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# Solving psychedelic trials' blinding problem with the Zelen design

Dr. Balázs Szigeti



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# Disclosures

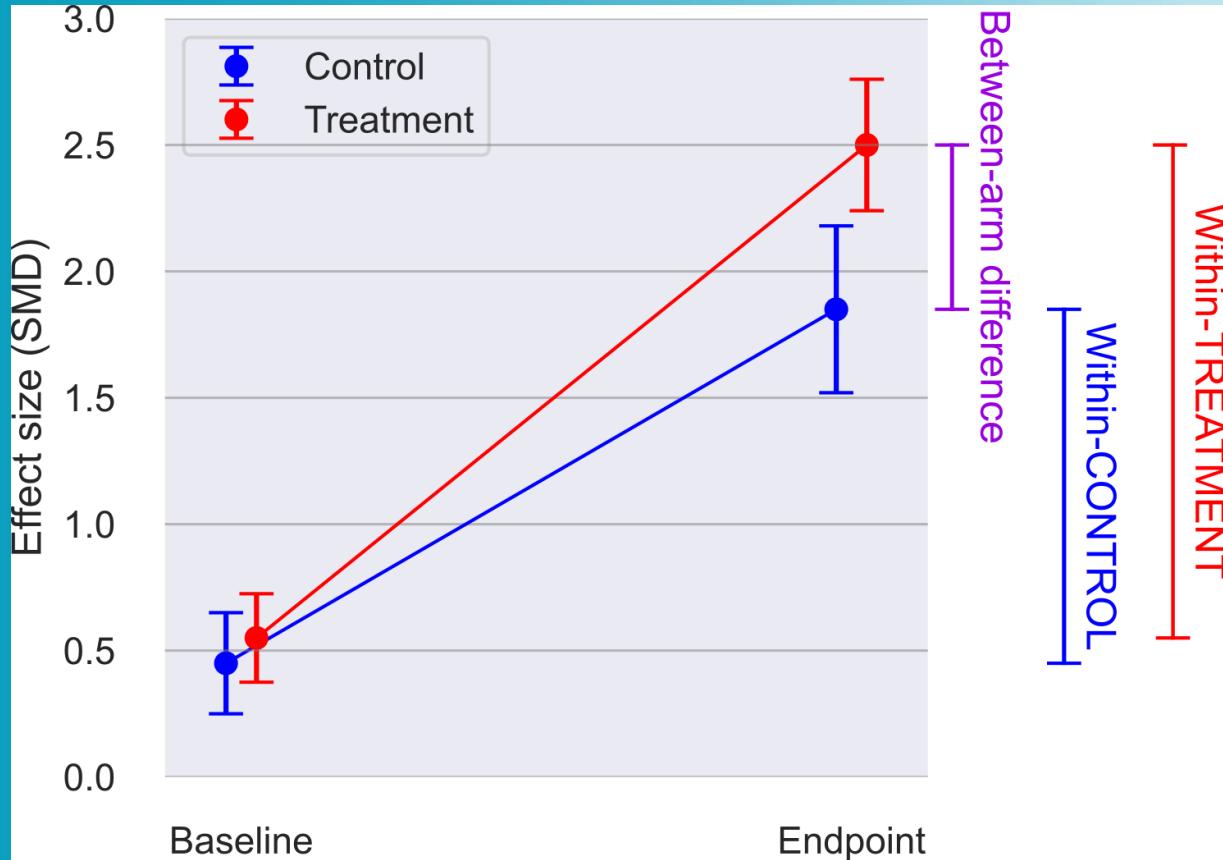
Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose."

# What is measured in a trial?



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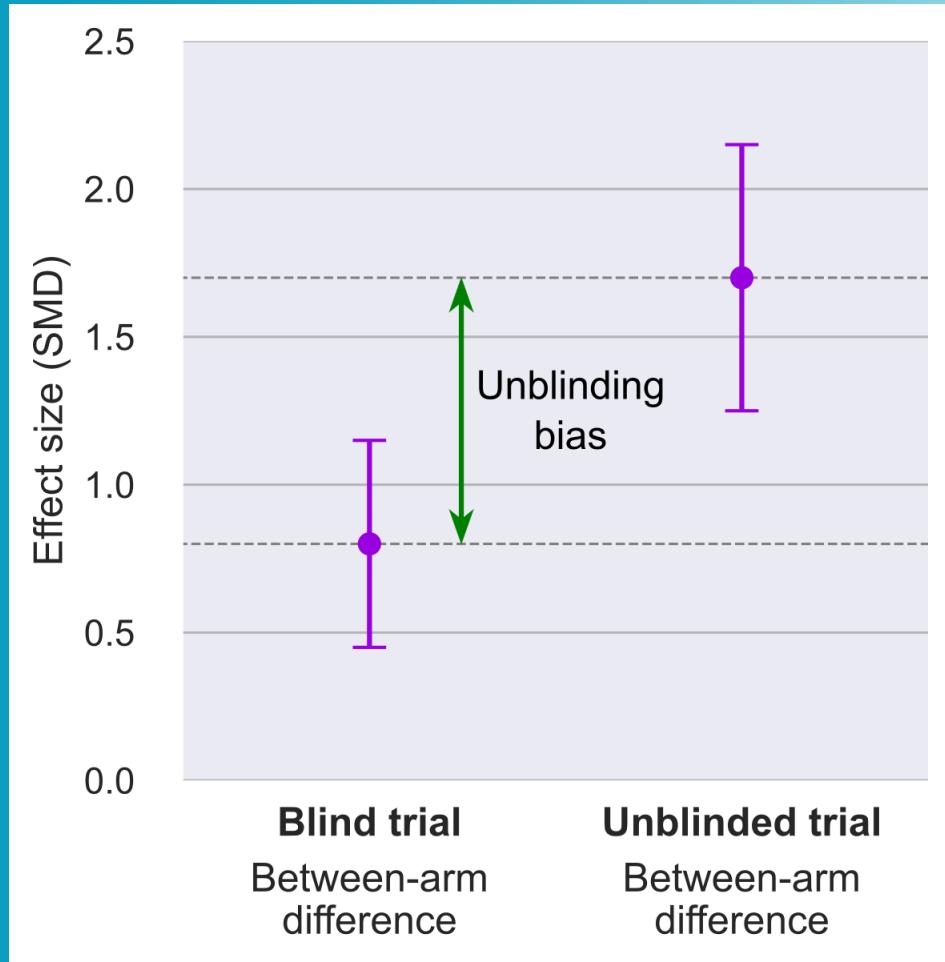
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There are 3 effect sizes in a trial with two groups:

- *Between-arm difference*  
(treatment vs. control)
- *Within-arm effect of the TREATMENT arm*
- *Within-arm effect of the CONTROL arm*

# What is unblinding bias?



**Unblinding bias** is the difference between the 'between-arm differences' of two trials that are identical, except one is unblinded, while the other is truly blind

Szigeti, et al. "Too big to fail? Comparing effect sizes of MDMA assisted therapy to unmasking bias." *Psychopharmacology* (2025): 1-4.

# Sources of unblinding bias



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## TREATMENT PATHWAY

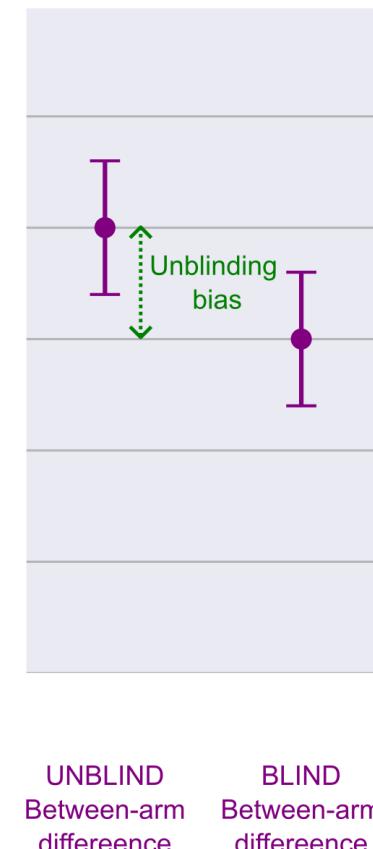
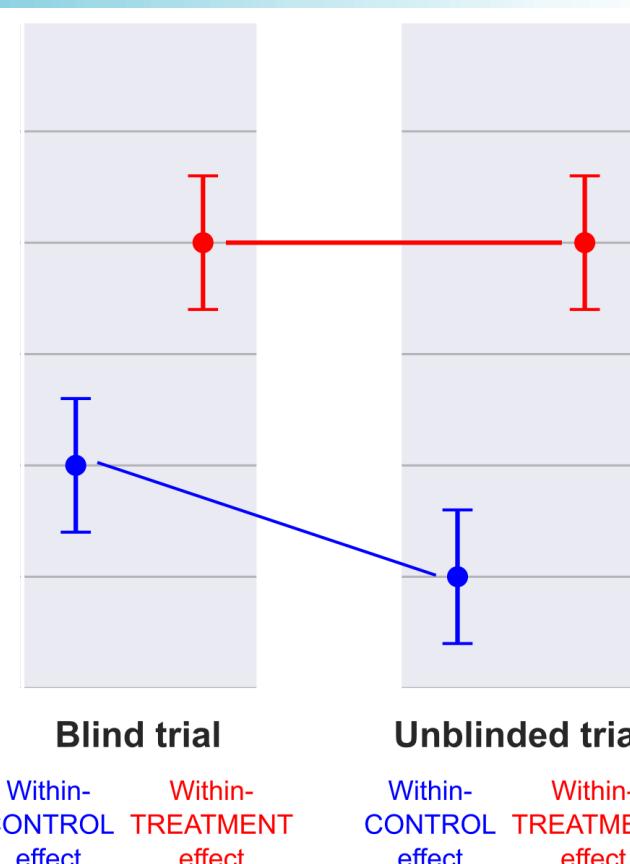
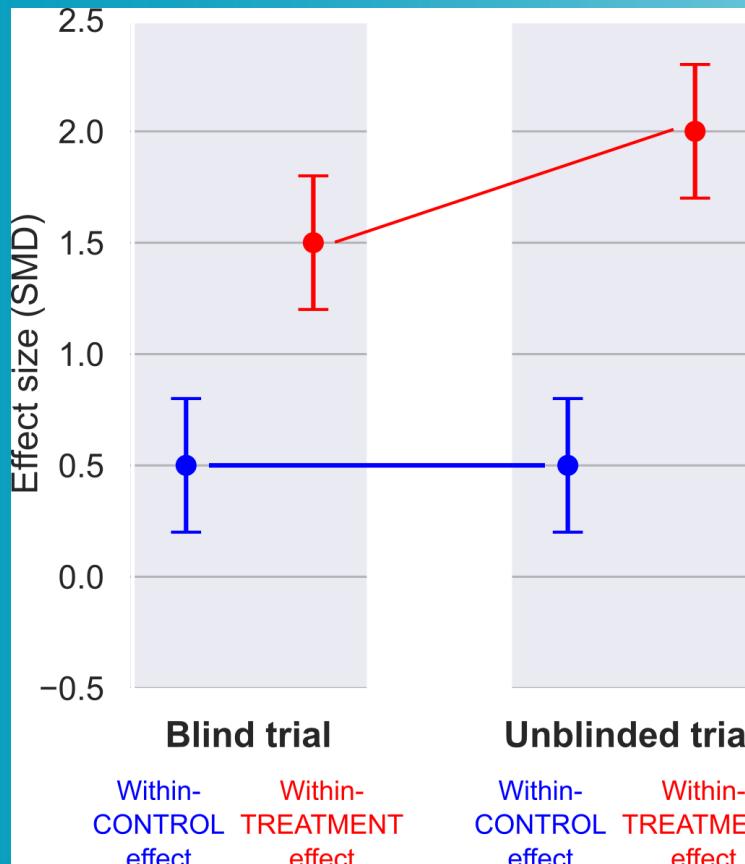
Within-Treatment **INCREASES**

