

Adaptive Interventions: Healing with Data

S.A. Murphy

Sante Fe Institute, Community Lecture

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50 min. Adaptive Interventions: Healing with Data

Why are treatments for chronic disease and addiction so often ineffective?

Statistician Susan Murphy believes that generalized treatment approaches simply don't take into account critical individual differences like patient response, risk, burden, adherence, and preference. By implementing a sequence of decision rules that dynamically adapt treatment to each individual's response over time, Murphy explores the promising potential of adaptive intervention to maximize treatment efficacy by avoiding over-treatment and providing increased treatment only to those who need it.

Susan Murphy is a 2013 MacArthur Fellow who teaches Statistics at the University of Michigan. Murphy is also a principal investigator at the Methodology Center of Pennsylvania State University.

Outline

- Adaptive Interventions
- SMART Designs
- Trial Design Principles and Analysis
- Exploring Individualization using the “Adaptive Interventions for Children with ADHD” study (W. Pelham, PI).

2

Other names are dynamic treatment regimes, treatment algorithms, stepped care models, expert systems, adaptive treatment strategy, treatment protocols. Structured treatment interruptions in the treatment of AIDS are a form of adaptive treatment strategy

Adaptive Interventions are individually tailored sequences of treatments, with treatment type and dosage changing according to patient outcomes. Operationalize clinical practice.

- Kasari et al. (2014) Treatment of Autism
- McKay (2009) Treatment of Substance Use Disorders
- Marlowe et al. (2008, 2012) Drug Court
- Adams et al. (2013) Improving Physical Activity

3

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 info (genetics, 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

Kasari C., Kaiser A., Goods K., Nietfeld J., Mathy P., Landa R., [Murphy S.](#), Almirall D. (2014) Communication Interventions for Minimally Verbal Children with Autism: Sequential Multiple Assignment Randomized Trial. *Journal of the American Academy of Child and Adolescent Psychiatry* 53(6):635-646.

Brooner (2002, 2007) uses a two component adaptive intervention, 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.

Article Source: [An Adaptive Physical Activity Intervention for Overweight Adults: A Randomized Controlled Trial](#)

Adams MA, Sallis JF, Norman GJ, Hovell MF, Hekler EB, et al. (2013) An Adaptive Physical Activity Intervention for Overweight Adults: A Randomized Controlled Trial. PLoS ONE 8(12): e82901. doi: 10.1371/journal.pone.0082901

Why Adaptive Interventions?

- 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 (→ relapse)
- Excessive burden (→ non-adherence) is common

4

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

Example of an Adaptive Intervention

- Adaptive Drug Court Program for drug abusing offenders.
- Goal is to minimize recidivism and drug use.
- Marlowe et al. (2008, 2009, 2012)

5

Cites are below.

See also

<http://www.ct.gov/dss/cwp/view.asp?a=2353&q=305266>

See the Connecticut Dept of Social Services. “Jobs First” program

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

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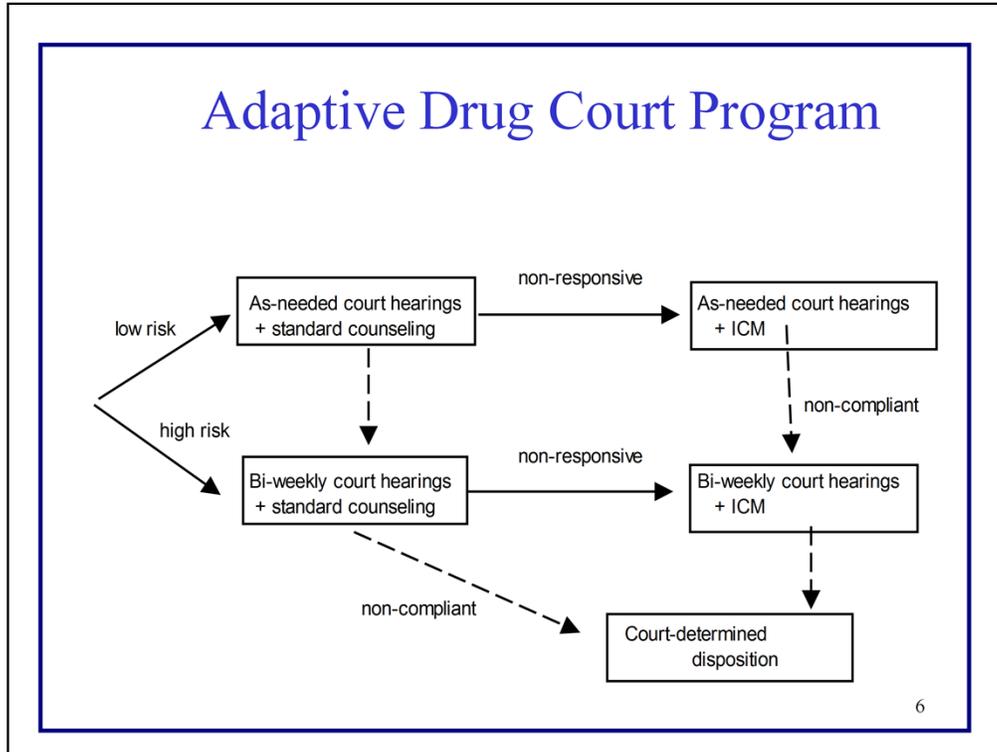
Marlowe DB, Festinger DS, Arabia PL, Dugosh KL, Benasutti KM, Croft JR.

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

**Adaptive Programming Improves Outcomes in Drug Court : An
Experimental Trial**

Criminal Justice and Behavior 2012 39: 514 Douglas B. Marlowe, David S.
Festinger, Karen L. Dugosh,
Kathleen M. Benasutti, Gloria Fox and Jason R. Croft

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 formal drug abuse 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?
(AKA: how do we individualize the sequence of treatments to the person?)

7

The design of the adaptive intervention involves a sequence of treatment decisions.

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

Also how to combine therapies?

