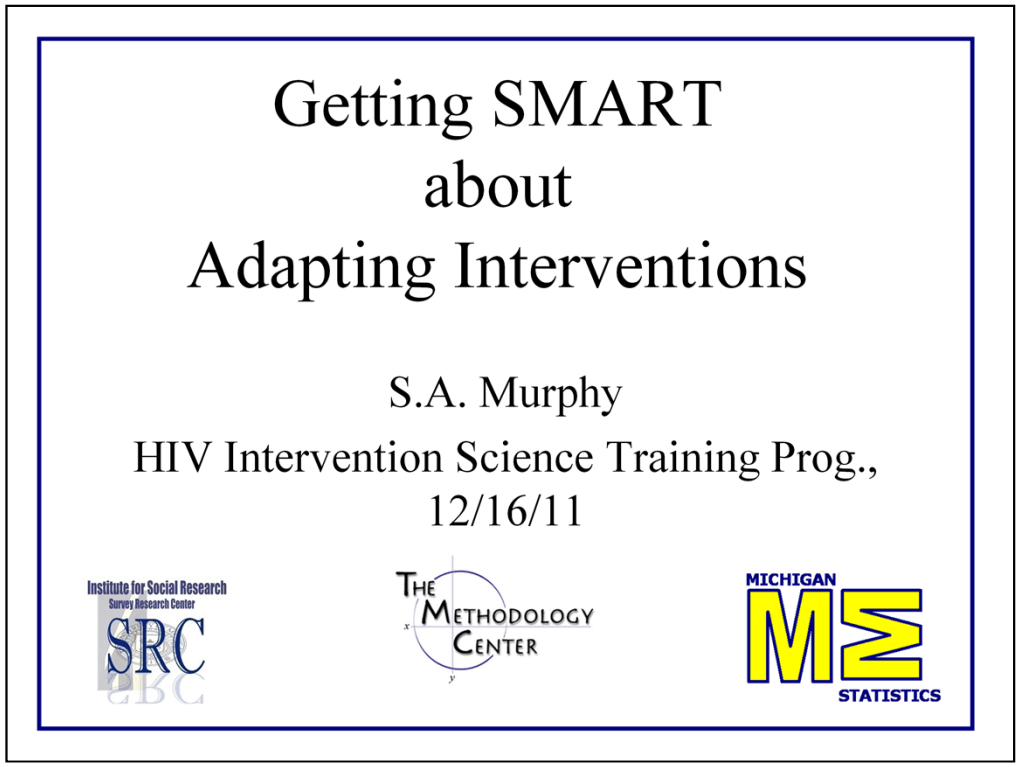

Getting SMART about Adapting Interventions

The effective treatment and management of many behavioral and health disorders often requires individualized, sequential decision making, in which the intervention is dynamically adapted over time based on an individual's changing course. Adaptive interventions operationalize individualized, sequential, decision making via a sequence of decision rules that specify whether, how, for whom, and when to alter the intensity, type, or delivery of psychosocial, behavioral, and/or pharmacological treatments. In this talk, we discuss how a novel, experimental design-sequential multiple assignment randomized trials (SMART) can be used in the development and optimization of adaptive interventions.

An emerging and exciting area of clinical science involves the use of data to directly inform the tactics and strategies used to individualize, adapt and readapt interventions to patient progress. Adaptive treatment strategies provide one way to operationalize this sequential clinical decision making. We review concepts behind adaptive treatment strategies and introduce Q-learning, a data analysis method that originated in the computer science field. Q-learning can be used to inform and improve sequential clinical decision making.

The data analysis method is illustrated using data from the "Adaptive Interventions for Children with ADHD" trial (W. Pelham, PI).

Outline

- Why Adaptive Treatment Strategies?
  - "new" treatment design
- Why SMART experimental designs?
  - "new" clinical trial design
- Trial Design Principles and Analysis
- Examples of SMART Studies
- Exploring Individualization using the "Adaptive Interventions for Children with ADHD" study (W. Pelham, PI).

2

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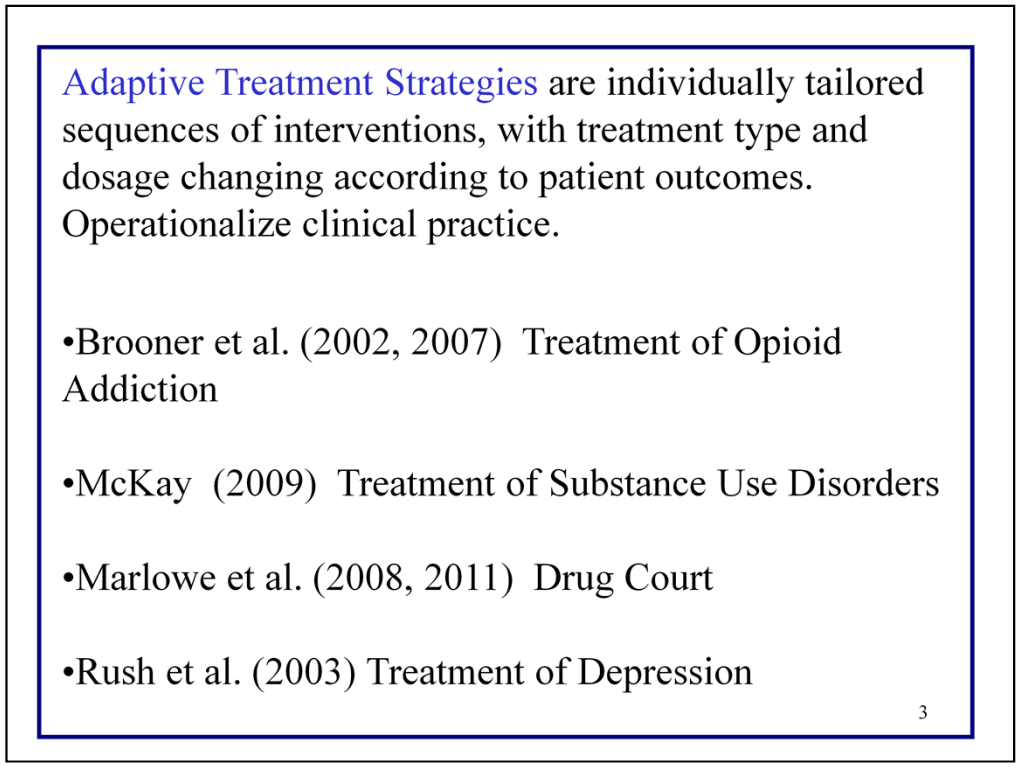
Individualized interventions



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

Most clinical scientists develop the decision rules using trial and error;
developmental and behavioral theories; clinical experience

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.
Benasutti, Jason R. Croft and James R. McKay
Adaptive Interventions in Drug Court: A Pilot Experiment

Adaptive interventions may optimize outcomes in drug courts: a pilot study.

Marlowe DB, Festinger DS, Arabia PL, Dugosh KL, Benasutti KM, Croft JR.

Curr Psychiatry Rep. 2009 Oct;11(5):370-6.

