ISCTM 2021

Studies integrating neurocognitive, social cognitive, or functional skills training with medication

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Disclosures

- I am an employee of Boehringer Ingelheim
- My spouse is an employee of Boehringer Ingelheim

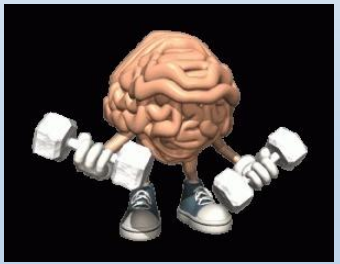
Agenda

- Background
- Methodology considerations
- Operational / Regulatory considerations

Why bother?

- To date, no compound has been successfully developed / registered that is effective in addressing critical impairments that people living with schizophrenia struggle with (cognitive, negative Sxs, social cognition) that are highly correlated with improvements in functioning

- Evidence exists for *benefit* of non-pharmacologic interventions
  - CBT for psychosis
  - Computerized Cognitive Remediation / Training
  - Social Skills Training
  - Virtual Reality Job Interview Training (VR-JIT)
  - Vocational Rehab



Research Questions to Consider

- What question do I really want to answer?
  - Does my digital training / therapeutic (DTx) work in the presence of the often-irrational polypharmacy that is the current state of schizophrenia treatment?
  - Is my DTx efficacious on its own?
  - Do I want to test it in combination with a compound in development?
  - How enduring is the effect?

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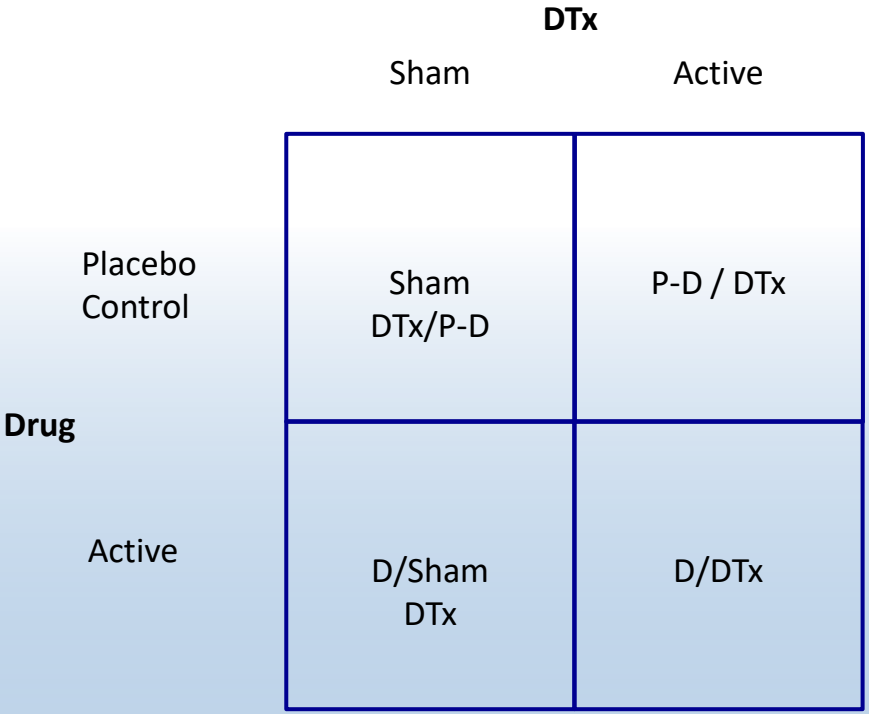
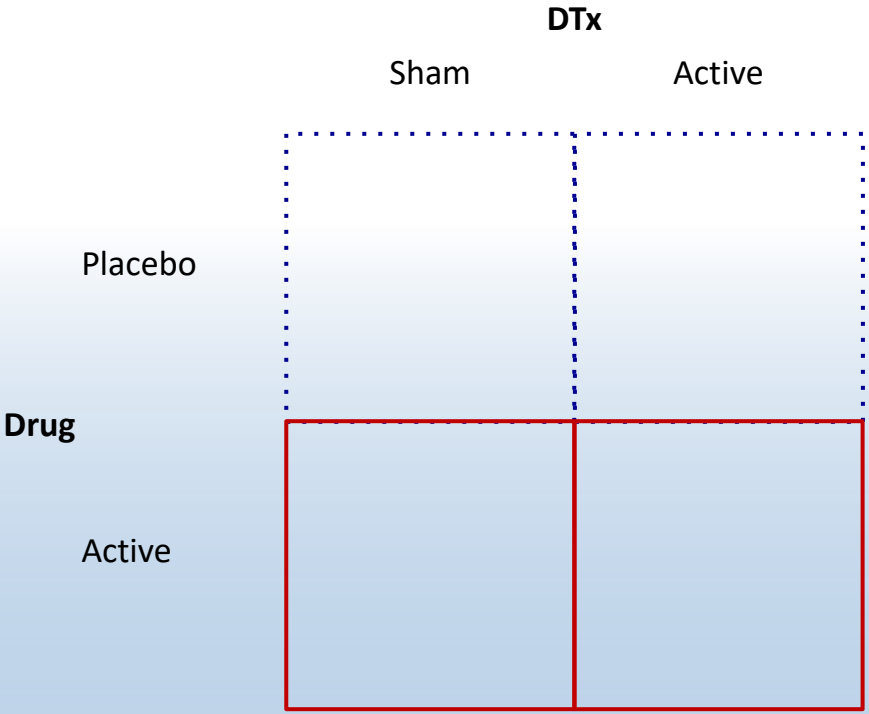


