

Interpreting Results from New Studies on Therapeutics: The Importance of Placebo

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NEITHER DANIEL PINE, MD NOR MARY SALCEDO, MD HAVE ANY FINANCIAL RELATIONSHIPS WITH COMMERCIAL INTERESTS TO DISCLOSE.

ACKNOWLEDGEMENTS

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us at info@rosscenter.com.

OBJECTIVES

1. Recognize factors that lead to variable response rates.
2. Compare efficacy across treatments and conditions.
3. Understand factors influencing placebo response.

Outline

- *Placebo in Disorders: Anxiety & MDD*
 - *How to Evaluate Future Studies*
 - *Understanding Placebo Response*

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MDD & Placebo Response

1. Care about both DIFFERENTIAL & OVERALL response
2. Placebo as universal control for treatments
3. Good for medication and psychotherapy
4. Focus on youth, but data in adults are similar

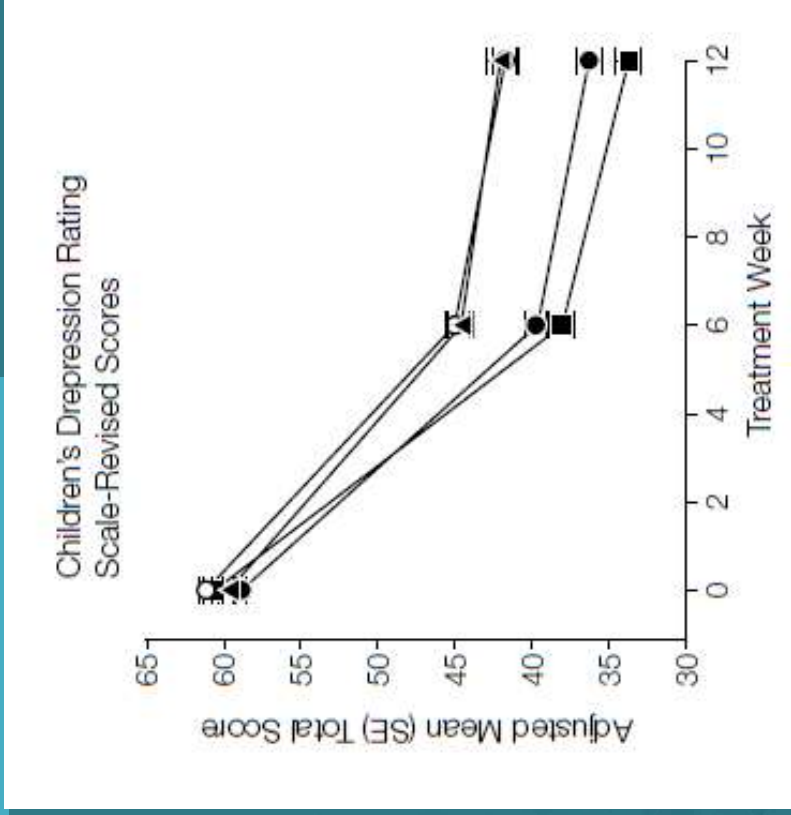
MDD & Placebo Response

JAMA. 2004;292:807-820

Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression

Treatment for Adolescents With Depression Study (TADS) Randomized Controlled Trial

