Getting SMART about Developing Individually-Tailored, Adaptive Health Interventions

Addiction Health Services Research - Monday, October 3, 1PM-5PM
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<table>
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<th>Module</th>
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| INTRODUCTION 1:00-1:10PM (10 min) | Course Outline, Structure, and Introductions  
*Exercises:* Identify working groups of 2-3 investigators by scientific interests/discipline. |
| MODULE 1 1:10-1:40PM (30 min) | What are Adaptive Treatment Strategies?  
- What are adaptive treatment strategies (ATS)? Give examples of ATSSs.  
- Discuss why ATSSs are needed and how they inform clinical practice.  
- Compare simple ATSSs versus more deeply tailored ATSSs. |
| Q&A 1:40-2:00PM (20 min) | Question, Answer, Discussion & Practice Exercise  
*Exercise:* Write down 2-3 simple ATSSs to address a condition in your research. |
| MODULE 2 2:00-2:40PM (40 min) | What are Sequential Multiple Assignment Randomized Trials (SMARTs)?  
- What are SMARTs? Why do we need SMARTs?  
- Compare SMARTs to using a multiple-RCT approach for building ATSSs.  
- Discuss SMART design principles. What are typical primary and secondary aims?  
- Address misconception that SMARTs necessarily require large sample sizes. |
| Q&A 2:40-3:10PM (30 min) | Question, Answer, Discussion & Practice Exercise  
*Exercise:* Using the 2-3 simple ATSSs written above, (a) construct a draft SMART design and (b) identify your primary scientific aim. |
| BREAK 3:10-3:30PM (20 min) | Break for water, snacks, and restrooms. |
| MODULE 3 3:30-3:55PM (25 min) | Primary Data Analytic Methods using Data Arising from a SMART  
- Discuss common primary research questions in a SMART.  
- Present SAS code and worked examples using simulated/fake data. |
| Q&A 3:55-4:10PM (15 min) | Question, Answer, Discussion & Practice Exercise  
*Exercise:* Write down a primary research question of interest to you. What data analysis approach would you use to address this primary question? |
| MODULE 4 4:10-4:35PM (25 min) | Secondary Data Analytic Methods using Data Arising from a SMART  
- Discuss common secondary research questions in a SMART.  
- Present SAS code and worked examples using simulated/fake data. |
| Q&A 4:35-4:50PM (15 min) | Question, Answer, Discussion & Practice Exercise  
*Exercise:* Write down a secondary research question of interest to you. What data analysis approach would you use to address this question? |
| WRAP-UP 4:50-5:00PM (10 min) | Wrap-up early to address final questions & to share contact information, etc. |
(TLC) and EMIT procedures for cocaine, alprazolam and clonazepam, and alcohol. Urine samples were included in the report only for subjects who remained active in the study (i.e., were in treatment and had not withdrawn consent or been removed from the evaluation).

2.2.3. Medication take-home doses. All subjects could earn methadone take-home doses after achieving 12 consecutive weeks of negative urine specimens and attendance to all scheduled counseling sessions. Employed subjects could also receive a second and a third weekly methadone take-home dose following additional 30-day periods of abstinence and attendance to scheduled counseling sessions. These incentives were available to all subjects independent of study assignment. Subjects could earn a range of 0–3 weekly take-homes of methadone during the study, although unemployed subjects could earn no more than one take-home per week.

2.2.4. Individual counseling. Individual drug abuse counseling was provided by the routine counseling staff with a bachelor’s degree in the behavioral sciences. Individual counseling sessions were approximately 30 min long (±10 min). Counselors completed a psychosocial assessment and master treatment plan for all subjects during the first 4 weeks of treatment (baseline period), and used cognitive-behavioral and motivational intervention approaches to help reduce drug and alcohol use and manage medical, occupational, and other psychosocial problems. Counselors were supervised weekly by masters-trained licensed professional counselors; all counselors worked with a similar number of subjects assigned to each of the four treatment conditions.

