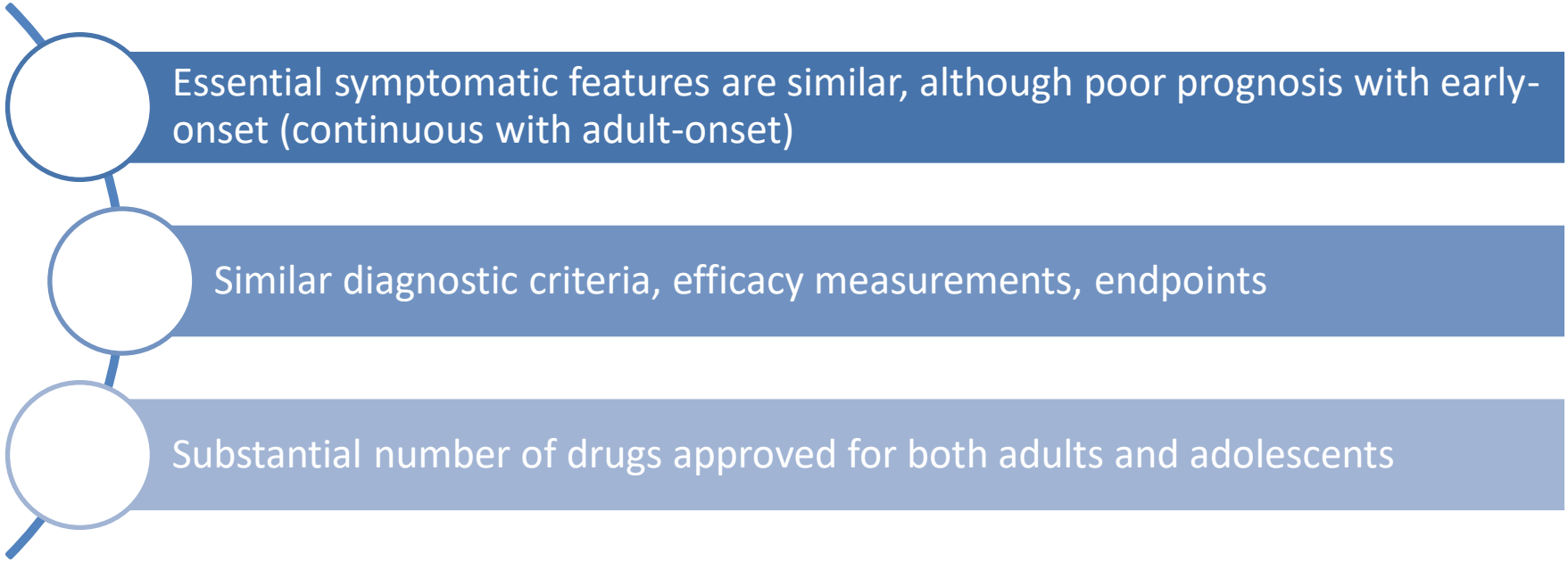
Pharmacokinetic Study

Placebo-Control, Fixed-Dose Design

Open-label Safety Study

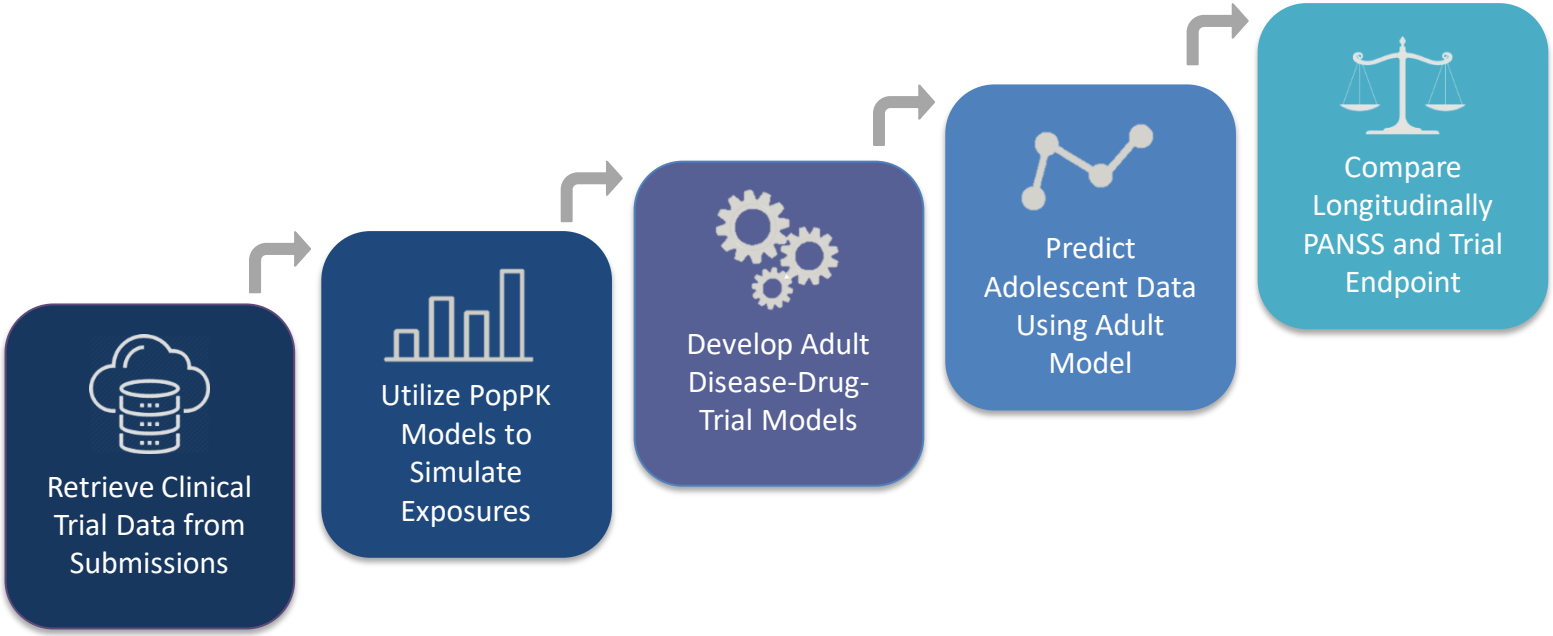
Applicable for the treatment of schizophrenia and for the treatment of manic episodes associated with bipolar I disorder