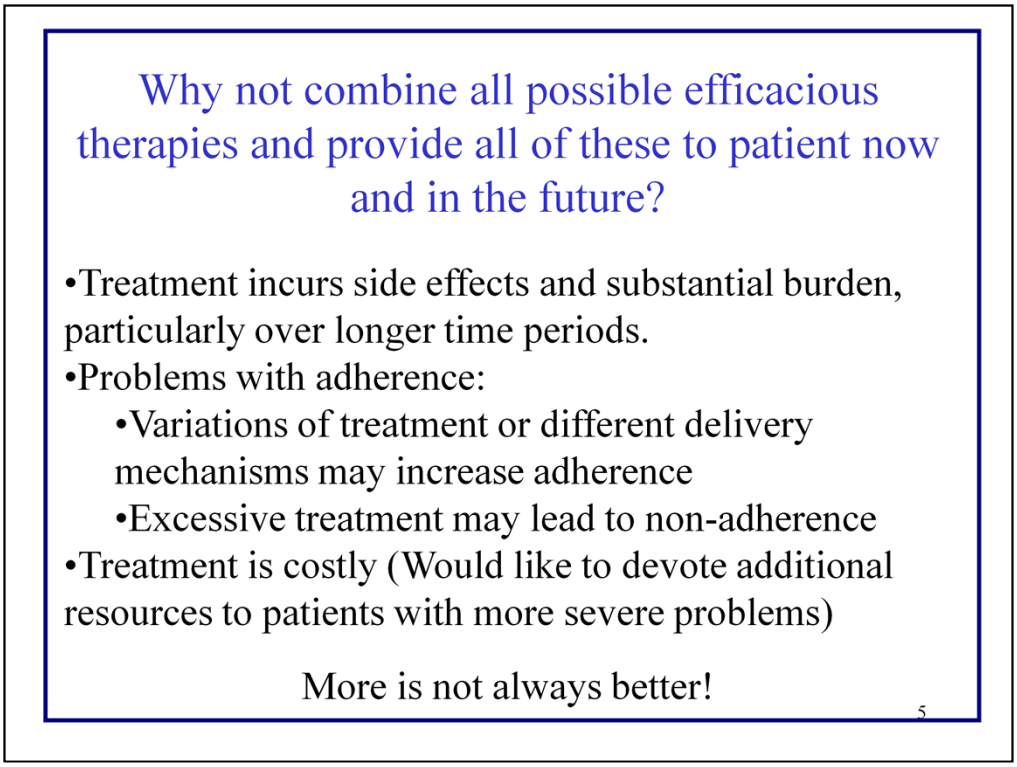
The decision rules used by Brooner et all, Marlowe et al., and McKay are quite detailed, and based on explicit actions by patient, whereas in contrast the Rush et al study (Texas Medication Algorithm Project) appears to be more losely structured; the clinician uses clinical judgment to decide if depression 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.

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 (and relapse is common)
- 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

4

These are all reasons why we need to plan ahead because we are likely to need to use a sequence of treatments



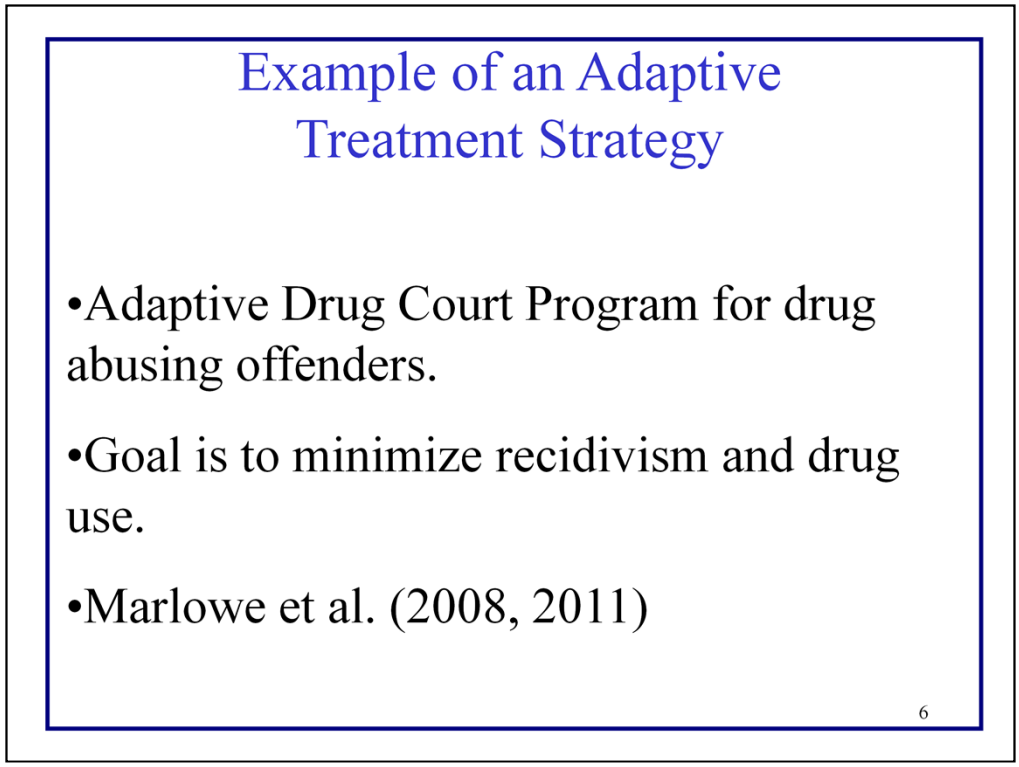
Why not give a universal intervention to all for a sufficiently long time??

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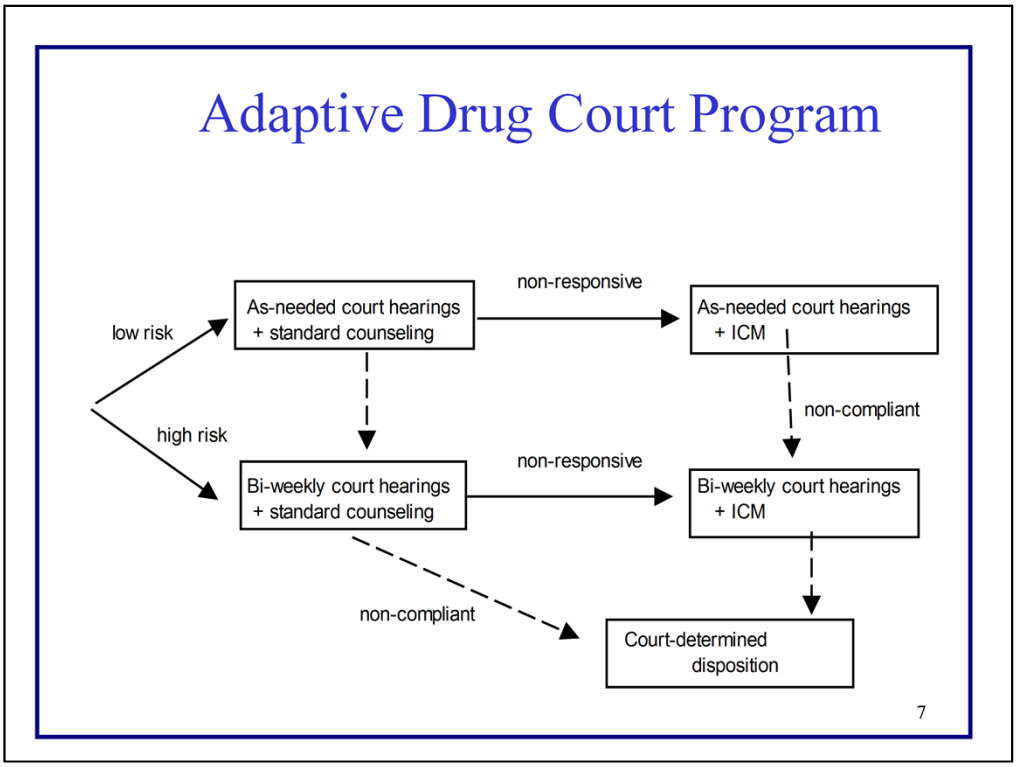
minimize recidivism and drug use is operationalized by graduating from the drug court program

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 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

Some Critical Decisions

- 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?)

