Introduction to Adaptive Treatment Strategies

What are adaptive treatment strategies (ATS)?
What are the pieces that make up an ATS?
Examples of ATSs: Compare simple versus deeply-tailored ATSs.
Discuss why ATSs are needed
Utilizing theory to design an ATS
How ATSs can be used to inform clinical practice
Other names are dynamic treatment regimes, treatment algorithms, stepped care models, expert systems, adaptive interventions, treatment protocols. Structured treatment interruptions in the treatment of AIDS are a form of adaptive treatment strategy.

Individualized interventions
Adaptive Treatment Strategies

• Are individually tailored time-varying treatments composed of
  • a sequence of critical treatment decisions
  • tailoring variables
  • decision rules, one per critical decision; decision rules input tailoring variables and output individualized treatment recommendation(s).

• Operationalize clinical practice.

Provide a paradigm whereby we can seek to improve clinical practice which by its nature is adaptive.

Tailoring is achieved by use of a decision rules. Takes ongoing info (past response, adherence, burden, etc) and outputs txt level type

Scientists develop ATSSs first. They are then used by clinicians to guide their thinking in actual clinical practice.

We use the term ATS but others might use the terms: dynamic treatment regimes, treatment algorithms, stepped care models, expert systems, adaptive interventions, treatment protocols.
Example: Adaptive Aftercare for Alcohol Dependent Individuals

- **Population**: alcohol dependent individuals who have graduated from an intensive outpatient program
- **Overall goal**: prevent relapse to alcohol abuse
- **Critical treatment decisions**: which treatment to provide first?; which treatment to provide second?
- **Tailoring variable**: heavy drinking days
Decision Rules

Alcohol dependent individuals are provided Naltrexone along with Medical Management.

**IF** an individual experiences 3 or more heavy drinking days prior to 8 weeks

**THEN** the individual’s Naltrexone treatment is augmented with Combine Behavioral Intervention.

**ELSE IF** the individual successfully completes 8 weeks with fewer than 3 heavy drinking days

**THEN** the individual is provided a prescription to Naltrexone along with Telephone Disease Management.

Individuals have weekly medical management visits

naltrexone medication (opiate antagonist—reduces the reinforcing or pleasurable effects of alcohol )

+ MM  is standard treatment

CBI is combine behavioral intervention  this is motivational enhancement and cognitive behavioral therapy—incorporates pharmacotherapy
Adaptive Treatment Strategies

- **From the individual/patient/client’s point of view**: a sequence of (individualized) treatments

- **From the clinician’s point of view**: a sequence of decision rules that recommend one or more treatments at each critical decision.
Other critical decisions: The individual’s participation in treatment (e.g., who should set health-related goals, the participant or the care provider?), the location of the intervention offered (e.g., is it better to offer treatment at home or at the clinic?), the provider of the intervention (e.g., should the parent or the teacher intervene?), the mode of delivery (e.g., is face-to-face delivery better than Internet-based delivery?), or the timing of treatment (e.g., is it better to intervene immediately or at some later point?)

More examples of critical treatment decisions

- How long should we use the first treatment before transitioning to a maintenance/relapse prevention treatment? And which treatment should this be?
- How long should we try the first treatment before declaring non-response and moving to another treatment? And which treatment should this be?
- How should a treatment be delivered?
- How do we re-engage patients who are non-adherent?
More examples of tailoring variables

- Age, Severity of illness, Presence of comorbid mental or physical conditions, Quality of family support, Past failed treatments
- Adherence to present treatment, Side effects while on present treatment, Symptoms while on present treatment
- Candidate tailoring variables include moderators, mediators or short-term outcomes or even proximal measures of the ultimate outcome of interest

Other tailoring variables are genetics, family background, proteomics
### Example: Adaptive Drug Court Program

- **Population:** drug abusing offenders assigned to drug court
- **Overall goal:** minimize recidivism and drug use
- **Critical treatment decisions:** which treatment to provide first?; which treatment to provide second?

