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Adaptive Interventions in Child and Adolescent Mental Health

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Abstract

The treatment or prevention of child and adolescent mental health (CAMH) disorders often requires an individualized, sequential approach to intervention, whereby treatments (or prevention efforts) are adapted over time based on the youth's evolving status (e.g., early response, adherence). *Adaptive interventions* are intended to provide a replicable guide for the provision of individualized sequences of interventions in actual clinical practice. Recently, there has been great interest in the development of adaptive interventions by investigators working in CAMH. The development of such replicable, real-world, individualized, sequences of decision rules to guide the treatment or prevention of CAMH disorders represents an important “next step” in interventions research. The primary purpose of this special issue is to showcase some recent work on the science of adaptive interventions in CAMH. In this overview article, we review why individualized sequences of interventions are needed in CAMH, provide an introduction to adaptive interventions, briefly describe each of the articles included in this special issue, and describe some exciting areas of ongoing and future research. A hopeful outcome of this special issue is that it encourages other researchers in CAMH to pursue creative and significant research on adaptive interventions.

Keywords

dynamic treatment regimens; personalized medicine; treatment effect heterogeneity

Introduction

In clinical practice, the treatment or prevention of child and adolescent mental health (CAMH) disorders often requires an individualized, sequential approach to intervention, whereby treatments (or prevention efforts) are adapted over time based on the youth's evolving status (e.g., early response, adherence). There are a variety of reasons for this, all owing to vast individual differences among youth with (or at risk for) mental illness, including between- and within-person heterogeneity in response to existing, evidence-based child and adolescent mental health interventions.

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Adaptive interventions are intended to provide a replicable guide for the provision of individualized sequences of interventions in actual clinical practice (Collins, Murphy, & Bierman, 2004; P. W. Lavori & R. Dawson, 2008; P. W. Lavori, R. Dawson, & A. J. Rush, 2000; S. A. Murphy, Collins, & Rush, 2007; Susan A Murphy, Oslin, Rush, Zhu, & MCATS Research Network, 2007). Recently, there has been great interest in the development of adaptive interventions by investigators working in child and adolescent mental health.

The primary purpose of this special issue is to showcase recent work on the science of adaptive interventions in CAMH. Given the novelty of adaptive interventions in CAMH research, much of this research is in the beginning stages. A hopeful outcome of this special issue is that it encourages other researchers in CAMH to pursue creative and clinically significant research on adaptive interventions to improve the lives of greater numbers of children and adolescents with (or at risk for) mental health disorders.

In this overview article, we (1) review why individualized sequences of interventions are needed in CAMH, (2) provide an introduction to adaptive interventions and discuss the need for more research in this area, (3) briefly describe sequential multiple assignment randomized trials (SMART), which is one of a variety of study designs that can be used in adaptive interventions research, (4) briefly describe each of the articles included in this special issue, and (5) describe some exciting areas of ongoing and future research.

Need for Individualized Sequences of Interventions in CAMH

There are various reasons why, in actual clinical practice, interventions are adapted and re-adapted over time based on the evolving needs of a child or adolescent. First, and foremost, a substantial number of children or adolescents may remain symptomatic at the conclusion of an evidence-based intervention (Kendall, Safford, Flannery-Schroeder, & Webb, 2004). For example, the estimated acute remission rate following 12 weeks of high-quality cognitive behavioral therapy (CBT) alone is 39.3% for pediatric obsessive-compulsive disorder (OCD; March et al., 2004), 16% for adolescent depression (B. Kennard et al., 2006), and up to 46.2% for pediatric anxiety (Ginsburg et al., 2011). Based on these same studies, estimated remission rates following 12 weeks of medication alone are 21.4% (OCD), 23% (depression), and up to 46.3% (anxiety). This suggests that across a wide variety of youth mental illnesses, there is a clear need for subsequent intervention for children who fail to respond to an initial course of treatment.