8

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 intervention is a multi-stage decision problem.

Also how to combine therapies?

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Individualized interventions

SMART Studies

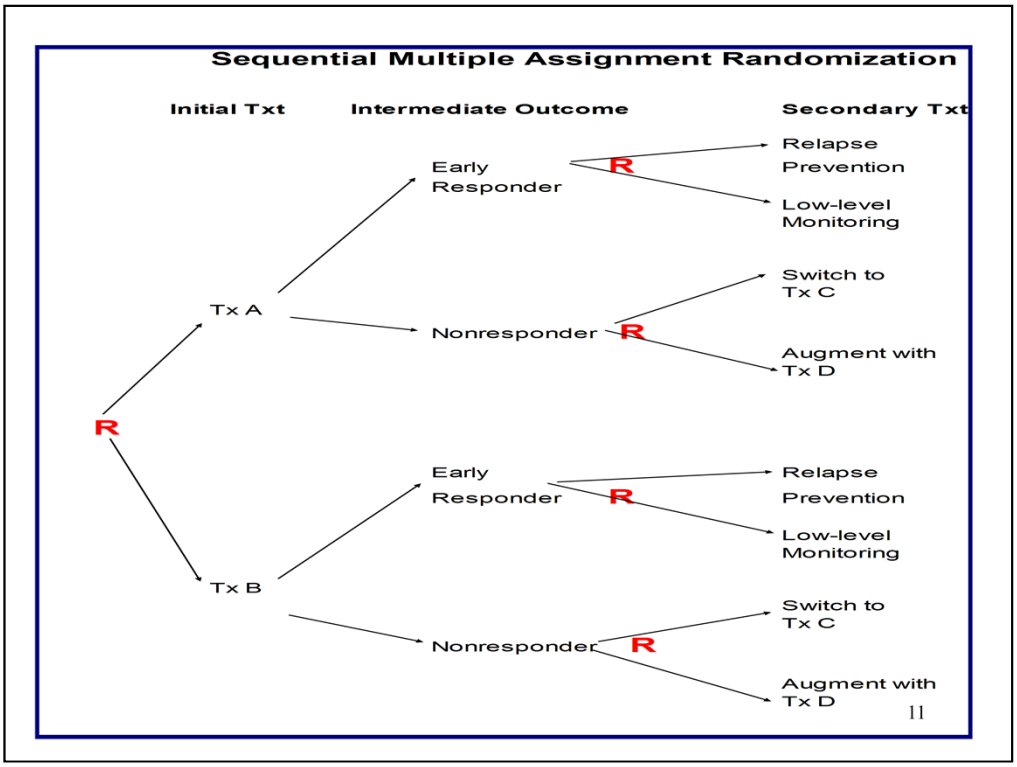
What is a sequential, multiple assignment, randomized trial (SMART)?

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

Goal of trial is to inform the construction of adaptive treatment strategies.

10

In stat. people may call these multistage trials (the randomization at each stage is assumed)



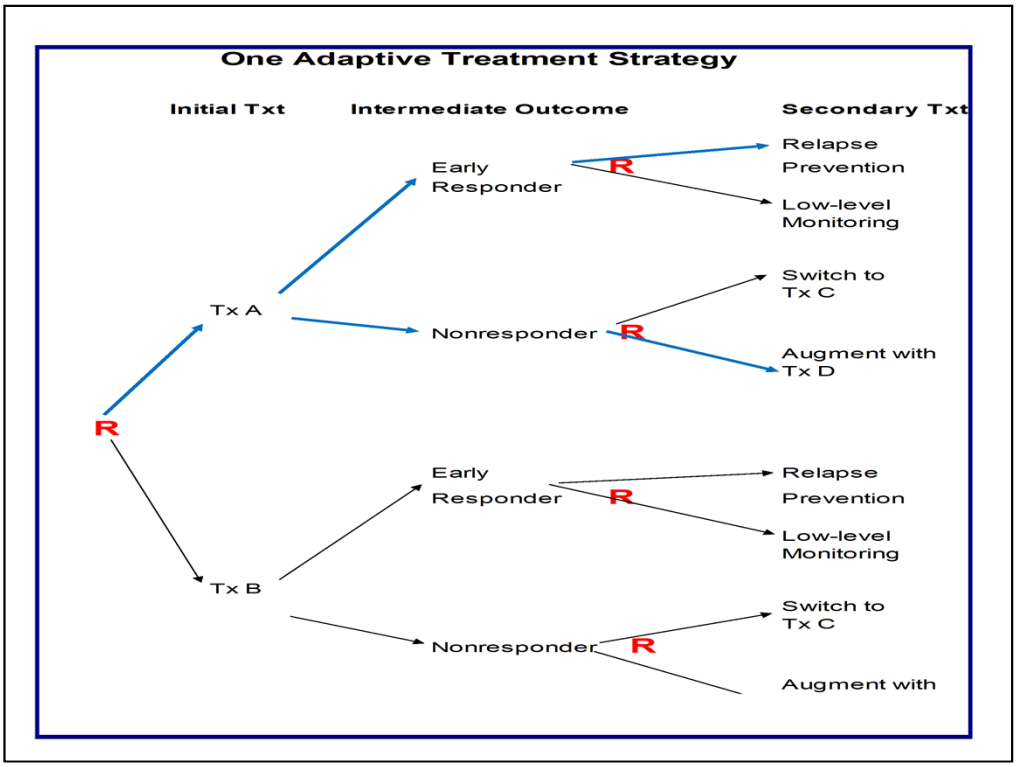
Hypothetical trial: Outcome is not shown but is on far right. The second randomization can take place up front (if you do not want to stratify or block by stage 1 outcomes such as adherence).

Equal randomization

Usual reaction is (1) I'm worried about sample size and

(2) This looks awfully complicated.

In reality, both of these problems are less worrisome than one might think—see following slides.



An adaptive treatment strategy is indicated in blue

Alternate Approach I to Constructing an Adaptive Treatment Strategy

- Why not use data from multiple 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.

Particularly attractive since potential initial treatment may have been evaluated in prior trials. So you propose a responder study or you propose a nonresponder study.

Or, why choosing the best initial treatment on the basis of a randomized trial of initial treatments and choosing the best secondary treatment on the basis of a randomized trial of secondary treatments is not the best way to construct an adaptive treatment strategy

Delayed Therapeutic Effects

Why not use data from multiple 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.

counseling and then if respond, monitoring with low level telephone counseling.

