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Quantifying Clinical Relevance: Introducing Effect Sizes

How NNT Can Help the Clinician Interpret Clinical Trial Results

Leslie Citrome, MD, MPH

Clinical Professor of Psychiatry and Behavioral Sciences, New York Medical College, Valhalla, NY

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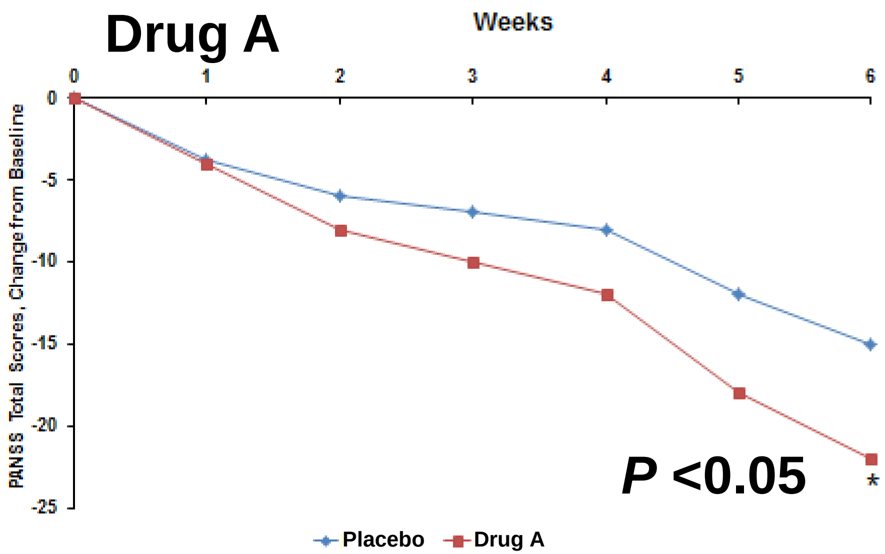
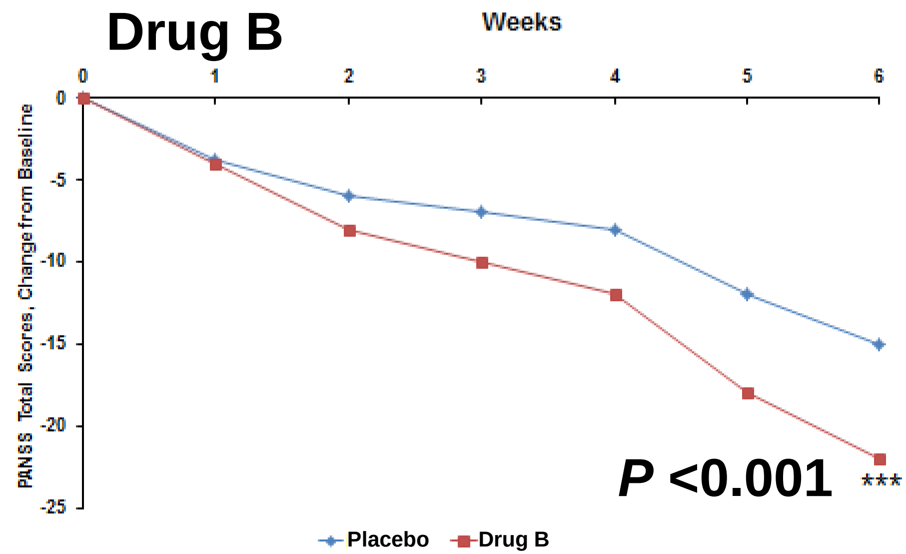
Choosing Between Drug A and Drug B for Acute Schizophrenia (Fictional Example)[1]

Drug A vs. placebo and Drug B vs. placebo in subjects with acute schizophrenia Positive and Negative Syndrome Scale (PANSS) total score change from baseline over time





- Is Drug B better because the *P* value is more impressive (<0.001 vs. <0.05)?