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8

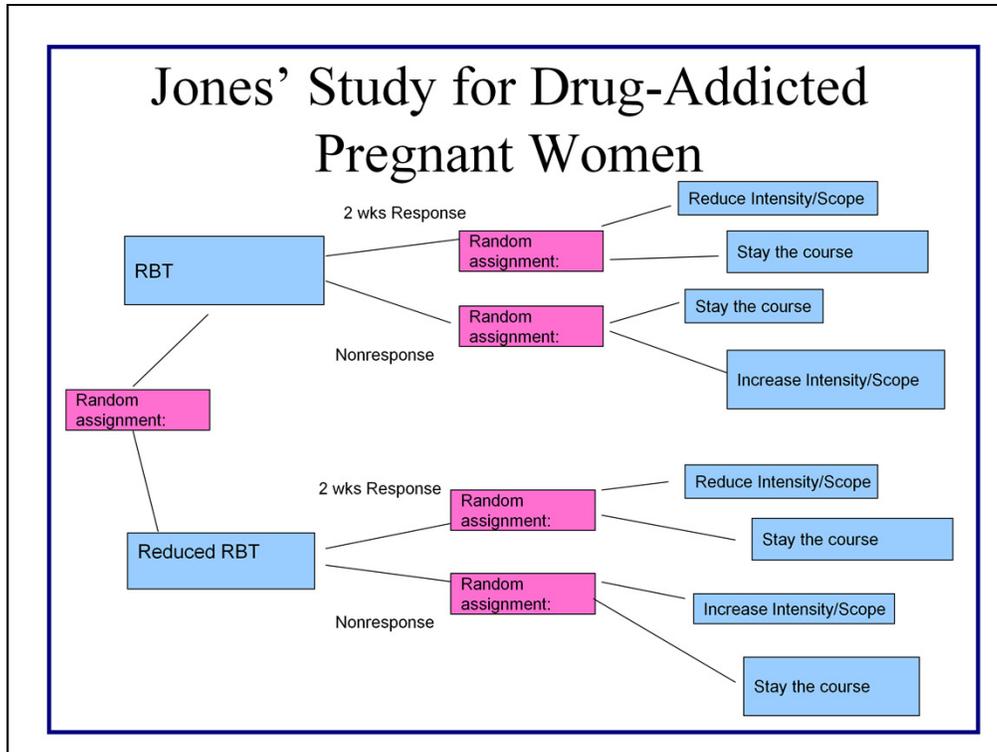
SMART Studies

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

These are multi-stage clinical trials; each participant proceeds through stages of treatment.

Each stage concerns a critical decision and randomization takes place at each critical decision.

Goal of trial is to inform the construction of an adaptive intervention.



This study was recently completed.

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

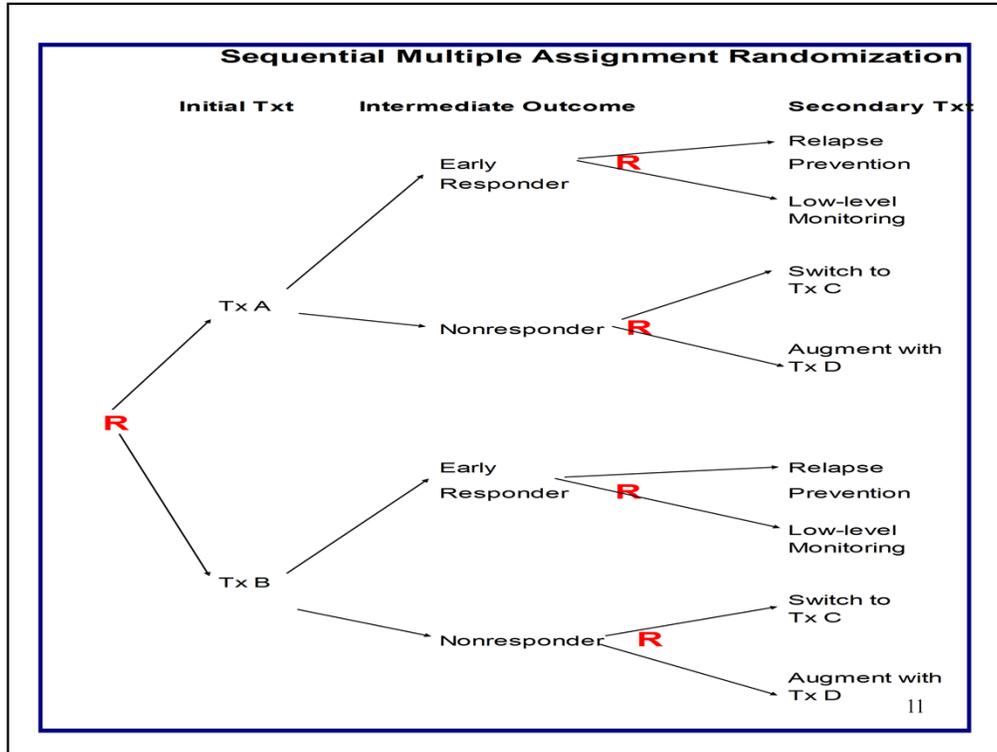
tRBT is traditional

eRBT is enhanced

This trial is designed to provide data regarding how the intensity and scope of reinforcement based treatment (RBT) might be adapted to

a pregnant woman’s progress in treatment. Components of RBT are:

1. Functional assessment of drug/alcohol use
2. Use of behavioral contracts
3. Motivational interviewing style of therapy
4. Graphing and monitoring of critical identified behaviors to sustain abstinence
5. Abstinence-contingent access to elements 8–11 below as well as other tangible reinforcers
6. Outreach upon first noncompliant event
7. Individual therapy
8. Recreation paid for by the program
9. Job club
10. Social club including free lunch
11. Skills-building modules



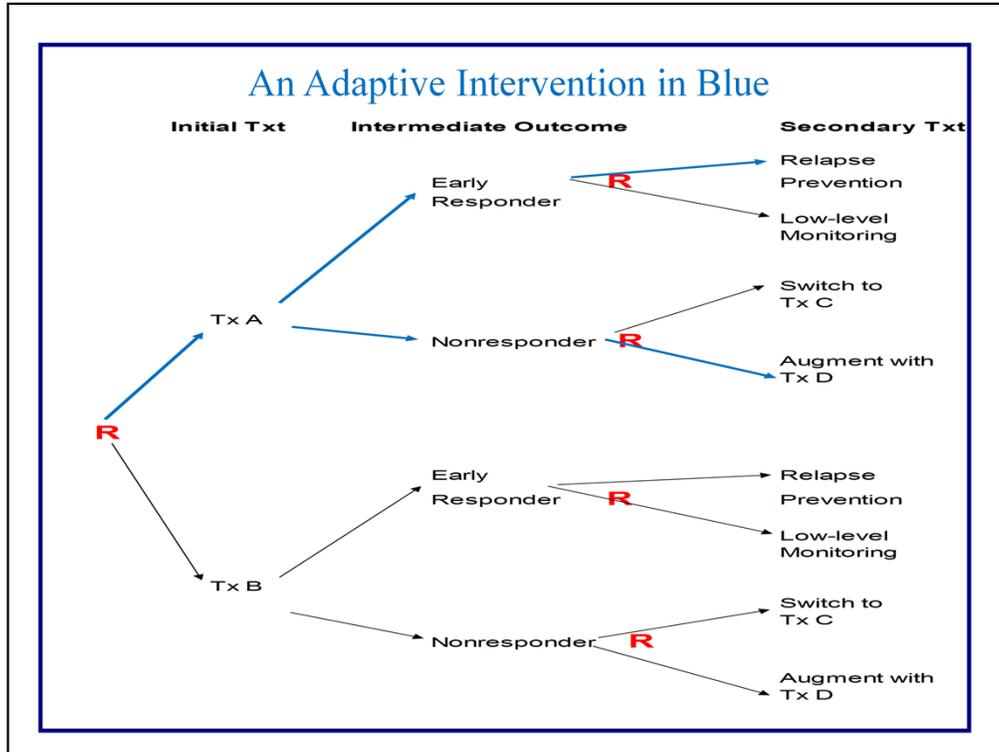
Hypothetical trial: Outcome is not shown but is on far right. The second randomization can take place up front (if you do not want to stratify or block by stage 1 outcomes such as adherence).