ORIGINAL CONTRIBUTION



1. Overall Change with Placebo
2. Placebo vs. CBT
3. Combination vs. Fluoxetine Alone

Anxiety & Placebo Response

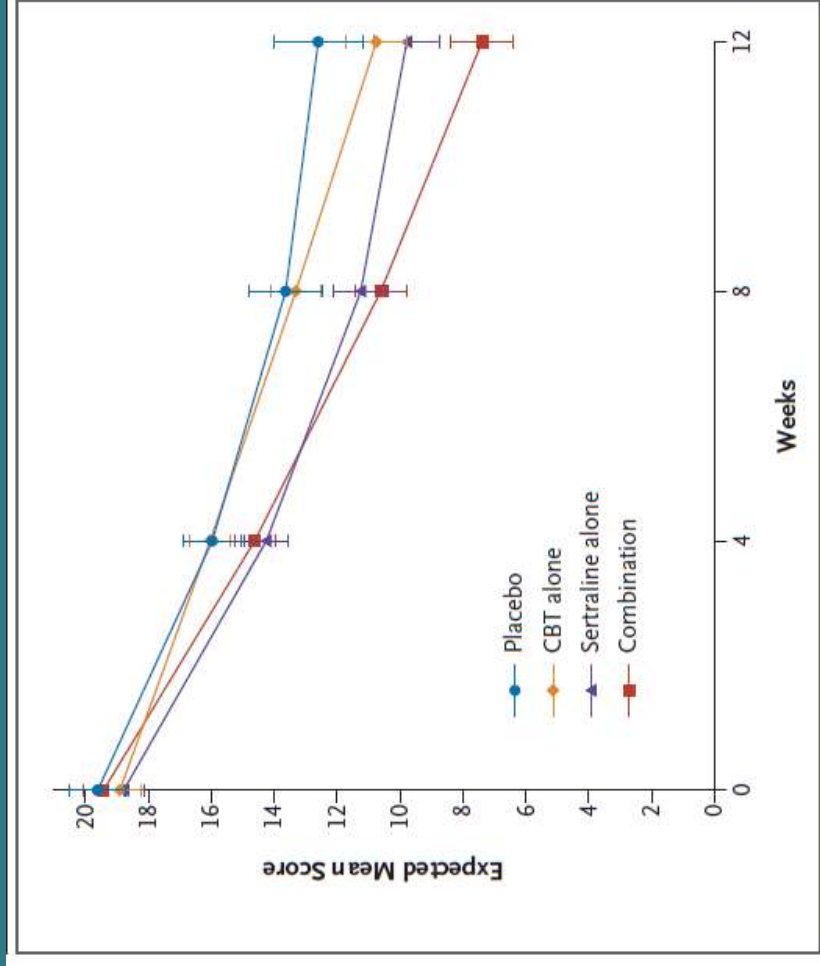
The **NEW ENGLAND**
JOURNAL of MEDICINE

Cognitive Behavioral Therapy, Sertraline,
or a Combination in Childhood Anxiety

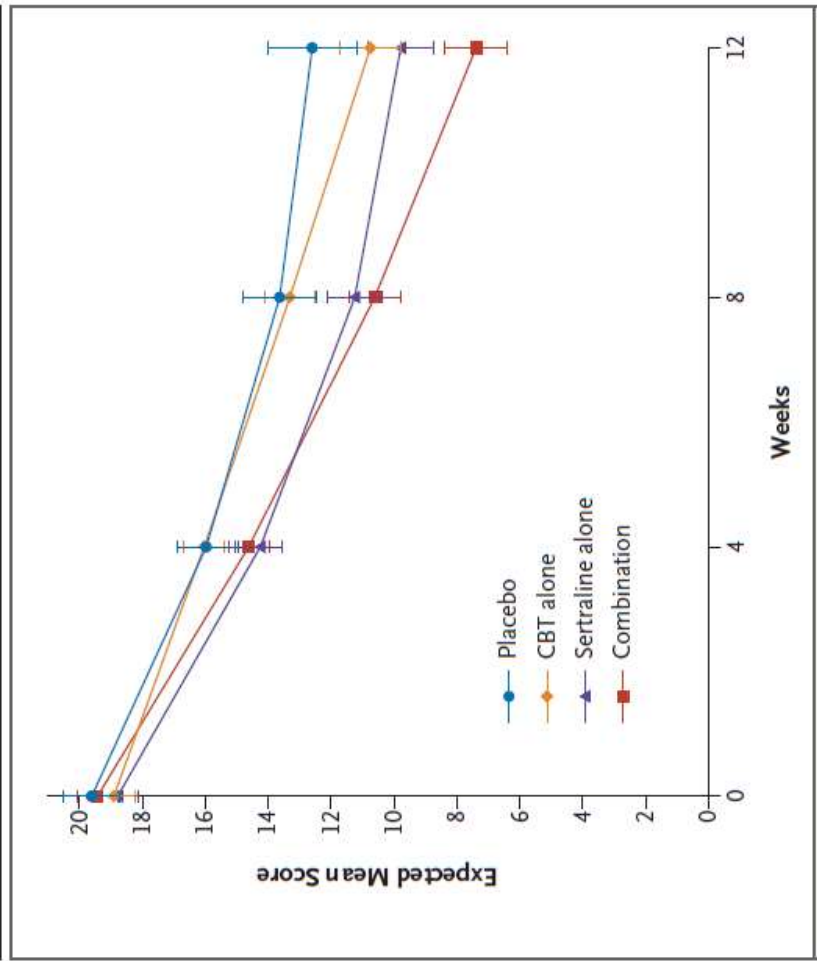
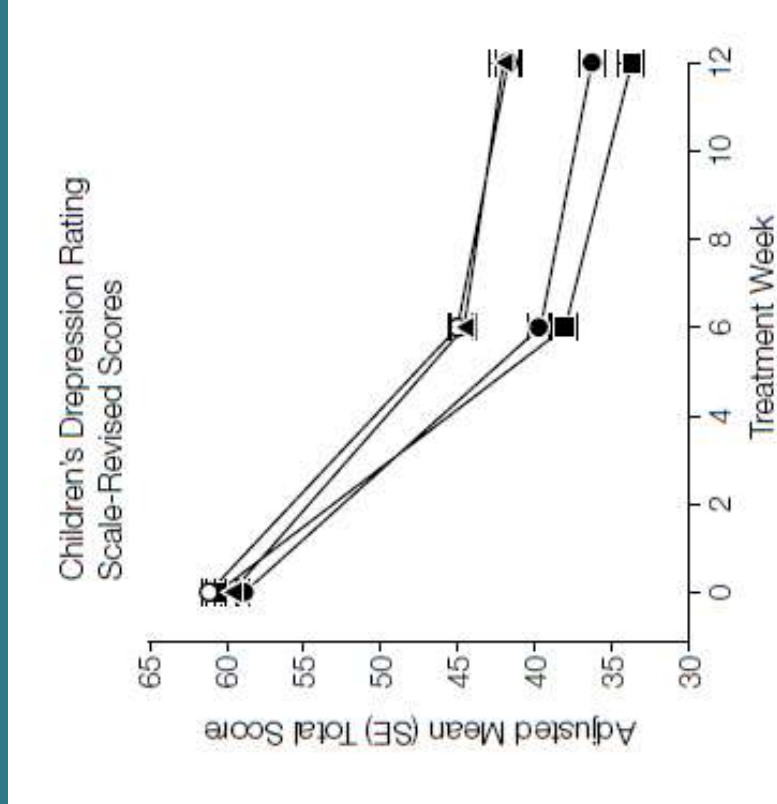
N Engl J Med 2008;359.

