Getting SMART about Adapting Interventions

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Early Childhood Interventions

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Adaptive Interventions are individually tailored sequences of interventions, with treatment type and dosage changing according to patient outcomes. Operationalizes many interventions in practice.

• Brooner et al. (2002, 2007) Treatment of Opioid Addiction

• McKay (2009) Treatment of Substance Use Disorders

• Marlowe et al. (2008, 2011) Drug Court

• Rush et al. (2003) Treatment of Depression
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 (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
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, 2011)
Adaptive Drug Court Program

- As-needed court hearings + standard counseling
  - low risk
  - high risk
  - non-responsive

- Bi-weekly court hearings + standard counseling
  - non-responsive

- As-needed court hearings + ICM
  - non-compliant

- Bi-weekly court hearings + ICM
  - non-compliant

- Court-determined disposition
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?)
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 interventions.
Example: Pelham ADHD Study

A. Begin low-intensity behavior modification

8 weeks
Assess:
Adequate response?

No

Random assignment:

Yes

A1. Continue, reassess monthly; randomize if deteriorate

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

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

B. Begin low dose medication

8 weeks
Assess:
Adequate response?

No

Random assignment:

B1. Continue, reassess monthly; randomize if deteriorate

B2. Increase dose of medication with monthly changes as needed

B3. Add behavioral treatment; medication dose remains stable but intensity of bemod may increase with adaptive modifications based on impairment
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.
SMART Design Principles

• Choose primary hypotheses that are both scientifically important and aid in developing the adaptive intervention.
  • Power trial to address these hypotheses.

• Conduct secondary analyses that further develop the adaptive intervention and that use the randomization to eliminate confounding.
SMART Designing Principles: Sample Size Formula

• EXAMPLE 1: (sample size is highly constrained): Hypothesize that beginning with low dose BMOD results in better classroom behavior than beginning with low dose MED. Sample size formula is same as for a two group comparison.

• EXAMPLE 2: (sample size is less constrained): Hypothesize that among non-responders, augmenting current treatment results in better classroom behavior than an intensification of current treatment. Sample size formula is same as a two group comparison of non-responders.
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
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 intervention.
- A subsequent trial would evaluate the proposed adaptive intervention.
Example: Pelham ADHD Study

A. Begin low-intensity behavior modification

B. Begin low dose medication

Assess-Adequate response?

Yes

Random assignment:

A1. Continue, reassess monthly; randomize if deteriorate

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

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

B1. Continue, reassess monthly; randomize if deteriorate

B2. Increase dose of medication with monthly changes as needed

B3. Add behavioral treatment; medication dose remains stable but intensity of bemod may increase with adaptive modifications based on impairment
Q-Learning using data on children with ADHD

• Stage 1 data: \((X_l, A_l, R_l)\)
  – \(R_l = 1\) if responder; \(=0\) if non-responder
  – \(A_l = 1\) if BMOD, \(A_l = -1\) if MED
  – \(X_l\) includes baseline school performance, \((Y_0)\) and prior medication \((S_l)\)
    • \(S_l = 1\) if prior use of medication; \(=0\), if not.

• Stage 1 involves all children
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 \((R_1 = 0)\).
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. $\hat{Y}$
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 ($M_2$)
Q-Learning using data on children with ADHD

• Stage 2 regression for $Y$:

$$(1, Y_0, S_1, A_1, M_2, S_2)\alpha_2 + A_2(\beta_2 + A_1\beta_2 + S_2\beta_3)$$

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

- A1=BMOD; S2=High Adherence (Difference=1.26, P<.01)
- A1=BMOD; S2=Low Adherence (Difference=1.61, P<.001)
- A1=MED; S2=High Adherence (Difference=1.46, P<.001)
- A1=MED; S2=Low Adherence (Difference=1.41, P= <.01)
Stage 1 Regression for All Children

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

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

$$\hat{Y} = (1, Y_0, S_1, A_1, M_2, S_2)\hat{\alpha}_2 + |\hat{\beta}_{21} + A_1\hat{\beta}_{22} + S_2\hat{\beta}_{23}|$$
Q-Learning using data on children with ADHD

• Stage 1 regression for $\hat{Y}$:

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

• Interesting stage 1 contrast: does the best initial treatment differ by whether a child received medication in the prior year for ADHD?
Stage 1 Regression for All Children

- $S_1 =$ Acceptability of medication
  - Difference $= 0.40$
  - Adaptive 95% CI: $(-1.1314, 0.2724)$

- $S_1 =$ No knowledge re Acceptability of Medication
  - Difference $= 0.49$
  - Adaptive 95% CI: $(0.0746, 0.8978)$
Adaptive Intervention 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 intensify current treatment.
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.
This seminar can be found at:

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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Jones’ Study for Drug-Addicted Pregnant Women

Random assignment:

Nonresponse

2 wks Response

rRBT

Random assignment:

tRBT

Random assignment:

tRBT

Random assignment:

eRBT

2 wks Response

rRBT

Random assignment:

Random assignment:

Random assignment:

Random assignment:

Nonresponse

rRBT

Random assignment:

tRBT

Random assignment:
	rRBT

Random assignment:
	rRBT

Random assignment:
	rRBT
Oslin ExTENd

- Early Trigger for Nonresponse
  - Random assignment:
    - 8 wks Response
      - Nonresponse
        - Random assignment:
          - 8 wks Response
            - Nonresponse
              - Random assignment:
                - TDM + Naltrexone
                - CBI
                - CBI + Naltrexone
              - Naltrexone
            - TDM + Naltrexone
          - CBI
        - CBI + Naltrexone
    - Naltrexone
- Late Trigger for Nonresponse
  - Random assignment:
    - 8 wks Response
      - Nonresponse
        - Random assignment:
          - TDM + Naltrexone
          - CBI
          - CBI + Naltrexone
        - Naltrexone
      - TDM + Naltrexone
    - CBI
    - CBI + Naltrexone
Kasari Autism Study

A. JAE+EMT

Random assignment:

B. JAE + AAC

12 weeks

Assess-
Adequate response?

Yes

Random assignment:

JAE+EMT

JAE+EMT+++

No

JAE+AAC

B1. JAE+AAC

B2. JAE +AAC ++

12 weeks

Assess-
Adequate response?

Yes

No