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 intervention is indicated in blue

Alternate Approach to Constructing an Adaptive Intervention

- Why not use data from multiple trials to construct the adaptive intervention?
- 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 intervention

Delayed Therapeutic Effects

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

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 interventions, 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 intervention?

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.

Sample Selection Effects

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

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, that are to be used as part of *a sequence of treatments*, we need to take into account, e.g. control, the effects of the secondary treatments thus SMART
- Standard single-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

Examples of “SMART” designs:

- Pelham (2012) Treatment of ADHD
- Oslin (2013) Treatment of Alcohol Dependence
- Kasari (multiple) Treatment of Children with Autism
- McKay (in field) Treatment of Alcohol and Cocaine Dependence
- Kilbourne (in field) “Treatment” to Improve Implementation of Effective Programs.

<http://methodology.psu.edu/ra/smart/projects>

18

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

Other trials in cancer.

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19

SMART Design Principles

- **Select the Critical Decisions**
- **Aim for Simplicity:** 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.

20

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 intervention.
 - Determine sample size of trial to address these hypotheses.
- Conduct secondary analyses that further develop the adaptive intervention—these analyses use the randomization to eliminate confounding.

21

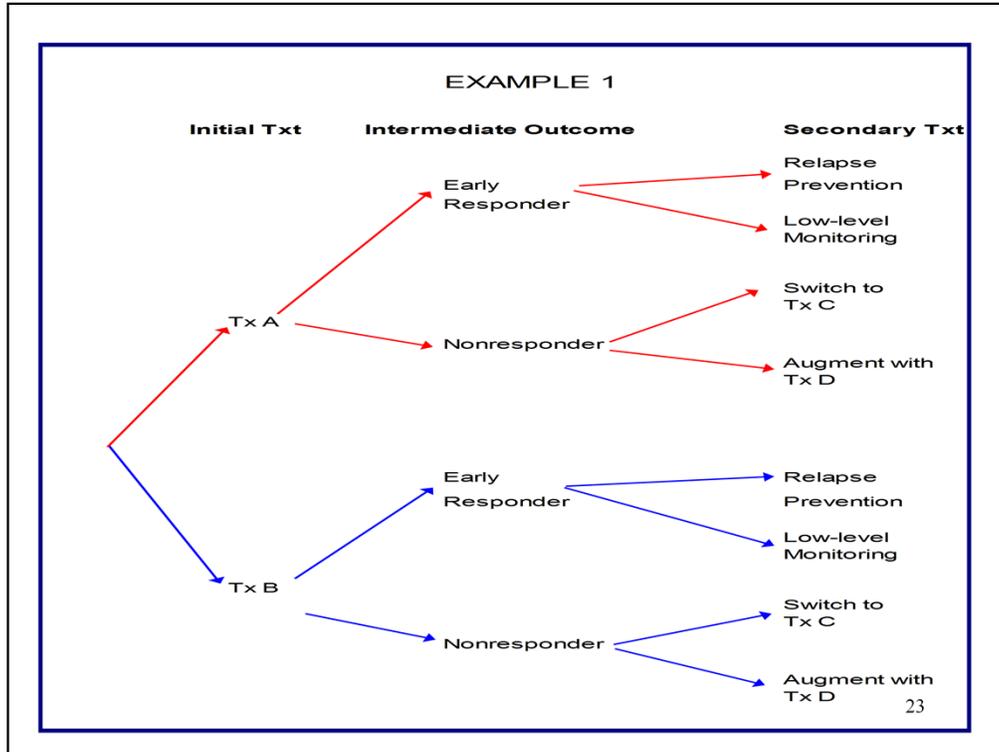
SMART Designing Principles: Primary Hypothesis

- EXAMPLE 1: (*sample size is highly constrained*):
Hypothesize that adaptive interventions beginning with treatment A result in lower symptoms than adaptive interventions beginning with 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

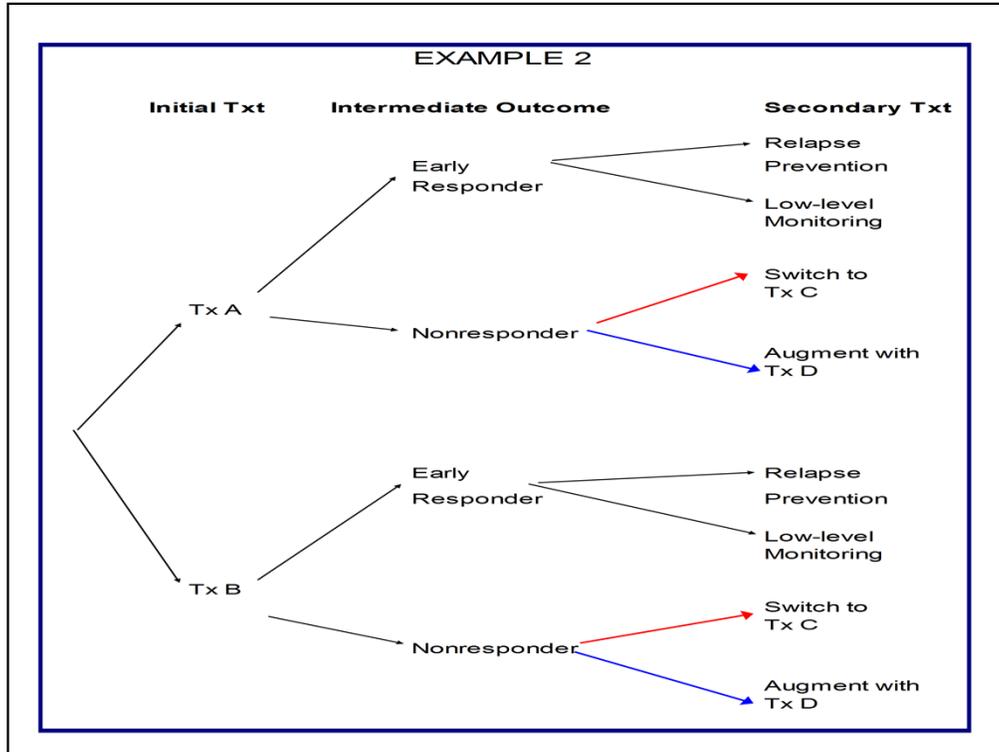
The second would be appropriate if you initially wanted to run a trial for non-responders and are now considering SMART