A consequence is that comparing two initial therapies based on a proximal outcome may produce different results from the comparison of two initial therapies when followed by a maintenance therapy and comparing more distal outcomes. Additionally, restricting comparisons to longer term outcomes, a comparison of two initial therapies followed by usual care or no therapy may yield different results from the comparison of two initial therapies when followed by one of several maintenance therapies.

We can expect that in an optimized adaptive treatment strategies, the best subsequent therapy will build on the gains achieved by prior therapies and thus these delayed effects should be common.

We want big positive delayed effects. We want profound positive cross-over effects!!!

Delayed Therapeutic Effects

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

Negative synergies: Treatment A may produce a higher proportion of 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.

treatment of psychosis: a medication may result in many immediate responders but Some patients are not helped and/or experience abnormal movements of the voluntary muscles (TDs). The class of subsequent medications is greatly reduced.

Or the kind of response produced may not be sufficiently strong so that patients can take advantage of maintenance care.

A negative delayed effect would occur if the initial treatment overburdens an individual, resulting decreased responsivity to future treatment; see Thall et al. (2007), Bembom and van der Laan (2007) for an example of the latter in cancer research.

Prescriptive Effects

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

Treatment A may not produce as high a proportion of 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.

Consider the issue of motivation as expressed via adherence; if tx A has provides less adherence support than tx B, then patients who require the adherence support will exhibit adherence problems during tx with A but not during tx with B. This is useful information as we then know that these patients, even if they respond will potentially need an enhancement of an adherence support during the maintenance or aftercare phase.

Sample Selection Effects

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

Subjects who ***will enroll in***, who ***remain in or*** who ***are adherent in*** the trial of the initial treatments may be quite different from the subjects in SMART.

Consider the issue of adherence; in many historical trials subjects were assigned a fixed treatment, that is, there were no options besides non-adherence for subjects who were not improving. This often leads to higher than expected drop-out or non-adherence. This is particularly the case in longer studies where continuing treatments that are ineffective is likely associated with high non-adherence. As a result the subjects who remained in the historical trial may be quite different from the subjects that remain in a SMART trial, which by design provides alternates for non-improving subjects. David Oslin made this point to me.

Consider the issue of motivation. Nonresponder trials recruit individuals who are not responding to their present treatment, say Med A. An important consideration is whether these nonresponders represent the population of individuals who do not respond to Med A or whether the nonresponders recruited into the trial are more motivated. Such selection bias will prevent us from realizing that we might need a behavioral intervention to encourage nonresponders to start again with treatment.

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.

Just because an initial txt looks best when looking at intermediate outcomes does not mean that it is best in an adaptive txt strategy

Alternate Approach II to Constructing an Adaptive Treatment Strategy

Why not use theory, clinical experience and expert opinion to construct the adaptive treatment strategy and then compare this strategy against an appropriate alternative in a confirmatory randomized two group trial?

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Don't know why your treatment strategy worked or did not work. Did not open black box. Should we wait until patient has had 5 heavy drinking days before giving up on this medication or should we give up on this medication after only 2 heavy drinking days?

Why constructing an adaptive treatment strategy and then comparing the strategy against a standard alternative is not always the answer.

- Don't know why your adaptive treatment strategy worked or did not work. Did not open black box.
- Adaptive treatment strategies are multi-component treatments
  - We need to address: when to start treatment?, when to alter treatment?, which treatment alteration?, what information to use to make each of the above decisions?

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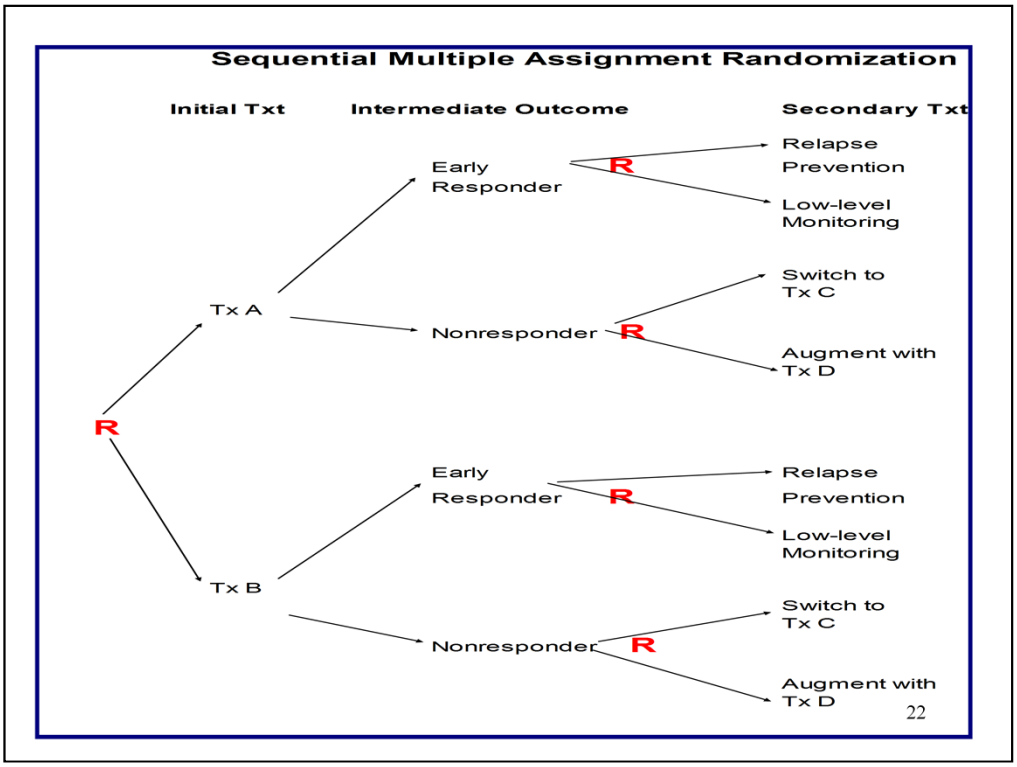
Individualized interventions



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Equal randomization

Usual reaction is (1) I'm worried about sample size and

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In reality, both of these problems are less worrisome than one might think—see following slides.

SMART Design Principles

•KEEP IT SIMPLE: At each stage (critical decision point), restrict class of treatments only by ethical, feasibility or strong scientific considerations. Use a low dimension summary (responder status) instead of all intermediate outcomes (adherence, etc.) to restrict class of next treatments.

•Collect intermediate outcomes that might be useful in ascertaining for whom each treatment works best (adherence, etc.); information that might be used to individualize subsequent treatment.

23

Note we considered different txt's for the responders as compared to the nonresponders.

In mental illness studies feasibility considerations may force us to use preference in this low dimensional summary.

SMART Design Principles

•Choose primary hypotheses that are both scientifically important and aid in developing the adaptive treatment strategy.

  •Power trial to address these hypotheses.

•Conduct secondary analyses that further develop the adaptive treatment strategy and that use the randomization to eliminate confounding.