Within-Control **CONSTANT**

## CONTROL PATHWAY

Within-Treatment **CONSTANT**

Within-Control **DECREASES**





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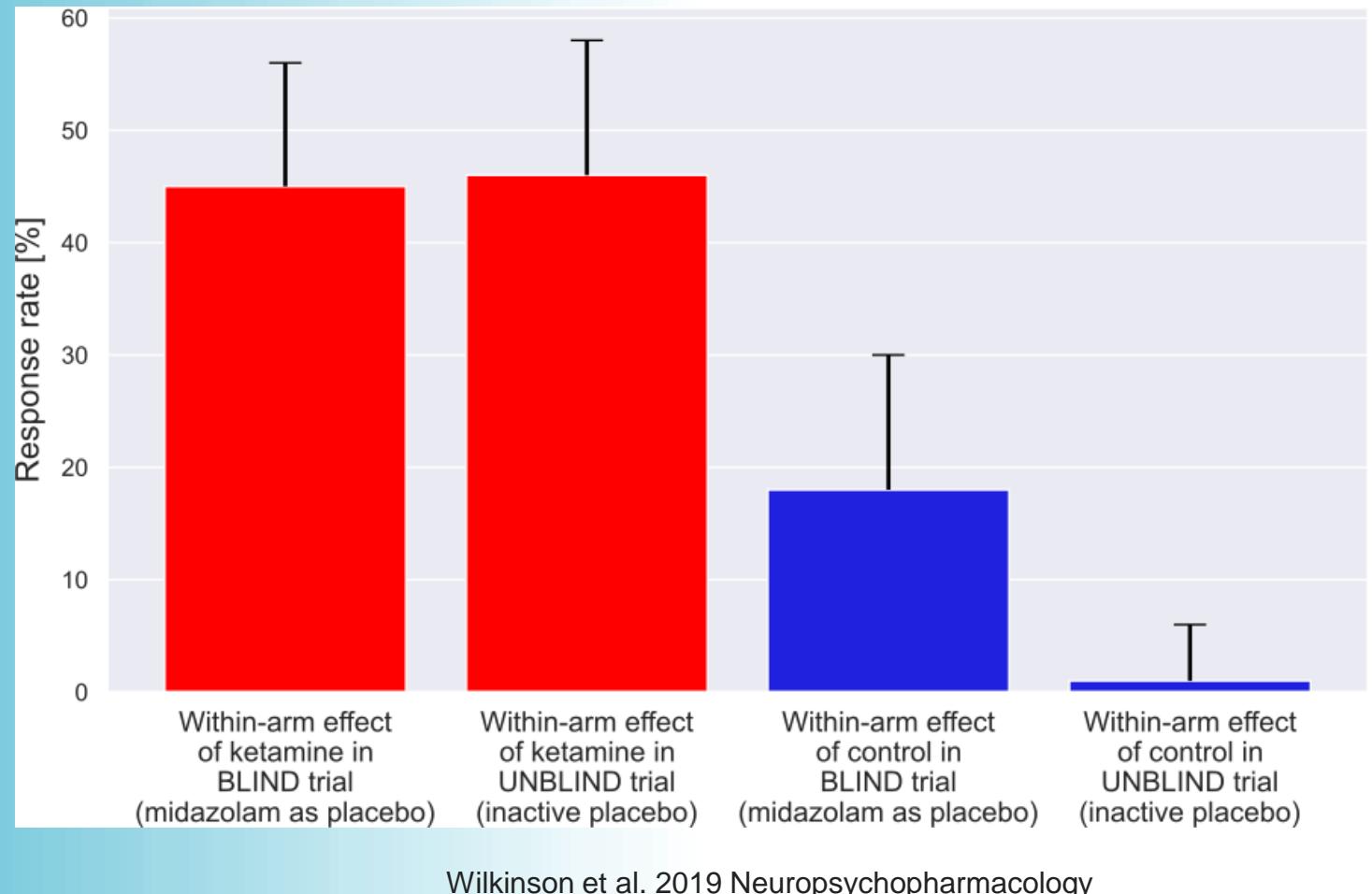
# Ketamine

- There are both BLIND and UNBLINDED trials:
  - Inactive placebo leads to functional unblinding
  - Midazolam as active placebo leads to adequate blinding



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Wilkinson et al. 2019 Neuropsychopharmacology

# Cannabis



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*[...] there was a significant association between blinding and placebo response wherein poor blinding was associated with lower placebo response. The same was not present in response to genuine treatment”*

Gedin et al. *Placebo response and media attention in randomized clinical trials assessing cannabis-based therapies for pain: a systematic review and meta-analysis*. JAMA Network Open 5.11 (2022): e2243848-e2243848.