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 is the 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 is same as for a two group comparison of non-responders.*

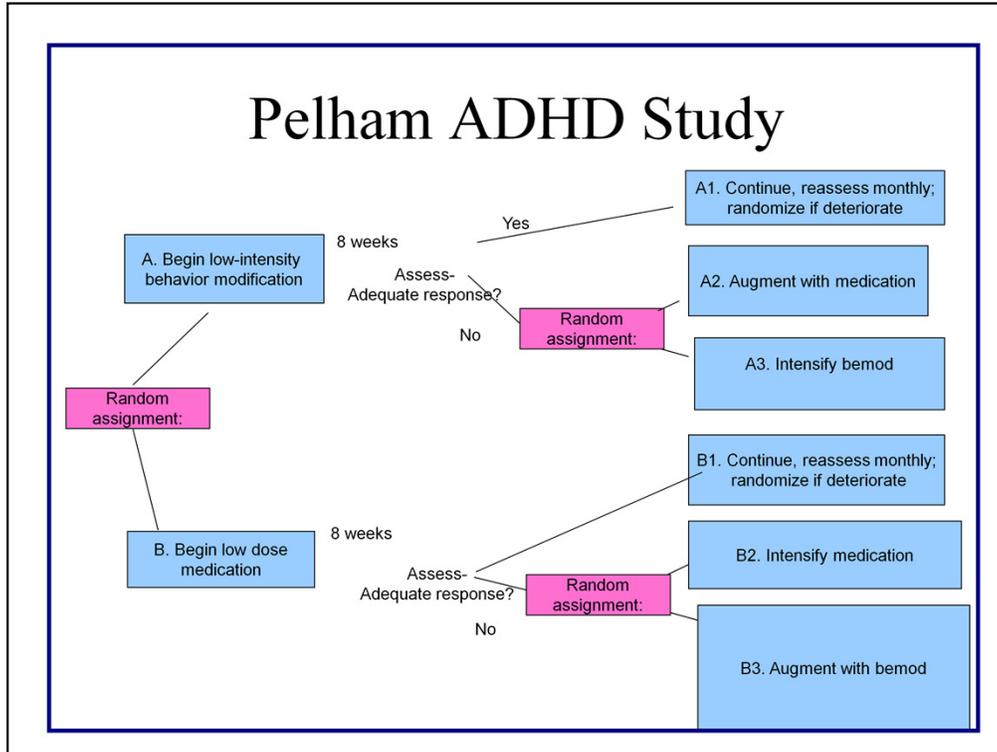
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26

a task force of the American Psychological Association recommends psychosocial first (Brown et al. 2007), whereas the guidelines of the American Academy of Child and Adolescent Psychiatry (2007) recommend using medication first.



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

- I. Nahum–Shani, M. Qian, D. Almiral, W.. Pelham, B. Gnagy, G. Fabiano, J. Waxmonsky, J. Yu and S.A. Murphy (2012). Experimental Design and Primary Data Analysis Methods for Comparing Adaptive Interventions. *Psychological Methods* 17(4), 457–477.
- II. I. Nahum–Shani, M. Qian, D. Almiral, W.. Pelham, B. Gnagy, G. Fabiano, J. Waxmonsky, J. Yu and S.A. Murphy (2012). Q–Learning: A Data Analysis Method for Constructing Adaptive Interventions. *Psychological Methods* 17(4):478–94.

William E. Pelham, Jr. (PI) , Lisa Burrows-MacLean, James Waxmonsky, Greta Massetti,
Daniel Waschbusch, Gregory Fabiano, Martin Hoffman, Susan Murphy, E. Michael Foster,
Randy Carter, Elizabeth Gnagy, Jihnhee Yu

(IES 2006-2010)

Exploring Greater Individualization via Q-Learning

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

- This regression results in a proposal for an optimal adaptive intervention.
- A subsequent trial might contrast the proposed adaptive intervention with standard practice.

28

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 , whether medicated in prior year (S_1), ODD (O_1)
 - $S_1=1$ if medicated in prior year; $=0$, otherwise.
- Stage 1 involves all children

29

N=138

A1=1 if BMOD, -1 if MED

A2=1 if intensify, -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 Intensify, $A_2=-1$ 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 ($R_1=0$).

30

A1=1 if BMOD, -1 if MED

A2=1 if intensify, -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 is a predictor of end of school performance, Y , under optimal treatment in stage 2.
 - Stage 2 analysis is used to construct the predictor, \hat{Y} of end of school performance, Y

31

A1=1 if BMOD, -1 if MED

A2=1 if intensify, -1 if augment

Stage 2 Regression for Non-responding Children

- Dependent Variable: Y (end of school year performance)
- Treatment: $A_2=1$ if Intensify, $A_2=-1$ 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)

32

$A_1=1$ if BMOD, -1 if MED

$A_2=1$ if intensify, -1 if augment

Q-Learning using data on children with ADHD

- Stage 2 regression—prediction of end of school year performance Y :

$$\alpha_{21} + \alpha_{22}Y_0 + \alpha_{23}S_1 + \alpha_{24}O_1 + \alpha_{25}A_1 + \alpha_{26}M_2 + \alpha_{27}S_2 \\ + (\beta_{21} + \beta_{22}A_1 + \beta_{23}S_2)A_2$$

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

33

$A_1=1$ if BMOD, -1 if MED

$S_2=1$ if adherent to initial txt; $S_2=0$ if nonadherent to initial treatment.

$A_2=1$ if intensify, -1 if augment

Q-Learning using data on children with ADHD

- Decision rule is “if child is non-responding then intensify initial treatment if $-.72 + .05A_1 + .97S_2 > 0$, otherwise augment”

Decision Rule for Non-responding Children	Initial Treatment =BMOD	Initial Treatment=MED
Adherent	Intensify	Intensify
Not Adherent	Augment	Augment

34

A1=1 if BMOD, -1 if MED

S2=1 if adherent to initial txt.