Second, acute response (or even remission) at the conclusion of an evidence-based intervention does not always imply response in the longer-term. It is generally well-accepted that many mental health disorders can be characterized as chronic (e.g., attention-deficit/hyperactivity disorder or ADHD; S. Pliszka & 2007); stressful life events may serve as the diathesis for recurrence (e.g., in depression; Liu & Alloy, 2010); co-morbidities, such as substance abuse or depression may arise secondary to childhood-onset disorders (Chronis-Tuscano et al., 2010; Molina & Pelham, 2003) and, generally, relapse is common (Bruce et al., 2008; Burcusa & Iacono, 2007). For example, analysis of participants in the Multimodal Treatment of ADHD (MTA) study demonstrated that (1) children who showed the most favorable clinical presentation at baseline and the best acute treatment response

(approximately 52% of the sample) fared better over time; yet, the majority of adolescents in the sample continued to demonstrate functional impairment in most domains compared to non-disordered peers 6–8 years following the conclusion of treatment (Molina et al., 2009). These ideas suggest the need for an approach to intervention which monitors or tracks youth for signs of non-response or worsening across development, including among youth demonstrating acute treatment response or remission.

Third, for some child and adolescent disorders, the most promising treatments may also be more costly, more difficult to find in the community, or more burdensome. For example, in the Child and Adolescent Anxiety Multimodal Study (CAMS), 81% of children who were offered sertraline combined with high-quality medication management and high-quality CBT were rated as very much or much improved at the end of 12 weeks (Walkup et al., 2008). In general, a number of large-scale efficacy trials have shown that the combination of psychotherapy plus medication leads to improved outcomes as compared to monotherapy (Ginsburg et al., 2011; The MTA Cooperative Group, 1999; Treatment for Adolescents With Depression Study (TADS) Team, 2004). However, in actual practice, some families may not have access to high-quality combination treatments such as those where behavior therapists and pharmacotherapists provide coordinated treatments; some families may have access to it yet it may be too costly to obtain; and for other families, combined treatment may be too burdensome (e.g., the need to meet with both a psychiatrist and a CBT-trained therapist weekly or every two weeks may not be feasible) (Reeves & Anthony, 2009). In such cases, the combined treatment (and, in general, costlier or more burdensome treatments) may be more suitable as a second-line treatment only for children who do not respond adequately to monotherapy.

Fourth, children may vary a great deal in the dose or duration of treatment that is necessary for longer-term response or remission. Some children may respond quickly to a first-stage treatment; these children may remain on their current treatment, discontinue treatment, or transition more quickly to a maintenance treatment. Other children will require a longer duration in first-stage treatment before making a decision about the need for subsequent treatment.

Fifth, in actual practice, many youth (or their parents) may not adhere to or remain engaged in treatment or may drop out from treatment prematurely. For example, approximately 40% of families who receive CAMH treatment services may terminate treatment prematurely (Miller, Southam-Gerow, & Allin Jr, 2008). Another report estimated that children entering mental health care attend a mean number of 3.9 visits within a six-month period (Harpaz-Rotem, Leslie, & Rosenheck, 2004). Given that youth who terminate treatment prematurely may be more likely to experience greater subsequent impairment (Kazdin, Mazurick, & Siegel, 1994), it is important to consider approaches to preventing treatment non-adherence or drop-out, for example, by improving parental engagement (Nock & Kazdin, 2005) or by employing other child and adolescent engagement strategies. In addition to considering treatment engagement strategies, youth and/or parents showing early signs of treatment non-adherence may benefit from changes in treatment, such as a switch in treatment or augmentation with another therapeutic approach (Nahum-Shani et al., 2012b).

Over the past two decades, researchers have begun to address questions related to individualizing sequences of treatments in CAMH: For instance, a number of studies have utilized “non-responder randomized trials” to study how best to intervene and improve longer-term outcomes among youth with CAMH disorders who do not respond sufficiently to a first-stage course of intervention (Brent et al., 2008; Franklin, Foa, & March, 2003; Goodyer et al., 2008; Skarphedinsson et al., 2014). Similarly, “responder trials” have been used to study how best to intervene in order to maintain early improvements over the longer-term (or prevent subsequent relapse) among youth with CAMH disorders who do respond to an initial course of treatment (Emslie et al., 2008; B. D. Kennard et al., 2008; Troost et al., 2005). Another emphasis has been the development of medication algorithms (e.g., individualized sequences of pharmacological treatments based on clear decision rules) via expert consensus panels (e.g., Hughes et al., 2007; S. R. Pliszka et al., 2006).

