Brain Injury Research: Keeping Up, Evaluating the Evidence

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The Problem

• Brain injury treatment information is accelerating at a dizzying pace
• PubMed search for “brain injury treatment” yielded more than 10,000 articles in last 5 years
• How can we keep up with this information?
• More importantly, how do we know what’s worth our time and effort to keep up with?
Overview of Workshop

• To be a good “consumer” of research, you need to know:

• Tessa:
  • What is research?
  • What are the different types of treatment research, and the strengths/weaknesses of each?
  • What should be “built in” to a study design in order for you to trust the results?

• Monica:
  • How to find brain injury research
  • How to evaluate the results that you find
What Is (Treatment) Research?

• How is it different from clinical practice? From program evaluation?

• Research involves a lot of the same activities, but the INTENTION is
  • To discover general principles/ knowledge that applies beyond your patients and your program
  • To disseminate this knowledge to other people through articles, presentations, etc.
A Key Distinction

• Research is strictly regulated through federal oversight (Institutional Review Boards; sometimes the FDA), where clinical practice / program evaluation are not.

• EVERY piece of research that is offered for your “consumption” must have been overseen by one or more IRBs.

• If it has not, it shouldn’t be presented as research.
What Is a Clinical Trial?

“An experiment testing (medical) treatments on human subjects.”

• Often used to refer to drug studies
• But can equally apply to behavioral trials, e.g.:
  • Studies on the efficacy of cognitive rehab
  • Comparisons of different methods of gait training
  • Speech and language therapies
  • Psycho-educational treatments

• Etc.
Example: Anger Self-Management Training for Traumatic Brain Injury

• 2-center clinical trial led by Moss
• Compares a treatment called ASMT with a different kind of treatment (more about this later)
• Will serve as an example running through the presentation (later)
2 Main Types of Treatment Research

• **Observational** research
  • OBSERVE what happens naturally when people receive treatments or doses X, Y, Z
  • No attempt to change treatment
  • Systematic observations of how patients change (or do not) in response to certain treatments or variations in treatment that are used in the “real world”

• **Experimental** research
  • The experimenter develops a new treatment and assigns people to receive it, OR manipulates existing treatment so that some get it and some do not
  • Vast majority of BI treatment research is in this category
Each Has Its Pros & Cons

• Advantages of Observational Research:
  • Examines what is actually done in the real world of clinical care
  • Avoids ethical problems in, e.g., withholding treatment

• Disadvantages:
  • Often difficult to define and measure “real” treatment
  • Takes VERY large numbers of patients (usually in the thousands) to draw causal inferences about treatment → outcome
  • Even in large samples, there may be hidden confounds:
Major Drawback to Observational Research

- Very difficult to draw cause-and-effect conclusions with regard to effects of *treatment alone*
- Often, the same factors that affect outcome also affect what treatments are given...
Example: The “Denmark Study”

• We collaborated with a TBI rehabilitation hospital in Copenhagen that had similar
  • Team composition
  • Types of treatments
  • Patients with TBI
  • Cultural factors & expectations about recovery

• Major difference:
  • Moss: ~4 weeks in rehab hospital for most severe patients
  • DK: ~18 weeks for comparable patients!
Denmark Study Hypotheses

Inpatient rehabilitation

Glostrup Hospital

MossRehab Hospital

Person variables

Inpatient rehabilitation

Discharge

Outcomes

6 months

12 months
Unfortunately....

• There were no differences in outcome between the 2 sites
• This wasn’t because the extra time in the hospital didn’t make any difference...
• It seemed that the patients weren’t that comparable after all
• DK had more patients who “needed” extended rehab care compared to Moss
• Although we carefully measured every treatment, we couldn’t “prove” that additional treatment improved outcomes
Experimental Treatment Research

• Instead of getting the treatments they would have naturally gotten, patients get treatments assigned to them by the experimenter.

• 2 concepts crucial to “trustworthiness” of the results of an experimental trial:
  • Control of extraneous variables
  • Minimizing bias
Experimental Control

• Everyone has heard of a “control group”....
• What exactly is being controlled?
• Anger study example:
  • Take people with anger problems
  • Give them ASMT treatment (1 session per week x 8 weeks)
  • See if their anger has gotten better
    • Let’s say, it does
• What’s wrong with that??
The Problem Is....

• Extraneous variables (= factors other than the treatment) could have helped them “get better”
  • Passage of time
  • Expectation that a treatment was going to help them (or, should help them)
  • Regression to the mean (extreme values on anything, such an anger scale, are likely to be less extreme the 2nd time around)
Control Groups

• Control for the extraneous variables that might affect the study results

• Many different types, with different pros & cons—none are perfect

• Medication trials can use placebos— inert pills that look exactly like the active treatment
  • “Double blind” trial—neither patient nor experimenter knows what treatment any patient is getting

• But there’s no true placebo for a behavioral trial
Control Groups for Behavioral Trials Such as the ASMT

- No-treatment control
  - People don’t like to sign up for these!
- Wait list control
  - Not feasible if you have a long treatment/ follow-up period; basically turns into a no- treatment control
- Usual Care (Treatment As Usual) control
  - Not feasible if there is no treatment usually given for the condition under study!
Our Solution: Everyone Gets Treatment

- Structurally equivalent alternative treatment
- Same as the ASMT in:
  - Number of 1:1 sessions, with same type of therapist
  - Opportunities to involve family member/significant other
  - Degree of planning, structure, and detail in sessions
- Different in:
  - Guiding philosophy of treatment
  - Activities and discussions included in the treatment sessions
How Are Patients Assigned to Treatments?

- *Random assignment* of patients to groups (“randomized controlled trial”) is the cornerstone of treatment research that minimizes *bias*.

