Adaptive Treatment Strategies

Getting SMART About Developing Individualized Sequences of Adaptive Health Interventions

Association for Behavioral and Cognitive Therapies
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40 minutes

What are adaptive treatment strategies (ATS)? Give examples of ATSs.

- Discuss why ATSs are needed and how they inform clinical practice.
- Compare simple ATSs versus more deeply tailored ATSs.

Give examples of ADHD

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

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 txt 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 ATSs first. They are then used by clinicians to guide their thinking in actual clinical practice.

Adaptive Aftercare for Alcohol Dependent Individuals

- 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

These individuals graduated from an Intensive Outpatient program.

Decision Rules

First 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.

Stepping up txt:

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

What does decision rule do?

When to start txt, when to stop txt, when to change txt, what txt to change to

Adaptive Treatment Strategies

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

- From the clinical scientist's point of view: a sequence of decision rules that recommend one or more treatments at each critical decision.

This is really related to clinical management of chronic disorders.

Take a broad view of what constitutes therapies: changing intensity, switching medication, augmenting medication, behavioral contingencies, monitoring schedules, motivational therapy, support networks.

The design of the adaptive treatment strategy is a multi-stage decision problem. In general the component treatments/therapies have been shown to be efficacious and "safe"; they require explication for appropriate implementation.

Also how to combine therapies?

More examples of critical treatment decisions and tailoring variables

- Critical treatment decisions: how long to try the first treatment?; how should a treatment be delivered?; how intensive should a treatment be? When to stop/start treatment?

- Tailoring variables: severity of illness, presence of comorbid mental or physical conditions, family support, adherence to present treatment, side effects resulting from present treatment, symptoms while in treatment.

Other tailoring variables are genetics, family background, proteomics

Another Example of an Adaptive Treatment Strategy

- Adaptive Drug Court Program for drug abusing offenders.
- Goal is to minimize recidivism and drug use.
- Marlowe et al. (2008)

Criminal Justice Review 2008; 33; 343 Douglas B. Marlowe, David S. Festinger, Patricia L. Arabia, Karen L. Dugosh, Kathleen M.

Benasutti, Jason R. Croft and James R. McKay

Adaptive Interventions in Drug Court: A Pilot Experiment

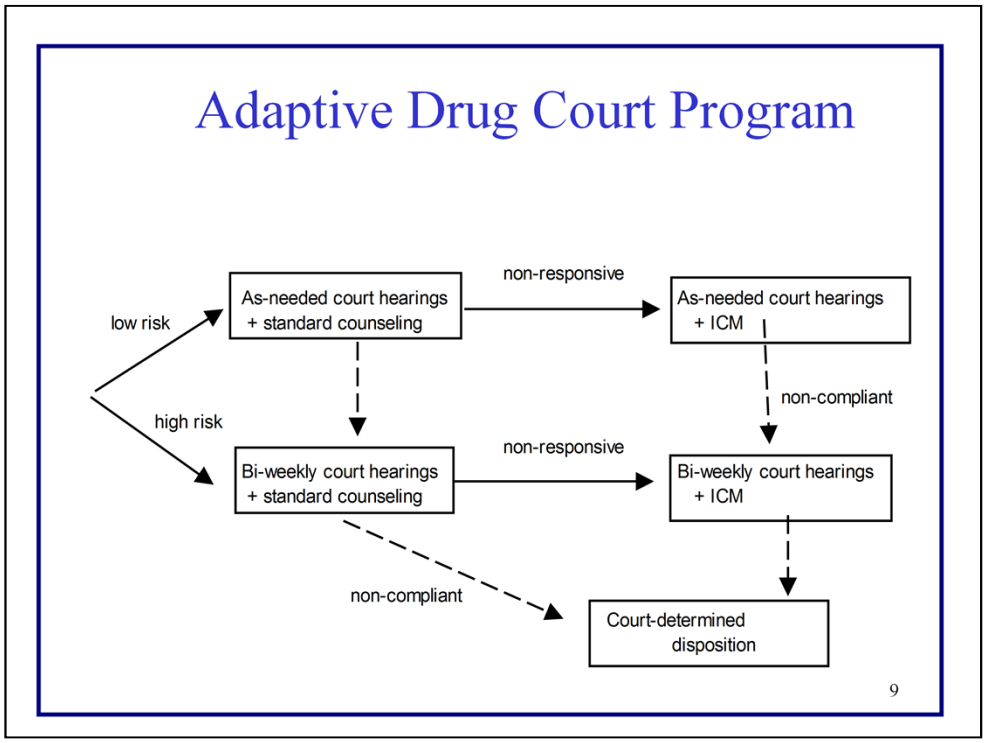
minimize recidivism and drug use is operationalized by graduating from the drug court program.