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**Adaptive Interventions in Drug Court: A Pilot Experiment**


minimize recidivism and drug use is operationalized by graduating from the drug court program

To graduate offender must attend 12 counseling sessions; provide 14 consecutive weekly negative drug urine specimens; remain arrest-free; obey program rules and procedures; pay 200 dollar court fee
All movement between steps or stages is operationalized.
High risk: ASPD or history of drug treatment otherwise low risk

These are assessed monthly:
Noncompliance: is (1) falls to attend 2 or more counseling sessions or (2) fails to provide 2 or more scheduled urine specimens

Nonresponsive = (1) is attending sessions and completing program requirements, and (2) is not committing new infractions, but (3) provides 2 or more drug-positive urine specimens.

(from Marlowe paper:) A jeopardy contract involves “zero tolerance” for further violations of the rules of the program. Any further violation leads to a termination hearing, at which the participant is terminated from the program and sentenced on the original charge or charges unless he or she can provide a good-cause reason to be given another chance. The decision whether or not to permit another chance is within the discretion of the judge and is generally granted in approximately 30% of cases
Adaptive Drug Court Program
Tailoring Variables

• Stage 1 Tailoring Variables: ASPD, Prior formal drug abuse treatment

• Stage 2 Tailoring Variables: Attendance at counseling sessions, Infractions, Providing scheduled urine screens, Positive urine specimens
ICM is intensive case management, includes individual counseling as well as help with other aspects of life (housing, etc.)

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**Adaptive Drug Court Program Decision Rules**

- **Stage 1 Decision Rule:** Provide group-based drug abuse counseling to all. **If** ASPD or Prior formal drug abuse treatment **then** provide bi-weekly court hearings. **Else** provide as-needed court hearings.

- **Stage 2 Decision Rule:** **If** committed an infraction or missed 2 or more counseling sessions or missed 2 or more urine screens **then** step up court supervision. **Else if** 2 or more positive urine specimens **then** step up treatment to ICM. **Else** continue on stage 1.
Other Examples of Adaptive Treatment Strategies

• Brooner et al. (2002, 2007) Treatment of Opioid Addiction
• McKay (2009) Treatment of Substance Use Disorders
• HIV-Causal Collaboration (2011) Treatment of HIV
• Rush et al. (2003) Treatment of Depression

Brooner uses a two component adaptive txt strategy, one component has to do with txt and the other with encouragement to adhere.
One steps up/down intensity and type of counseling sessions based on negative urines and adherence.
One steps up/down behavioral contingencies based on adherence to counseling sessions.
Rules are explicit.

McKay has a book on this topic– see Treating Substance Use Disorders With Adaptive Continuing Care (Hardcover) by James R. McKay

When to initiate combined antiretroviral therapy to reduce mortality and AIDS-defining illness in HIV-infected persons in developed countries: an observational study.

The decision rules used by Brooner et all and McKay are quite detailed, and based on explicit actions by patient, whereas in contrast the Rush et al study (Texas Medication Algorithm Project) appears to be more losely structured; the clinician uses clinical judgment to decide if depression levels are clinically significant and thus an augmentation or switch in treatment intensity is needed. The particular secondary treatment is chosen out of a set of specified alternatives and depends on clinical judgment/patient preference.
Outline

- What are Adaptive Treatment Strategies?
- Why use Adaptive Treatment Strategies?
- Adaptive Treatment Strategy Design Goals
- What does an Adaptive Treatment Strategy include?
- Summary & Discussion
Why Adaptive Treatment Strategies?

1) High heterogeneity in need for or response to any one treatment

What works for one person may not work for another, thus often need a sequence of treatments just to obtain an acute response

This is really “why do we need to consider a sequence of treatments?”
Why Adaptive Treatment Strategies?

2) Chronic or Waxing and Waning Course

Improvement often marred by relapse

Intervals during which more intense treatment is required alternate with intervals in which less treatment is sufficient
Why Adaptive Treatment Strategies?

3) Treatment is burdensome

Treatment required over long time periods is burdensome

Non-adherence leads to relapse or loss of positive effect
Why not combine all possible efficacious therapies and provide all of these to the patient now and in the future?