Other CAMH studies have also developed or evaluated flexible treatments (Chorpita & Daleiden, 2014; Weisz et al., 2012) or prevention programs (K. Bierman et al., 1992; Connell, Dishion, Yasui, & Kavanagh, 2007; Dishion, Andrews, Kavanagh, & Soberman, 1996; McMahon et al., 1999) that involve individualized sequences of intervention.

Building on this early and important work, more recently, researchers have begun to focus on *adaptive interventions* in CAMH (e.g., K. L. Bierman, Nix, Maples, & Murphy, 2006; Dawson, Lavori, Luby, Ryan, & Geller, 2007; S.A. Murphy, Van Der Laan, & Robins, 2001).

What is an Adaptive Intervention?

An adaptive intervention is a sequence of decision rules that operationalizes whether, how or when—and, importantly, based on which measures—to alter the dosage (frequency, duration or amount), type, or delivery of treatment(s) at critical decision points in the course of care (Collins et al., 2004; Philip W Lavori & Ree Dawson, 2008; S.A. Murphy, Lynch, Oslin, McKay, & TenHave, 2007; Nahum-Shani et al., 2012a). Such decision rules lead to individually-tailored sequences of treatment.

The key elements of an adaptive intervention include critical decision points (i.e., points at which treatment decisions are made), tailoring variables (i.e., measures that are used to make personalized treatment decisions at each decision point), intervention options (e.g., medication vs. psychosocial treatment), and the decision rule at each critical decision point which is used to link the tailoring variable(s) with the intervention options (Almirall, Nahum-Shani, Sherwood, & Murphy, 2014).

The tailoring variable(s) in an adaptive intervention may include baseline or intermediate (i.e., on-going) information about the child or adolescent. Baseline information is used to tailor the first treatment decision (i.e., which treatment to begin with); baseline or intermediate information is used to tailor subsequent treatment decisions. Baseline information may include demographic information (e.g., developmental level, race/ethnicity, gender, educational attainment), clinical characteristics (e.g., symptom severity, presence of co-morbid conditions, history of treatment), or biological indicators (e.g., genetic tests).

Intermediate or on-going information includes proximal outcomes of prior treatment decisions or early indicators of successful outcomes in the longer-term, such as short-term change in symptoms or functioning (collected by clinical observation or measuring biological markers), or adherence to prior treatment. The decision rules making up an adaptive intervention may depend on a single tailoring variable or on multiple tailoring variables; some decisions in an adaptive intervention may involve no tailoring variables.

Adaptive interventions are also known as “adaptive treatment strategies” (Philip W Lavori & Ree Dawson, 2008; S. A. Murphy et al., 2007), “dynamic treatment strategies” (Philip W Lavori & Dawson, 2014), or sometimes simply “treatment strategies” (Philip W Lavori, Ree Dawson, & A John Rush, 2000). In the statistical literature, they are commonly referred to as “dynamic treatment regimens” (Chakraborty & Moodie, 2013; Laber, Lizotte, Qian, Pelham, & Murphy, 2014; P. W. Lavori & Dawson, 2004; S. A. Murphy, 2003; S. A. Murphy & Almirall, 2009; Shortreed & Moodie, 2012), “treatment policies” (Lunceford, Davidian, & Tsiatis, 2002; Wahed & Tsiatis, 2004), or “multi-stage” or “multi-course treatment strategies” (Thall, Millikan, & Sung, 2000; Thall, Sung, & Estey, 2002).

Special cases of adaptive interventions include medication algorithms (Hughes et al., 2007; S. R. Pliszka et al., 2006), which focus on individualized sequences of pharmacotherapy, and stepped-care interventions (Bower & Gilbody, 2005; Haaga, 2000; Sobell & Sobell, 2000), which focus on providing gradually more intensive services in a sequence that begins with a lower-intensity (and typically lower initial cost) intervention (McDermott & Cobham, 2014). Adaptive interventions are more general in that they may involve a combination of sequences of psychosocial and pharmacological interventions; and they may step-up or step-down the intervention (or components of an intervention) over time.