# Psychedelics – positive expectancy



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- Expectancy is a component of unblinding; use it as proxy

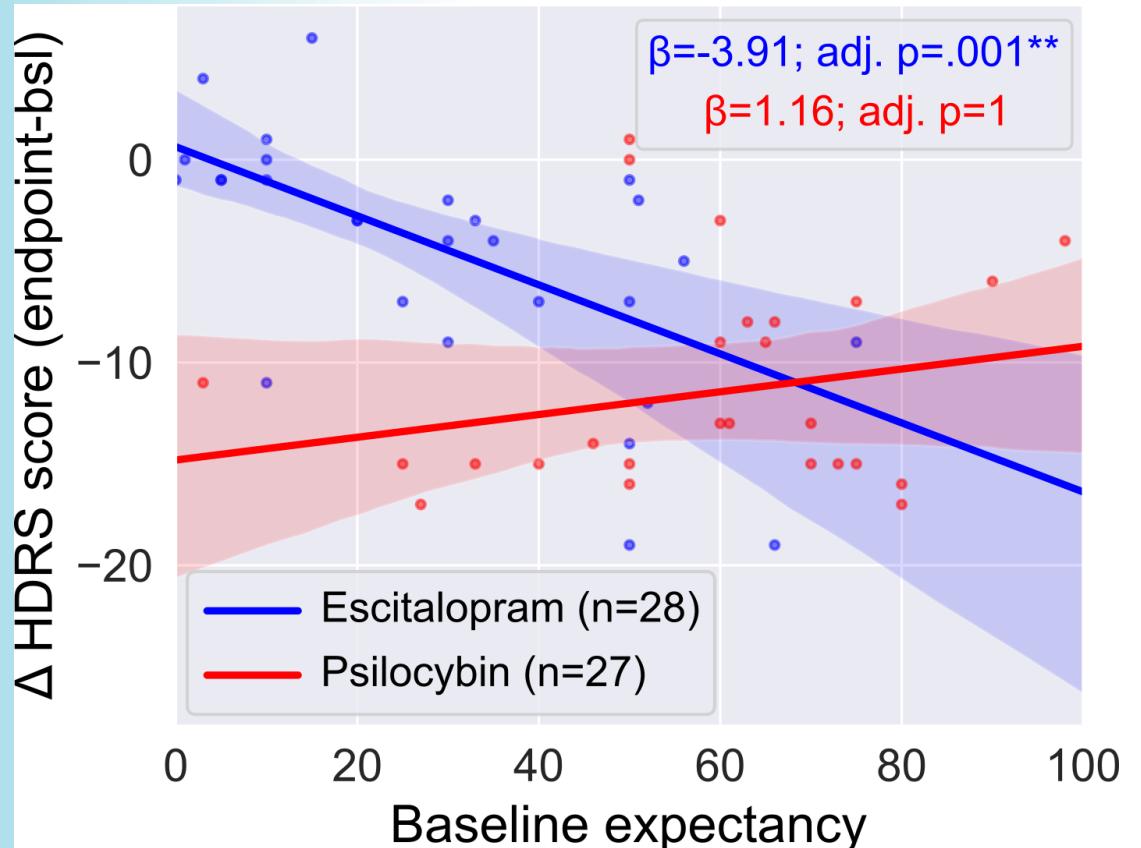
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- There is no evidence of expectancy bias in either psychedelic trials that measured expectancy:
  1. Szigeti et al. 2023: *Assessing expectancy and suggestibility in a trial of escitalopram v. psilocybin for depression*
  2. Szigeti et al 2025: *An open-label, dose-escalation trial of psilocybin-assisted therapy for bipolar 2 depression* (pre-print available)



\* HDRS: Hamilton Depression Rating Scale (17item)