High risk: ASPD or history of drug treatment otherwise low risk

Noncompliance: is(1) falls below threshold for attendance in counseling sessions or status hearings, (2) fails to provide scheduled urine specimens, **or** (3) commits a new crime or serious rule infraction

Nonresponsive = (1) is attending sessions and completing program requirements, **and** (2) is not committing new infractions, **but** (3) continues to provide drug-positive urine specimens.

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



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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.

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 below threshold for attendance in 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.

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

Other Examples of Adaptive Treatment Strategies

- Brooner et al. (2002, 2007) Treatment of Opioid Addiction
- McKay (2009) Treatment of Substance Use Disorders
- Marlowe et al. (2008) Drug Court
- 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

Criminal Justice Review 2008; 33; 343 Douglas B. Marlowe, David S. Festinger, Patricia L. Arabia, Karen L. Dugosh, Kathleen M.

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Adaptive Interventions in Drug Court: A Pilot Experiment

The decision rules used by Brooner et all, Marlowe et al., 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.

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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

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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

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Why not combine all possible efficacious therapies and provide all of these to 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!

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Why not give a universal intervention to all for a sufficiently long time??

More is not always better.

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!

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Treatment Design Goals

- Maximize the strength of the adaptive treatment strategy
  - by well chosen tailoring variables, well measured tailoring variables, & well conceived 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".

Treatment Design Goals

- Maximize replicability in future experimental and real-world implementation conditions
  - by fidelity of implementation & by clearly defining the treatment strategy

To achieve this goal, ATS should be explicit.

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 intervention 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 denotes one txt. Condition

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.

Adaptive Aftercare for Alcohol Dependent Individuals

- Individuals who return to heavy drinking while on Naltrexone need additional help to maintain a non-drinking lifestyle.
- Tailoring variable is heavy drinking
- Providing CBI to individuals who are maintaining a non-drinking lifestyle is costly.

tailoring variable: heavy drinking proximal outcome!

CBI is a cognitive behavioral therapy --combine behavioral intervention this is motivational enhancement and cognitive behavioral therapy—incorporates pharmacotherapy

This is one of those cases where a cost might be incorporated into the response, Y.

Suppose we took people on naltrexone and randomized some to cbi and others to no cbi. Then we expect that the effect of cbi will be positive for individuals who have returned to heavy drinking and will be nonexistent or negative for individuals who are maintaining a non-drinking lifestyle.

Technical Interlude!

s=tailoring variable

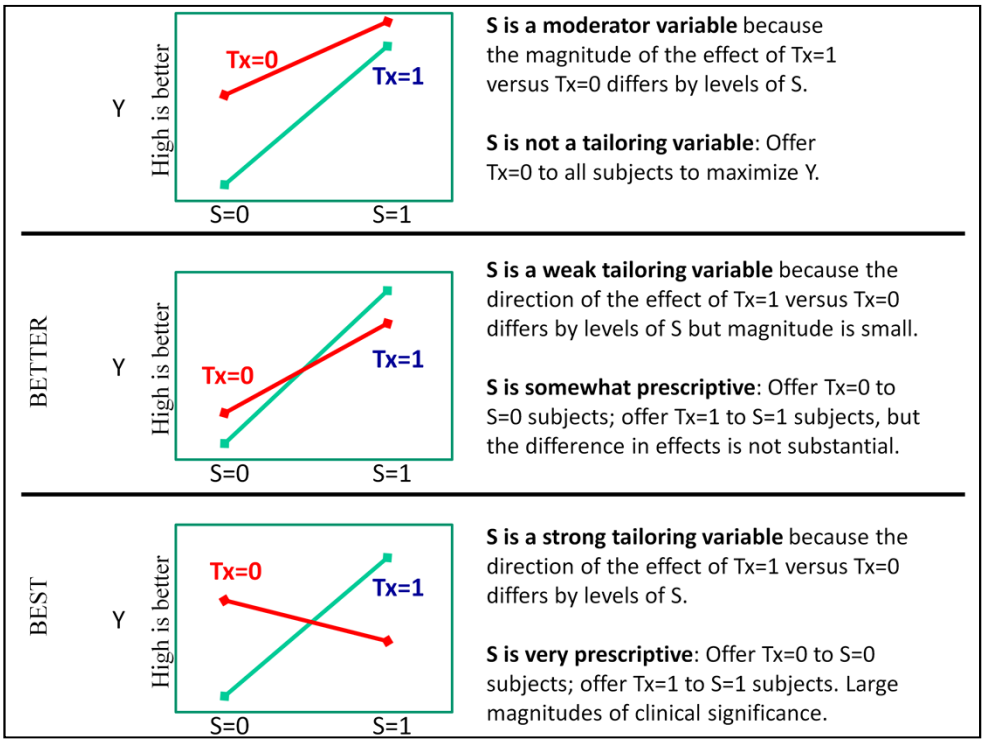
t=treatment type (0 or 1)

Y=primary outcome (high is preferred)

$$Y=\beta_0 + \beta_1 s + \beta_2 t + \beta_3 st + error$$

$$= \beta_0 + \beta_1 s + (\beta_2 + \beta_3 s)t + error$$

If $(\beta_2 + \beta_3 s)$ is zero or negative for some s and positive for others then s is a tailoring variable.


