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The Perils of Attention Controls in Behavioral Intervention Research

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Purpose-Guided Trial Design

- ***The design of a behavioral trial should be guided by its purpose.***
- The fundamental principle of Purpose-Guided Trial Design (PGTD).
- Seems obvious, like it should go without saying.
- Yet many of our trials are *not* designed this way.

The Opposite of PGTD

- PGTD is antithetical to *misguided* trial design, i.e., design errors that can easily occur when we:
  - rely on unquestioned methodological traditions, beliefs, or norms,
  - pretend that difficult dilemmas, tradeoffs, and compromises in the trial design process either do not exist or that they can simply be ignored,
  - choose a comparator simply because it's popular,
  - craft a comparator that doesn't serve its intended purpose,
  - select a trial design without considering whether it's fully compatible with the research question, or
  - allow the trial design to passively define the purpose of the study, instead of thinking through the purpose and designing it accordingly.

Misguided Trial Design

- Inappropriate use and/or design of so-called attention control (AC) groups is one of the most common and problematic examples of MTD.
- There are others, but this talk will focus on AC controls because this is an especially important issue in behavioral trial methodology.

Attention Controls

- Countless behavioral trial proposals have been shot down for “failing to control for attention.”
- Many published trials have been condemned for this unforgivable sin as well.
- “Attention Control” is an ambiguous shorthand label for a variety of conditions that supposedly control for attention and/or placebo and/or other nonspecific effects.

Drug Trials

- To understand why attention controls (ACs) have been so controversial, it helps to start by examining how drug trials are designed.
- Randomized, double-blind, placebo-controlled trials are gold standard efficacy tests for drugs.
- They’re also one of the main inspirations for the use of attention control groups in RCTs of behavioral interventions.

Drug Trials

- Obviously, drugs are *chemicals*.
  - The primary purpose of a standard drug trial is to determine the effects of a particular chemical.
- Why not simply compare drug vs. no drug?
  - Because double-blinding would impossible.
  - Because the chemical's effect would be seriously confounded by two other factors.

Drug Trials

- The “placebo” in a drug trial is an object that is superficially identical to the drug but that lacks its chemical ingredient.

- Familiar characteristics of this physical object imbue it with *generic* placebo value.

These look like pills, so we expect them to be medicinal.

These sort of look like pills, but we know they’re chocolates, so don’t expect them to be medicinal.

Drug Trials

- Without any *extrinsic information*, these pill-like objects would have little or no *specific* placebo value.
  - Is it a pain pill? A blood pressure drug? A cure for AIDS?
  - Study participants are given information via recruitment materials, informed consent forms, etc. that shape the object's specific placebo value.
  - They wouldn't know what kind of effects to expect from an unlabeled pill without this information.
  - This information does not emanate from the pills; it comes from elsewhere.

Drug Trials

- These extrinsic sources of information also shape the pill's *nocebo* effects.
  - They tell the patients about certain side effects that the pills might produce.
  - Heartburn? Rash? Erection lasting over 4 hours?

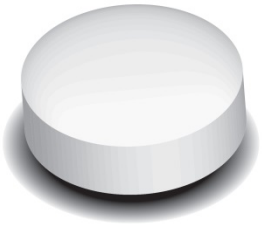
Drug Trials

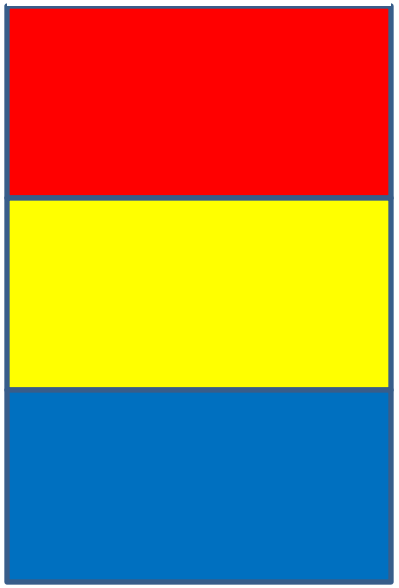
- Thanks to double-blinding and superficially identical pill-like objects, it's possible to completely extract the active ingredient from a pill and leave only its placebo value behind.
- Also thanks to double-blinding, all patients in a drug trial (regardless of random assignment to drug or placebo) can be given standardized *clinical attention* that does not differ qualitatively or quantitatively between the groups.