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SMART Designing Principles: Primary Hypothesis

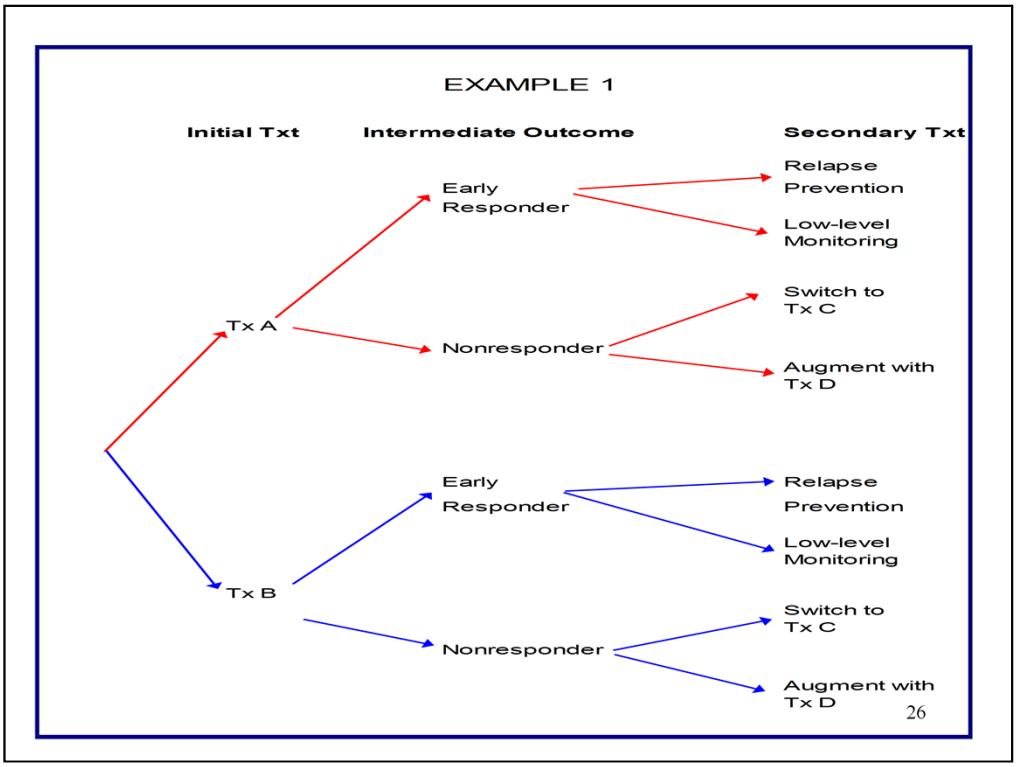
•EXAMPLE 1: (*sample size is highly constrained*): Hypothesize that controlling for the secondary treatments, the initial treatment A results in lower symptoms than the initial treatment B.

•EXAMPLE 2: (*sample size is less constrained*): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D.

These are main effects a la' ANOVA

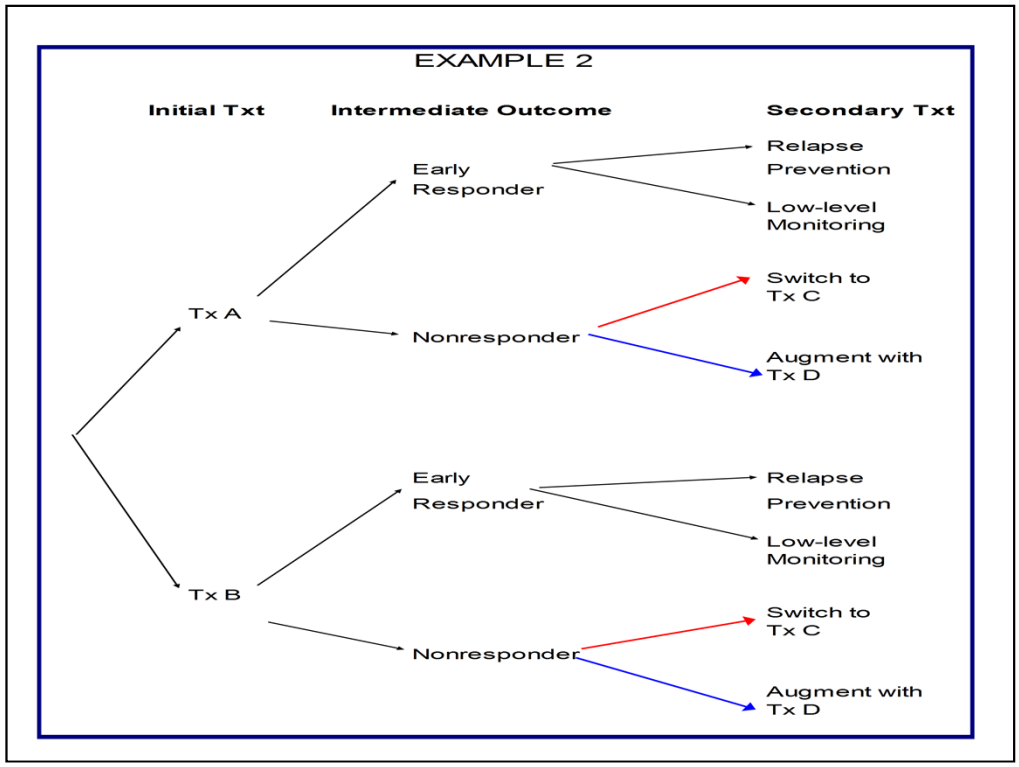
The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

Example 1: Effects of secondary treatments are controlled by experimental design –not by statistical analysis



A study of initial tx's in which subsequent tx's are controlled.

Here you can use a variety of analyses, growth curve models, survival analysis, etc.



A study of nonresponders in which one controls the tx's to which people don't respond to.

SMART Designing Principles: Sample Size Formula

•EXAMPLE 1: (sample size is highly constrained): Hypothesize that given the secondary treatments provided, the initial treatment A results in lower symptoms than the initial treatment B. *Sample size formula is same as for a two group comparison.*

•EXAMPLE 2: (sample size is less constrained): Hypothesize that among non-responders a switch to treatment C results in lower symptoms than an augment with treatment D. *Sample size formula is same as a two group comparison of non-responders.*

These are main effects a la' ANOVA

Sample Sizes

N=trial size

	Example 1	Example 2
$\Delta\mu/\sigma$ =.3	N = 402	N = 402/initial nonresponse rate
$\Delta\mu/\sigma$ =.5	N = 146	N = 146/initial nonresponse rate

α = .05, power =1 – β=.85

Sigma for example 1 is the std of primary outcome of patients initially assigned tx A (or B)

Sigma for example 2 is the std of primary outcome of non-responding patients who are assigned a switch (or augment)

Throughout working assumptions are equal variances and normality

Sample sizes calculated on the website:
http://hedwig.mgh.harvard.edu/sample_size/quan_measur/para_quant.html

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Individualized interventions

Examples of "SMART" designs:

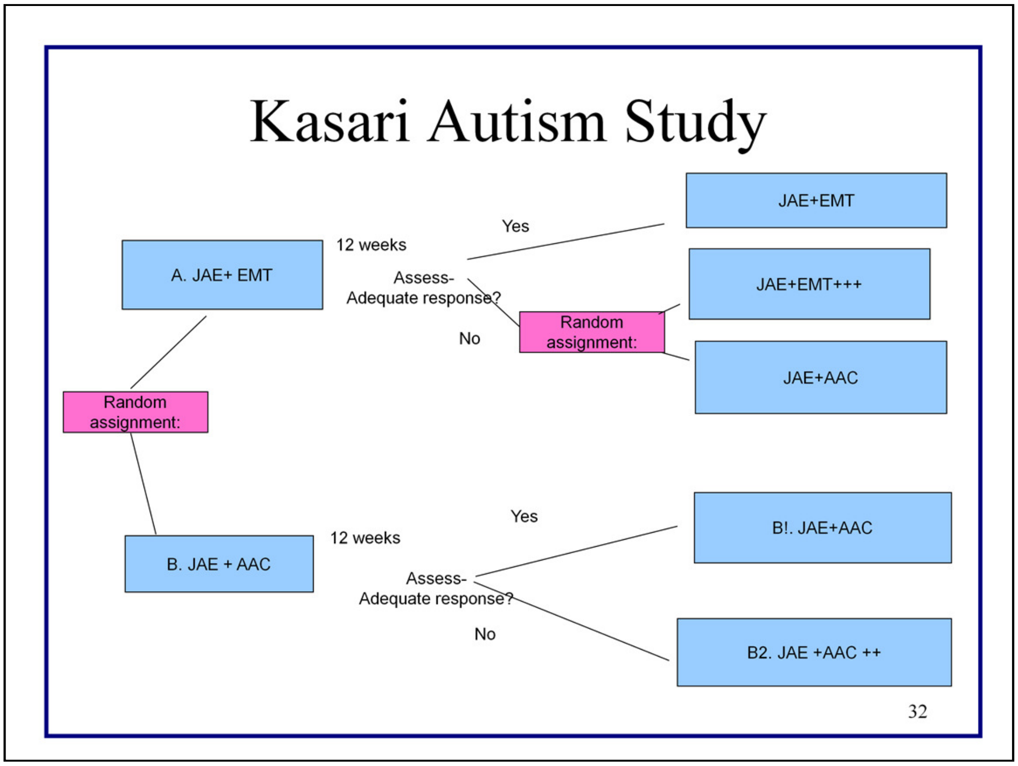
- CATIE (2001) Treatment of Psychosis in Schizophrenia
- Pelham (primary analysis) Treatment of ADHD
- Oslin (primary analysis) Treatment of Alcohol Dependence
- Jones (in field) Treatment for Pregnant Women who are Drug Dependent
- Kasari (in field) Treatment of Children with Autism
- McKay (in field) Treatment of Alcohol and Cocaine Dependence

31

These are intervention development trials. These trials are not confirmatory in the sense of confirming that one adaptive intervention is best.

The primary analyses are being conducted with the second two

Other trials in cancer.



Pop'n: children who are nonverbal (not

using spoken language) by 5 years of age despite involvement in traditional intervention programs

N=90 6 month trial

cutoff for nonresponse at 12 weeks (three measures of communication to yield our ***response/non-response indicator*****: number of words used spontaneously during parent-child interaction, number of communicative**

functions used for each word during parent-child interactions, and generalization of spontaneous

words to express multiple communication functions.) Responder status—increase of 25% over baseline in at least half of 14 assessment measures

JAE *Joint attention and joint engagement*

Enhanced Milieu Teaching (EMT) is a

naturalistic language intervention that promotes functional use of new language forms in the context of every

day interactions with parents and teachers. EMT uses environmental arrangement, responsive interaction,

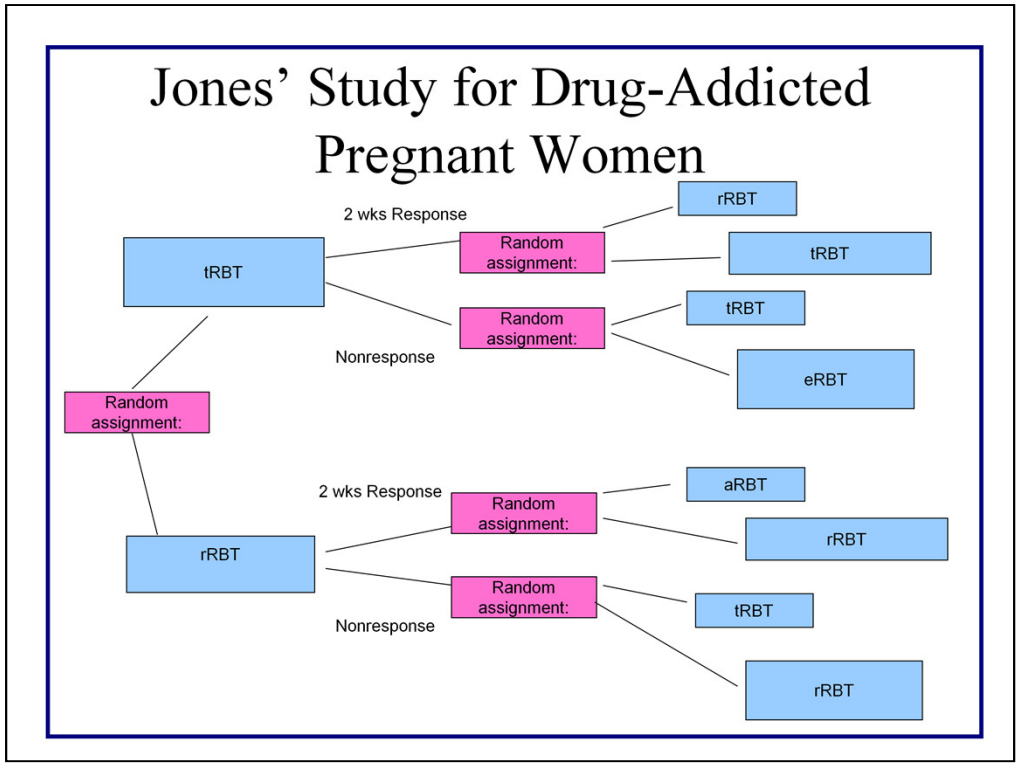
language modeling, and systematic prompting procedures to teach functional language.

augmentative and alternative communication interventions (AAC)

Primary Aim:

1) To compare the slopes in outcome measures of communication and language across three time periods

(times 0, 3 months and 6 months) for the two treatments: JAE +AAC strategy vs enhanced JAE strategy



This study is in the field n=300 primary hypothesis compared always traditional RBT vs always reduce RBT

Primary outcome is "in treatment when child born"

Nonresponse ==missed unexcused tx day or positive urine for opioid or cocaine use or self report of opioid/cocaine use