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1. Overall Change with Placebo
2. Placebo vs. CBT
3. Combination vs. Sertraline Alone



MDD, Anxiety, & Placebo Response



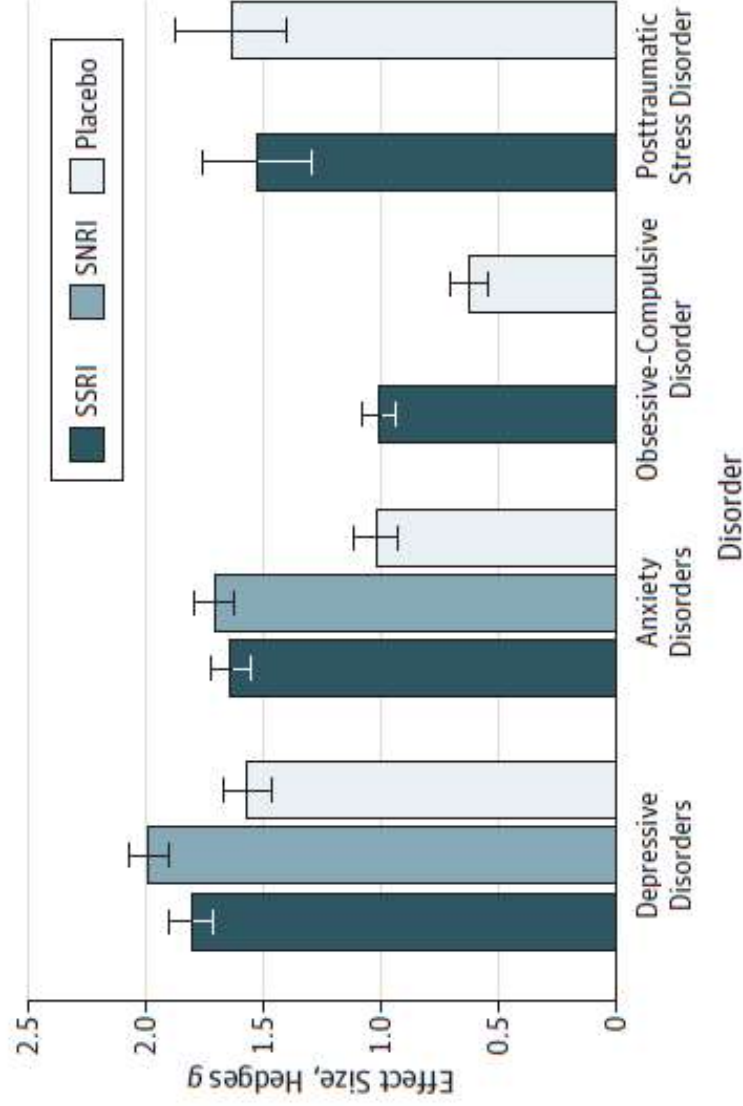
Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors and Placebo for Common Psychiatric Disorders Among Children and Adolescents