Drug Trials

- Clinical attention in a drug trial takes the form of clinical management and focuses on compliance, signs, & symptoms.
- It enhances the *generic* placebo effect.
- Its contributions to the *specific* placebo & nocebo effects of the pills are relatively minor, compared to the roles that other sources of extrinsic information usually play.
- It's a potential confounder primarily because clinical management can be therapeutic in its own right.
- In short, attention and placebo are fairly *distinct* ingredients in a drug trial, and both are completely distinct from the active chemical ingredient.

Drug Trials

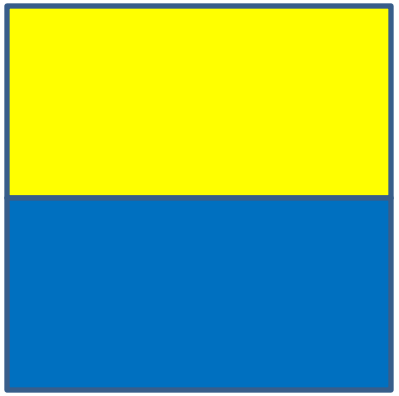




Active Ingredient
(Chemical)

Placebo

Clinical Attention



Drug Arm

Placebo Arm

These aren't really "drug *vs.* placebo" trials; *both* groups receive placebo & attention!

Drug Trials

- Thus, drug trials isolate the effects of the chemical in an intervention that has 3 distinct components (chemical + placebo + attention).
- This is necessary because, for medical, ethical, and financial reasons, patients shouldn't be given chemicals that provide no real benefit.
- Thus, double-blind, placebo-controlled drug trials are *intervention-oriented* studies.
  - Their primary purpose is to *dismantle* the treatment.

Drug Trials

- Since placebo-controlled trials are the gold standard, how can drug researchers ever move beyond basic proof of chemical efficacy to evidence that clinical outcomes can be *improved*?
  - **Indirect method:** Show a *larger* benefit, relative to placebo, than other drugs have shown.
    - Primary purpose = intervention-oriented
    - Secondary purpose = outcomes-oriented
  - **Direct method:** Show superiority to other drugs in head-to-head comparisons.

Attention Controls in Behavioral Trials

- We try to bolster the rigor of behavioral trials by emulating drug trials.
- Unfortunately, a lot gets lost in translation between drug & behavioral RCTs.
- Starting with the fact that with few exceptions, behavioral trials cannot be double-blinded; they can only be single-blinded.
  - The patients know which group they're in.
  - They're informed about ways that their group differs from the other group(s).
  - Consequently, the operative extrinsic information that shapes the placebo values of the treatment & AC conditions differs between the groups.
  - **Thus, we aren't comparing the active ingredients + placebo in one arm to the *same* placebo in the other arm; we're comparing it to a *different* placebo.**
  - This is very different than how drug trials work.

Attention Controls in Behavioral Trials

- There's no such thing as bare, naked clinical attention in a clinical trial.
- You can't just sit and stare at the patient.

Attention Controls in Behavioral Trials

- The attention has to be delivered in the guise of some sort of “therapeutic” activity.

Attention Controls in Behavioral Trials

- In drug trials, the clinical attention is delivered in the form of a necessary and purposeful activity, i.e., clinical management.
  - Monitor signs and symptoms
  - Track compliance and address noncompliance
  - Address other clinically relevant issues
- This activity doesn't differ between groups.