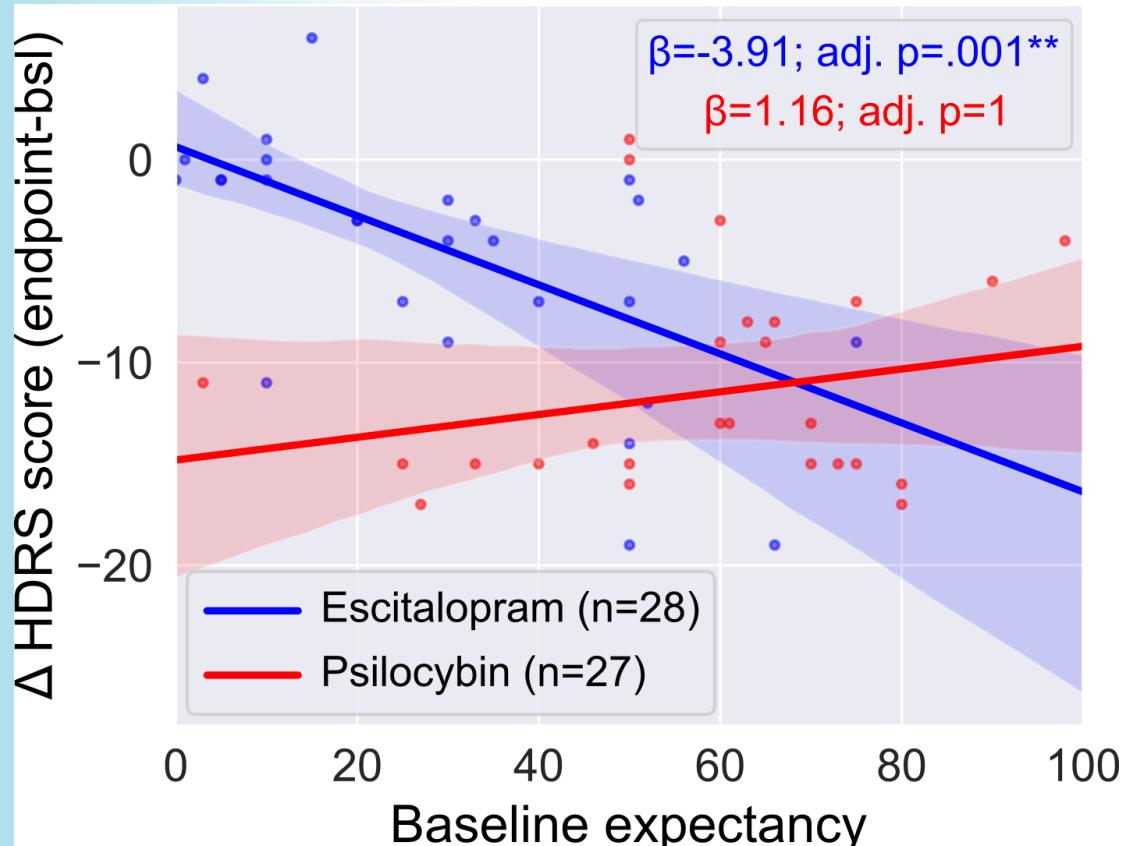
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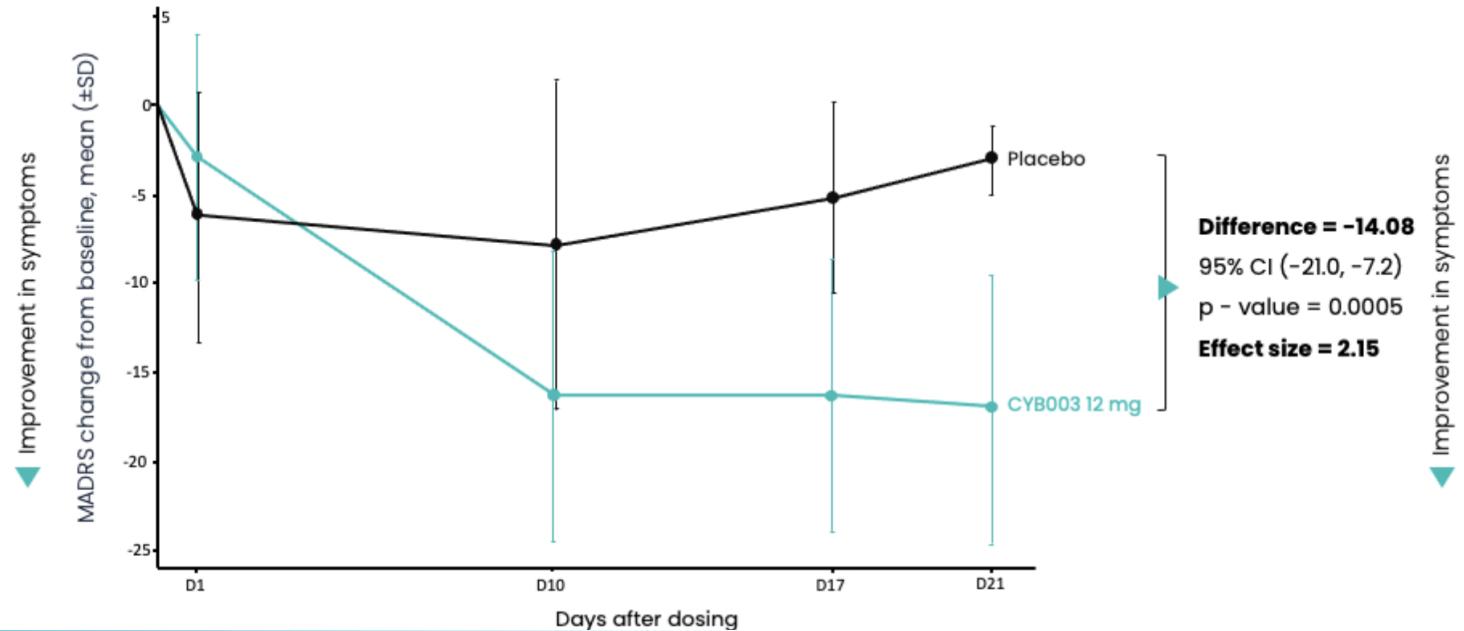
# Psychedelics – placebo suppression



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## Rapid reduction in symptoms after a single dose



<https://www.businesswire.com/news/home/20231031220551/en/Cybin-Announces-Unprecedented-Positive-Phase-2-Interim-Data-for-CYB003-in-Major-Depressive-Disorder-Meeting-Primary-Efficacy-Endpoint-with-Rapid-and-Significant-Improvements-in-Depression-Symptoms-After-Single-Dose>