Qualitative and Clinical Assessment of Disease Similarity



Chen L, et al. Risk factors in early and late onset schizophrenia. *Compr Psychiatry.* 2018;80:155-62
Coulon N, et al. Early and very early-onset schizophrenia compared with adult-onset schizophrenia: French FACE-SZ database. *Brian Behav.* 2020;10:e01495

Model-Based Approach to Justify Disease and Exposure Response Similarity

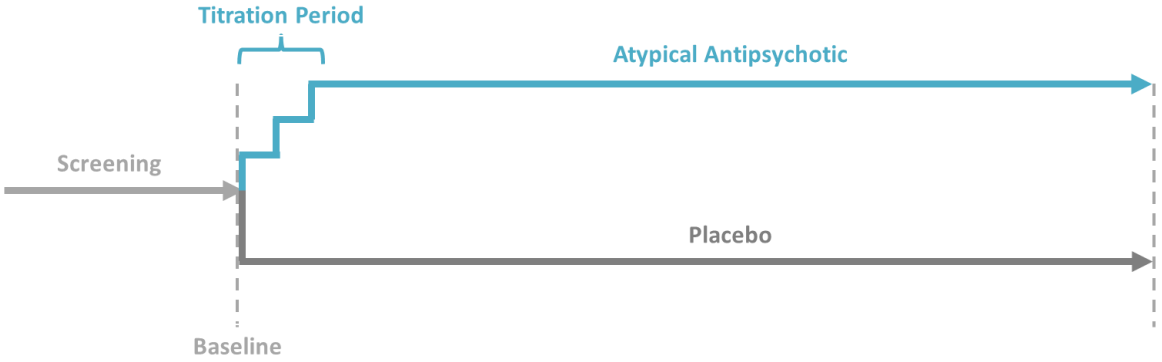


Leveraging Current Knowledge of Antipsychotic Use in Adults and Adolescents: Schizophrenia

9 Adult Programs

7 Adolescent Programs

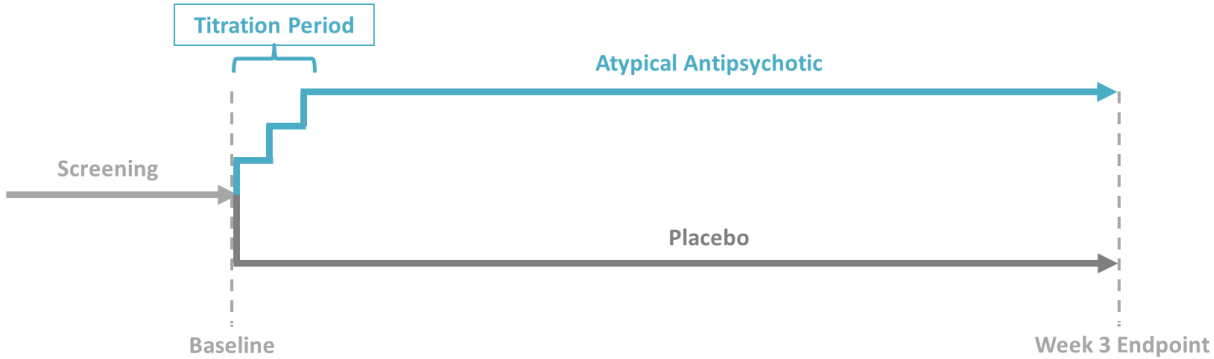
2 Adolescent Negative Trials



Adult Sample Size:
17,778
Adolescent Sample Size:
2,122

***Primary Endpoint**: Change from Baseline in Total PANSS Scores*

Leveraging Current Knowledge of Antipsychotic Use in Adults and Adolescents: Bipolar I Disorder