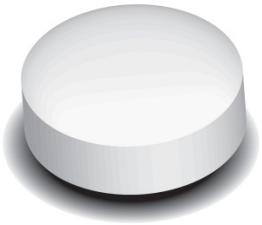
Attention Controls in Behavioral Trials

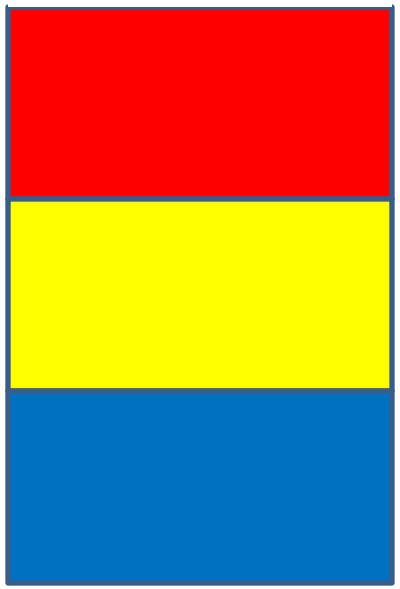
- In many “attention-controlled” behavioral trials, the activity in the AC arm is an artificial quasi-intervention intended to serve both as a placebo and as a delivery vehicle for attention.
- The attention it provides inevitably differs from the attention that the experimental intervention provides.
- Unlike in drug trials, attention isn’t extrinsic to the experimental intervention in most behavioral trials; it’s an *intrinsic ingredient* of the intervention; the intervention wouldn’t be the same without it.
  - Although attention may help to explain the effects of a behavioral intervention, it’s not a *rival* explanation.
  - In other words, clinical attention isn’t a potential confounder in most behavioral trials in the same sense that it is in a drug trial.

Attention Controls in Behavioral Trials

- The placebo elements of the AC arm usually differ from those of the behavioral intervention arm, for 2 reasons:
  - Differential extrinsic information differentially influences the placebo elements of the groups.
  - Unlike in drug trials, it's usually impossible to omit the active ingredients from a complex behavioral intervention, and leave only the placebo elements behind.
- When we try to do this anyway, what usually gets left behind is a *different* placebo than the one to which the patients in the active arm will be exposed.

Drug Trials

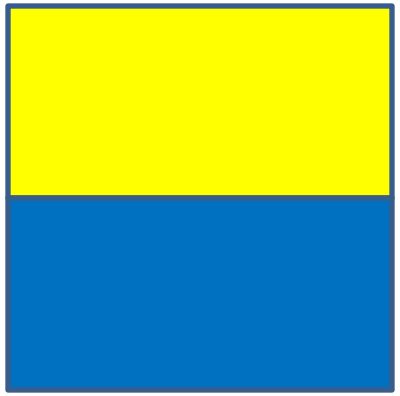




Active Ingredient
(Chemical)