Adaptive interventions can also be used to guide “service-level decision making”, where, for example, the goal is to inform the individualized sequencing of child and adolescent levels of care (Mee-Lee, 1996), rather than specific treatments, or both. Following Rush and Thase (1996), adaptive interventions may be “strategic” (e.g., selecting among specific treatments), “tactical” (e.g., whether or when to continue, intensify, augment, or switch treatment(s)), or some combination of both.

Next, we provide two concrete examples of an adaptive intervention in CAMH. (Many other examples are included in the papers in this special issue.)

A first example concerns the provision of treatment following an initial diagnosis of pediatric generalized anxiety disorder (GAD): “First treat with the medication sertraline (SERT) for 12 weeks. If the child has not achieved an adequate response to initial SERT (at week 12), augment by initiating a combination of sertraline + individual cognitive behavioral therapy (CBT) for 12 additional weeks; otherwise, if child shows adequate response, maintain SERT alone for another 12 weeks” (Almirall, Compton, Gunlicks-Stoessel, Duan, & Murphy, 2012). In this example: The critical decision points are at baseline and end of week 12. SERT is the only intervention option at baseline; the decision rule at baseline is not tailored. SERT and SERT+CBT are the two intervention options at the end of week 12. The tailoring variable used in the decision rule at the end of week 12,

“adequate response,” is defined as a score of less than 3 on the Clinical Global Impression-Improvement (CGI-I) scale at the end of week 12.

A second example of an adaptive intervention in CAMH is given by Dawson et al. (2007, p. 761) for the management of childhood mania after medication dose has been stabilized. This adaptive intervention tailors the post-stabilization medication regimen (i.e., strategies for augmenting vs. switching vs. staying the course) based on change in the Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP; Spearing, Post, Leverich, Brandt, & Nolen, 1997). A novel aspect of this adaptive intervention is that, in addition to guiding changes in the medication regimen, it also operationalizes the level of monitoring (weekly vs. monthly) based on the child’s current needs: specifically, if the child is currently markedly ill based on the CGI-BP, then monitor on a weekly basis; otherwise, monitor on a monthly basis.

Adaptive interventions are intended to serve as guides for clinical practice. For example, adaptive interventions could be incorporated into practice parameters (or practice guidelines) to improve the management of various CAMH disorders (e.g., Birmaher, Brent, & Benson, 1998; M. Dulcan, 1997; McClellan & Werry, 1997; Szymanski & King, 1999; Volkmar, Cook, Pomeroy, Realmuto, & Tanguay, 1999). In order to help accomplish such a broad goal, a first important design consideration in the development of an adaptive intervention is that its elements be clear and well-operationalized, so that the adaptive intervention can be replicated both by clinicians in clinical practice, and by researchers who seek to evaluate or further refine the adaptive intervention in subsequent research.

A second important design consideration is that the adaptive intervention be feasible (or viable) in actual clinical practice, for example, by accounting for common contingencies that may arise such as the inability to collect early indicators of response due to missed clinic visits (Almirall et al., 2012) or side effects that might rule out subsequent intervention options (Wang, Rotnitzky, Lin, Millikan, & Thall, 2012).

Another set of important intervention design considerations concerns the choice of tailoring variable(s), including whether there is (are) a single or multiple tailoring variables, how the tailoring variable(s) is (are) measured, who is (are) the most appropriate informant(s) (e.g., self-report by youth, parent, teacher or clinician), and the feasibility of measuring the tailoring variable(s) in real-world clinical practice. In the first example given above, a single, clinician-measured CGI is used at the second decision point. In other examples, such as in school-based treatments for ADHD or autism, it may be observations or measures collected by a teacher, paraprofessional (e.g., a school aide during recess), parent, or some combination of these. Other adaptive intervention design considerations are discussed in Collins et al. (2004) and Almirall et al. (2012).

The development of such replicable, real-world, individualized, sequences of decision rules to guide the treatment or prevention of CAMH disorders represents an important “next step” in interventions research. For example, developing adaptive interventions fits squarely with Objective 3 of the National Institute of Mental Health’s strategic plan for research which is explicit about the need to “Foster personalized interventions and strategies for sequencing or

combining existing and novel interventions that are optimal for specific phases of disease progression, different stages of development, and other individual characteristics” (Insel, 2009, Objective 3; National Institute of Mental Health, 2015, Strategy 3.2).