A2=1 if intensify, -1 if augment

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), baseline ODD, (O_1)

35

A1=1 if BMOD, -1 if MED

A2=1 if enhance, -1 if augment

Constructing the Dependent Variable, \hat{Y} for the Stage 1 Regression

Stage 1 dependent variable: $R_1Y + (1 - R_1)\hat{Y}$

where

$$\hat{Y} = \hat{\alpha}_{21} + \hat{\alpha}_{22}Y_0 + \hat{\alpha}_{23}S_1 + \hat{\alpha}_{24}O_1 + \hat{\alpha}_{25}A_1 + \hat{\alpha}_{26}M_2 + \hat{\alpha}_{27}S_2 \\ + |\hat{\beta}_{21} + A_1\hat{\beta}_{22} + S_2\hat{\beta}_{23}|$$

Q-Learning using data on children with ADHD

- Stage 1 regression for \hat{Y} :

$$\alpha_{11} + \alpha_{12}Y_0 + \alpha_{13}S_1 + \alpha_{14}O_1 \\ + (\beta_{11} + \beta_{12}S_1)A_1$$

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

37

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

Q-Learning using data on children with ADHD

- Decision rule is “Begin with BMOD if $.17 - .32S_1 > 0$, otherwise begin with MED”

Initial Decision Rule	Initial Treatment
Prior MEDS	MEDS
No Prior MEDS	BMOD

38

$S_1 = 1$ if prior meds, $=0$ if not.

$A_1 = 1$ if BMOD, -1 if MED

1st Adaptive Intervention Proposal

IF medication was not used in the prior year
THEN begin with BMOD;
ELSE select MED.

IF the child is nonresponsive and was non-adherent, **THEN** augment present treatment;
ELSE IF the child is nonresponsive and was adherent, **THEN** intensify current treatment.

39

ADHD Example

- The adaptive intervention is quite decisive. We developed this adaptive intervention using a trial on *only 138 children*. We need to quantify our uncertainty!
- Would a similar trial obtain similar results?
- There are strong opinions regarding how to treat ADHD.
- One solution –use confidence intervals.

40

a task force of the American Psychological Association recommends psychosocial first (Brown et al. 2007), whereas the guidelines of the American Academy of Child and Adolescent Psychiatry (2007) recommend using medication first.

ADHD Example

Treatment Decision for Non-responders. Positive Treatment Effect → Intensify

	90% Confidence Interval for second stage Treatment Effect
Adherent to BMOD	(-0.08, 0.69)
Adherent to MED	(-0.18, 0.62)
Non-adherent to BMOD	(-1.10, -0.28)
Non-adherent to MED	(-1.25, -0.29)

41

ADHD Example

First State Treatment Decision: Positive Treatment Effect → BMOD

	90% Confidence Interval for First Stage Treatment Effect
Prior MEDS	(-0.48, 0.16)
No Prior MEDS	(-0.05, 0.39)

42

2nd Adaptive Intervention Proposal

IF medication was not 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 nonresponsive and was adherent, **THEN** select either intensification or augmentation of current treatment.

43

Our present work.....

- Increasing use of wearable computers (e.g smart phones, etc.) to both collect real time data and provide *just-in-time* adaptive interventions.
- We have developed study designs aimed at providing data for use in constructing and optimizing just-in-time adaptive interventions.
 - Participants are randomized 100's or 1000's of times in these designs.

44

This seminar can be found at:

<http://www.stat.lsa.umich.edu/~samurphy/seminars/SanteFe.04.08.15.ppt>

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 with questions or if you would like a copy:

samurphy@umich.edu

Adaptive Implementation Intervention of “Replicating Effective Programs”

“Treatments”:

- External Facilitators (EF) and
- Internal Facilitators (IF)

46

Replicating Effective Programs (REP) is an implementation intervention to promote use of psychosocial txt in community-based settings (site)

But, 50-75% of sites do not respond to REP alone

There are two types of REP augmentation options

External Facilitators (EF, less expensive): Reside outside of the site, provide technical expertise by phone

Internal Facilitators (IF, more expensive): Employed by sites, direct relationship to site leaders, protected time specifically for improving EBP adoption

Some sites need augmented REP, but not all sites require REP+EF+IF; Cannot do IF without EF

REP was used successfully in previous literature to help HIV/AIDS community-based settings/clinics adopt behavioral interventions for prevention and treatment.

EBP for mood disorders is Life Goals CC

Despite availability of EBPs, quality of life and outcomes for persons with mental disorders remain suboptimal because of organizational barriers.

Challenges to community-based settings include

Lack tools to embed EBPs into routine clinical care
Lack of provider training, on-going support
Lack of awareness of EBPs among leaders
Providers face competing demands

In a previous preliminary study comparing REP vs REP+IF+EF, the augmented REP did much better. However, not all sites may need the IF and it is costly.

Therefore, an adaptive implementation intervention approach is necessary, whereby the implementation intervention may need to be augmented if sites are not responding (i.e., not adopting EBPs) to REP alone. In contrast to measuring correlates of implementation non-response, adaptive implementation interventions are augmented, or stepped, in direct response to limited uptake of EBPs among specific sites based on circumstances that may not be observable at baseline.

Two Critical Decisions

- (1) Which treatment to provide to sites that are insufficient responders to standard REP?
- (2) Which treatment to provide to the sites that continue to show non-response?

47

Primary Aim: To examine, among sites that do not respond to **REP** at month 6, the effect of **REP+EF+IF** versus **REP+EF** on changes (6mo to 18mo) in MH-QOL (primary), # LG encounters, psych sx, functionality, cost-effectiveness (\$/QOL) (secondary).

Aim 2: To determine, among **REP+EF** sites with continued non-response after 12 months, the effect of continued **REP+EF** vs. **REP+EF+IF** on outcomes at 24 months.