2.2.5. Intensified counseling sessions. Group-based counseling was primarily used to intensify the counseling schedule and overall care of subjects. Subjects were referred to one or more of the following groups based on assigned step of care: (1) chemical dependency education (CDEG; 1 × per week), (2) coping skills (CSG; 2 × per week), (3) community support (CST; 1 × per week), (4) relapse control (RCG; 2 × per week), and/or (5) cognitive-behavioral therapy (CBT; 2 × per week). Each group was manual-guided, with the exception of the cognitive-behavioral therapy group. In general, subjects in Step 1 were assigned to attend CDEG, those advanced to Step 2 were referred to RCG, and those moved to Step 3 were assigned to attend CSG, CST, and CBT groups. Exceptions to this schedule were occasionally made to accommodate subjects with specific time constraints or other obstacles to attendance (e.g., previously scheduled appointments; work schedule). Groups were led by licensed professional counselors with a master’s degree in the behavioral sciences, licensed clinical psychologists, or board-certified psychiatrists; all staff had a minimum of 3 years of experience in the treatment program. The only group that was not manually guided (cognitive-behavioral therapy) was led by a licensed clinical psychologist or psychiatrist.

2.3. Description of study conditions

All subjects were administered the Structured Interview for the DSM-IV (SCID-IV; First et al., 1995a,b) and other study assessments during the 4-week baseline. They were stratified on three variables commonly associated with treatment outcome: current cocaine dependence (e.g., Kidof et al., 1998), antisocial personality disorder (APD; e.g., Woody et al., 1985; King et al., 2001), and current non-substance use Axis I or II psychiatric disorder other than APD (e.g., Rounsaville et al., 1986; Brooner et al., 1997), and then randomly assigned to one of four treatment conditions for 6 months.

2.3.1. Condition 1: motivated stepped care (MSC-only). MSC is an adaptive stepped care service delivery model that adapts intensity of service delivery to objective indices of treatment performance. Subjects with a partial and poor treatment response (i.e., missed counseling sessions and/or drug-positive urine samples) are advanced to more intensive steps of weekly counseling. These subjects are returned to less intensive weekly counseling schedules after achieving a good clinical response (i.e., attendance to scheduled counseling and drug-negative urine samples).

As shown in Fig. 1, subjects began at Step 1 and were scheduled to attend one individual drug abuse counseling session per week (30 min). Subjects who missed a scheduled counseling session or produced a drug-positive urine specimen (any tested substance) during any two consecutive weeks were advanced to Step 2 for 2–4 weeks. Subjects advanced to Step 2 were scheduled to attend one individual counseling session, and two group sessions per week. They returned to Step 1 after submitting drug-negative urine specimens and attending all scheduled counseling sessions for two consecutive weeks. Failure to meet the criterion for return to Step 1 within 4 weeks resulted in their movement to Step 3 for 8 weeks. Once in Step 3, subjects were scheduled to attend 2 individual counseling sessions and 5 h of group sessions. They returned to Step 1 by submitting drug-negative urine specimens and attending all scheduled counseling for four consecutive weeks. Those who failed to meet this criterion within 8 weeks were started a 30-day methadone dose taper in preparation for discharge.

Additional behavioral contingencies to reinforce counseling attendance and reduced drug use were introduced in Step 3. Subjects who missed scheduled counseling sessions within the first 4 weeks of Step 3 were placed on a series of Fig. 1. Subjects receiving MSC move to Step 2 for 2–4 weeks after missing any counseling sessions and/or submitting any drug-positive urine specimens during two consecutive weeks; they return to Step 1 after attending all scheduled counseling sessions and producing drug-negative urine specimens for two consecutive weeks. Subjects that do not produce at least two consecutive weeks of counseling attendance with drug-negative urine specimens are advanced to Step 3 (4–8 weeks) and must attend all scheduled counseling and provide drug-negative urine samples for four consecutive weeks to return to Step 1. Subjects that do not produce four consecutive weeks of counseling attendance with drug-negative urine specimens in Step 3 begin a 30-day methadone dose taper in preparation for discharge from the program which is discontinued by attending all counseling sessions for 1 week and providing a drug-negative urine specimen. Step 3 subjects tapered to a methadone dose of 0 are discharged and offered rapid readmission, starting at Step 3.
contract involves “zero tolerance” for further violations of the rules of the program. Any further violation leads to a termination hearing, also known as a show-cause hearing. At the termination hearing, the individual is terminated from the program and sentenced on the original charge or charges unless he or she can provide a good reason to be given another chance. The decision of whether or not to grant another chance is within the discretion of the judge.