Many Scientific Questions Remain Unanswered

Despite the clear need for guidance on how to individualize and sequence interventions in CAMH, the fact that much of clinical practice unfolds in this way, and the early research in this area, many questions remain about how best to develop and evaluate the effectiveness of real-world, high-quality adaptive interventions in CAMH.

The existence of evidence-based treatments in CAMH, including evidence from large or very well-conducted efficacy randomized trials, does not imply that we know how best to individualize or sequence such treatments over time to the specific needs of the child or adolescent. Indeed, despite our major advances in treatment, many of the practical concerns raised over a decade ago by Dulcan (2005) about existing professional practice guidelines at the time remain relevant today. Some of these include: “lack of belief that implementing the guideline improves patient outcomes”, “[guidelines] must be flexible enough to allow for the values, preferences, and goals of the patient and family”, “attempts to include all possible aspects and complexities result in [guidelines] so lengthy that they are unlikely to be read and impossible to execute,” and “guidelines on the same topic from different sources may conflict.”

As a first example, consider that scientists have not reached consensus on the best way to begin a sequence of treatments for youth with ADHD, one of the longest-studied disorders in CAMH. The American Academy of Pediatrics (AAP; 2011) advises that, for preschool-aged children (4–5 years of age), the primary care clinician “should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first line of treatment and may prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child’s function” (p. 1008). If behavior therapy is not available, the AAP recommends careful consideration of the costs/benefits of prescribing medication. For elementary-school-aged children, the AAP recommends that the primary care clinician should prescribe FDA-approved medications for ADHD and/or behavior therapy, preferably both, but provides no guidance on how to sequence these treatments.

Similarly, the American Academy for Child & Adolescent Psychiatry practice parameters (2007) acknowledge that ADHD is a chronic disorder in need of ongoing treatment which “may consist of psychopharmacological and/or behavior therapy.” AACAP points out the importance of considering patient preferences but provides no other guidance on the selection of medication vs. behavior therapy or sequencing of the two. Later in their guidelines, AACAP recommends that if none of the FDA-approved medications are helpful, the clinician should “consider behavior therapy and/or the use of medications not approved by the FDA for the treatment of ADHD.” These practice parameters are based on what is considered the best available evidence and consensus of a panel of experts. In light of these conflicting recommendations and lack of clear evidence to address these important clinical

decisions, studies are critically needed to guide clinicians on how to optimally select and sequence treatments for children with ADHD, as well as how to proceed in the case of nonresponse. This ongoing debate in the treatment and management of youth ADHD suggests the need for additional research. While the illustration above focuses on the example of ADHD, similar questions are likely to arise for other disorders in CAMH.

More recently, Markowitz and Milrod (2015) discussed the critical need for additional research on sequencing and individualizing treatments in mental health. Their commentary, which focuses on the need for sequences of treatments that begin with psychotherapies, states “ignorance of whether or how to change psychotherapies is a major and persisting gap in psychiatric knowledge.” While their editorial focuses on gaps in our understanding of treatment strategies for adult mental health illnesses that begin with psychotherapies, much the same can be said of the gaps in our science base for sequencing treatments in CAMH, whether or not they begin with psycho- or pharmacotherapies.

Table 1 presents examples of open scientific questions that may prevent researchers from developing high-quality adaptive interventions. The list includes questions about how best to sequence or time treatments (or treatment changes) in the context of an adaptive intervention, as well as questions concerning tailoring variables. Many such questions remain unanswered in CAMH. Filling these gaps in CAMH research is critically important given that the treatment or prevention of child and adolescent mental health disorders often requires an individualized, sequential approach. The research presented in this special issue begins to tackle questions such as these in the development and evaluation of adaptive interventions in CAMH.