A Systematic Review and Meta-analysis

JAMA Psychiatry. 2017;74(10):1011-1020. doi:10.1001/jamapsychiatry.2017.2432
Published online August 30, 2017.

Cosima Locher, PhD; Helen Koehn, MSc; Sean R. Zoon, MA; Christoph Werner, BSc; Daniel S. Pine, MD; Irving Kirsch, PhD; Ronald C. Kessler, PhD; Joe Kosowski, PhD, MMSc

Figure 2. Drug and Placebo Effect Size by Disorder Category



Disorder- Specificity & Placebo Response Rates

Placebo Response

- ADHD & Stimulant: Low Placebo Response
- Schizophrenia & Antipsychotics: Low Placebo Response
- OCD & SSRIs: Low Placebo Response
- Anxiety & SSRIs: Moderate Placebo Response
- MDD & SSRIs: High Placebo Response
- PTSD & SSRIs: High Placebo Response

How to Understand?

Disorder- Specificity & Placebo Response Rates

- Unlikely to reflect severity of untreated disorder
- Unreliability in diagnosis?
- Unreliability in outcome response measure?
- Procedures for recruiting participants?
- A study's measure of "assay sensitivity"

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Placebo Response

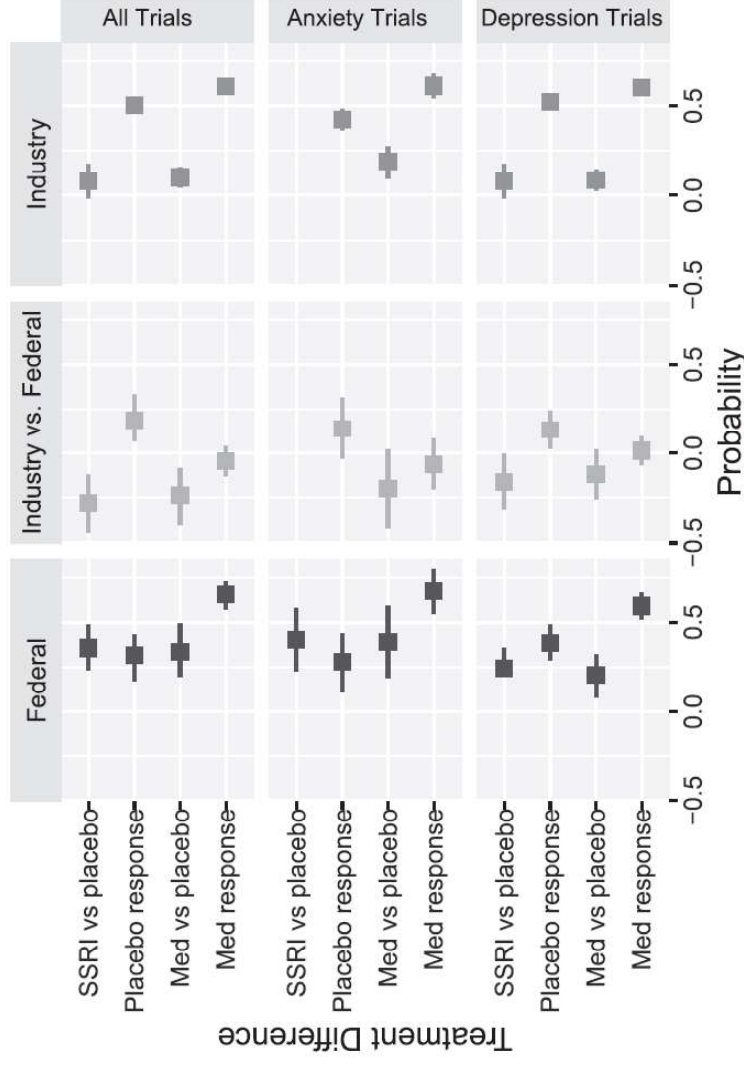
- Source of Study
- Number of Sites
- Methods



