Integrating Multiple Therapeutic Modalities Framework and Design Challenges

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Disclosures of support

- Alkermes
- Lundbeck
- Otsuka
- Teva

Outline of Presentation

- History
  - Exemplar trial designs and rationales
- Modern Definitions
- Conceptual framework for studies
- Trial Designs
  - Challenges

1965
Treatment of Schizophrenia
A comparative study of five treatment methods
PRA May and colleagues

- Five Arms — Rationale for inclusion
  - Psychotherapy alone — Belief in efficacy
  - Antipsychotic(AP) alone — Newly available modality with efficacy data
  - AP and psychotherapy — Integrate competitors
  - ECT — Prior evidence of efficacy
  - Milieu — Control

1974

Relapse Prevention in Schizophrenia
Chlorpromazine, Placebo and Psychosocial Treatment
Hogarty et al

- Four arms
  - Chlorpromazine alone
  - Chlorpromazine and Major Role Therapy
  - Placebo alone
  - Placebo and Major Role Therapy

Rationale

Evidence of efficacy

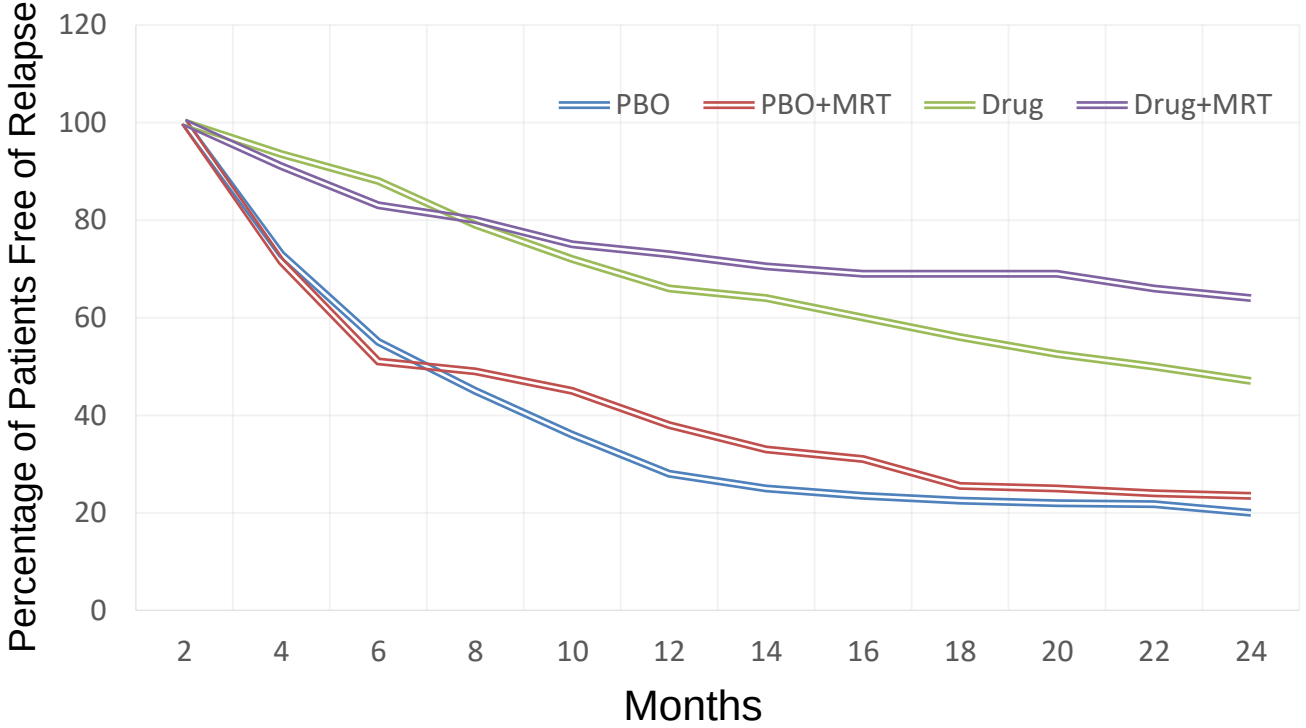
Hypothesis: added benefit

Control for drug

Control for behavioral intervention

- Study design
  - 2 X 2 Factorial
    - Allows assessment of effect of each and/formal interaction