Placebo

Clinical Attention

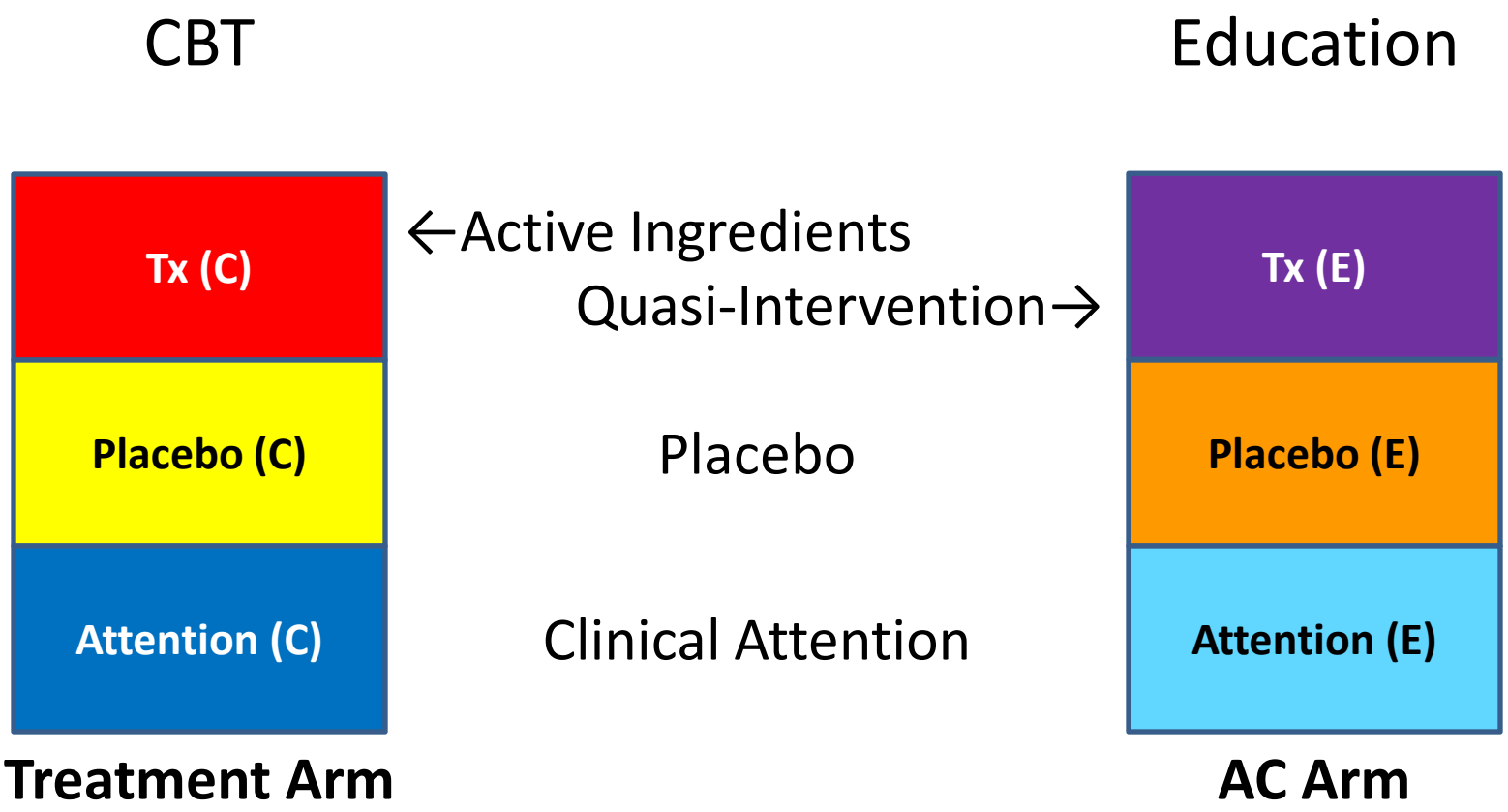


Drug Arm

Placebo Arm

This design effectively isolates the effect of the active ingredient.

Attention-Controlled Behavioral Trials



This design *doesn't* isolate (deconfound) the treatment's active ingredients!

Attention Controls in Behavioral Trials

- Because attention is not a legitimate rival explanation, it's a mistake to assume that *control* is the primary purpose of an AC comparator.
  - The primary purpose, per force, is *comparison*, i.e., of two different ways of inducing change in the outcome variable.
  - But it tends to be a very problematic comparison.
    - Apples to oranges
    - Low clinical relevance
      - Most AC interventions aren't bona fide, evidence-based treatments.
      - **Comparison to AC often supplants comparisons to more clinically relevant existing practices or evidence-based interventions.**

Attention Controls in Behavioral Trials

- Concerns about confounding aren't the only reason why we often face demands to "control for attention." Two other reasons:
  - Skepticism that the ostensibly active, special, or unique ingredients of behavioral interventions are truly active, special, or unique.
    - This is known as the Dodo Bird Conjecture.

  - Concern about the burden, complexity, or expense of an intervention.

Attention Controls in Behavioral Trials

- Different concerns tend to lead researchers to fashion different kinds of AC interventions.
  - Confounding: quasi-intervention
  - Dodo Bird conjecture: generic supportive therapy
  - Expense, complexity, burden: cheaper, simpler, easier intervention

Attention Controls in Behavioral Trials

- Concerns about confounding:
  - AC quasi-interventions (e.g., “education”) are often designed to have weak effects on the outcome of interest yet they’re presented to patients as if they’re genuine alternatives to the intervention being tested.
  - They’re usually clinically irrelevant, i.e., they don’t have a legitimate role in clinical practice.
  - They’re even irrelevant in some cases to the study’s primary outcome (e.g., health ed. in a depression trial)
  - It’s hard to claim that we’re truly in equipoise when we make such questionable comparisons.

Attention Controls in Behavioral Trials

- Concerns about confounding:
  - Also, AC trials that are designed around concerns about confounding must be interpreted with caution.
  - If adequately powered and *positive*, "the intervention is superior to AC" is a justifiable conclusion.
  - But if the trial is *negative*, "the intervention is no better than AC" is not a justifiable conclusion.
  - It's siding with the null hypothesis.
  - It's more accurate to say that the trial did not show that the intervention is superior to the AC condition.

Attention Controls in Behavioral Trials

- Proof of active, special, or unique ingredients:
  - Failure to demonstrate superiority to nonspecific therapy is a good way to cast doubt on questionable claims that are often made about interventions.
  - But *intervention-oriented* trials that do this only prove that a supposedly new & improved intervention doesn't actually yield better outcomes, so patients aren't much better off than they were before.
  - *Outcomes-oriented* trials aim to improve outcomes by *surpassing* current approaches, not by dwelling on the lowest common denominator (nonspecific therapy).