Sequential Multiple Assignment Randomized Trials

Several manuscripts in this special issue describe studies which utilize a sequential multiple assignment randomized trial (SMART) design (Philip W Lavori & Dawson, 2000; P. W. Lavori & Dawson, 2004; S. A. Murphy, 2005). A SMART is a multi-stage randomized trial design, which is used explicitly for the purpose of developing a high-quality adaptive intervention (Almirall et al., 2014; Chakraborty, 2011; Nahum-Shani et al., 2012a, 2012b). Each participant in a SMART may move through multiple stages of treatment. All participants are randomized at least once; some participants may be re-randomized at multiple stages of treatment. Re-randomizations may depend on prior treatment, response (e.g., change in symptoms, adherence) to prior treatment, or neither (e.g., in the case of a non-restricted SMART). Ideally, research outcomes are collected for all participants throughout the entire study (across all stages of treatment).

All SMART studies are designed to answer multiple open scientific questions that are useful for the development of an adaptive intervention or sequences of interventions (see Table 1 for examples). However, not all research on adaptive interventions requires a SMART study. For example, the last question in Table 1 could be addressed using a standard two-arm randomized clinical trial.

SMARTs have been used to develop adaptive interventions across a wide range of disciplines (see Kidwell (2014) for a review of the past, present and future of SMARTs in oncology). In oncology research, SMART designs have been used to develop adaptive interventions for prostate cancer (Thall, Wooten, Logothetis, Millikan, & Tannir, 2007; Wang et al., 2012). Lei, Nahum-Shani, Lynch, Oslin, and Murphy (2012) provide an excellent review of four example SMART studies to develop behavioral adaptive interventions, one each in autism and ADHD, and two in adult substance use; this paper includes a description of each SMART and the types of scientific questions they were designed to answer. The Clinical Antipsychotics Trial of Intervention Effectiveness in schizophrenia (CATIE; Lieberman et al., 2005; Shortreed & Moodie, 2012) and the Sequenced Treatment Alternatives to Relieve Depression in depression (STAR*D; Philip W Lavori et al., 2001; Rush et al., 2004) are examples of early precursors to the SMART in adult mental health research.

Overview of the Articles in the Special Issue

This special issue includes nine articles across six areas of CAMH research (ADHD, depression, autism, anxiety, conduct disorder and obesity), each with a focus on adaptive interventions.

Two of the nine manuscripts describe interesting secondary data analyses aimed at generating hypotheses about potential tailoring variables for the development of adaptive interventions in anxiety (Pettit, Silverman, Rey, Marin, & Jaccard, 2015) and autism (Shih, Patterson, & Kasari, 2014). These two papers nicely complement other, recent work, which uses different methodology for identifying critical treatment decision points during the course of intervention (Fitzpatrick et al., 2014; Gunlicks-Stoessel & Mufson, 2011; Steidtmann et al., 2013).

Pettit et al. (2015) describe the importance of identifying youth (ages 6 to 16) who are not making adequate progress while receiving CBT for anxiety, as a way to begin thinking about adaptive interventions that begin with an initial course of CBT. The authors use a latent profile analysis (with data from two separate studies) to inform the development of a candidate tailoring variable based on anxiety symptom profiles at the mid-point (i.e., after 8 sessions) of CBT. They end the article by describing the design of a subsequent, novel randomized trial (the proposed study is novel in that it combines a responder trial with a non-responder trial) to empirically evaluate the utility of the tailoring variables *and* the effectiveness of different second-stage treatment options for both responders and non-responders.

Shih et al. (2014) describe the need to develop school-based, adaptive social skills interventions in school-children (grades 1 to 5) with autism spectrum disorder (ASD). They use a regression tree approach to identify four meaningful subgroups of children, based on trajectories of observed peer engagement on the playground during social skills intervention, which could be used in a future study to adapt this social skills intervention in children with ASD.

Four manuscripts in this special issue present results from SMART studies in CAMH. Pelham et al. (2015) present the primary results of a SMART study designed to develop an adaptive intervention over the course of a school year for children (ages 5 to 12) with ADHD. The study addresses two key questions: (1) whether it is better to begin with low-dose medication (MED) or behavior modification (BMOD); and (2) among children identified as non-responders, whether it is better to intensify the initial intervention (INTENSIFY) or to augment with combined MED+BMOD. To address these questions, all children were randomized initially to MED vs. BMOD; and re-randomized non-responders to INTENSIFY vs. MED+BMOD. Children who were never identified as non-responders remained on initial treatment. This work is significant because it begins to shed light on the long-standing question concerning the sequencing of behavioral and pharmacological interventions in children with ADHD described previously. The adaptive interventions considered are novel. For example, response vs. non-response is measured monthly, and children may transition to second stage treatment at different time points. In a second manuscript by the same research team (Page et al., 2015), cost outcomes are presented. Together, the two manuscripts begin to shed light on the cost-effectiveness of different adaptive interventions in children with ADHD.