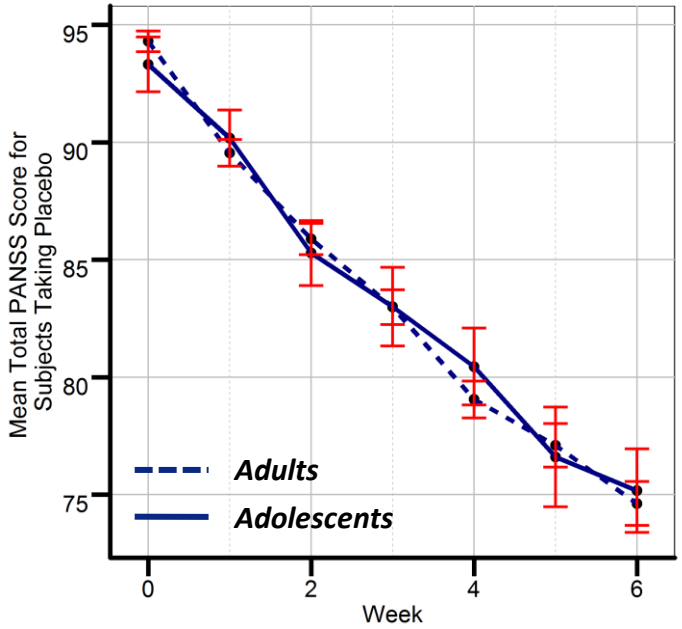


Adult Sample Size:
6,781
Adolescent Sample Size:
2,087

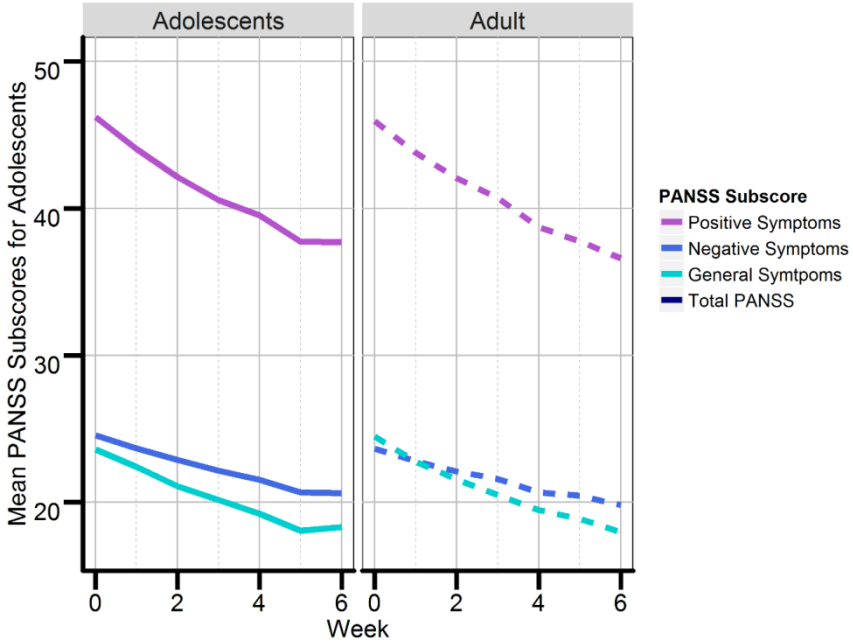
***Primary Endpoint**: Change from Baseline in Total YMRS Scores*

Assessment of Similarity in Symptomatic Changes during an Acute Exacerbation of Schizophrenia

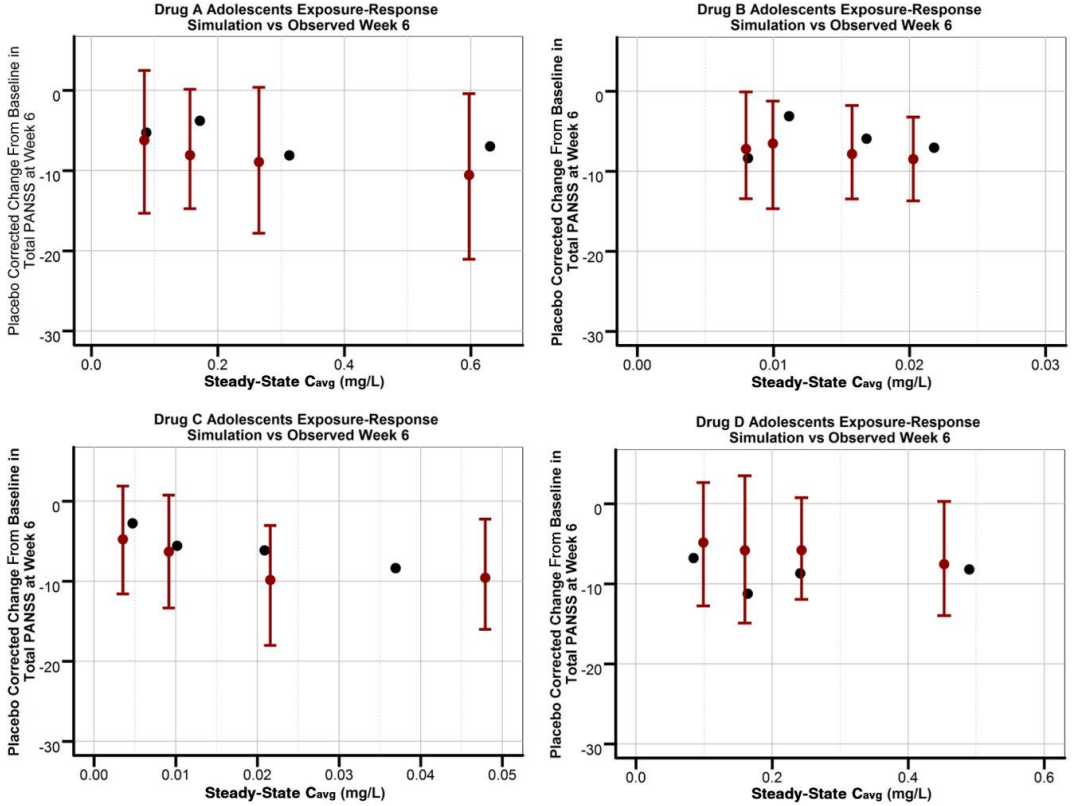
Disease Progression over a Typical 6-Week Trial is Similar Between Adult and Adolescent Completers



Longitudinal Mean PANSS-Sub Scores are Similar Between Adults and Adolescents



Exposure-Response Assessment



Safety Analysis to Inform Regulatory Policy

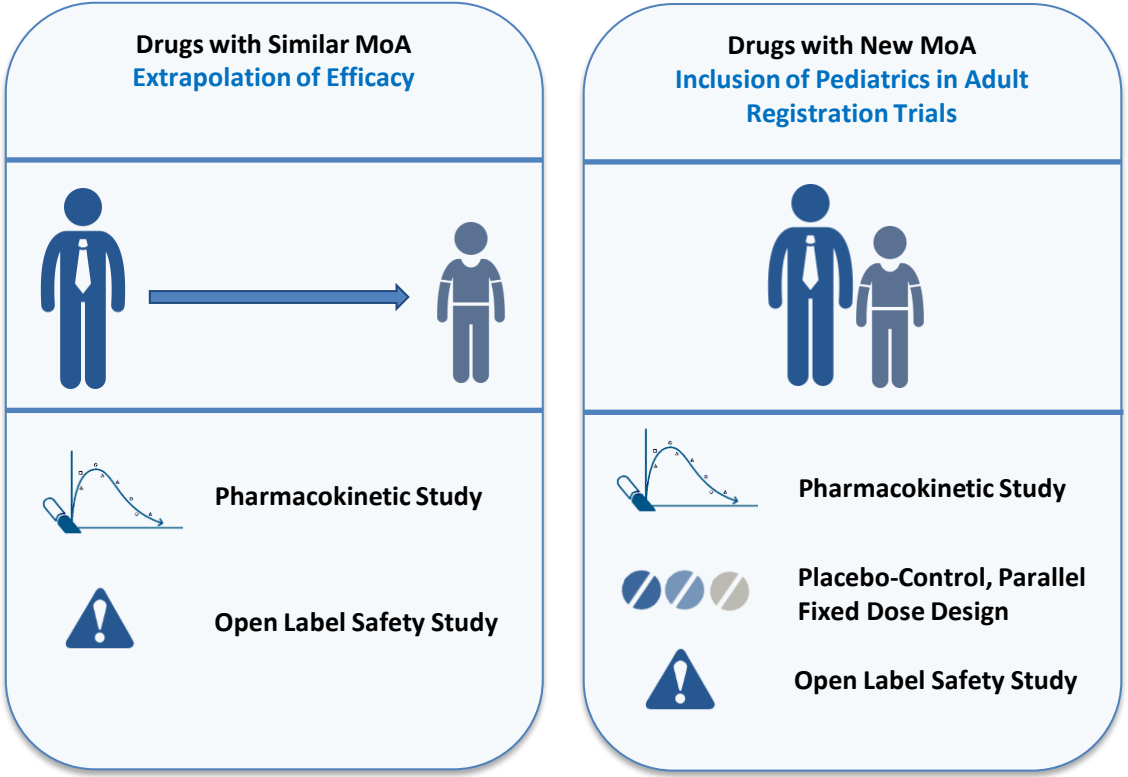
- **Incidence of metabolic adverse effects (AEs) and movement disorders were similar across different drug programs**
  - *Incidence of AEs were similar when comparing subjects with bipolar disorder and schizophrenia at Week 3*