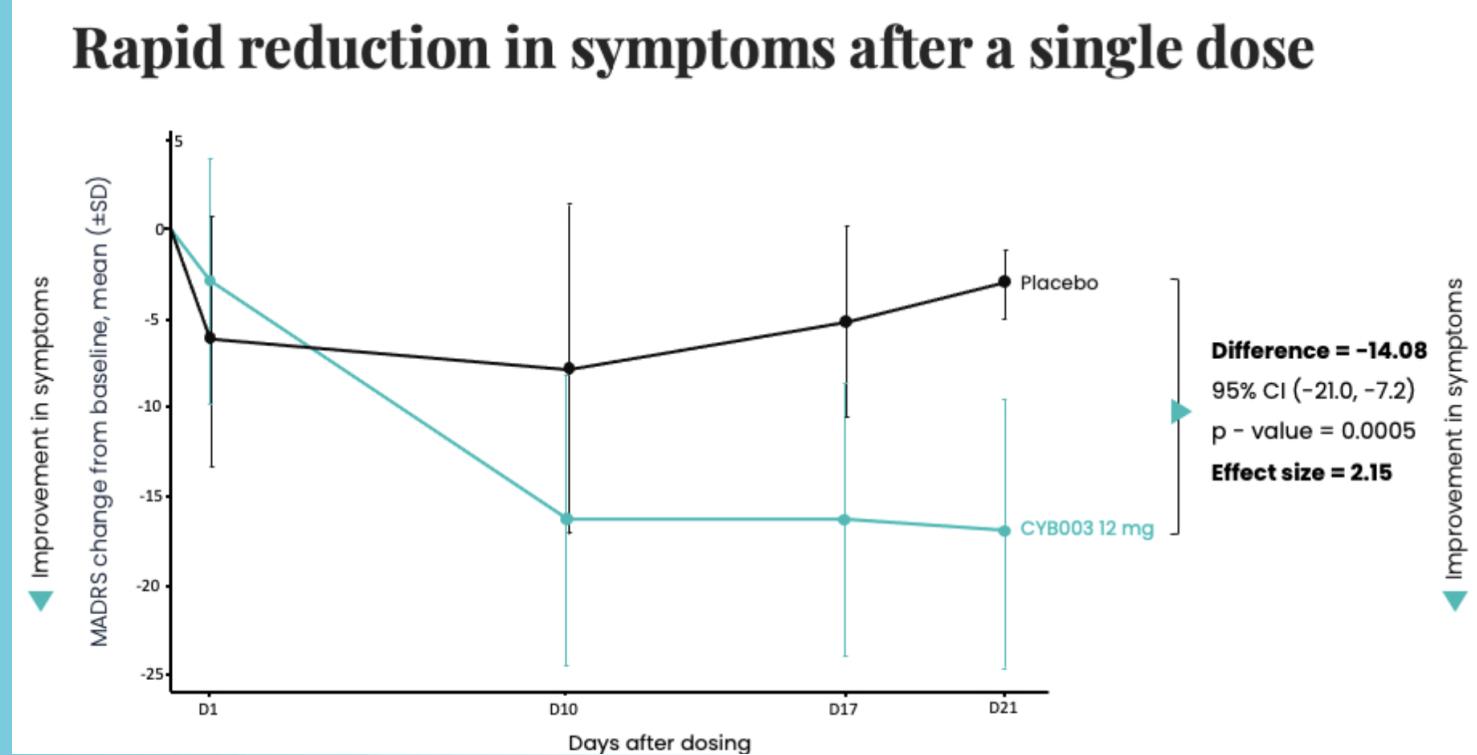
# Psychedelics – placebo suppression



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- Patients get WORSE in psychedelic trials' placebo arm – **UNIQUE**
- Compared to traditional antidepressants, the placebo response is ~4 HRSD units less in psychedelic trials (Hsu et al. BMJ 386; 2024) – **LARGE EFFECT**