Attention Controls in Behavioral Trials

- Concerns about burden, expense, or complexity:
  - Of course it's legitimate to seek less burdensome, cheaper, or simpler ways to intervene.
  - The question is whether it's possible to do this without sacrificing effectiveness.
  - This is a *utility-oriented* question (in PGTD terms), and a superiority trial comparing a complex treatment to a bogus AC condition is the wrong way to answer it.
  - The right way requires a noninferiority trial with a legitimate alternative intervention, tight margins, and a cost-effectiveness analysis.

Example

Brenes GA, et al. Telephone-Delivered Cognitive Behavioral Therapy and Telephone-Delivered Nondirective Supportive Therapy for Rural Older Adults With Generalized Anxiety Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* 2015;72:1012-20.

- IMPORTANCE: Generalized anxiety disorder (GAD) is common in older adults; however, access to treatment may be limited, particularly in rural areas.
- OBJECTIVE: To examine the effects of telephone-delivered cognitive behavioral therapy (CBT) compared with telephone-delivered nondirective supportive therapy (NST) in rural older adults with GAD.
- *There is a mismatch between the "Importance" and the "Objective" of this trial.*

Brenes et al. (2015)

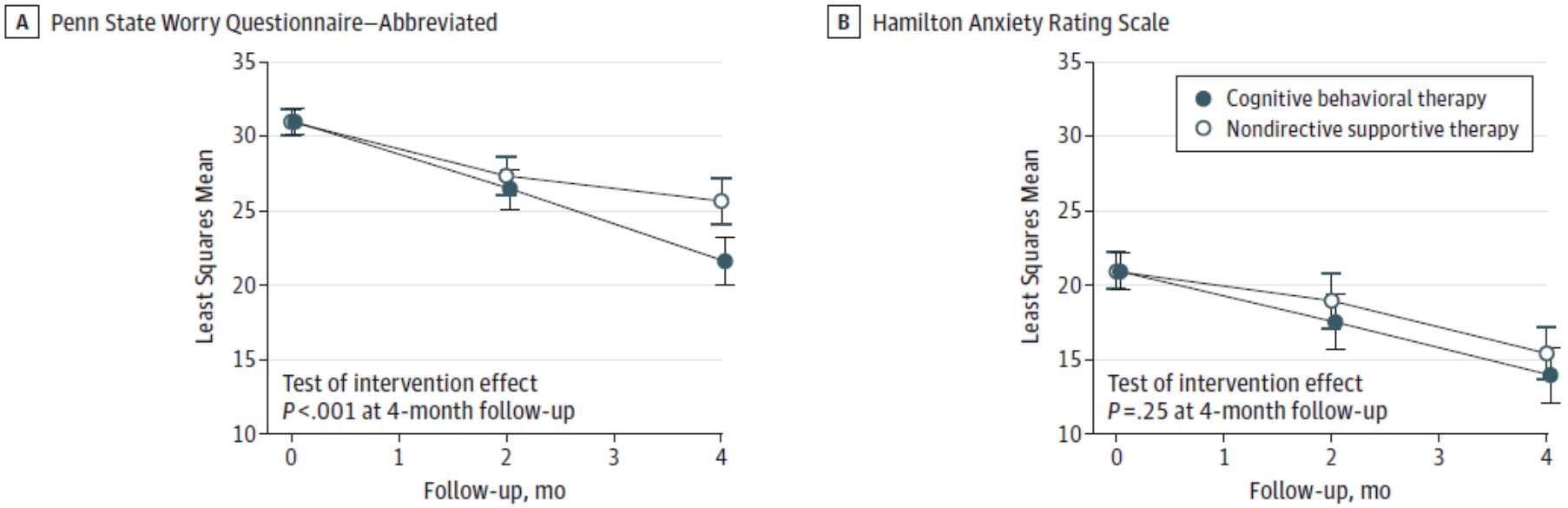
- “There are a number of barriers that older adults face, particularly those who live in rural areas. Mobility and transportation limitations can make travel to a professional’s office difficult.”

- “Thus, alternate methods of providing treatment may increase mental health care utilization by this underserved population.”