• Treatment incurs side effects and substantial burden, particularly over longer time periods.
• Problems with adherence:
  • Variations of treatment or different delivery mechanisms may increase adherence
  • Excessive treatment may lead to non-adherence
• Treatment is costly (Would like to devote additional resources to patients with more severe problems)

More is not always better!

Why not give a universal intervention to all for a sufficiently long time?? These are all reasons why you should not provide MORE treatment than is needed. Only provide MI to people who need motivation to adhere. That is a multi-component fixed treatment is not practical or is too costly or would not result in good adherence A principle of adaptive tx strategies is to provide no more than needed to accomplish desired result!
Outline

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Adaptive Treatment Strategy
Design Goals

• Maximize the strength of the adaptive treatment strategy
  • by well chosen tailoring variables, well measured tailoring variables, well conceived decision rules & well implemented decision rules

CLARIFICATION NOTE: Here we are discussing the design of the adaptive treatment strategy (hence “treatment design”). We are not discussing the design of a trial to inform the development of an ATS—that’s the next module on “trial design”.

Use behavioral/social/biological theory, clinical experience, expert opinion, consultation with clinical staff, review of extant literature to help select the tailoring variables and form the decision rules.
To achieve this goal, ATS should be explicit. We have the most confidence in an adaptive treatment strategy when its effects are replicable with different experimenters, different clinical staff, different locations, etc.
Recall

- Adaptive treatment strategies are individually tailored time-varying treatments composed of
  - a sequence of critical treatment decisions
  - tailoring variables
  - decision rules, one per critical decision; decision rules input tailoring variables and output individualized treatment recommendation(s).

Tailoring is achieved by use of a decision rules. Takes ongoing info (past response, adherence, burden, etc) and outputs txt level type
Considerations re Critical Decisions

• Which treatment decisions are critical and need to be guided (e.g. manualized, structured)?

  • Which decisions are likely influenced by non-systematic variance?
  • Which decisions are likely influenced by systematic bias?

variance: different staff would provide the same individual with different treatments

Non-systematic variance: this variance is due to issues unrelated to the individual (staff member is in a hurry, staff member is tired, last patient of the day, etc.)

Systematic variance: this variance is due to (unconscious) bias on the part of the staff member. One staff member connects to the individual whereas the other staff member does not. Racial or gender or age bias lead to different treatment recommendations.
Adaptive Treatment Strategy
Design Considerations

• Choice of the Tailoring Variable
• Measurement of the Tailoring Variable
• Decision Rules linking Tailoring Variables to Treatment Decisions
• Implementation of the Decision Rules

In order to understand how to achieve our design goals it is important to understand what constitutes the treatment.

Aspects of the site such as individual staff, schools, treatment sites, etc. are not part of the intervention. Rather, they are sources of extraneous variance.

Measurement is particularly an issue if you have a theory based adaptive txt strategy.

This bundle (tailoring variable→ decision rule→ implementation) denotes one txt. Condition
Considerations re Tailoring Variables

• Significant differences in effect sizes in a comparison of fixed treatments as a function of characteristics.

• That is, some values of the tailoring variable should indicate a particular treatment decision is best while other values of the tailoring variable should indicate that a different treatment decision is best.

Actually it is the optimal txt varies by individual characteristics.
To help understand this consider the following example.
Adaptive Aftercare for Alcohol Dependent Individuals

• Hypothetical Study: Alcohol dependent individuals on NTX; after 8 weeks randomize individuals to continue on NTX or to an augment of NTX with CBI

• Result of hypothetical study: Among individuals who had returned to heavy drinking, NTX+CBI performs better than NTX only. However there is little or no difference for individuals who were maintaining a more sober lifestyle.
Adaptive Aftercare for Alcohol Dependent Individuals

• Individuals who return to heavy drinking while on Naltrexone (NTX) need additional help to maintain a non-drinking lifestyle.
• Tailoring variable is heavy drinking
• Providing CBI to individuals who are maintaining a non-heavy drinking lifestyle is costly.
• Implication: Provide NTX+CBI to individuals who are drinking heavily. NTX only is sufficient for individuals who are maintaining a non-heavy drinking lifestyle.

tailoring variable: proximal measure of heavy drinking –a proximal value of primary outcome!
This is one of those cases where a cost might be incorporated into the response, Y.
Technical Interlude!