Implementation of EBPs in Mental Health

Takes years to translate evidence-based practices (EBPs) into community-based settings (clinic sites)

An example

Life Goals Collaborative Care

- This is the EBP intervention they are trying to get community based practices to take up
- An evidence-based psychosocial treatment shown to improve outcomes among patients with mood disorders (depression and bipolar) in 6 RCTs across mental health and primary care settings.
 - Outcomes include: 3 point decrease in PHQ-9 scores, 9 fold increase in prob of depression remission; 4 point increase in physical and mental health quality of life

- Effective in patients with co-occurring substance use disorders
- Based on social cognitive theory
- Delivered in 4 two-hour weekly group sessions (see below) + at least 6 individualized care management contacts
 - Contacts are designed to encourage active discussions focused on individuals' personal goals that are aligned with healthy behavior change

More details on Life Goals Components Group Sessions

Four sessions lasting 60-80 minutes focused on active discussions around personal goals, psychiatric symptoms, stigma, and health behaviors

Session 1: Personal goals

Personal goals and self-management; Understanding stigma; Symptoms & wellness

Session 2: Depressive symptoms (sx)

Overview, triggers to depressive episodes; Action plan for depression, self-assessment

Session 3: Anxiety/manic sx

Overview, triggers to episodes; Action plan: anxiety/mania, self-assessment

Session 4: Wellness plan

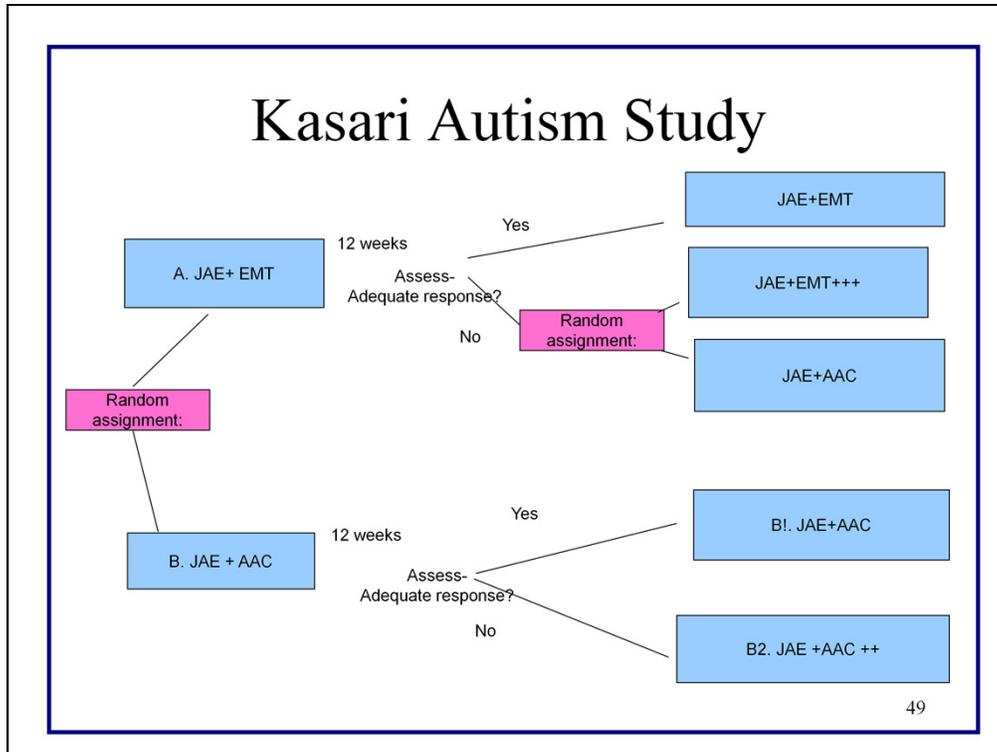
Building behavior change goals; Relapse prevention and monitoring, medications

More details on Life Goals Individualized sessions

Provider makes 6 regular individual contacts (15-20 min), encouraging ongoing healthy behavior change tied to symptom coping strategies, addressing barriers to behavior change, and encouraging ongoing symptom and behavior monitoring

month 6 on (change in) outcomes **at month 18**.

Secondary outcomes include: # Life Goals encounters (recall max is 10 for each patient), psychiatric symptoms, functional impairment, and cost-effectiveness.



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.

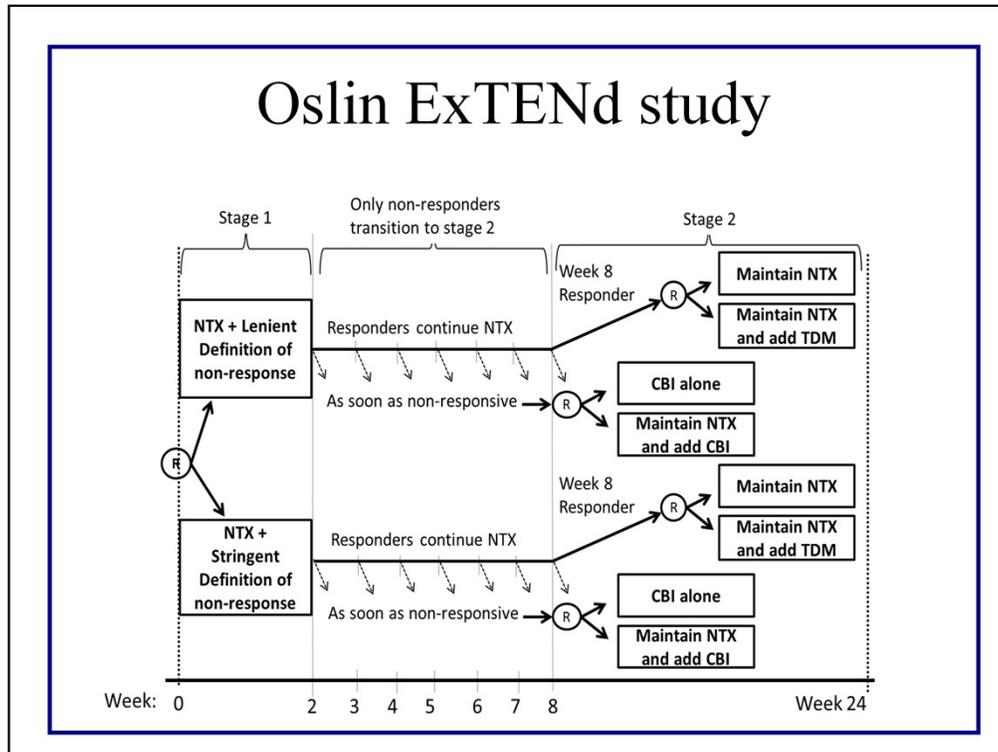
augmentative and alternative communication interventions (AAC)