The Impact of Failed Antidepressant Trials on Outcomes in Children and Adolescents with Anxiety and Depression: A Systematic Review and Meta-Analysis

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 31, Number 4, 2021

Sarah A. Mossman, MACPR,¹ Jeffrey A. Mills, PhD,² John T. Walkup, MD,³ and Jeffrey R. Strawn, MD¹



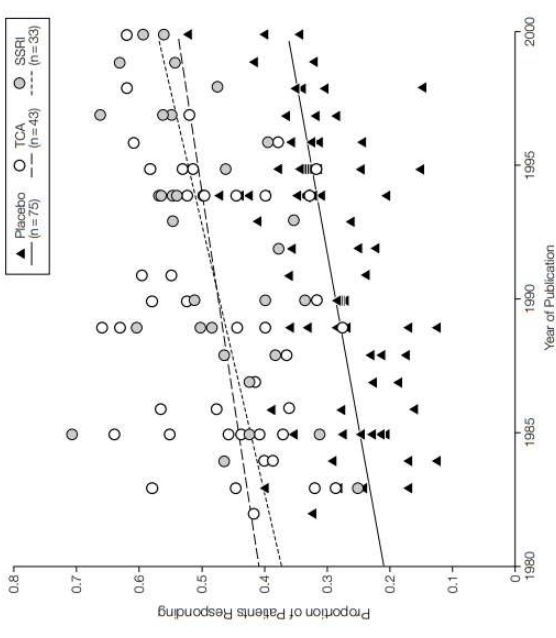
Process

- Time Trends

Placebo Response in Studies of Major Depression Variable, Substantial, and Growing

JAMA. 2002;287:1840-1847

REVIEW



Process

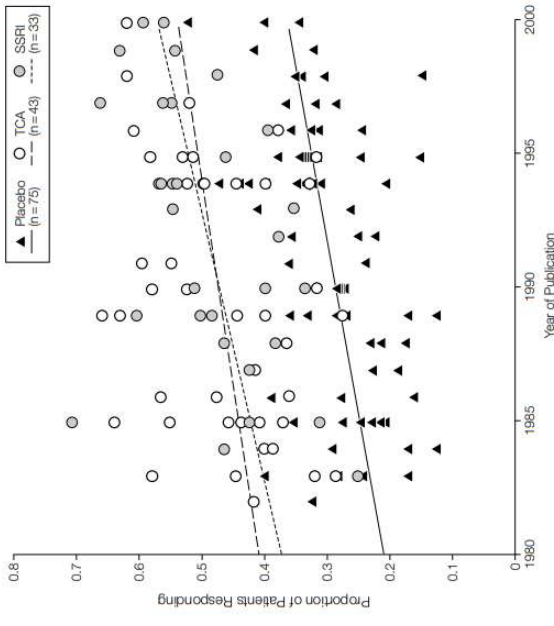
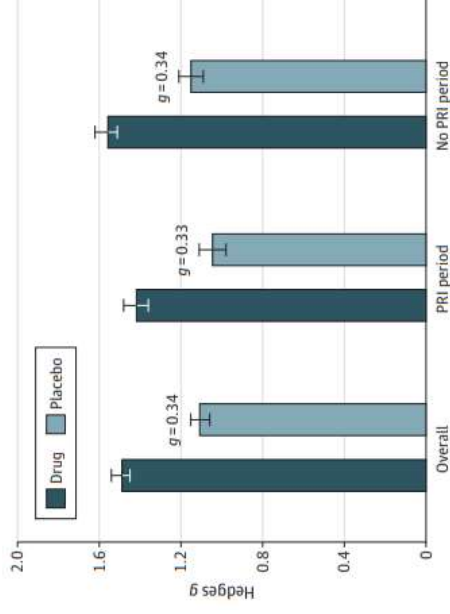
- Time Trends
- How to Reduce?
- **Run in?**
- **Withdrawal?**

Placebo Response in Studies of Major Depression

Variable, Substantial, and Growing

JAMA. 2002;287:1840-1847

REVIEW



JAMA Psychiatry | Original Investigation

Association of Single-blind Placebo Run-in Periods With the Placebo Response in Randomized Clinical Trials of Antidepressants: A Systematic Review and Meta-analysis

JAMA Psychiatry. 2022;79(1):42-49.

