Adaptive Treatment Strategies
&
SMART Studies

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What is an Adaptive Treatment Strategy?

Adaptive Treatment Strategies are individually tailored treatments, with treatment type and dosage changing according to patient outcomes.

Operationalize clinical practice.
Why Adaptive Treatment Strategies?

– High heterogeneity in response to any one treatment
  • What works for one person may not work for another
  • What works now for a person may not work later
– Improvement often marred by relapse
– Lack of adherence or excessive burden is common
– Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient
An Adaptive Treatment Strategy for ADHD

- No prior med.
  - Low Intensity BMOD
    - Non-responsive & non-adherent: Augment with other Therapy
  - Prior med.
    - Low Dose Med.
      - Non-responsive & adherent: Intensify Current Therapy
      - Responsive: Continue Current Therapy
The Big Questions

• What is the best sequencing of treatments?

• What is the best timings of alterations in treatments?

• What information do we use to make these decisions? (how do we individualize the sequence of treatments?)
Why SMART Trials?

What is a sequential multiple assignment randomized trial (SMART)?

These are multi-stage trials; each stage corresponds to a critical decision and a randomization takes place at each critical decision.

Goal is to inform the construction of adaptive treatment strategies.
Sequential Multiple Assignment Randomization

**Initial Txt**

- Tx A
- Nonresponder

**Intermediate Outcome**

- Early Responder
- Nonresponder

**Secondary Txt**

- Relapse
  - Prevention
  - Low-level Monitoring
- Switch to Tx C
- Augment with Tx D

- Early Responder
  - Relapse
    - Prevention
    - Low-level Monitoring
- Switch to Tx C
- Augment with Tx D
One Adaptive Treatment Strategy

Initial Txt  Intermediate Outcome  Secondary Txt

Tx A

Early Responder

Tx B

Nonresponder

Nonresponder

Switch to Tx C

Switch to Tx C

Augment with Tx D

Augment with

Early Responder

Relapse Prevention

Low-level Monitoring

Relapse Prevention

Low-level Monitoring
Alternate Approach to Constructing an Adaptive Treatment Strategy

• Why not use data from multiple clinical trials to construct the adaptive treatment strategy?

• Choose the best initial treatment on the basis of a randomized trial of initial treatments and choose the best secondary treatment on the basis of a randomized trial of secondary treatments.
Delayed Therapeutic Effects

Why not use data from multiple clinical trials to construct the adaptive treatment strategy?

**Positive synergies**: Treatment A may not appear best initially but may have enhanced long term effectiveness when followed by a particular maintenance treatment. Treatment A may lay the foundation for an enhanced effect of particular subsequent treatments.
Delayed Therapeutic Effects

Why not use data from multiple clinical trials to construct the adaptive treatment strategy?

**Negative synergies:** Treatment A may produce a higher proportion of early responders but also result in side effects that reduce the variety of subsequent treatments for those that do not respond. Or the burden imposed by treatment A may be sufficiently high so that nonresponders are less likely to adhere to subsequent treatments.
Prescriptive Effects

Why not use data from multiple clinical trials to construct the adaptive treatment strategy?

Treatment A may not produce as high a proportion of early responders as treatment B but treatment A may elicit symptoms that allow you to better match the subsequent treatment to the patient and thus achieve improved response to the sequence of treatments as compared to initial treatment B.
Selection Effects

Why not use data from multiple clinical trials to construct the adaptive treatment strategy?

Subjects who will enroll in, who remain in or who are adherent in the trial of the stand-alone treatments may be quite different from the subjects in SMART.
Summary:

• When evaluating and comparing initial treatments, *in a sequence of treatments*, we need to take into account, e.g. control, the effects of the secondary treatments thus SMART.

• Standard one-stage randomized trials may yield information about different populations from SMART trials.
Pelham ADHD Study

A. Begin low-intensity behavior modification

B. Begin low dose medication

A1. Continue, reassess monthly; randomize if deteriorate

A2. Add medication; bemod remains stable but medication dose may vary

A3. Increase intensity of bemod with adaptive modifications based on impairment

B1. Continue, reassess monthly; randomize if deteriorate

B2. Increase dose of medication with monthly changes as needed

B3. Add behavioral treatment; medication dose remains stable but intensity of bemod may increase with adaptive modifications based on impairment
Jones’ Study for Drug-Addicted Pregnant Women

Random assignment:

- tRBT
  - 2 wks Response
    - Random assignment:
      - rRBT
    - Nonresponse
      - eRBT

Random assignment:

- rRBT
  - 2 wks Response
    - Random assignment:
      - aRBT
    - Nonresponse
      - tRBT
Kasari Autism Study

A. JAE+ EMT

Random assignment:

12 weeks

Assess-
Adequate response?

Yes → JAE+EMT

No → B. JAE + AAC

Random assignment:

B. JAE + AAC

12 weeks

Assess-
Adequate response?

Yes → B1. JAE+AAC

No → B2. JAE + AAC ++

JAE+EMT

JAE+EMT+++

JAE+AAC

B1. JAE+AAC

B2. JAE +AAC ++
Osling ExTENd

Early Trigger for Nonresponse

Random assignment:

Nonresponse

Random assignment:

8 wks Response

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone

Late Trigger for Nonresponse

Random assignment:

Nonresponse

Random assignment:

8 wks Response

Naltrexone

TDM + Naltrexone

CBI

CBI + Naltrexone
Discussion

• Interesting primary hypotheses are tested using the primary outcome of all participants.

• Secondary analyses can use pretreatment variables and outcomes to provide evidence for more deeply individualized adaptive treatment strategies are available. (when and for whom?)

• Sample Size formulae are available; data analysis software is available. See http://methodology.psu.edu/ra/adap-treat-strat

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