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

Oslin ExTEND study



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

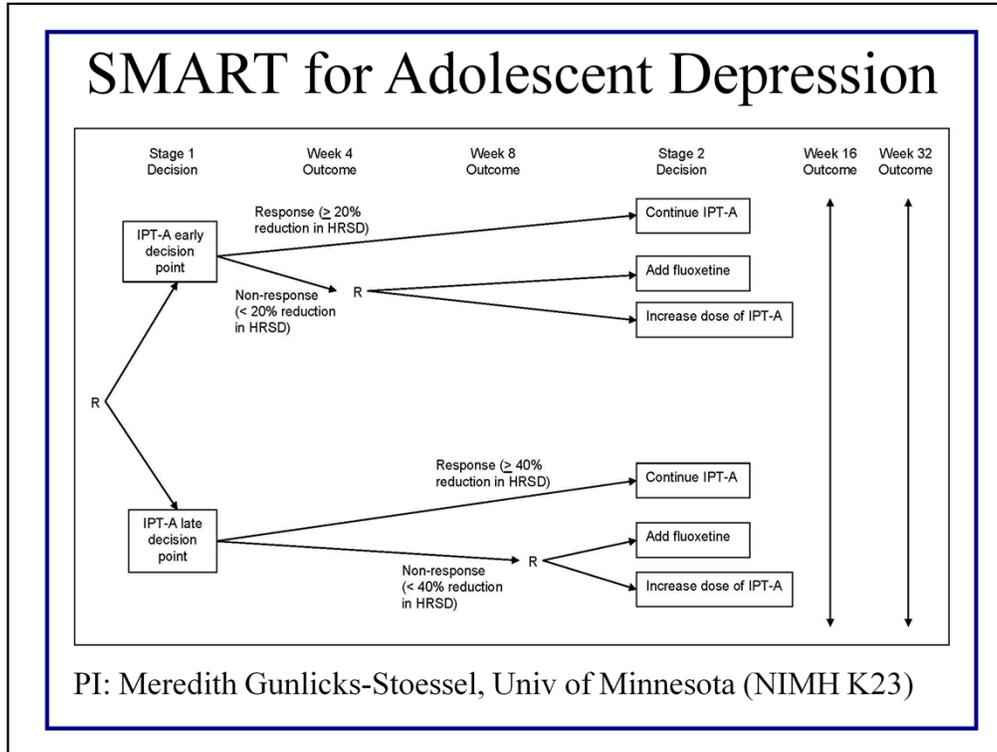
Early trigger 2 or more hdd

Late trigger 5 or more hdd

N=302

See H. Lei, I. Nahum-Shani, K. Lynch, D. Oslin and [S.A. Murphy](#) (2012). [A SMART Design for Building Individualized Treatment Sequences](#), *The Annual Review of Clinical Psychology, Review in Advance first posted online on December 12, 2011* Vol. 8: 21-48.

for a description of this study as well as the following studies



This SMART addresses the two critical questions on the previous slide.

The unit of randomization, intervention and outcome/analysis is the child.

Approximately 46 adolescents are planned to be recruited for this pilot. Meredith is half-way as of October 2, 2013.

Treatment definitions:

IPT-A: Time-limited psychotherapy that aims to decrease depressive symptoms by helping adolescents improve their relationships and interpersonal interactions

Fluoxetine:

- 10 mg per day for the first week
- 20 mg per day for the following 5 weeks
- If no treatment response is observed by week 6, the dosage can be increased to 40 mg per day
- Pharmacotherapy sessions scheduled weekly for the first 4 weeks and every other week thereafter.

The embedded tailoring variable is a cut-off on the HSRD. HSRD = Hamilton Rating Scale for Depression

The research outcomes are collected at Baseline, 4, 8, 12, 16 weeks. They include

- **Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Chaput, et al, 1999)**
- **Children's Depression Rating Scale-Revised (CDRS-R; Poznanski & Mokros, 1996)**
- **Beck Depression Inventory-II (BDI-II; Beck et al., 1996)**
- **Global Assessment Scale for Children (C-GAS; Shaffer et al., 1983)**
- **Client Satisfaction Questionnaire (CSQ-8; Larsen, et al., 1979)**
- **Adaptive Treatment Attitudes Questionnaire (ATA, Gunlicks-Stoessel, unpublished)**

Inclusion Criteria:

DSM-IV diagnosis of MDD, Dysthymic Disorder, or DD NOS

Children's Depression Rating Scale (CDRS-R) raw score ≥ 36

Children's Global Assessment Scale (CGAS) ≤ 65

Exclusion Criteria:

DSM-IV diagnosis of Psychotic Disorder, Bipolar Disorder, OCD, Substance Abuse, Conduct Disorder, Eating Disorder, or Pervasive Developmental Disorder

Active suicidality with plan and/or intent

Mental retardation

Already receiving treatment for depression

Taking antidepressant medication

Non-responder to past adequate trial of IPT-A or fluoxetine

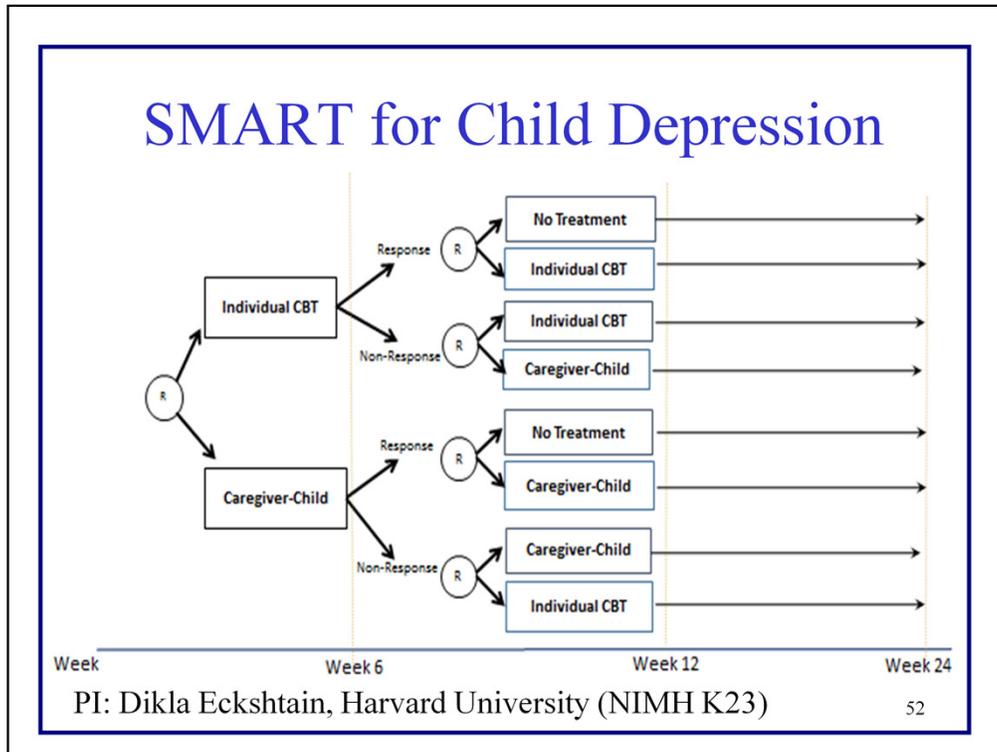
Female adolescents who are pregnant or breastfeeding

Outcomes:

- Will families report that a change in

the treatment plan, if indicated, is acceptable?