Relapse Prevention in Schizophrenia
Chlorpromazine, Placebo and Psychosocial Treatment



From Hogarty , Goldberg, Schooler et al Arch Gen Psychatry1974

2000
Cognitive Adaptation Training (CAT) to Prevent Schizophrenia Relapse
Velligan et al

- Three arms — Rationale
  - Medication management(MM) — Platform for CAT
  - MM and CAT — Active treatment
  - MM and non-specific activities — Control condition

1989
Psychotherapies for Depression
Elkin et al

	Rationale
• Four arms	
– Cognitive Behavior Therapy	Experimental treatment
– Interpersonal therapy	Experimental treatment
– Clinical Management & medication	Established treatment
– Clinical management and placebo	Control for medication

Four arms but not a factorial design

1992
PET changes in OCD for both behavior therapy & fluoxetine
Baxter et al

- Two treatment arms
  - Fluoxetine and behavior therapy
  - Not randomly assigned
- First study (I think) to demonstrate biomarker changes with psychosocial treatment

Examples of Platforms in regulatory labeling based on clinical trials

- FDA
- Naltrexone for alcohol dependence
  - "**adjunct** to social and psychotherapeutic methods under conditions that enhance compliance"
- Bupropion for smoking cessation
  - "in **conjunction** with individual smoking cessation counseling
- EMA
  - Naltrexone/buproprione for weight management
    - "**adjunct** to a reduced calorie diet and increased physical activity in adults ≥ 18 years
  - Buproprione for nicotine dependent patients
    - **"aid** to smoking cessation in combination with motivational support

Note – clinical trials in schizophrenia used medication as platform
Drugs used psychosocial treatment as platform

Modern Terms
More than one treatment/intervention – the topic of the symposium

- **Definition** **Source**
  - Multimodal therapy — National Academy of Sciences -2017
    - "Two or more modalities that *target different aspects of a disease*"
  - Integrated Therapeutics — ISCTM Working Group
    - Multiple hypothesized relationships between treatments focused on drug or device and learning-based intervention
  - Combination products — FDA (for drugs and devices)
    - "Both are required to achieve the intended use, indication or intended effect"
  - Multiple therapeutic modalities — This presentation
    - agnostic

Modern Terms
Treatments/Interventions

- FDA
  - Drugs
  - Devices
  - No regulatory authority over other interventions or global term

- National Academy of Sciences – 2017
  - Neuromodulation
  - Pharmacotherapy
  - Psychosocial therapy

- ISCTM Working Group
  - Biologic/neurotherapeutic intervention
  - Learning based intervention

Contrasting Assumptions in multimodal studies

- Historical
  - RCTs designed primarily for comparative efficacy
    - Defined by independent or additive effects
  - Secondary aim to identify sub groups with differential benefit
    - moderators
- Contemporary
  - Identify “target of engagement” – biological substrate that the treatment engages
  - Either
    - each treatment targets a different substrate leading to additive effect
    - One treatment facilitates the other such that only combination is effective