1. Citrome L. *Innov Clin Neurosci*. 2014;11(5-6):26-30.

P-Values Can Be Misleading[1]

- Assuming equivalent tolerability, cost, and overall patient acceptability, many people will say Drug B looks better because the *P*-value is lower
- However, all a *P*-value tells us is about statistical significance:
  - The lower the *P*-value, the more convinced we are that the results observed are less likely due to chance, and thus we must be dealing with "the truth"
- Unfortunately, "the truth" may not be clinically relevant or clinically significant

1. Citrome L. *Innov Clin Neurosci*. 2014;11(5-6):26-30.

Effect Size Can Help

- The effect size of a treatment represents how large a clinical response is observed[1]
- For continuous outcome measures such as point change on a rating scale, the effect size can be standardized so that it is easier to compare treatment effects in a meta-analysis[1]
- Clinically we are very interested in categorical outcomes, such as whether or not response was achieved, and an effect-size measure that is useful here is the number-needed-to-treat (NNT)[1,2]

1. Citrome L. *Innov Clin Neurosci*. 2014;11(5-6):26-30.
2. Citrome L. *Acta Psychiatr Scand*. 2010;121(2):94-102.

Number-Needed-to-Treat[1,2]

- NNT answers the question "How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional positive outcome of interest?"
- Complementing NNT is NNH
  - NNH answers the question "How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to avoid?"

NNH, number-needed-to-harm; NNT, number-needed-to-treat.

1. Citrome L. *Innov Clin Neurosci*. 2014;11(5-6):26-30.
2. Citrome L. *Acta Psychiatr Scand*. 2008 ;117(6):412-9.

Calculating NNT Is Easy[1]

What is the NNT for an outcome for Drug A vs Drug B?

f_A = frequency of outcome for Drug A

f_B = frequency of outcome for Drug B

$$NNT = 1/[\, f_A - f_B \,]$$

By convention, and to avoid exaggerating differences, we round up the NNT to the next *highest* whole number

For example, Drug A results in response 50% of the time, but Drug B results in response 20% of the time.

NNT = 1/[0.50-0.20] = 1/0.30 = 3.33 → Round up to 4

NNT, number-needed-to-treat.

1. Citrome L, Ketter TA. *Int J Clin Pract*. 2013;67(5):407-11.

What Is a Clinically Important NNT?[1,2]

- A small NNT of 2 would be an extremely important difference
- Single-digit NNTs are important enough to notice in day-to-day clinical practice
- A large NNT of 100 or more means that there is little difference between choosing Drug A or Drug B for the outcome measured
- Some NNTs may be clinically important, even if they are relatively large, for example, when the outcome is death
- Some NNTs may be clinically irrelevant, even if they are relatively small, for example, when the outcome is a mild dry mouth

NNT, number-needed-to-treat.

1. Citrome L. *Acta Psychiatr Scand*. 2008 ;117(6):412-9.
2. Citrome L, Ketter TA. *Int J Clin Pract*. 2013;67(5):407-11.

Choosing Between Drug A and Drug B for Acute Schizophrenia[1]

Number-needed-to-treat (NNT) and number-needed-to-harm (NNH) for Drug A vs. placebo and Drug B vs. placebo in 6-week randomized controlled trials

Outcome	Drug A			Drug B		
	Rate on drug, %	Rate on placebo, %	NNT (NNH)	Rate on drug, %	Rate on placebo, %	NNT (NNH)
Response	35%	10%	4	30%	15%	7
Akathisia	15%	4%	9	10%	6%	25
Sedation	10%	8%	50	25%	10%	7
Weight gain	5%	3%	50	15%	2%	8

1. Citrome L. *Innov Clin Neurosci*. 2014;11(5-6):26-30.

Caveats[1]

- NNT and NNH differ from relative measures of effect size
  - Relative measures can be misleading. For example, if the rate of an adverse event with a certain medication is 1% and that for another agent is 0.5%, it may be stated that the risk of the former agent is twice that of the latter but the NNH is 200
- It is important to always report the NNT with the rates that were used to calculate it
  - A NNT of 10 when it is calculated from rates of 20% vs. 10% is a very different scenario then when it is calculated from rates of 80% vs. 70%
- The effect of time on benefits such as treatment response can be profound
  - The longer the clinical trial, the greater the opportunity for treatment response
  - The longer the clinical trial, the greater the opportunity for harms such as adverse events to occur or resolve

NNH, number-needed-to-harm; NNT, number-needed-to-treat.

1. Citrome L. *Innov Clin Neurosci*. 2014;11(5-6):26-30.

Conclusions[1]

- Interpreting clinical trial results requires consideration of effect size in order to quantify the clinical relevance of the results
- *P*-values are not informative regarding the size of treatment effects
- NNT and NNH can provide additional information that clinicians may find useful in clinical decision-making, and although limited to dichotomous outcomes, NNT and NNH are clinically intuitive

NNH, number-needed-to-harm; NNT, number-needed-to-treat.

1. Citrome L. *Innov Clin Neurosci*. 2014;11(5-6):26-30.

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Thank you

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