Amelia J. Scott, PhD; Louise Sharpe, PhD; Veronica Quinn, PhD; Ben Colagiuri, PhD

Process

- Assay Sensitivity

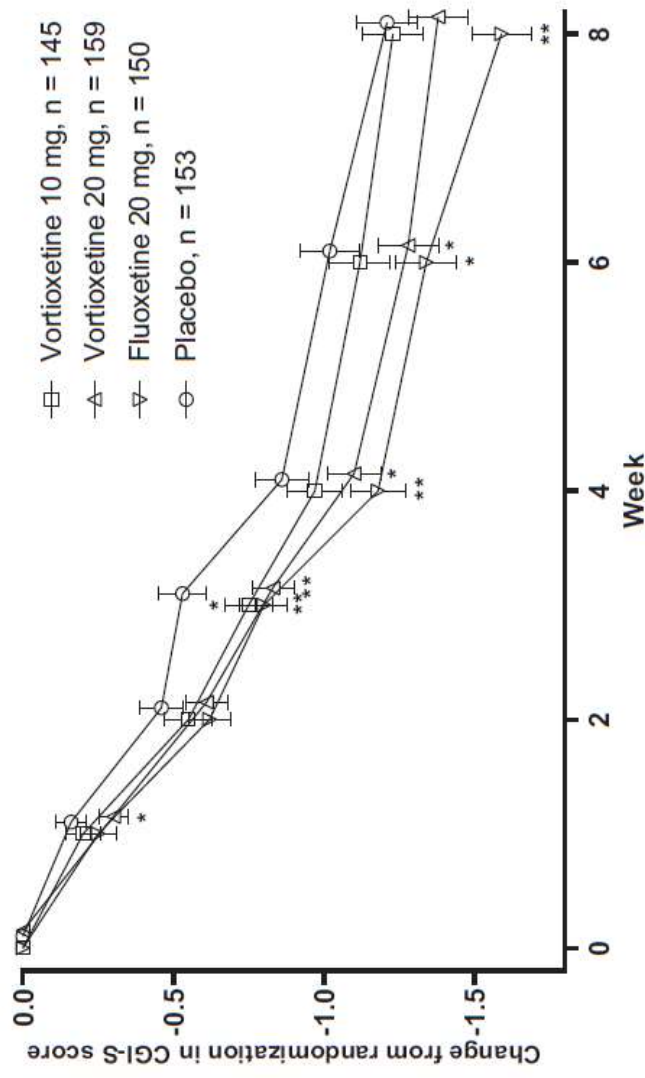
Process

- Assay
- Sensitivity

Vortioxetine for Major Depressive Disorder in Adolescents: 12-Week Randomized, Placebo-Controlled, Fluoxetine-Referenced, Fixed-Dose Study

J Am Acad Child Adolesc Psychiatry 2022;61(9):1106-1118

Robert L. Findling, MD, MBA , Melissa P. DelBello, MD, MS , Alessandro Zuddas, MD ,
Graham J. Emslie, MD , Anders Ettrup, PhD , Maria L. Petersen, MD ,
Simon N. Schmidt, MSc , Monika Rosen, PhD 