Brenes et al. (2015)

- "…we adapted CBT for administration by telephone in an effort to overcome barriers to care while still providing an evidence-based treatment."
- "We compared telephone-delivered CBT (CBT-T) with telephone-delivered nondirective supportive therapy (NST-T), a structurally equivalent comparison group with similar levels of outcome expectations and credibility."
- "Thus, this design allowed for a comparison between the gold standard for anxiety disorders and a commonly available type of psychotherapy in clinical practice."

Brenes et al. (2015)



Brenes et al. (2015)

- The investigators tested whether telephone CBT is superior to telephone NST in rural older adults.
- *But this wasn't the question they intended to ask.*
- They could have compared telephone CBT to:
  - Usual care as delivered by the patients' own health care system
    - Many patients would have received minimal or no treatment for GAD.
    - But the question is whether telephone CBT can help patients with limited access to clinic-based care, and a usual care comparator would have addressed this question.
  - Clinic-based CBT delivered by study therapists
    - Adherence would have been poor and attrition would have been high.
    - This would be a difficult trial and the statistical analysis would be challenging.
    - If there's a clinical or health care system commitment to provide CBT to patients like the participants, this design would have addressed the modality question.

Brenes et al. (2015)

- The NST comparator gives this trial an *appearance* of scientific rigor by "controlling" for attention and nonspecific or placebo elements.
  - Not exactly the *same* attention, nonspecific, and placebo ingredients that are integral to CBT, but close enough to please (fool?) reviewers and other judges of study quality.
- *Truly* rigorous behavioral trials are optimally designed to answer the question at hand.
  - The investigators had an important question.
  - But despite its many strengths, this trial was not designed to answer their question.
  - That's one of the kinds of prices we pay for well-intended but misguided behavioral trial design.

Attention Controls in Behavioral Trials

- *Implementation* of ACs is often problematic too.
- In behavioral trials, the clinical attention usually differs both qualitatively and quantitatively between groups.
  - Despite best intentions, treatment and AC groups tend to receive different doses of attention.
  - AC groups are often less engaging, less convincing, and more repetitive than active interventions.
  - This leads to low adherence & differential attrition.
    - See Popp & Schneider, *Trials* (2015) for an interesting example.

Attention Controls in Behavioral Trials

- Even if comparing two bona fide treatments, equalizing attention doesn't necessarily make sense.
- Example: You hypothesize that a relatively lengthy intervention is superior to a briefer form of the same intervention.
  - Full = 10 sessions, Brief = 4 sessions.
  - The dosage of attention differs between the arms.
  - Are the effects "confounded" by differential attention?
  - Would it make any sense to try to equalize the dosage of attention between the arms in this trial?
- Equal attention isn't always necessary or appropriate in behavioral trials; insisting on it anyway is an example of MTD.

Attention and Placebo Effects

- The roles of attention and placebo in some interventions do deserve careful scrutiny, e.g.,
  - Does mindful aerobic exercise produce better fitness outcomes than mindless aerobic exercise?
  - Do eye movements augment desensitization in EMDR?
  - Is acupuncture nothing more than a placebo?

"Extraordinary claims require extraordinary evidence."

– Carl Sagan

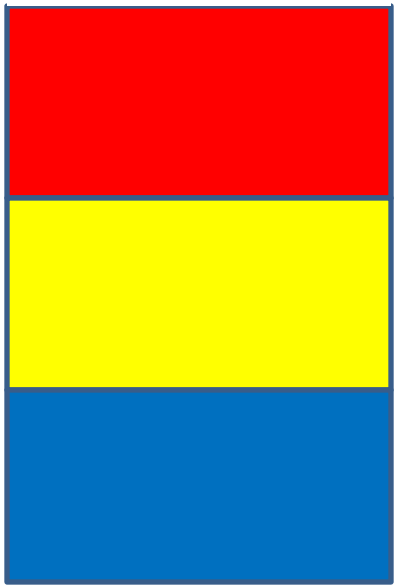
Attention and Placebo Effects

- These interventions have something in common.
  - The supposedly “active” ingredient can be extracted from the intervention *without* distorting it OR the other ingredients (although this must be done carefully).
  - This means that the questionable ingredient is *dissociable* from the rest of the intervention, and that it isn’t *intrinsic* to the intervention.
  - Thus, it’s possible to test it in a way that resembles the test of chemical efficacy in a drug trial.