Y
High is better
Tx=0
Tx=1
S=0
S=1
S is a moderator variable because the magnitude of the effect of Tx=1 versus Tx=0 differs by levels of S.
S is not a tailoring variable: Offer Tx=0 to all subjects to maximize Y.
BETTER
Y
High is better
Tx=0
Tx=1
S=0
S=1
S is a weak tailoring variable because the direction of the effect of Tx=1 versus Tx=0 differs by levels of S but magnitude is small.
S is somewhat prescriptive: Offer Tx=0 to S=0 subjects; offer Tx=1 to S=1 subjects, but the difference in effects is not substantial.
BEST
Y
High is better
Tx=0
Tx=1
S=0
S=1
S is a strong tailoring variable because the direction of the effect of Tx=1 versus Tx=0 differs by levels of S.
S is very prescriptive: Offer Tx=0 to S=0 subjects; offer Tx=1 to S=1 subjects. Large magnitudes of clinical significance.

Measurement of Tailoring Variables

- Reliability -- high signal to noise ratio
- Validity -- unbiased

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!.

Self-report:Time-Line Follow-Back (TLFB).

Biological: Carbohydrate Deficient Transferrin (CDT).

Derivation of Decision Rules

- Articulate a theoretical model for how treatment effect on key outcomes should differ across values of the moderator.
- Use prior clinical experience.
- Use prior experimental and observational studies.
- Discuss with research team and clinical staff, "What dosage would be best for people with this value on the tailoring variable?"

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 naltexone 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.

Greater than 1 heavy drinking day within a two month period.

In weeks 3-8 can be declared a nonresponder and switched to NTX+MM+CBI

Implementation

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

- Document values of tailoring variable!

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. The non systematic component of these factors introduces random error into the treatment, thereby lessening its effectiveness. The systematic component of these factors harms replicability by introducing confounders into the experimental comparison of the preventive intervention with other conditions. That is we have alternate explanations for txt effect.

Staff perceive dosage rules are inappropriate in a particular case

missing needed tailoring variables, measure of tailoring variable lacks validity, the way the tailoring variable weighs different criteria may be questioned.

Rules are stated ambiguously or staff person is insufficiently trained.

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.

Implementation

- Exceptions to the rules should be made only after group discussions and with group agreement.
- If it is necessary to make an exception, document this so you can describe the implemented treatment.

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

•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

Txt bundle effect should be robust to context, family, individual characteristics

Do this by making txt rules sensitive to context, family individual characteristics.

In clinical judgment—how can local knowledge be used in a replicable way? Should local knowledge be used to choose between equivalent txt's?.

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 (-way to efficiently encode expert knowledge- R. Shachter, S. Lauritzen)

A Dynamic Bayesian Network to evaluate the performance of Intensive Care Units.

Davide Luciani, MD

John Rust has a good bit of work in econometrics that assumes expert knowledge and then finds best decision rules.

Questions?

More information

L.M Collins, S.A. Murphy and K.A. Bierman (2004), A Conceptual Framework for Adaptive Preventive Interventions, *Prevention Science* 5:185-196.

S.A. Murphy & J.R. McKay (2004), Adaptive Treatment Strategies: an Emerging Approach for Improving Treatment Effectiveness. Clinical Science (Newsletter of the American Psychological Association Division 12, section III: The Society for the Science of Clinical Psychology) Winter 2003/Spring 2004

L.M. Collins, S.A. Murphy, V. Nair & V. Strecher (2005), A Strategy for Optimizing and Evaluating Behavioral Interventions , *Annals of Behavioral Medicine.* 30:65-73.

S.A. Murphy, L.M. Collins, A.J. Rush (2007). Customizing Treatment to the Patient: Adaptive Treatment Strategies. *Drug and Alcohol Dependence,*. 88(2):S1-S72.

Discussion & Practice Exercise

Exercise: Write down 2-3 simple ATSs to address a chronic disorder in your field!

Next up!: Experimental Study designs for use in finding good tailoring variables and rules.