- Full evaluation of interactions between DTx and drug
- Best way to interpret effects

Volkswagen



- Compare drug to drug + Dtx
- Standard outcome measures
- Explicitly ask if DTx enhances drug effect
- Negative result difficult to interpret without full placebo control (e.g. has active worked in this population? Effect size of DTx alone effect compared to active alone effect?)

Operational Issues to Consider (very short list)

- WHAT DTx are you going to deliver? How do you choose? Irrespective of choice, will my label only reflect the specific DTx I've studied? Put differently, to the FDA, is all CCT equivalent?
- WHERE is it going to be delivered? In clinic? Remotely? If latter, how? If former, what are the concerns re inflating placebo, "coaching", etc?
- HOW do you choose the dose of the DTx? How do you limit it? Do you monitor in real time and adjust?
- What is your sham (hint – not quite as simple as a placebo pill)
- What are your best endpoints? "Standard" scales? Digital EMA?

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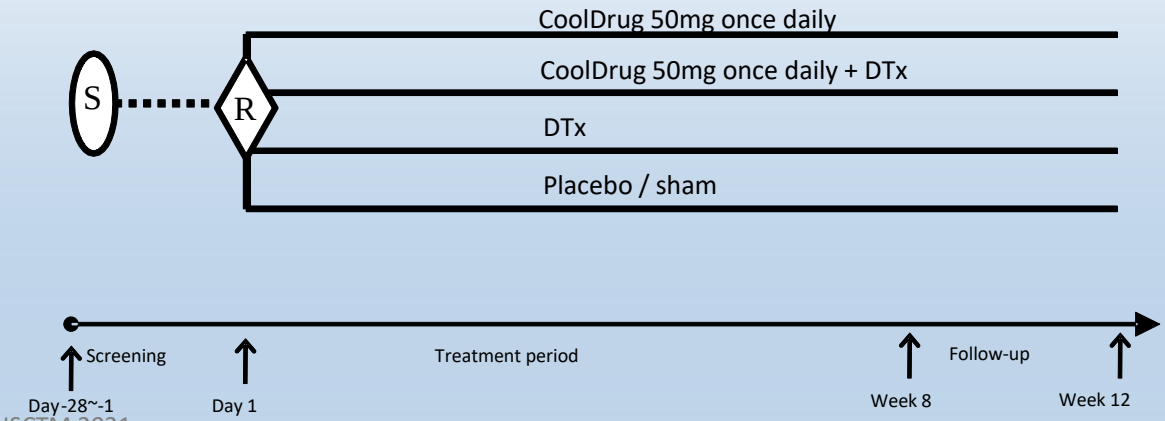
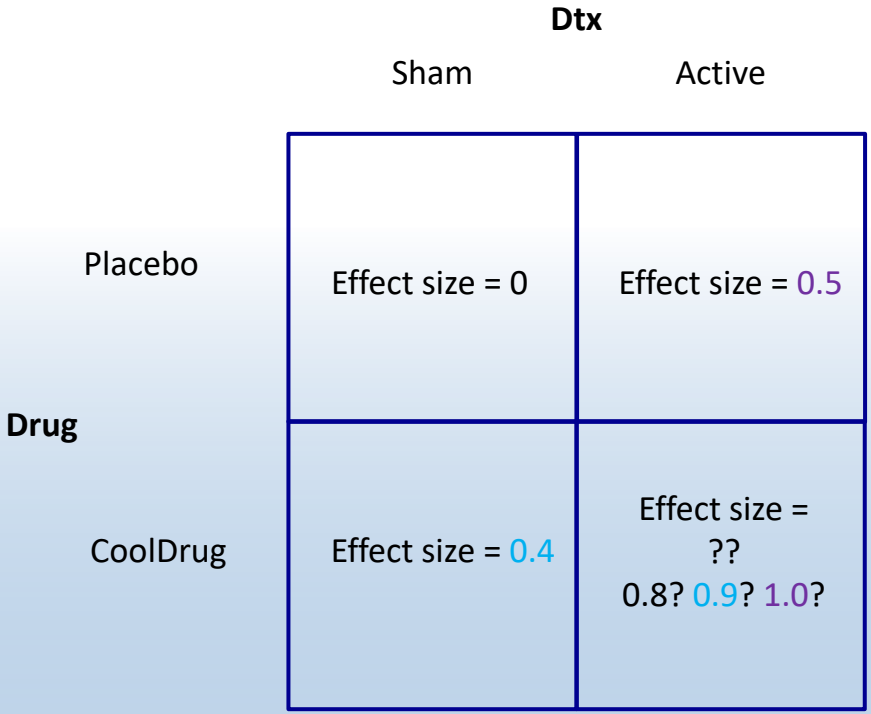
Objective:

To investigate the efficacy, safety and tolerability of CoolDrug 50mg alone vs. CoolDrug 50mg in combination with DTx, vs DTx alone, compared to placebo / sham given for 8 weeks in patients with schizophrenia on stable antipsychotic treatment.

N= ? patients to be randomised at a ratio of 1:1:1:1



Recommendation : Power calculations for 80% power



Effect size	N per group
0.2	394
0.25	253
0.3	176
0.35	130
0.4	100
0.45	79
0.5	64

What about a “standalone” DTx (Negative Sxs)

- What’s the right population? All-comers? Significant residual neg sxs?
- All the same operational questions apply (dose, duration, delivery, etc….)
- How do you target an “MOA”? Or conversely, what can you build that you think might have a salutary effect on certain neg sxs? Is a DTx targeting anhedonia likely to improve social isolation? Avolition?
- If your DTx contains components of CBT, how do you establish a “therapeutic alliance” with a DTx?
- Can you really achieve Voc training / rehab effects without other support, e.g., supportive employment?
- How do you monitor AEs? How do assess if you have a signal?

Summary Thoughts

- DTx are not going away; they are accelerating at an exponential rate
- Like all good research, identify the hypotheses you wish to test.
- “Measure twice, cut once”
- We are in the infancy of this kind of research; be prepared to fail
- When it comes to partners / vendors…….choose wisely.
- Collaborate widely and frequently – anyone who tells you they have the answers, doesn’t.

Selected References

- Rector, N. A., & Beck, A. T. (2001). Cognitive behavioral therapy for schizophrenia: an empirical review. *The Journal of nervous and mental disease*, *189*(5), 278-287.

- Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. *American Journal of Psychiatry*, *171*(5), 523-538.

- Harvey, P. D., & Sand, M. (2017). Pharmacological augmentation of psychosocial and remediation training efforts in schizophrenia. *Frontiers in Psychiatry*, *8*, 177.

- Smith, M. J., Fleming, M. F., Wright, M. A., Roberts, A. G., Humm, L. B., Olsen, D., & Bell, M. D. (2015). Virtual reality job interview training and 6-month employment outcomes for individuals with schizophrenia seeking employment. *Schizophrenia research*, *166*(1-3), 86-91.

- McGurk, S. R., Twamley, E. W., Sitzer, D. I., McHugo, G. J., & Mueser, K. T. (2007). A meta-analysis of cognitive remediation in schizophrenia. *American Journal of Psychiatry*, *164*(12), 1791-1802.

- Software as a Medical Device (SAMD): Clinical Evaluation - Guidance for Industry and Food and Drug Administration Staff (fda.gov)

Thank you!

Questions?