- **Onset of metabolic AEs generally occur much later into the trial, whereas movement disorders occur relatively earlier with a shorter duration**

- **Comparison of active treatment in short term RCTs versus naïve treatment subjects in open-label safety studies demonstrate similar trends at Week 3 and 6**
  - *Demonstrates the ability to use open-label safety studies to derive information on safety risks at Week 3 and 6 for subjects receiving active therapy for the first time*

Extrapolation of Efficacy from Adults to Pediatrics

January 2020 General Advice Letter



*Juvenile animal studies needed for bipolar I indications less than 12 years of age

**Open label safety studies could concurrently enroll patients with bipolar I and schizophrenia adult and pediatric patients

Approvals based on current policy:
Brexpiprazole

Additional Information

Clinical Pharmacology & Therapeutics

Article | Full Access

A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials

Shamir N. Kalaria, Hao Zhu, Tiffany R. Farchione, Mitchell V. Mathis, Mathangi Gopalakrishnan, Ramana Uppoor, Mehul Mehta, Islam Younis

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Pharmacodynamics | Full Access

Assessment of Similarity in Antipsychotic Exposure-Response Relationships in Clinical Trials Between Adults and Adolescents With Acute Exacerbation of Schizophrenia

Shamir N. Kalaria PharmD, Tiffany R. Farchione MD, Mitchell V. Mathis MD, Mathangi Gopalakrishnan PhD, Islam Younis PhD, Ramana Uppoor PhD ... See all authors

The Journal of Clinical Pharmacology
Official Publication of the American College of Clinical Pharmacology

Supplement Article | Full Access

Extrapolation of Efficacy and Dose Selection in Pediatrics: A Case Example of Atypical Antipsychotics in Adolescents With Schizophrenia and Bipolar I Disorder

Shamir N. Kalaria PharmD, PhD, Tiffany R. Farchione MD, Ramana Uppoor PhD, Mehul Mehta PhD, Yaning Wang PhD, Hao Zhu PhD

What about Major Depressive Disorder?

Only fluoxetine (age 8-17) and escitalopram (age 12-17) are approved for pediatric patients

Of 56 adult antidepressant trials, **53% were positive**. Of 22 pediatric trials, only **18% were positive** (two fluoxetine trials, one citalopram trial, and one escitalopram trial)

Reasons for differences in trial outcomes are unclear

Research Questions

3. Clinical Trial Design

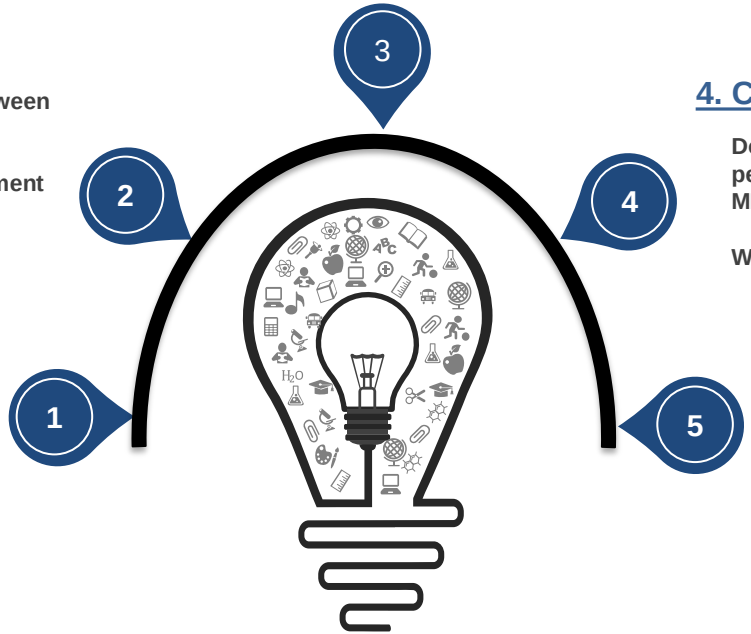
Are the proposed sample sizes and trial designs justified?

What are the optimal trial design elements for increasing probability of trial success?

2. Placebo Response

How does placebo response compare between adults and pediatrics?

What are predictors for placebo and treatment response?



4. Clinical Outcomes

Do clinical outcome assessments used in adult and pediatric clinical trials capture different aspects of MDD?

Which specific items track with response?

1. Dosing

How does the dose/exposure-relationship compare between adults and pediatrics with MDD?

Is the current method for dose-selection for pediatric MDD trials justified?

5. Clinical Population

How does the clinical heterogeneity in MDD trials differ between adults and pediatrics?

How does baseline disease severity or presence of other psychiatric comorbidities impact antidepressant response?

What is the impact of concomitant psychotherapy on antidepressant response?