- Will adolescents be adherent to treatment and complete the treatment protocol?
- Will adolescents and parents report satisfaction with the adaptive treatment strategies?
- Will clinicians report satisfaction with the adaptive treatment strategies?
- Will clinicians implement the adaptive treatment strategies with fidelity?
- Will families consent to a sequence of treatments?



children aged 8-12 years, and their caregivers

Treatments involve

Individual CBT :

The treatment manual includes psychoeducation and five skills from the

Primary and Secondary Control Enhancement Training (PASCET; Weisz et al., 1999) manual

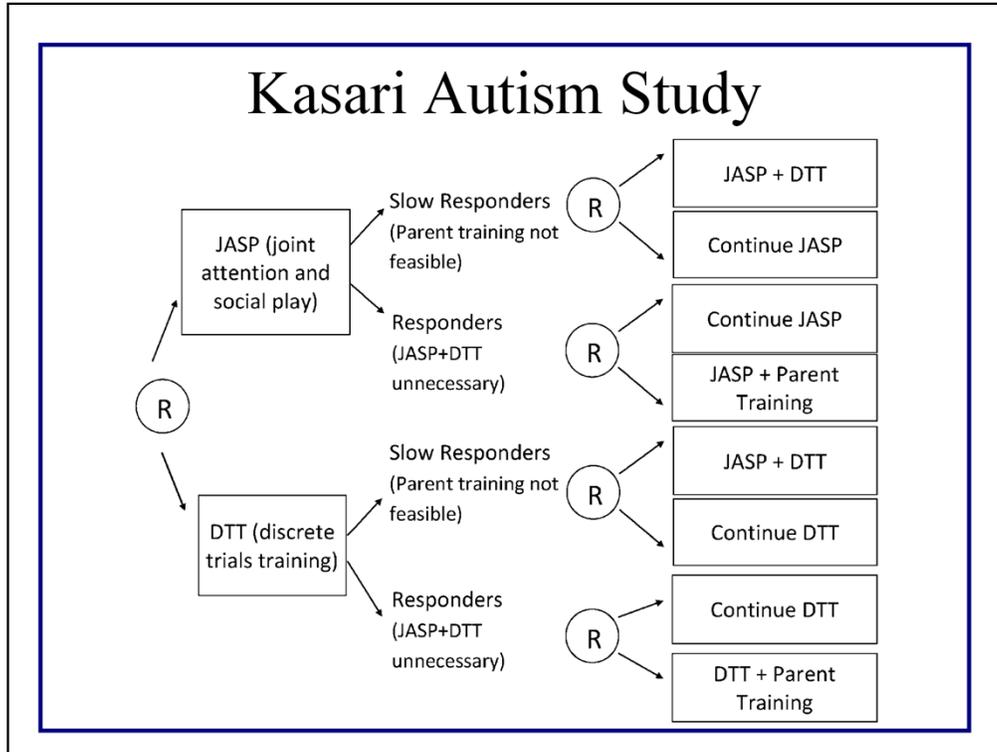
- (1) Problem Solving
- (2) Activity Scheduling
- (3) Cognitive
Restructuring
- (4) Relaxation
- (5) Social Skills Self-

Modeling

□ Caregiver–Child

treatment: The treatment manual includes pschoeducation and five skills, all from in the Caregiver-Child Relationship Enhancement Training (C-CRET-Revised; Eckshtain, 2012) manual

- (1) Special Time
- (2) Family Problem Solving
- (3) Negotiation and Conflict Resolution
- (4) Positive Communication
- (5) Positive Mood and Behavior Management



Connie and Danny's study

CORE-DTT is based on behavioral learning theory in which communication and related skills are taught

through systematic direct instruction. The goal of CORE-DTT is to help children be successful in learning

communication skills by breaking these skills down into small steps, providing systematic direct instruction on

each step, and reinforcing children (e.g., with praise or access to preferred items) for demonstrating skills. While many children will have been exposed to DTT prior to entering this trial, it is important to insure that children (a) receive quality DTT, and (b) have exposure to CORE

elements related to language learning, specifically joint attention and requesting gestures, in order to make the comparison with JASP-EMT.

JASP-EMT is a developmentally anchored behavioral intervention that assumes that communication

develops from social interactions in which specific social engagement strategies, symbolic representations, and early communication forms are modeled and naturally reinforced by adult partner responses to the child. The goal of JASP-EMT is to increase (a) joint engagement, (b) initiating joint attention gestures, (c) social play involving objects and persons, and (d) verbal and nonverbal communication by facilitating meaningful social interactions. The social interaction foundation of JASP-EMT is critical. Modeling and expansions of communicative behaviors and play are used strategically within meaningful social interactions with therapists and caregivers. Unlike COREDTT, JASP-EMT is likely to be a novel intervention to which few children will have had previous exposure.

These are the aims before we added the JASP+DTT arm to Slow responders.

Primary Aim: To determine which intervention for minimally verbal children (JASP-EMT vs. CORE-DTT) produces greater increases in socially communicative spontaneous utterances (SCU; primary outcome) and symbol-infused joint engagement, number of unique words, and object play level (secondary outcomes).

Primary Hypothesis: Adaptive interventions that begin with JASP-EMT will improve primary and secondary outcomes more than those that begin with CORE-DTT.

Secondary Aim 1: To determine whether adding a parent training component provides additional benefit among participants who demonstrate a positive early response to either JASP-EMT or CORE-DTT.

Hypothesis 1: Adding parent training to promote generalization for early responders in JASP-EMT or CORE-DTT will improve the primary and secondary outcomes more than just continuing the initial

interventions.

Secondary Aim 2: To compare and contrast four pre-specified adaptive interventions in terms of primary and secondary outcomes.

Hypothesis 2: The adaptive intervention that begins with JASP-EMT and (a) augments with parent

training for responders and (b) augments with CORE-DTT for slow responders will improve the primary

and secondary outcomes more than the other 3 adaptive interventions.

Tertiary Aim 3—Identifying Moderators: To determine whether (a) baseline repetitive behavior, (b) baseline

object interest, and (c) parent expectations for the specific intervention moderate intervention outcomes.

Hypothesis 3a: Participants with more interfering repetitive behaviors at baseline will demonstrate

greater increases in SCU in initial CORE-DTT than in JASP-EMT. Hypothesis 3b. Greater object

interest at baseline will predict better response to initial JASP-EMT than to initial CORE-DTT.

Hypothesis 3c. Among parents of children who are early responders to initial treatment (JASP-EMT or

CORE-DTT), those who indicate greater expectations for the initial treatment will benefit more from

parent training to promote generalization than from only continuing initial treatment.