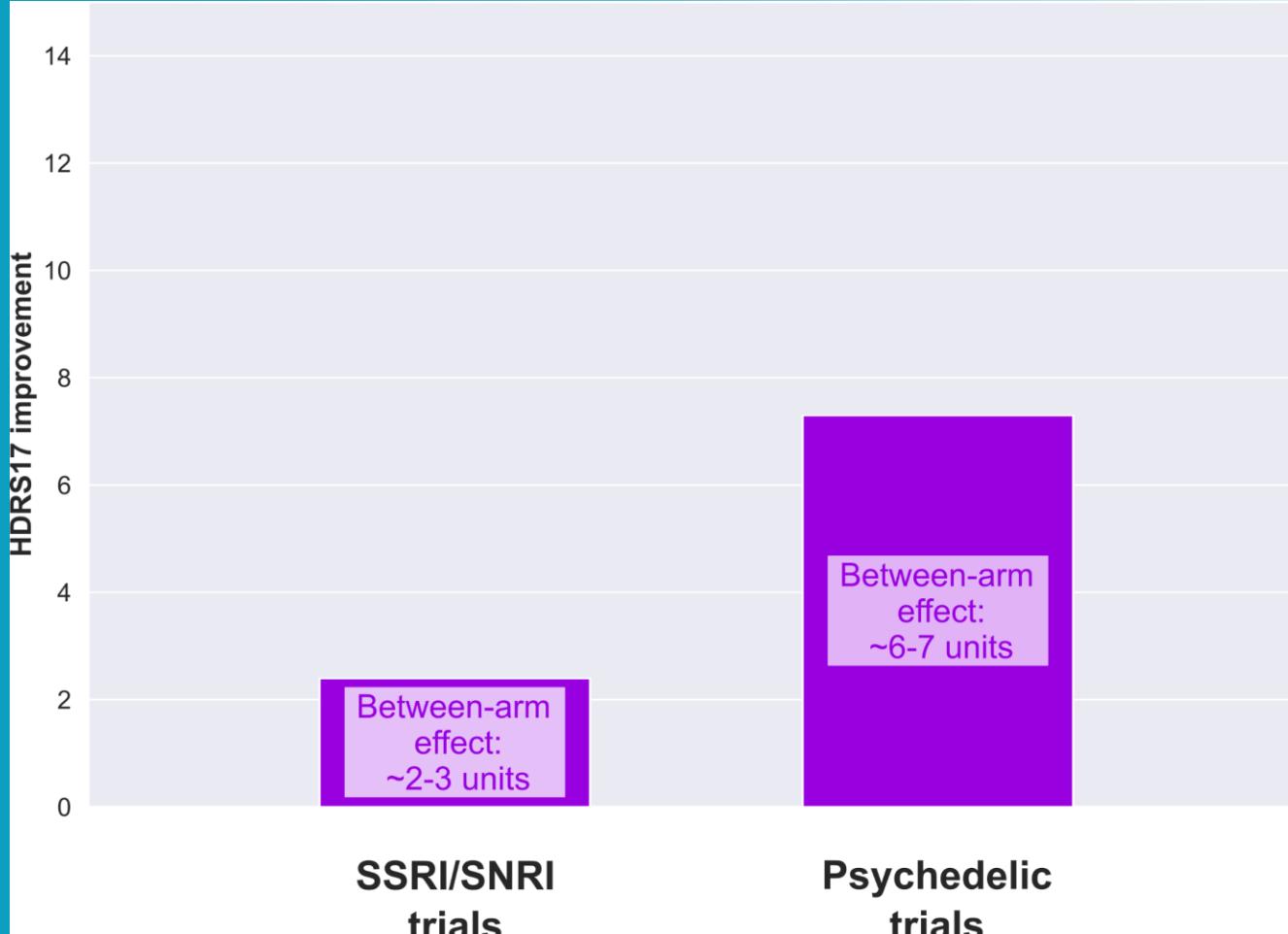
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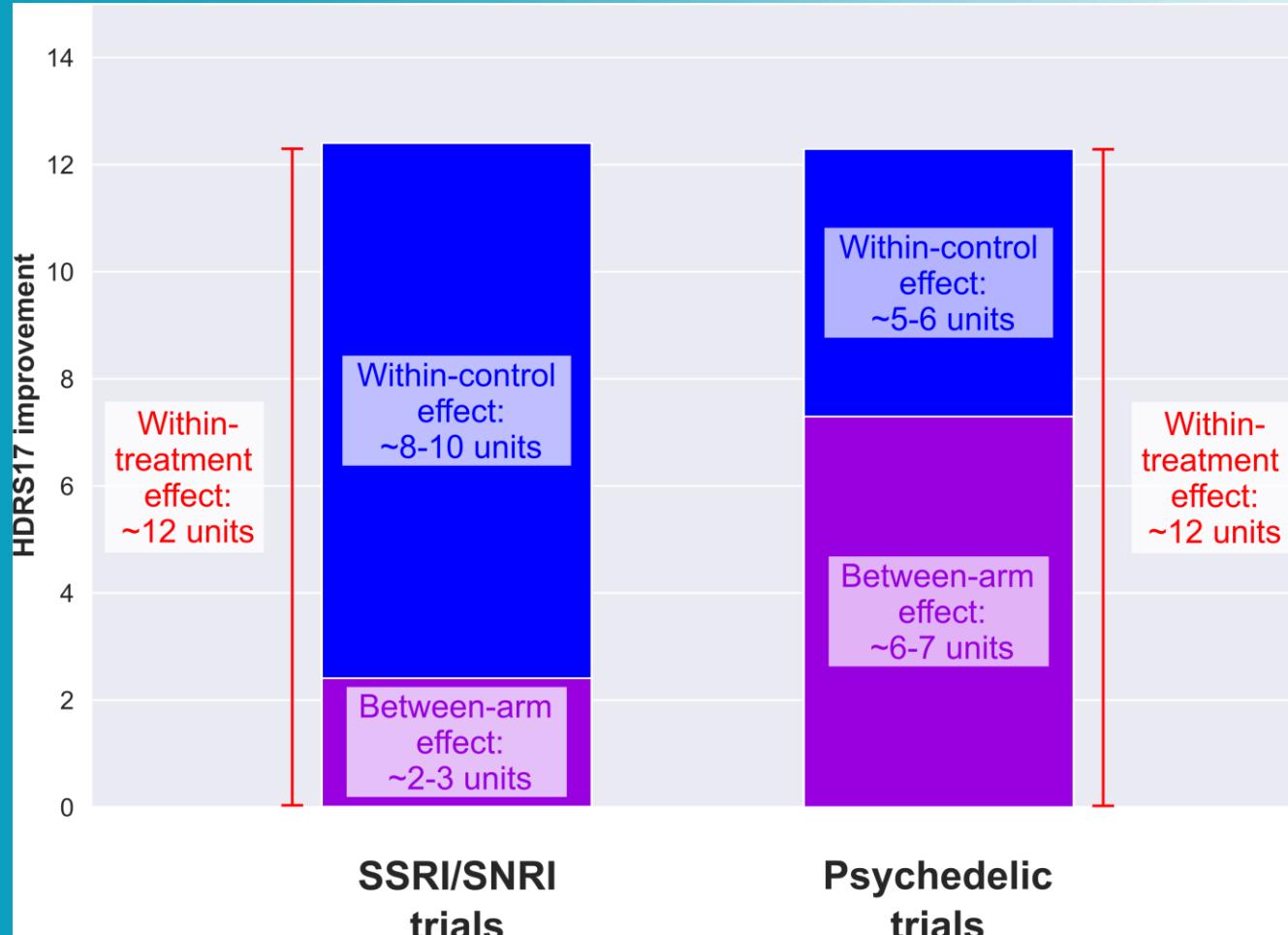
- Szigeti et al. 'Equal-unblinding' meta-analysis of psychedelic therapy vs. antidepressants for the treatment of depression (under review; pre-print available on OSF)
- Ko, Kwonmok, et al. "Psychedelic therapy for depressive symptoms: A systematic review and meta-analysis." *Journal of Affective Disorders* 322 (2023): 194-204.
- Stone, Marc B., et al. "Response to acute monotherapy for major depressive disorder in randomized, placebo-controlled trials submitted to the US Food and Drug Administration: individual participant data analysis." *Bmj* 378 (2022).
- Cipriani, Andrea, et al. "Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis." *The Lancet* 391.10128 (2018): 1357-1366.
- Hsu, Tien-Wei, et al. "Comparative oral monotherapy of psilocybin, lysergic acid diethylamide, 3, 4-methylenedioxymethamphetamine, ayahuasca, and escitalopram for depressive symptoms: systematic review and Bayesian network meta-analysis." *bmj* 386 (2024).