Naar-King et al. (2015) present the results of a SMART study designed to develop an adaptive intervention for weight loss in African-American adolescents (ages 12–16). This study addresses two key questions: First, it examines whether it is better to begin with a home-based (HOME) vs. office-based (OFFICE) motivational interviewing and skills intervention. Second, among children identified as non-responders after 3 months of initial treatment, the study examines whether it is better to intervene with 3 additional months of continued skill building in the home (CS) vs. with a contingency management (CM) intervention offering competing behavioral incentives. To examine these questions, all participating children were randomized initially to HOME vs. OFFICE; and re-randomized non-responders to CS vs. CM. Children identified as responders received a relapse prevention intervention in the same setting (home- or office-based) to which they were originally assigned treatment. The cost and added burden of CS in the home and CM made these interventions ideal candidates for second-stage treatment for children showing early signs of non-response.

Almirall et al. (2015) present results of a secondary analysis of a SMART study designed to develop an adaptive intervention for 5–8 year-old minimally-verbal children with ASD (Kasari et al., 2014). The overarching aim of this SMART was to examine whether and how best to incorporate the use of a speech-generating device (SGD) in the context of naturalistic communication intervention known as joint attention symbolic play, engagement and regulation intervention combined with enhanced milieu training (JASP-EMT; Kaiser & Roberts, 2013; Kasari, Paparella, Freeman, & Jahromi, 2008). All children were randomized initially to JASP-EMT vs. JASP-EMT+SGD. Children identified as responders at week 12 remained on their initially assigned treatment. Children identified as slower responders to JASP-EMT+SGD received intensified JASP-EMT (i.e., increased number of sessions per week). Children identified as slower responders to JASP-EMT were re-randomized to intensified JASP-EMT vs. add the SGD. The manuscript in this special issue focused on a comparison of the three adaptive interventions embedded in this SMART based on key

longitudinal communication outcomes. The analysis uses a recently developed analytic method (Lu et al., in press) for comparing adaptive interventions with repeated measures outcome data arising from a SMART.

Three manuscripts are from SMART Pilot studies that are currently in progress in the areas of adolescent depression, conduct disorder prevention, and maternal ADHD. Gunlicks-Stoessel, Mufson, Westervelt, Almirall, and Murphy (2015) present results from their SMART pilot study designed to examine feasibility and acceptability considerations of four, two-stage, adaptive interventions for adolescents ages 12 to 17 with depression. All four adaptive interventions begin treatment with interpersonal psychotherapy for depressed adolescents (IPT-A; Mufson, Dorta, Moreau, & Weissman, 2011) and assess for sufficient vs. insufficient response to IPT-A based on change on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1967). The four adaptive interventions differ in terms of the criteria used to determine sufficient vs. insufficient response (based on a combination of first-stage treatment duration and HSRD), as well as the type of second-stage treatment for insufficient responders (add fluoxetine medication vs. increase the dose of IPT-A). The authors identify a number of interesting feasibility and acceptability considerations and propose a plan for how to improve the adaptive interventions in preparation for a full-scale SMART study.

August, Piehler, and Bloomquist (2014) present the design and rationale of a SMART pilot study to examine feasibility and acceptability considerations in the development of an adaptive preventive intervention for youth (ages 13–17) identified by law enforcement as early stage offenders and referred to pre-court juvenile diversion programming. The goal of the adaptive interventions is to prevent subsequent conduct disorder or substance use disorder.