- Bias = conditions within a treatment trial that (often unintentionally) skew the results in favor of one group or the other.

- Random assignment assures that *nothing* except pure chance affects the allocation of a given patient to a treatment group.
Why is Random Assignment Important?

- Why not just assign “every other patient” to groups 1 and 2?
  - 2 patients come in on the same day....
- Why not people who take the bus in Group 1 and people who drive in Group 2?
- Why not M-W people in Group 1 and Th-Sat people in Group 2?
- *Random assignment* with concealed allocation minimizes all detectable--and undetectable--biases related to group assignment.
  - Over time, differences in extraneous factors even-out and don’t affect the trial results
Concealed Allocation ("Blinding" or "Masking")

• This means no one knows what treatment the participant has been assigned to

• But in a behavioral study, there’s no double-blind... the treater and the patient both know what the patient gets

  • So to avoid bias, the outcomes must be measured by someone who doesn’t know the treatment allocation
What’s the Big Deal About Masked Outcome Assessment?

• In a meta-analysis of 1346 clinical trials (Wood et al., 2008), incomplete masking of outcome evaluation produced bias in both drug and non-drug studies except when outcome was objective:
  • Death
  • Certain lab results

• Standardized tests and questionnaires are NOT objective measures!
Outcome Masking in the ASMT Trial

• The randomization schedule is kept hidden from the person who does tests and questionnaires
  • To minimize “guessing” what group this person or the next person will be assigned to

• Treatment and outcome assessment are “geographically” distinct
  • So that outcome assessor won’t run into patients with their therapists

• Careful control of what’s said during meetings where outcome assessor is present

• “Script” used to remind patients not to reveal their treatment allocation

• Documentation of unblinding, when it does occur
Pros and Cons of Experimental Treatment Research

• Advantages:
  • Can make very strong causal inferences about treatment → outcome (as long as well-controlled and free of bias)
  • Does not need huge samples as in observational research

• Disadvantages:
  • Often done on a “pure” sample without a lot of additional problems— as an initial step in testing the treatment in pure form
  • Therefore, difficult to generalize to “real world” patients who may have other problems
2 Other Types of Research to Mention

• Single-Case Designs/ Multiple Single-Case
  • Can be controlled similarly to experimental studies; multiple treatment/control conditions applied to same person(s) and differences recorded
  • Most effective when treatments are not expected to have permanent effects or widespread effects (i.e., not good for “teaching” treatments)

• Qualitative Research
  • Systematic exploration of themes extracted from transcripts of structured interviews
  • Good for developing, but not testing, hypotheses about treatment effects
  • Not the same as “testimonials”
And one more question to ask yourself...

• Who funded the treatment study?
• “Industry” trial
  • Pharmaceutical company wants to test a drug
  • Manufacturer of device, equipment, etc. being tested
• Vs. “Investigator-initiated” trial
  • Scientist has an idea for a trial, competes to get funding from a federal agency or foundation
  • E.g., ASMT study funded by NIH
• Industry trials are NOT all biased
  • Science may not be quite as “sharp” because less competition for funding

• Investigator trials are NOT all unbiased!
  • Many scientists “favor” an outcome even if they are careful to keep it to themselves

• Still, ask yourself if whoever initiated the trial stands to gain from a certain kind of result...

• Examine “conflict of interest” statements carefully.
How to find and evaluate research on brain injury topics
Types of Information

• Original research publications
• Narrative summaries
  • Literature review, subset of studies on a topic, broad perspective
• Systematic reviews
  • Search strategy and plan, meta-analysis component, synthesis
• Lay summaries
  • Summary of research in language that is understandable by general, non-scientific audience
Resources
Pubmed


• more than 24 million citations for biomedical literature
  • from MEDLINE, life science journals, and online books.

• Example:
  Emotion Perception After Moderate-Severe Traumatic Brain Injury: The Valence Effect and the Role of Working Memory, Processing Speed, and Nonverbal Reasoning.
PsycBITE

http://www.psycbite.com/

- database of treatments for psychological problems and issues occurring as a consequence of acquired brain impairment (ABI).

- studies are rated for their methodological quality, evaluating various aspects of scientific rigor.

- Free access to clinicians, students and researchers

- Example:

  A Randomized Controlled Trial of Prospective Memory Rehabilitation in Adults with Traumatic Brain Injury
Clinical Trials.gov

https://clinicaltrials.gov/

• registry and results database of publicly and privately supported clinical studies
• Basic and advanced searches
• Provides details about studies (status, description, aims, recruitment info, results if completed)

Example:
Anger Self-Management in Traumatic Brain Injury
Institute of Medicine

http://www.iom.edu/

• independent, nonprofit organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public.

• Search by keywords for reports, activities, meetings, directories

• Example:
  Report Release: Sports-Related Concussions in Youth: Improving the Science, Changing the Culture
Model Systems Knowledge Translation Center (MSKTC)

http://www.msktc.org/tbi

Summarizes research from the Model Systems programs

- Research database – studies conducted within TBIMS programs
  http://www.msktc.org/publications?sys=T
  - Citations, abstract, author contact info
  - Example: Effect of severity of posttraumatic confusion and its constituent symptoms on outcome after traumatic brain injury

- Systematic reviews
  http://www.msktc.org/tbi/research/systematic-reviews
  - Citation, lay summary
    Example: Treatment for Depression after Traumatic Brain Injury: A Systematic Review
Brainline

http://www.brainline.org

Research Update Section
  Lay summaries
  Links to original publication (limited access)
  Links to related information (non-research)

Example:
The Effect of Hyperbaric Oxygen on Military-Related Post-Concussive Symptoms