Pediatric Dataset Collection and Preparation

Trial Listings

Drug	Trial	Age Range (year)	Treatment N=3,767	Placebo N=1,992	Total N=5,759
Vilazodone	VLZ-MD-21	12 to 17	355	171	616
	VLZ-MD-22	7 to 17	284	186	526
Vortioxetine	12710A	12 to 17	316	154	470
Desvenlafaxine	B2061014	7 to 17	222	109	331
	B2061032	7 to 17	238	119	357
Duloxetine	HMCK	7 to 17	225	103	328
	HMCL	7 to 17	331	117	448
Escitalopram	SCT-MD-32	12 to 17	130	128	258
	SCT-MD-15	6 to 17	129	132	261
Citalopram	CIT-MD-18	7 to 17	93	85	178
	94404	13 to 18	124	120	244
Levomilnacipran	LVM-MD-11	12 to 17	406	140	546
	LVM-MD-14	7 to 17	328	159	487
Fluoxetine	HCJE	8 to 18	110	109	219
	x065	7 to 17	48	48	96
	TADS	12 to 17	327	112	439

Adult Dataset Collection and Preparation

Trial Listings

Drug	Number of Trials	Age Range (years)	Placebo N=8,429	Antidepressant N=16,431	Total N=24,860
Duloxetine	6	18-83	576	993	1569
Desvenlafaxine	9	18-85	1108	2047	3155
Escitalopram	4	18-76	587	1111	1698
Venlafaxine	4	18-77	400	763	1163
Mirtazapine	10	16-93	462	771	1233
Paroxetine	5	18-85	505	1124	1629
Vortioxetine	10	18-88	1625	3940	5565
Levomilnacipran	4	18-78	772	1324	2096
Fluoxetine	7	18-91	834	1609	2443
Vilazodone	9	18-70	1560	2749	4309

Dataset Collection and Preparation

Variable listings

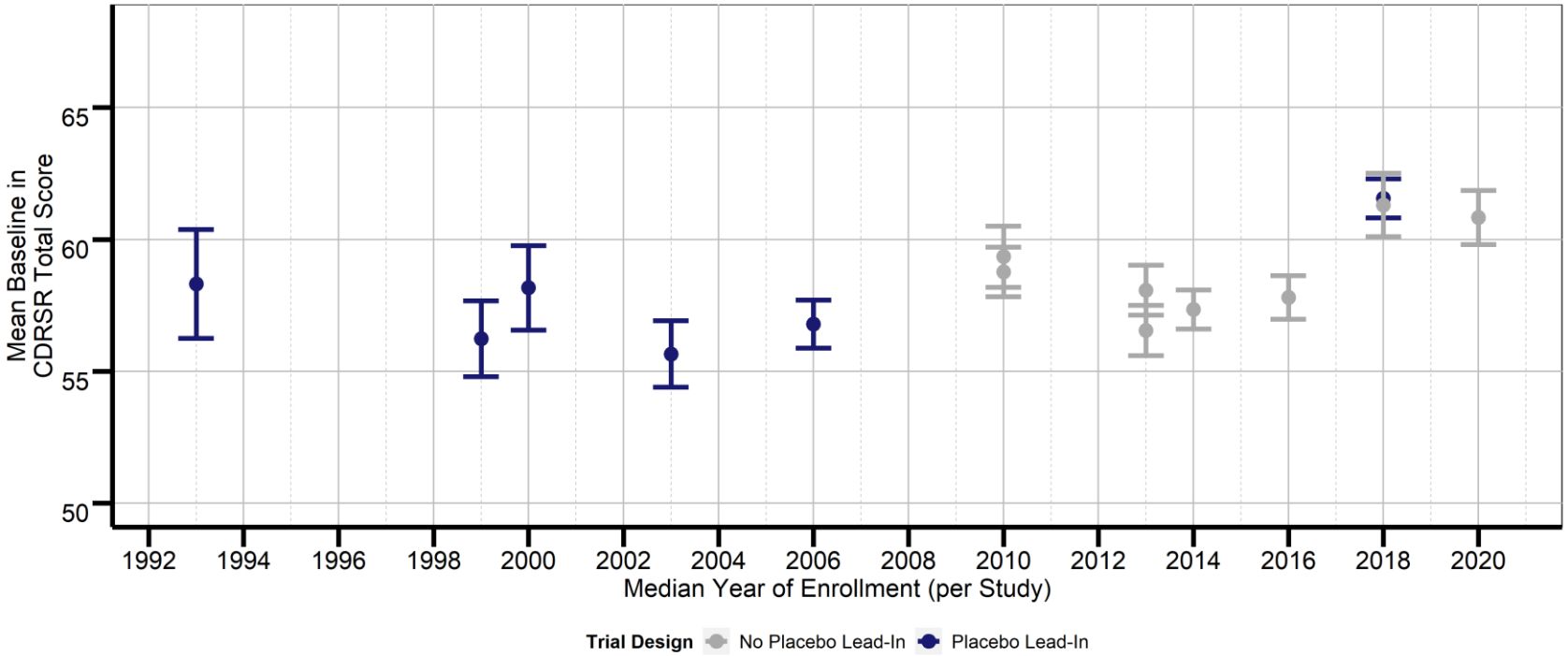
List of Data Variables Collected	
Demographics	Country, Gender, Age, Race, Height, Weight, BMI, School Setting, Primary Caregiver
Depression History	Age of First MDD Episode Onset, Duration of Current MDD Episode, Number of Previous MDD Episodes, History of Suicidal Ideation and Behavior Anxiety, ADHD, and Other Psych Disorder Flags,
Treatment History	Previous Usage, Previous NonAntidepressant-response to Antidepressant, Ongoing Cognitive Therapy Use + Indication, Response to Cognitive Therapy, Ongoing Concomitant Psychotropic Medications + Indication,
Trial	Protocol Number, Subject ID, Center ID, Visit Week, Completer Status, Termination Reason
Efficacy Variables	CDRSR-Total Score, CDRSR-Item Level Scores, CGII, CGIS
Suicidal Ideation and Behavior	C-SSRS based Suicidal Ideation, C-SSRS based Suicidal Behavior,