RBT==reinforcement based tx

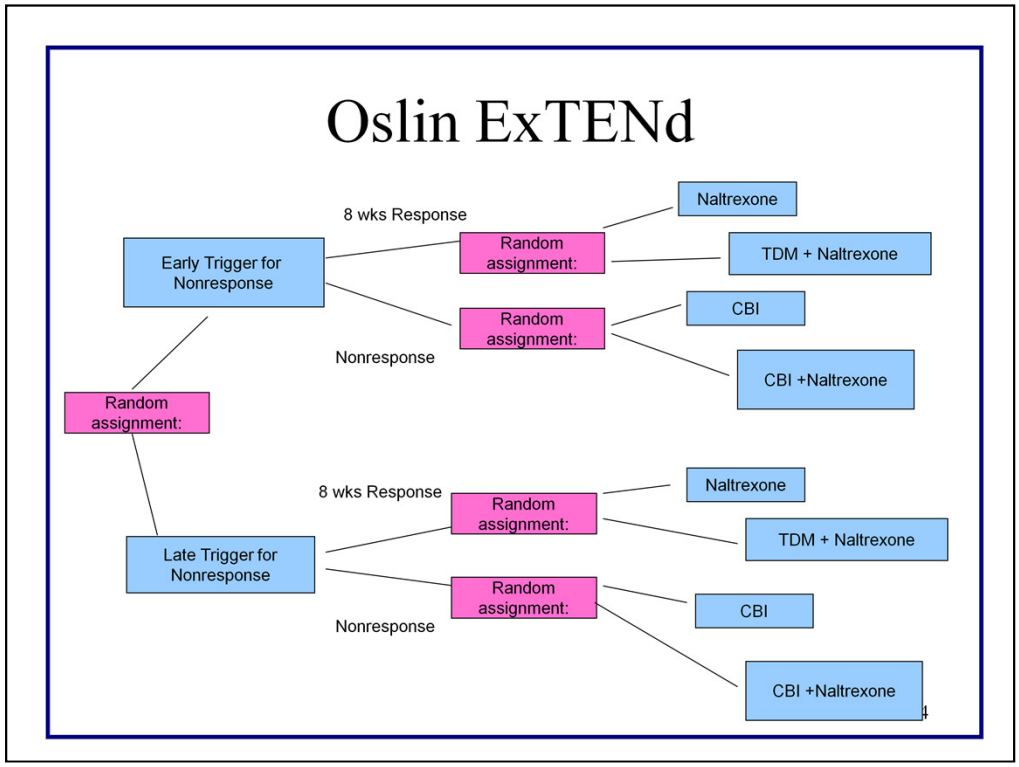
These differ in intensity and scope (in increasing order below)

aRBT is abbreviated RBT

rRBT is reduced RBT

tRBT is traditional

eRBT is enhanced



Alcohol dependent subjects begin on Naltrexone, an opioid receptor antagonist then in ensuing two months are monitored for heavy drinking

Trigger for nonresponse is heavy drinking days

Early trigger 2 or more hdd

Late trigger 5 or more hdd

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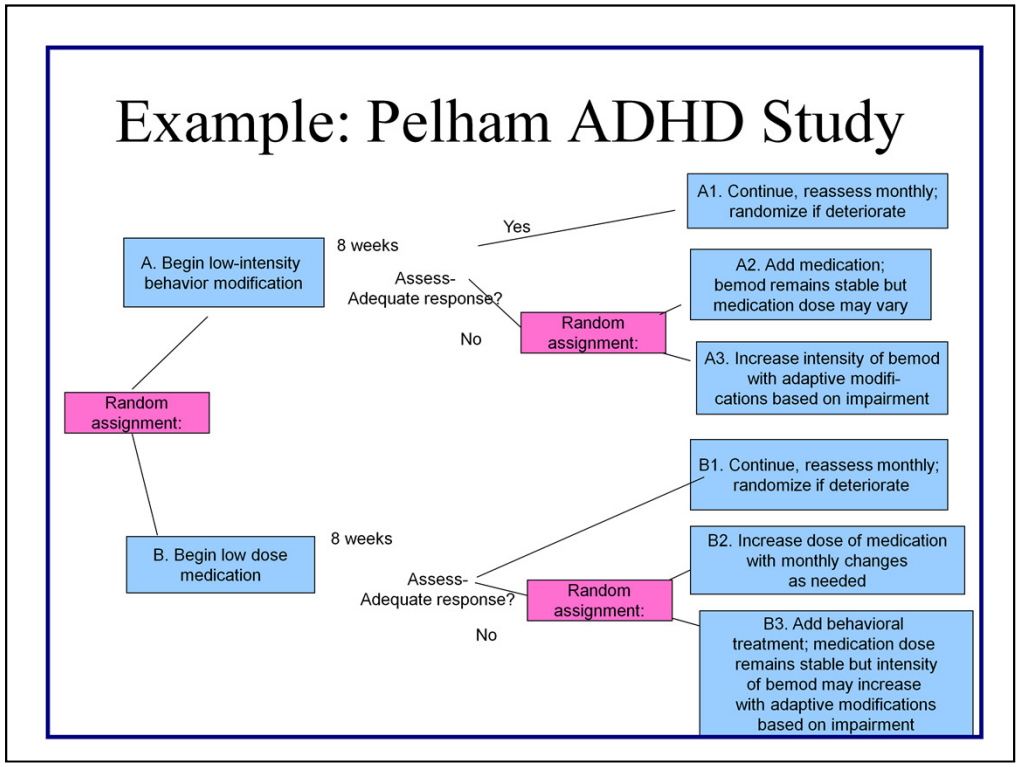

The medication is Ritalin

Adaptive Pharmacological and Behavioral Treatments for Children with ADHD: Sequencing, Combining, and Escalating Doses

(1) Average performance on the teacher rated Individualized Target Behavior Evaluations – ITB-- is less than 75% AND
(2) Rating by teachers as impaired (i.e., greater than 3) on the (Impairment Rating Scale) IRS in at least one domain.

Our outcome will be a teacher rated classroom performance recorded at 8 months. N=149

Exploring Greater Treatment Individualization via Q-Learning

Q-Learning is an extension of regression to sequential treatments.

- This regression results in a proposal for a more deeply tailored adaptive treatment strategy.
- A subsequent trial would evaluate the proposed adaptive treatment strategy.

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Q-Learning using data on children with ADHD

- Stage 1 data: (X_1, A_1, R_1)
  - $R_1=1$ if responder; $=0$ if non-responder
  - $A_1 =1$ if BMOD, $A_1=-1$ if MED
  - X_1 includes baseline school performance, (Y_0) and prior medication (S_1)
    - $S_1 =1$ if prior use of medication; $=0$, if not.
- Stage 1 involves all children

38

Since the primary analyses are being written up at this time we use altered data

A1=1 if BMOD, -1 if MED

A2=1 if enhance, -1 if augment

Q-Learning using data on children with ADHD

- Stage 2 data: (X_2, A_2, Y)
  - Y = end of year school performance
  - $A_2=1$ if Enhance, $A_2=-1$ if Augment
  - X_2 includes the month of non-response, (M_2) and a measure of adherence in stage 1 (S_2)
    - $S_2=1$ if adherent in stage 1; $=0$, if non-adherent
- Stage 2 involves only children who do not respond in Stage 1 $(R_1=0)$.