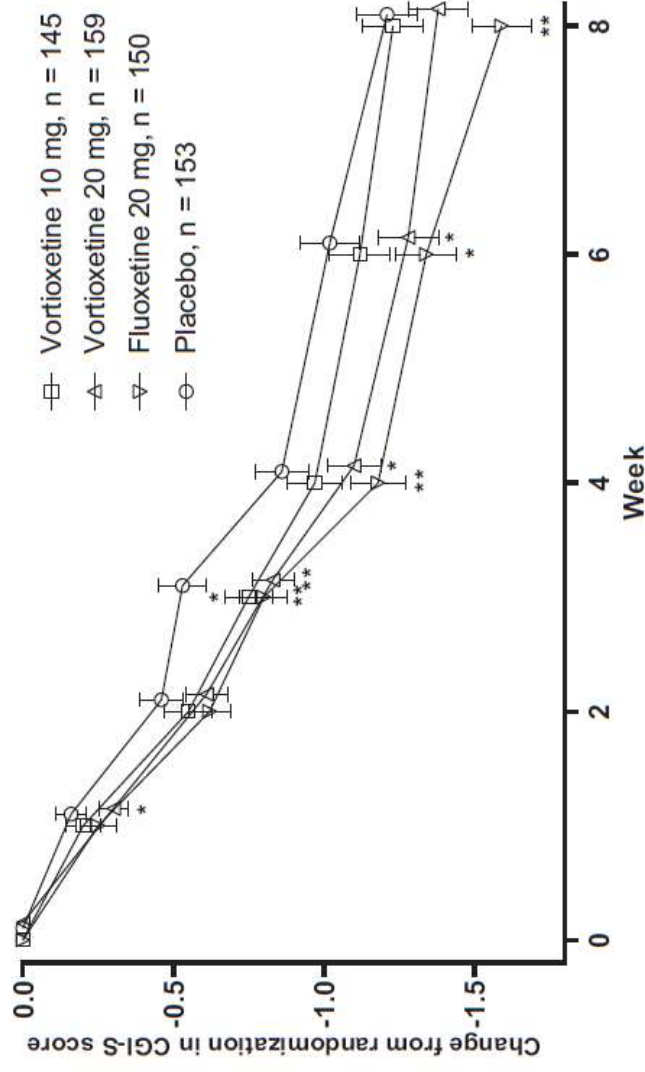
Process

- Assay
- Sensitivity
- Future
- Studies

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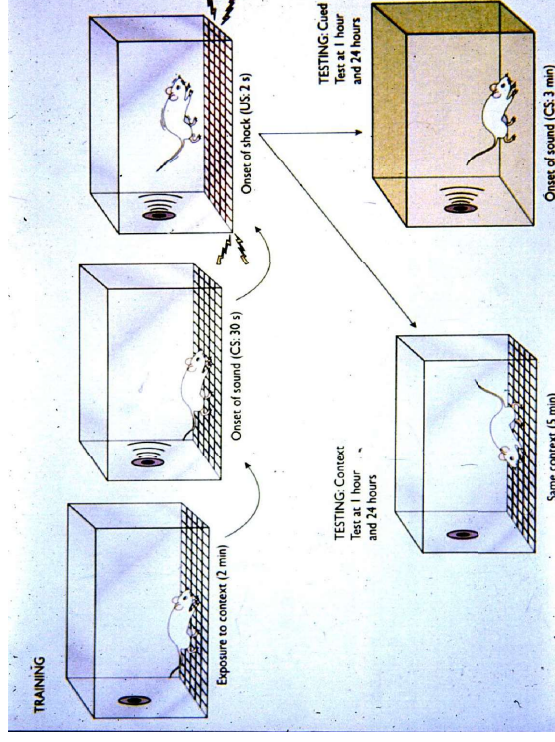


Outline

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- *How to Evaluate Future Studies*
- **Understanding Placebo Response**