Pediatric Baseline Demographic and Clinical Characteristics

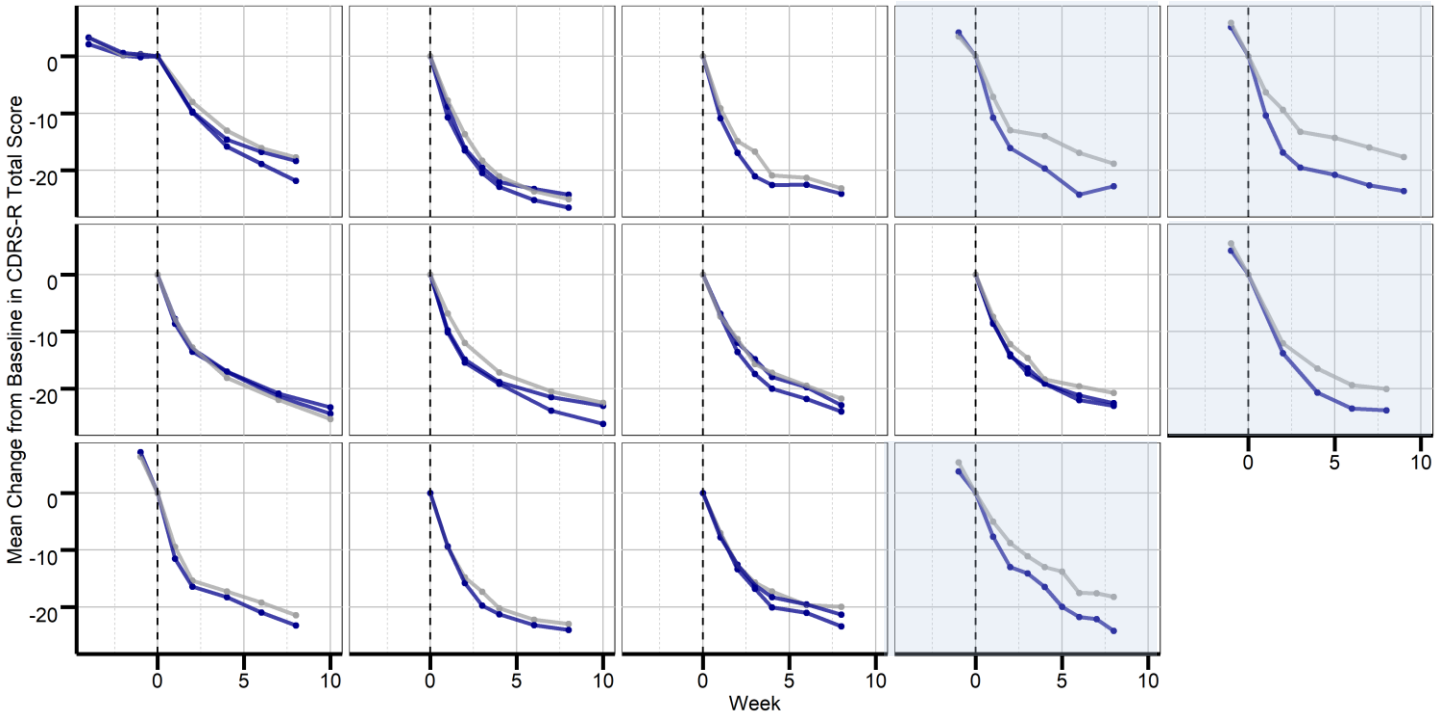
Demographic and Clinical Characteristics*	Placebo N=1,722	Antidepressant N=3,011
Age (years)	13.7 ± 2.7	13.7 ± 2.7
Race (%)		
Asian	21 (1.2)	28 (0.9)
Black	292 (17.0)	563 (18.7)
White	1243 (72.1)	2,116 (70.3)
Other	166 (9.6)	304 (10.1)
Male sex (%)	738 (42.9)	1281 (42.5)
Duration of Current MDD Episode (months)	12.7 (13.5)	12.2 (15)
History of Suicidal Ideation or Behavior (%)	56 (3.3)	75 (2.5)
Previous Antidepressant Therapy (%)	261 (22.6)	531 (26.8)
Age of First MDD Episode (years)	11.7 ± 3.2	11.5 ± 3.3
Number of Previous Episodes (%)		
0	235 (31.6)	585 (41.9)
1	335 (45.1)	493 (35.3)
≥ 2	173 (23.3)	318 (22.7)
Comorbid Disorders (%)		
Anxiety	133 (12.2)	221 (11.2)
ADHD	177 (16.2)	295 (14.9)
Other	235 (21.5)	374 (18.9)
Prior Psychotherapy (%)	106 (6.3)	208 (6.9)
Baseline CDRS-R Total Score	57.8 ± 9.8	58.6 ± 9.9
Baseline CGIS Score	4.5 ± 0.6	4.6 ± 0.7

*Plus–minus values are means ±SD. Total number of patients may differ for each characteristic due to missing data.

Trend in Baseline CDRS-R Total Scores over Time



Analysis of Drug and Placebo Response by Study



*Blue and gray line represents patients among the active treatment and placebo groups, respectively. Shaded regions indicated trials that demonstrated a positive statistical finding.

Assessment of CDRS-R and MADRS Items

Current Impressions

- Items related to affective symptoms and anhedonia on the CDRS-R and MADRS appear to be sensitive to change
- Several CDRS-R items exhibit a floor effect and may contribute to decreased instrument sensitivity
- Limited separation between drug and placebo groups across each item on the CDRS-R relative to MADRS

Assessment of CDRS-R and MADRS Items

Strength of CDRS-R and MADRS Items

Sensitive CDRS-R Items
1. Impaired schoolwork
2. Difficulty having fun
3. Social withdrawal
10. Low self-esteem
11. Depressed feelings
15. Depressed facial affect
16. Listless speech
8. Irritability

Insensitive CDRS-R Items
12. Morbid ideation
13. Suicidal ideation
9. Excessive guilt
14. Excessive weeping
4. Sleep disturbance
5. Appetite disturbance
6. Excessive fatigue
7. Physical complaints
17. Hypoactivity