Attention and Placebo Effects

- But generic AC conditions aren't the right comparators for questions like these.
- What are needed instead are *residual* comparators, i.e., whatever's left over after the putative active ingredient has been removed from the intervention, or *sham* comparators, *i.e.,* inert substitutes.
  - Exercise with vs. without "mindfulness"
  - EMDR with vs. without eye movements
  - Acupuncture with traditional vs. sham needle placements
  - Etc.

Drug Trial



Active Ingredient
(Chemical)

Placebo

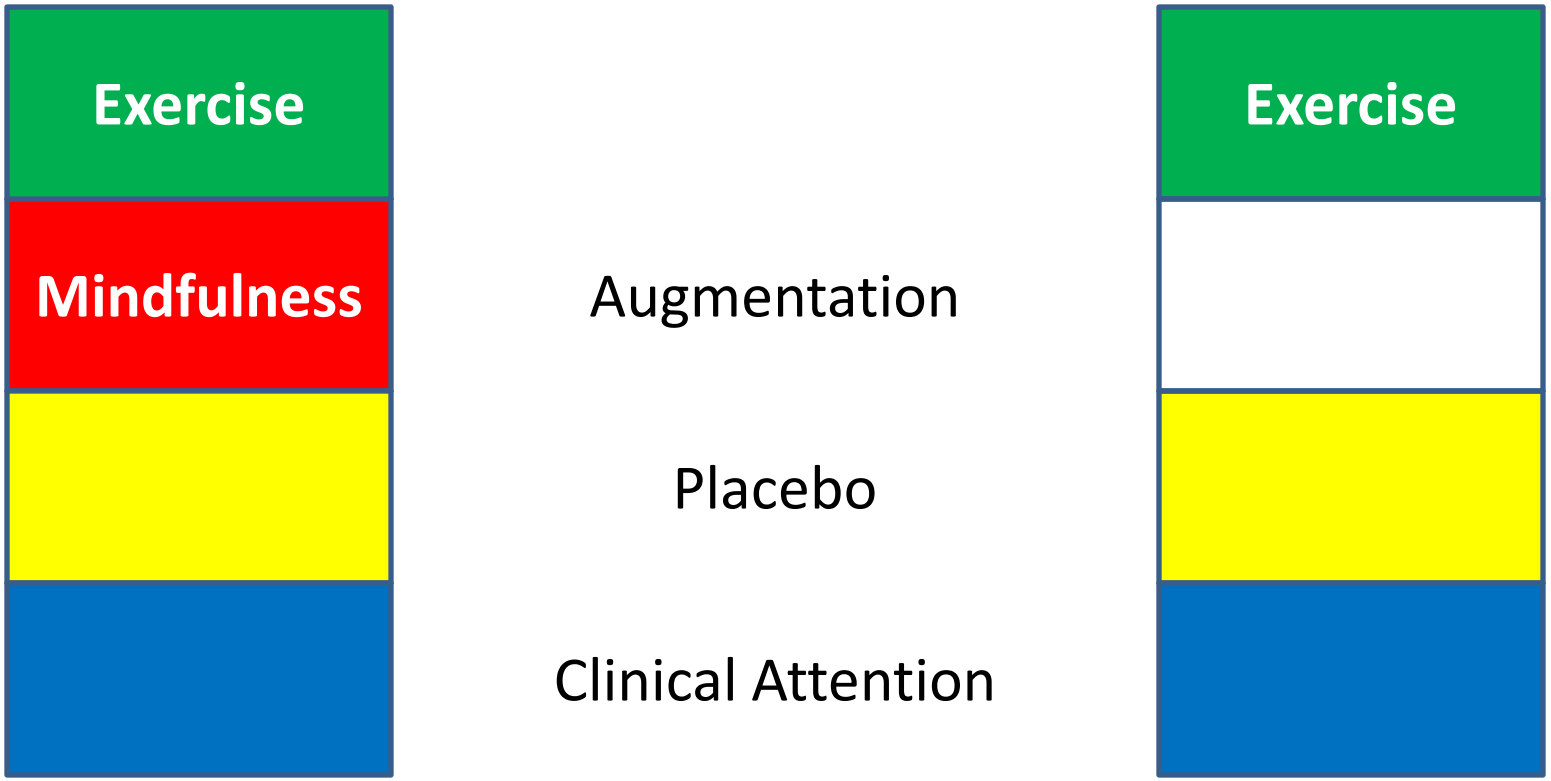
Clinical Attention

Drug Arm

Placebo Arm

This design effectively isolates the effect of the active ingredient.