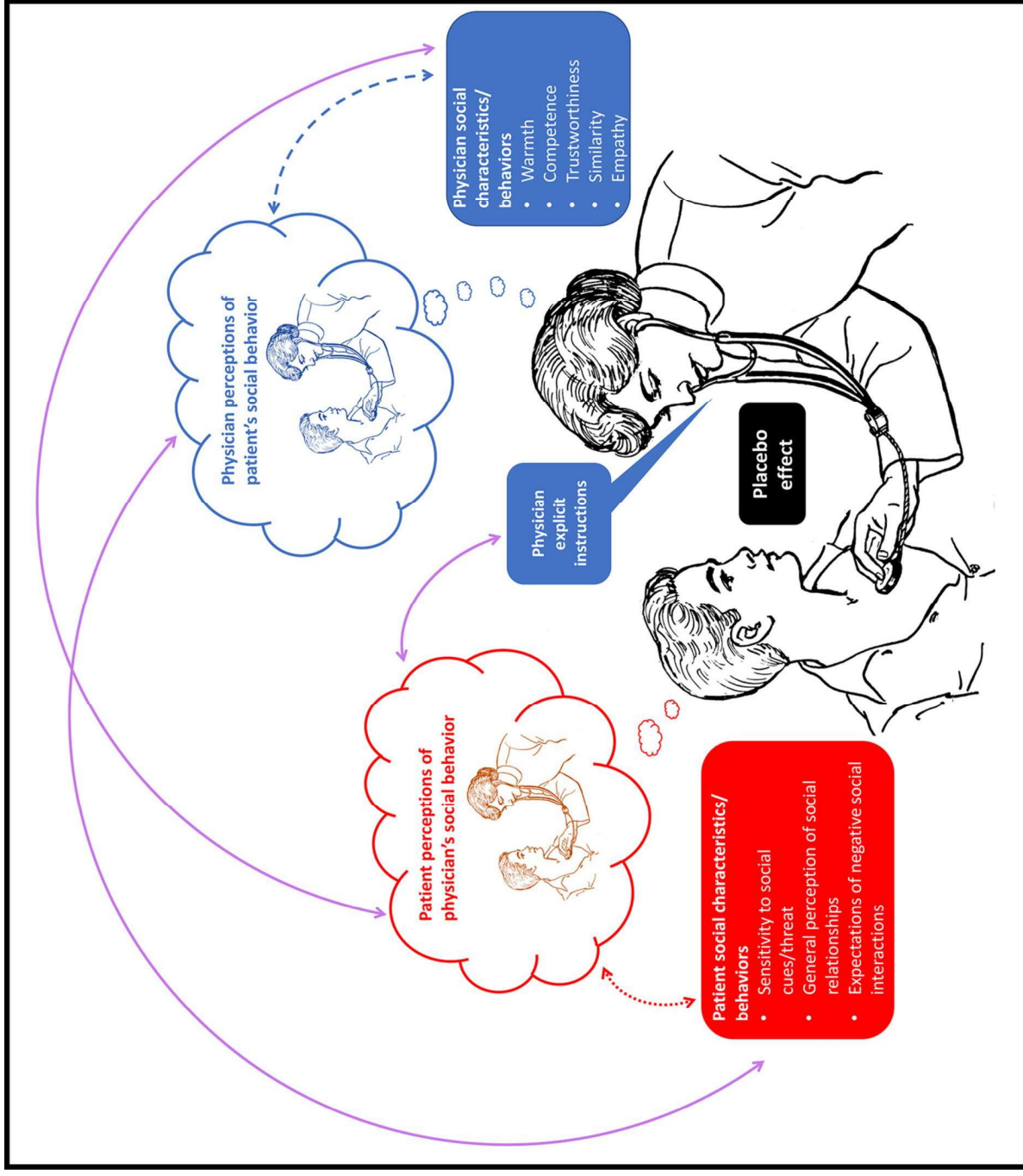
Process

- Expectancy
- Conditioning



Process

- Expectancy
- Data in Pain



Process

• Conditioning

• Remove

Expectation

• Data



Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks

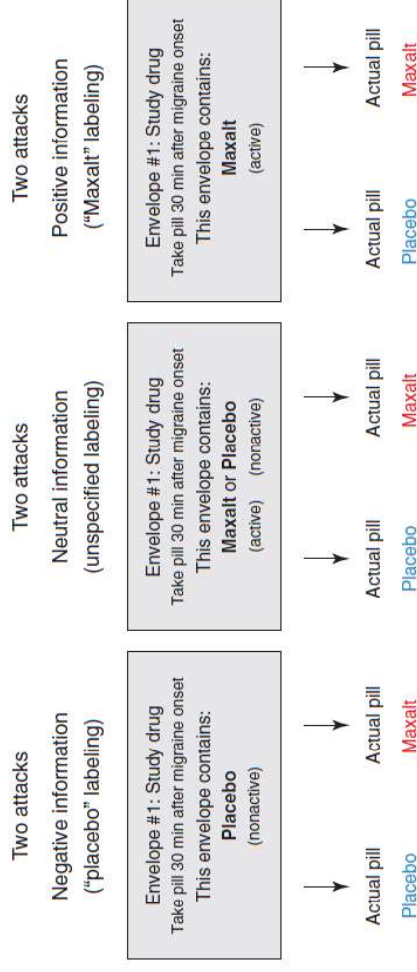
Slavenka Kam-Hansen,¹ Moshe Jakubowski,² John M. Kelley,^{3,4,5} Irving Kirsch,^{5,6} David C. Hoaglin,⁷ Ted J. Kaptchuk,^{5*} Rami Burstein^{2,*†}

www.ScienceTranslationalMedicine.org 8 January 2014 Vol 6 Issue 218 218ra5

No treatment (first attack)

Rescue medication
1 Maxalt and 2 naproxen
If you are not pain-free 2.5 hours
after migraine onset, you may take all 3
pills in this envelope at the same time

Study drug labels (attacks 1–6)



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References

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- Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Science Translational Medicine*, 6(218). <https://doi.org/10.1126/scitranslmed.3006175>
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- Towbin, K. E. (2022). Editorial: Not the same as adults: Vortioxetine in adolescents with major depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, 61(9), 1081–1083. <https://doi.org/10.1016/j.jaac.2022.03.019>