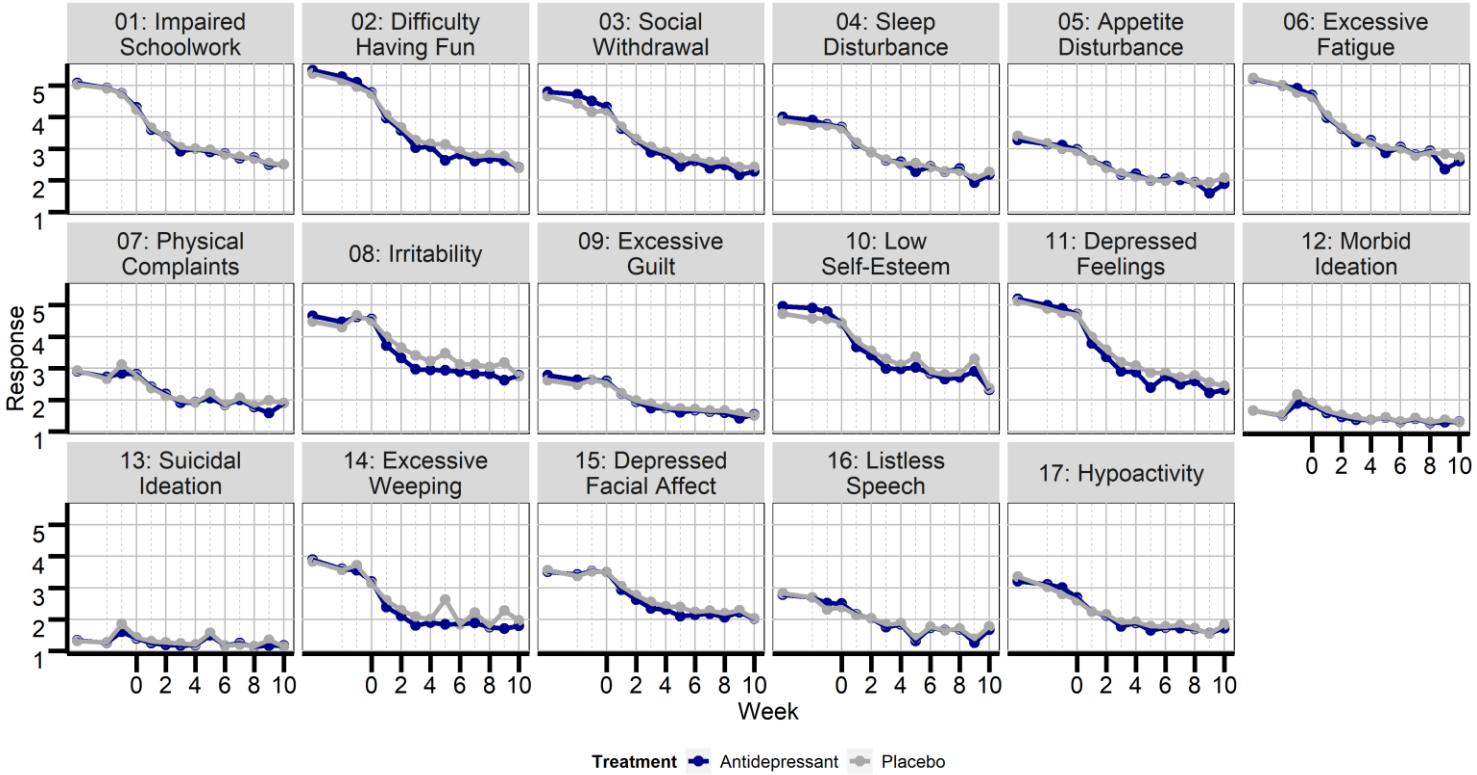
Sensitive MADRS Items
1. Apparent sadness
2. Reported sadness
8. Inability to feel
7. Lassitude
6. Concentration difficulties
4. Reduced sleep
3. Inner tension

Insensitive MADRS Items
9. Pessimistic thoughts
10. Suicidal thoughts
5. Reduced appetite

- Item sensitivity potential was based on several factors including:
  - Item-total correlation
  - Longitudinal trends by treatment arm
  - Changes from baseline through end-of-study
  - Between group effect sizes
  - Frequency and severity of item reporting
- Affective symptoms appear consistently as sensitive items on both scales
- Physical symptoms (e.g., sleep, appetite, fatigue) don't appear to be strongly associated with the total score
- Apparent flooring effect observed with items related to suicidal and morbid ideation