Aspirational Designs

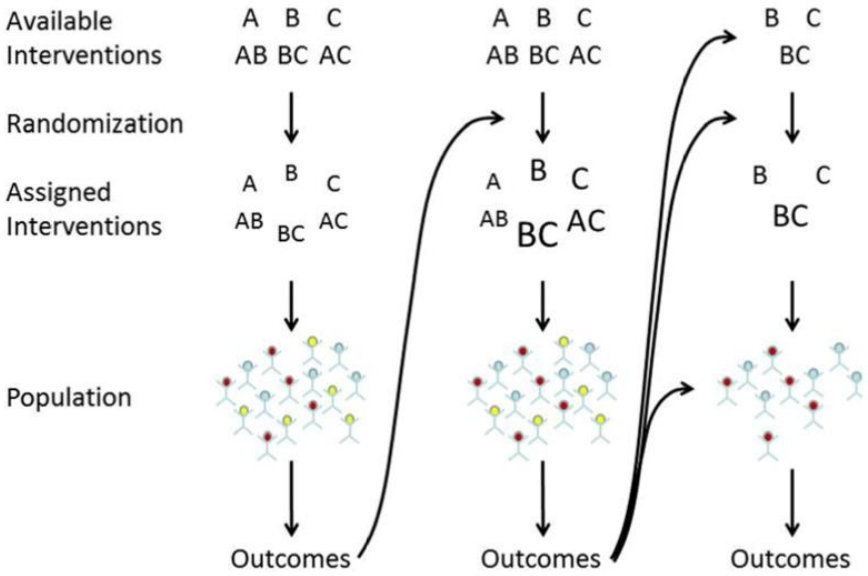


FIGURE 5-1 Evolution of a platform trial over time. In the first stage of a plat-

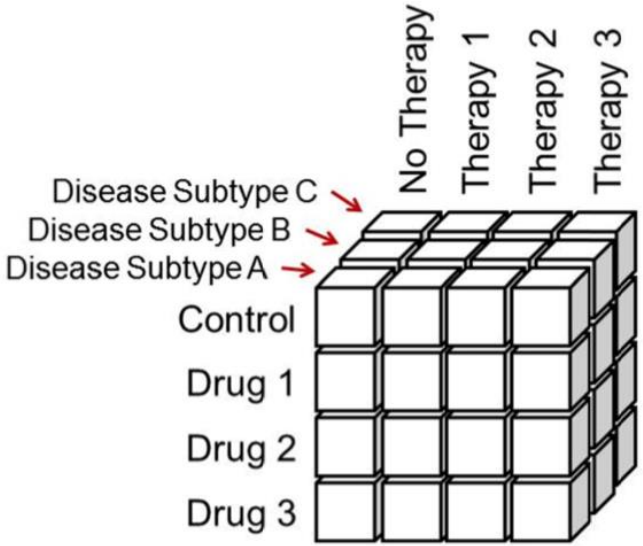


FIGURE 5-2 Building a platform trial for multimodal therapy. In a trial com-

National Academy of Sciences 2017

RCT Designs When Each Modality is Hypothesized to Have Independent Effect

- Classic factorial – 2 X 2, 2 X 3, n X n
  - Allows test of each modality, simple additive or interactive effects
  - Cells can be added to either or both factors
  - Can incorporate multiple outcomes if relevant
    - Defined as Co primary or primary and secondary

  The ideal design.

  Can incorporate mechanism of action or multiple targets of engagement

  Accommodates multiple doses or timing of interventions

RCT Designs When One Modality's Effect Established and the Second is Hypothesized to Have Independent Effect

- Platform of Established modality and comparisons of the second
  - Can address dose or timing for randomized modality
  - Only outcomes that are targeted by the randomized modality can be assessed

Not different from historical studies

Will only address mechanism of action or target of engagement for the experimental modality

RCT Designs When Interventions are Hypothesized to be Synergistic or Interdependent

- Hypothesis: Modality A is ineffective unless Modality B is present
  - Design Modality A is platform and Modality B is experimental
    - Modality B cells can be “doses”
- Hypothesis: Effectiveness of Modality A is Enhanced by Modality B
  - Design Factorial
- Hypothesis: Modality A is effective but unsafe without Modality B
  - Design: AB vs B
  - Must B have some efficacy or can it be considered as a placebo?

Study Challenges

- Adequate power
  - Complex designs can be difficult to conduct large scale/multi-center
- Required expertise in each modality being studied
- Blinding
- Fidelity to treatment delivery
- Use of weak designs to compensate for complexity
  - Cross over
  - Wait list
  - Changing study parameters during study course
  - Completer-only analysis
- Inadequate sample size
- Including timing of an intervention as a design feature

Last Thoughts
Not Conclusions

- It’s complicated
- Pre-specified adaptive design models can address some issues
- Drug development Phases are relevant
  - Phase 2 may be critical to establish study parameters
  - Dose for drugs
  - Relative timing of interventions
- Parameters of psychosocial/non-drug interventions
  - Defining dosage of interventions that cannot be measured in mg
  - Fidelity to intervention
  - Provider credentials