$S=$ tailoring variable (heavy drinking)
$Tx=$ treatment type (NTX vs NTX+CBI)
$Y=$ primary outcome (days abstinent, high is preferred)

$Y = \beta_0 + \beta_1 S + \beta_2 Tx + \beta_3 S \times Tx + \text{error}$

$= \beta_0 + \beta_1 S + (\beta_2 + \beta_3 S)Tx + \text{error}$

If $(\beta_2 + \beta_3 S)$ is zero or negative for some $S$ and positive for others then $S$ is a tailoring variable.
**S is a moderator variable** because the magnitude of the effect of \( Tx=NTX+CBI \) versus \( Tx=NTX \) differs by levels of \( S \).

However, **S is not a tailoring variable**: \( Tx=NTX+CBI \) is better for all subjects.

**S is a weak tailoring variable** because the direction of the effect of \( Tx=NTX+CBI \) versus \( Tx=NTX \) differs by levels of \( S \) but magnitude is small.

**S is somewhat prescriptive**: Offer \( Tx=NTX+CBI \) to \( S=1 \) subjects; the difference in effects is not substantial for \( S=0 \) subjects.

**S is a strong tailoring variable** because the direction of the effect of \( Tx=NTX+CBI \) versus \( Tx=NTX \) differs by levels of \( S \).

**S is very prescriptive**: Offer \( Tx=NTX \) to \( S=0 \) subjects; offer \( Tx=NTX+CBI \) to \( S=1 \) subjects. Large magnitudes of clinical significance.
Tailoring variables

- Tailoring variables are moderators but they may also be
  - Baseline variables
  - Mediators
  - Short-term outcomes
  - Proximal measures of the ultimate outcome of interest.
Unreliability means that you are making unsystematic assignment of dose – getting close to random assignment.

Invalid measure will weaken intervention effect (assuming your theory is correct) as you will be systematically assigning the wrong dose.

Alcohol aftercare study included weekly self report, but biological and from collaterals is not weekly – oh no!.


Biological: Carbohydrate Deficient Transferrin (CDT).
Timing of Tailoring Variable Collection

• Tailoring variable should be assessed at sufficiently frequent intervals so that non-response is detected in a timely manner.

• Too infrequent and an individual’s condition may deteriorate so much that readily available rescue options are ineffective.

• Too frequent assessment may result in dependence or non-adherence

How frequently to measure a tailoring variable may be a critical decision!
Adaptive Aftercare for Alcohol Dependent Individuals

• Example: The tailoring variable is heavy drinking days. Should we measure this variable weekly or twice a week?
In order to achieve a particular desired treatment effect different amounts or types of treatment may be needed by different individuals.

In alcohol aftercare study they know from prior studies that people who relapse to heavy drinking while on naltrexone within first two months rarely recover.
Derivation of Decision Rules

- Good decision rules are objective, are operationalized.
- Strive for comprehensive rules (this is hard!) – cover situations that can occur in practice, including when the tailoring variable is missing or unavailable.

Use staff to help brainstorm about operationalizing the rules.
Operationalize the Decision Rules

• **Bad**: Individuals who are drinking excessively are nonresponders and are switched to NTX +MM+CBI

• **Better**: Individuals who experience 3 or more heavy drinking days are nonresponders and are switched to NTX +MM+CBI.

An even better example: As soon as 3 or more heavy drinking day occur within weeks 3-8 the person is declared a nonresponder and switched to NTX+MM+CBI
Adaptive Aftercare for Alcohol Dependent Individuals

• Example: Suppose an individual misses his weekly clinic visit. Then the number of heavy drinking days in the prior week is missing.