Participants who provided two or more drug-positive urine specimens were determined to be nonresponsive to the clinical interventions in the program. Those individuals were referred to an intensive clinical case management program administered by the local TASC (Treatment Accountability for Safer Communities) office. Participants in the TASC program are required to meet twice weekly with an intensive clinical case manager who provides individual substance abuse counseling with an emphasis on motivational enhancement, relapse prevention, and cognitive restructuring (“criminal thinking”) techniques. This differs from the standard treatment regimen delivered in the drug court program in that it is administered individually as opposed to predominantly in groups. In addition, the case manager
Figure 1. Strategies for the treatment of nonpsychotic major depressive disorder. Asterisk indicates consider TCA/VLF if not tried; dagger, lithium, thyroid, buspirone; double dagger, skip if lithium augmentation has already failed; section mark, most studied combination. BUP<sub>bp</sub> indicates bupropion sustained release; cital, citalopram; fluox, fluoxetine; MAOI, monoamine oxidase inhibitor; MRT, mirtazapine; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; VLF, venlafaxine. This figure is published with permission from the Texas Department of Mental Health and Mental Retardation and is part of a state-funded project.

Multiple tools were used to enhance adherence to the algorithm. A detailed treatment manual was used for initial didactic training and ongoing consultations with clinicians (available at: http://www.mhmr.state.tx.us/centraloffice/medicaldirector/timamddman.pdf). The manual identified critical decision points (e.g., weeks 4, 6, 8, 10, and 12) for each medication when revisions in treatment strategies or tactics were to be undertaken based on degree of symptom change and side effect burden (Figure 1 and Figure 2).

Symptom severity and side effect burden were routinely monitored at each treatment visit to guide treatment implementation, with the aim of ensuring an adequate duration and dose of medication. Clinical assessments at each visit included a global assessment of symptoms and associated symptoms, IDS-C<sub>30</sub> and IDS-SR<sub>30</sub>, and side effect burden by a 10-point global scale. A standard clinical record form was completed at each clinic visit by those implementing the ALGO intervention. The symptom severity assessments were conducted by clinical coordinators before the physician visits.

Each ALGO patient also received a stepwise education package that provided information about the disease, prognosis, treatment options, and medication side effects. This package encouraged patients to participate in treatment decisions and adhere to the treatment.6,7

**PATIENT SELECTION**

Male and female outpatients 18 years or older with a clinical diagnosis of MDD (psychotic or nonpsychotic) were eligible for the study. Patients entered ALGO if their treating physician judged that they required an antidepressant medication change or were starting antidepressant therapy. Entrance into TAU initially used the same criteria. However, because medication changes were made less frequently in TAU, patients were also recruited if their quarterly, routinely administered 24-item Brief Psychiatric Rating Scale (BPRS-24) total score was higher than the median for that clinic’s routine quarterly evaluation of each patient. Once approached, another BPRS-24 interview was conducted. Patients with BPRS-24 total scores no more than 1 SD below enrolled ALGO patient average scores were asked to participate. This procedure ensured a minimal level of symptom severity for participation in TAU in the absence of a medication change. Thus, in both ALGO and TAU
ADHD in Children SMART Design

Principal Investigator: W. Pelham

- **Medication**
  - Responders
  - Non-Responders

- **Behavioral Intervention**
  - Responders
  - Non-Responders

- For Responders:
  - Continue Medication
  - Increase Medication Dose
  - Add Behavioral Intervention
  - Continue Behavioral Intervention
  - Increase Behavioral Intervention
  - Add Medication

- For Non-Responders:
  - Continue Behavioral Intervention

O1 —— A1 —— O2 / R Status —— A2 —— Y