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# Unblinding bias is driven by the control pathway



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Unblinding bias	
Treatment pathway	Control pathway
Ketamine	
Direct experimental evidence of no effect	Direct experimental evidence of a large effect
Cannabis	
Indirect evidence of no effect	Indirect evidence of a moderate effect
Psychedelics	
Indirect evidence of no effect	Indirect evidence of a large effect (know-cebo)

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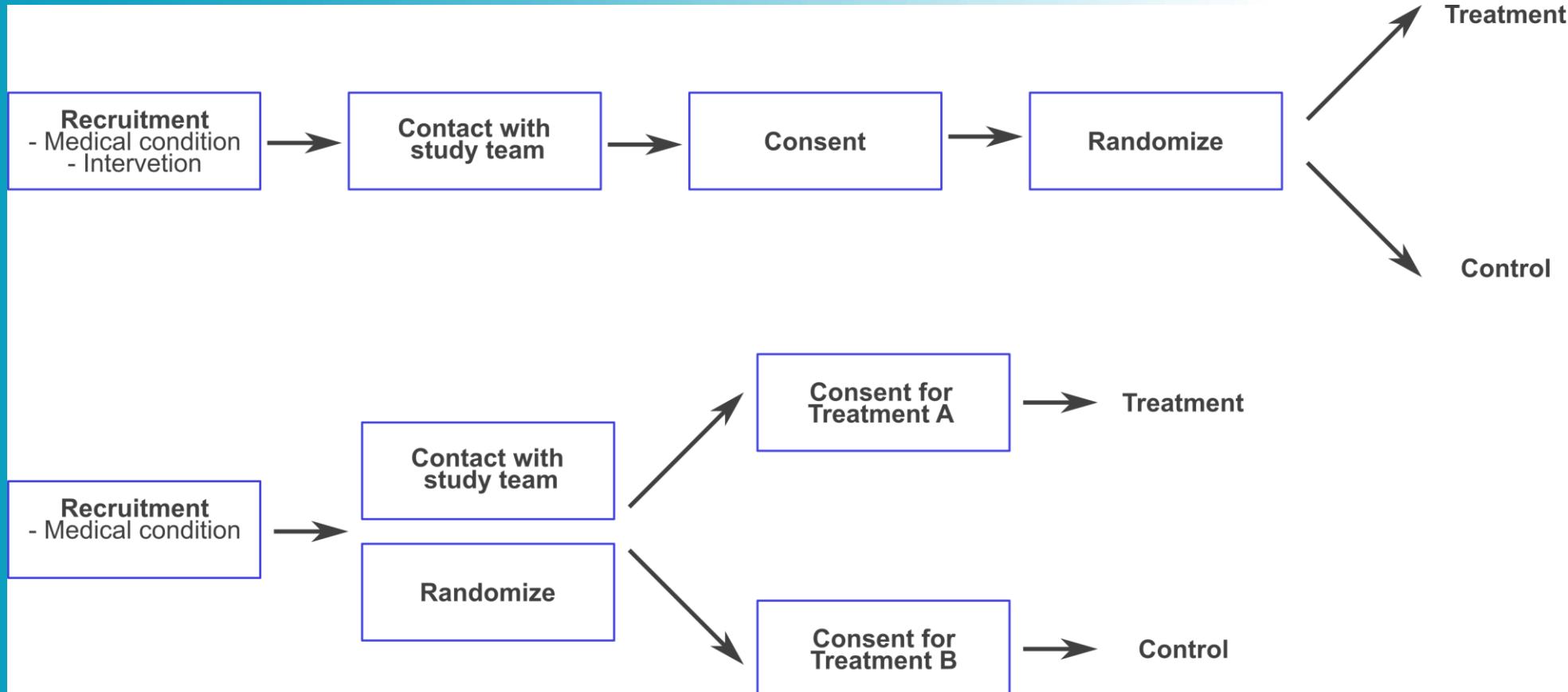
*"No evidence was found for an average difference in estimated treatment effect between trials with and without blinded patients [...]. These results could reflect that blinding is less important than often believed or meta epidemiological study limitations"* - Moustgaard et al. "Impact of blinding on estimated treatment effects in randomised clinical trials: meta-epidemiological study." *bmj* 368 (2020).

# Traditional vs. Zelen RCT



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Simon, Gregory E., Susan M. Shortreed, and Lynn L. DeBar. "Zelen design clinical trials: why, when, and how." *Trials* 22 (2021): 1-8.

# Summary



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## What is unblinding bias

- Difference of between-arm differences in a perfectly blind vs. unblind trial
- Two pathways of unblinding bias:
  - Treatment pathway
  - Control pathway

## Solving unblinding bias

- Control pathway is driving unblinding bias
- In Zelen design patients not even aware that there are two arms



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