39

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A2=1 if enhance, -1 if augment

Q-Learning for SMART Studies

- Conduct the regressions in backwards order! E.g. Stage 2 first, then Stage 1.
- Why?
  - Stage 1 dependent variable must control for Stage 2 treatment.
  - Stage 1 dependent variable is a predictor of Y under optimal treatment in stage 2.
  - Stage 2 analysis is used to construct the predictor of Y, e.g. $\hat{Y}$

40

A1=1 if BMOD, -1 if MED

A2=1 if enhance, -1 if augment

Stage 2 Regression for Non-responding Children

- Dependent Variable: Y (end of school year performance)
- Treatment: $A_2=1$ if Enhance, $A_2=-1$ if Augment
- Interactions with Treatment, A_2: stage 1 treatment (A_1) and adherence (S_2)
- Controls: baseline school performance, (Y_0) and baseline prior medication (S_1), month of non-response (M_2)

41

A1=1 if BMOD, -1 if MED

A2=1 if enhance, -1 if augment

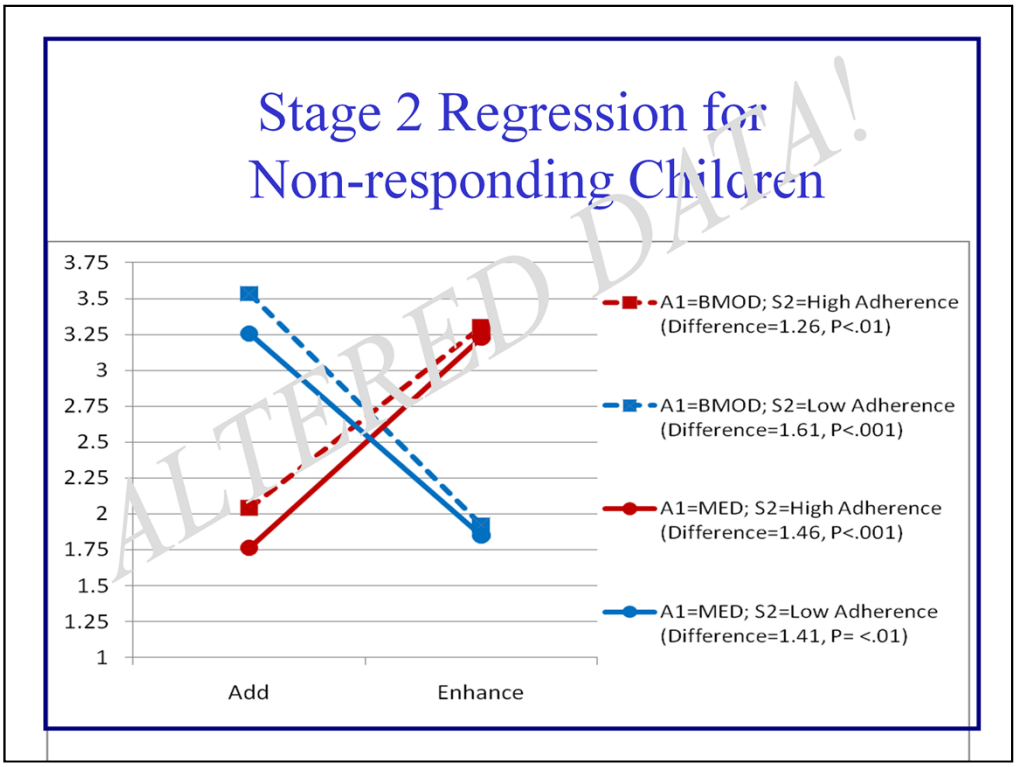
Q-Learning using data on children with ADHD

- Stage 2 regression for Y:

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_{21} + A_1\beta_{22} + S_2\beta_{23})$$

- Interesting Stage 2 contrast: Does the best stage 2 tactic (enhance versus augment) differ by whether the child/family is adherent?

42



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Stage 1 Regression for All Children

- Dependent Variable: $\hat{Y}$ (predicted end of school year performance under optimal stage 2 treatment)
- Treatment: $A_1=1$ if BEMOD, $A_1=-1$ if MED
- Interactions with Treatment, A_1: prior medication (S_1)
- Control: baseline school performance, (Y_0)

44

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Dependent Variable for Stage 1 Regression

- Stage 2 regression for Y:

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_{21} + A_1\beta_{22} + S_2\beta_{23})$$

- Stage 1 dependent variable:

$$R_1 Y + (1 - R_1)\hat{Y}$$

$$\hat{Y} = (1, Y_0, S_1, A_1, M_2, S_2)\hat{\alpha}_2 + |\hat{\beta}_{21} + A_1\hat{\beta}_{22} + S_2\hat{\beta}_{23}|$$

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Q-Learning using data on children with ADHD

- Stage 1 regression for $\widehat{Y}$:

$$(1, Y_0, S_1)\alpha_1 + A_1(\beta_{11} + S_1\beta_{12})$$

- Interesting stage 1 contrast: does the best initial treatment differ by whether a child received medication in the prior year for ADHD?

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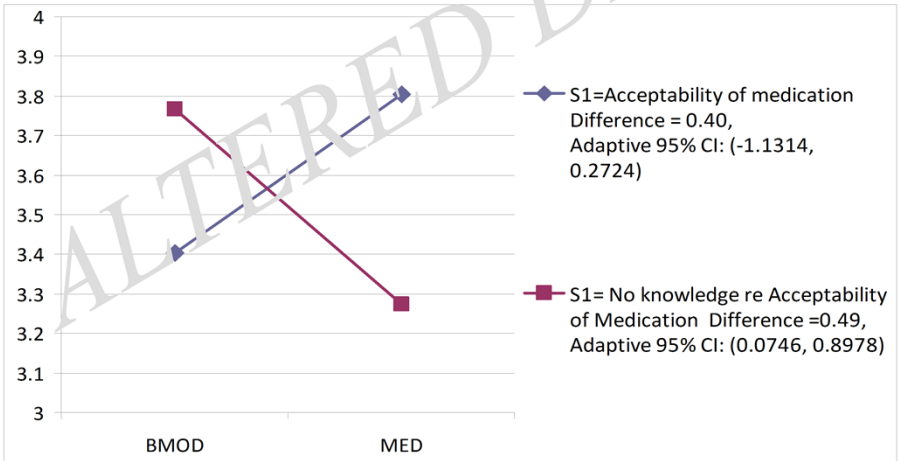
Since the primary analyses are being written up at this time we use altered data

S1=1 if on med in prior year, =0 otherwise

Stage 1 Regression for All Children



Adaptive Treatment Strategy Proposal

IF medication has not been used in the prior year
THEN begin with BMOD;
ELSE select either BMOD or MED.

IF the child is nonresponsive and was non-adherent, THEN augment present treatment;
ELSE IF the child is nonresponse and was adherent, THEN select intensification of current treatment.

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Discussion

- Confidence Intervals have been developed!
- Software in R for Q-Learning out and, in SAS, is coming out soon!

https://methodology.psu.edu/ra/adap-treat-strat/qlearning

- Aside: Non-adherence is an outcome (like side effects) that indicates need to tailor treatment.

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Adherence is not a statistical nuisance; adherence indicates need to tailor treatment.

This seminar can be found at:

http://www.stat.lsa.umich.edu/~samurphy/seminars/HIV Intervention Science Training Prog.12.16.11.pdf

This seminar is based on work with many collaborators some of which are: L. Collins, E. Laber, M. Qian, D. Almirall, K. Lynch, J. McKay, D. Oslin, T. Ten Have, I. Nahum-Shani & B. Pelham. Email me with questions or if you would like a copy:

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