• Should we wait until the following week to decide if the individual is a non-responder or should we call the individual a non-responder immediately?
Clinical judgment is used to inform the development of the decision rules and to produce structured measurements of tailoring variable.

Should clinical judgment be used to select among a limited set of dosages? (Although using clinical judgment to inform dosage decisions in this way may seem useful from a clinical standpoint, it is important to consider that this procedure renders clinical judgment a part of the decision rules, and therefore a part of the overall treatment.)

Is the following desirable?: Decision rules may include the less structured clinical judgment, e.g. Clinician selects one treatment in a set of recommended treatments for non-responders who are non-adhering. Clinician can declare non-response only after 6 weeks (with guidelines for what constitutes non-response).

In clinical judgment—how can local knowledge be used in a replicable way? Should local knowledge be used to choose between equivalent txt’s?
If rules are not implemented universally, some persons are treated differently from others, because the dosage assignment is based in part on factors that do not figure in the decision rules and may be unique to a certain individual, time, or situation.

**Implementation in an Intervention Trial**

- Try to implement decision rules universally, applying them consistently across subjects, time, site & staff members.

- We want to avoid treating some subjects differently from others due to factors that are not in the decision rules.
  - The non-systematic component introduces random error and increases variance.
  - The systematic component harms replicability by increasing the plausibility of alternative explanations for the (in)effectiveness of the adaptive treatment strategy.
Implementation in an Intervention Trial

- Try to implement rules universally, applying them consistently across subjects, time, site & staff members.
- Staff may be resistant to implementing the rules universally because
  - Missing but needed tailoring variables
  - Measured tailoring variable lacks validity
  - The way the tailoring variable weighs different criteria may be questioned.
  - Decision rules are ambiguous
  - Insufficient training

Staff perceive dosage rules are inappropriate in a particular case
To the extent that individuals with the same tailoring variable values are assigned dosages by relying on ad hoc procedures rather than the established dosage assignment rules, there will be problems with replicability.

The rule is like the manual in a manualized therapy.
If it is a big deal to make an exception then staff must come up with a cogent argument that you can use to help plan future implementations.

This helps you
1) Future revision of rule
2) Indicates if there is a need for further staff training
3) May indicate that you need to be clearer in articulating the purpose of a txt component.
Summary & Discussion

• Adaptive treatment strategies are attractive alternatives to fixed treatments
  • if in a comparable fixed treatment, significant variation in treatment effect would be expected as a function of identifiable tailoring variables, across participants and/or within participants over time
Summary & Discussion

Adaptive treatment strategies enhance the potency of the treatment if

- by increasing salience and negative effects, they improve adherence
- by reducing waste it becomes possible to devote additional resources to higher-risk individuals who can benefit from them.
Summary & Discussion

• Research is needed to build a theoretical literature that can provide guidance:
  • in identifying tailoring variables,
  • in the development of reliable and valid indices of the tailoring variables that can be used in the course of repeated clinical assessments
  • on when/how to allow clinical judgment.
Summary & Discussion

• Given a structural model of the causal chain relating the tailoring variables, decisions and outcome, statistical methods can help construct the decision rules

  • Influence diagrams and graphical models (a way to efficiently encode expert knowledge—R. Shachter, S. Lauritzen)

A Dynamic Bayesian Network to evaluate the performance of Intensive Care Units. By Davide Luciani, MD
Questions?

More information


Discussion & Practice Exercise

Exercise 1: Write 2-3 critical decisions that should be investigated to address a disorder in your field.

Exercise 2: Specify potential tailoring variables for each critical decision.
Discussion & Practice Exercise

Exercise 3: Identify 2-3 treatment options for each critical decision.

Exercise 4: Write down 1 simple ATS that links the tailoring variables to the treatment options at each critical decision.

Exercise 4: Write down a second ATS.
Discussion & Practice Exercise

Exercise 3: Write 2 simple ATSs to address a disorder in your field. These ATSs should differ only in terms of their first-stage treatment.

Exercise 2: Write down 2 simple ATSs that differ only in terms of their second-stage treatment.