Mindful Exercise Trial



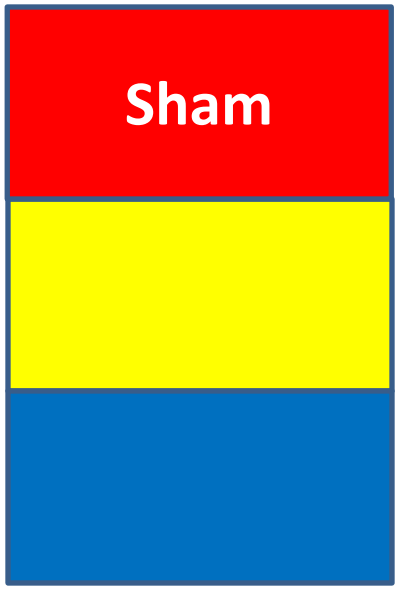
This design effectively isolates the effect of mindfulness.

Acupuncture Trial

Needle Placement

Placebo

Clinical Attention



Tx Group

Control Group

This design effectively isolates the effect of traditional needle placement

Attention and Placebo Effects

- Thus, we have two kinds of interventions:
  - Ones in which the putative active ingredient can be dissociated from the other ingredients, and
  - Ones in which this cannot be done (at least not very well).
- If it's both important and feasible to determine whether an intervention is more than a placebo, that's okay.

Attention and Placebo Effects

- But that's an *intervention-oriented* question.
- What are we left with after we answer it?
  - Interventions that are not superior to placebo, or
  - Ones that are marginally superior to placebo.
- If an intervention is superior to UC, it may still be clinically useful, even if its benefit is due primarily to attention and placebo effects.

Attention and Placebo Effects

- At best, though, this leaves some patients with a treatment that is only modestly beneficial and non-responders with one that's no help at all.
- Whether or not superiority to placebo is established, our goal should be to find ways to do *better,* not to be satisfied with marginally beneficial therapies.
- We need sophisticated treatment development research and *outcomes-oriented* trials more than we need intervention-oriented trials that endlessly dwell on the roles of attention & placebo.

Where Does All of This Leave Us?

- Double-blind, placebo-controlled trials deserve their gold-standard status in drug research.
- Single-blind, attention-controlled trials don't deserve the unquestioned faith that many behavioral researchers have placed in them.
- Most are consistent with MTD, not with PGTD.
- What should we do instead???

Toward Better Behavioral Trials

- Improve the quality of intervention-oriented studies by finding alternatives to flawed AC designs.
  - E.g., use the ORBIT model (Czajkowski et al., 2015) and MOST designs (Collins & Murphy) to develop and refine complex interventions rather than conducting dismantling studies to discredit them.
- Conduct only as much intervention-oriented research as necessary.
  - Conduct intervention-oriented research not as an end in itself, but to pave the way for outcomes-oriented trials.

Toward Better Behavioral Trials

- Define the primary purpose of the trial and choose the comparators that best serves it.
  - Even if at the expense of less important objectives.
  - Especially at the expense of misguided objectives.
- Engage in long-term, programmatic, treatment development and outcomes-oriented research, to discover over time how to *improve* outcomes.
- In other words, make *genuine progress* the goal.

Toward Better Behavioral Trials

- Recognize that “simpler” or “cheaper” or “more practical to implement” may come at the expense of efficacy in some cases.
  - When these goals conflict with one another, confront the question of which one should take priority, and which one should be deferred.
  - It takes programmatic research to establish behavioral interventions that are not only inexpensive and practical, but efficacious as well.
  - ACs don’t play a very useful role in these endeavors.

Conclusions

- “Always control for attention” was the wrong lesson for us to draw from drug trials.
- AC conditions do not serve behavioral trials the same way that pill placebos serve drug trials.
- Giving them undue primacy undermines our ability to answer more important questions and leaves us forever chasing Dodo birds.

Conclusions

- Misguided trial design gets us nowhere.
- Purpose-guided trial design facilitates *progress-oriented* behavioral intervention research.
- Real progress is what patients need from us, even if it's incremental rather than dramatic.
- Real progress means better outcomes.