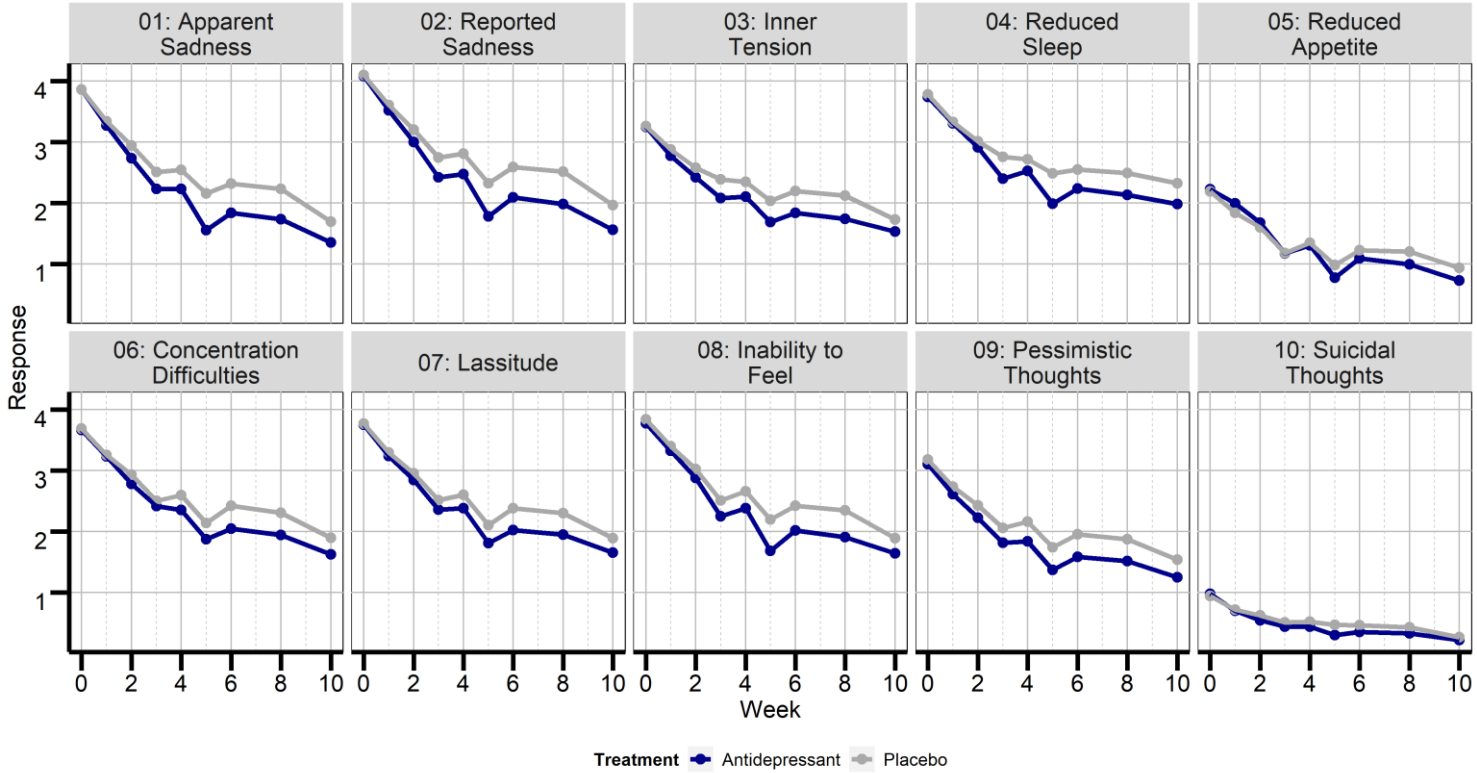
Assessment of CDRS-R and MADRS Items

Average CDRS-R Scores over Time

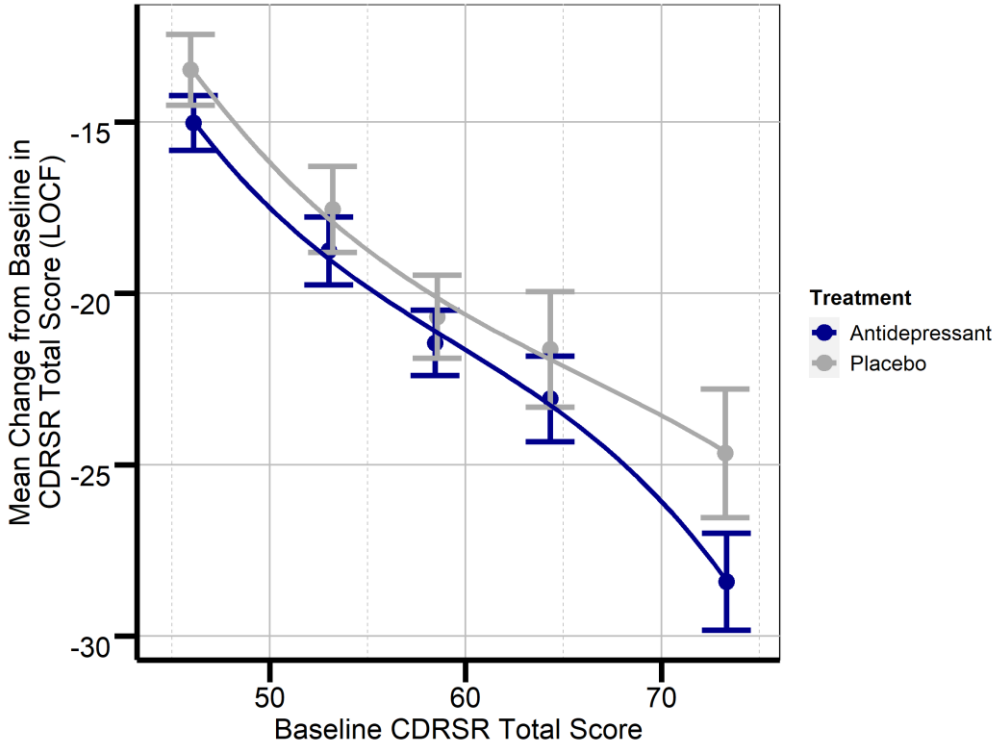


Assessment of CDRS-R and MADRS Items

Average MADRS Scores over Time



Assessment of Baseline Severity on Response



Does Disease Severity Differ Between Pediatrics and Adults?

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A Psychometric Evaluation of the CDRS and MADRS in Assessing Depressive Symptoms in Children

Shailesh Jain, M.D., M.P.H.[1], Thomas Carmody, Ph.D.[1,a], Madhukar H. Trivedi, M.D.[1], Carroll Hughes, Ph.D.[1], Ira Bernstein, Ph.D.[2,a], David W. Morris, Ph.D.[1], Graham J. Emslie, M.D.[1], and A. John Rush, M.D.[1]

Inclusion Criteria Cutoffs for Baseline Severity:

Pediatrics: CDRSR > 40

Adults: MADRS > 28/ HAMD > 22

Conversion between CDRS-R and MADRS at Exit for Children[a]

CDRS-R Total Score	MADRS Total Score (Child)	CDRS-R Total Score	MADRS Total Score (Child)
17–20	0–0	65–68	29–31
21–24	1–3	69–72	31–33
25–28	4–5	73–76	33–35
29–32	6–8	77–80	35–37
33–36	9–11	81–84	38–40
37–40	11–13	85–88	40–42
41–44	14–16	89–92	43–44
45–48	16–18	93–96	45–46
49–52	19–21	97–100	46–48
53–56	22–23	101–104	49–51
57–60	24–25	105–113	52–60
61–64	26–28		

[a] Due to the length of the table, 4-point intervals have been used. The complete table is available from the authors.

CDRS-R= Child Depression Rating Scale-Revised; MADRS= Montgomery-Asberg Depression Rating Scale

Next Steps

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- Mehul Mehta
- Islam Younis
- And more…