Chronis-Tuscano, Wang, Strickland, Almirall, and Stein (2015) present the design and rationale of a SMART pilot study to examine feasibility and acceptability considerations in the development of an adaptive intervention for mothers with ADHD with children (ages 3–8 years) who are at risk for ADHD by virtue of genetics and environmental factors. The pilot considers four sequences of interventions, which differ in terms of (i) whether to begin treatment with behavioral parent training (BPT) alone or maternal stimulant medication (MSM) alone, and, in the second stage, (ii) whether to continue with first-stage treatment or combine BPT+MSM. In a future full-scale SMART, the investigators aim to compare these four sequences, and to examine baseline and intermediate tailoring variables that could be used to individualize these four sequences of treatment. An especially novel aspect of this SMART is that it aims to develop an adaptive intervention which can be categorized as both treatment (in terms of maternal ADHD outcomes, e.g., maternal functioning and parenting quality) and prevention (in terms of child outcomes, e.g., course of ADHD symptoms and related impairment).

Finally, the issue concludes with a commentary from Dr. Joel Sherrill, Chief of the Psychosocial Treatment Research Program and Associate Director of the Division of Services and Interventions Research at NIMH. The commentary by Dr. Sherrill

contextualizes the theme of adaptive interventions within the mission of the NIMH and its recent strategic plan (National Institute of Mental Health, 2015).

Ongoing and Future Work

The contributions in this special issue represent only a small subset of current or ongoing work on adaptive interventions in CAMH. Based on a search of studies identified in early August 2015 via the www.clinicaltrials.gov website (search terms [“adaptive treatment” or “adaptive intervention” or “adaptive strategy” or “sequential treatment”] crossed with [“children”, “child”, “adolescent” or “youth”], or with the terms [“sequential multiple assignment randomized trial” or “sequential, multiple assignment, randomized trial”]), we wish to note that there is other exciting work on adaptive interventions being done in the areas of adolescent marijuana use (Budney, Stanger, & colleagues, 2014; Kaminer & colleagues, 2012), prevention of oppositional behavior (Dishion et al., 2014), child depression (Eckshtain, 2013), autism (Kasari & colleagues, 2012), college student suicide prevention (Pistorello & colleagues, 2015), child trauma (Salloum, Robst, et al., 2014; Salloum, Scheeringa, Cohen, & Storch, 2014), and child and adolescent obsessive-compulsive disorder (Shavitt & colleagues, 2010).¹

In addition, we wish to highlight two exciting new directions for future research on adaptive interventions in CAMH and ways that adaptive interventions could complement ongoing work. The first novel area is the development of adaptive interventions in settings where the unit of intervention is at the group level (e.g., classroom, school or other contextual-level interventions), but where the group-level intervention is meant to improve outcomes at the level of the children or adolescents that comprise the group. Other examples include family-level interventions (e.g., many preventive interventions are intended to impact outcomes for all members of the family), or service-provider level interventions (below is an example). In all of these cases, the group-level intervention may be adapted and re-adapted over time in response to the needs or evolving status of the group (e.g., using a group-aggregated measure of response/non-response) or may be subsequently adapted for some individuals in the group and not others based on individual change within the group.

A recent example of this type of research is the development of an *adaptive implementation intervention* (Kilbourne et al., 2013) in adult mental health services research. Implementation science focuses on understanding how best to promote the uptake of evidence-based interventions in routine, authentic healthcare settings; often, interventions are at the level of the service-provider (e.g., the community-based mental health site). In an adaptive implementation intervention, the intervention options, which correspond to different types and intensities of implementation strategies, can be tailored over time to site-specific contextual factors (i.e., site-specific tailoring variables). For example, not all sites require more intensive (and costly) implementation strategies such as provider coaching, and may adopt an evidence-based treatment (EBT) for mental health disorders via less costly approaches such as provider training; whereas these costlier implementation strategies could

¹The Methodology Center at Penn State University hosts a website with a basic description of various SMART studies (completed or underway) across a variety of scientific disciplines (The Methodology Center: Projects Using SMARTs).

be used to improve the likelihood of adoption for sites that do not adopt the EBT after 6 months of less intensive intervention. The NIMH-funded ADEPT study (Kilbourne et al., 2014)—the first-ever, cluster-randomized SMART—aims to develop a high-quality adaptive implementation intervention to improve the uptake/adoption of a brief, evidence-based intervention for mood disorders, known as Life Goals (Bauer et al., 2006a, 2006b), in community mental health settings.

A second, novel area is the development of just-in-time adaptive interventions (JITAI) in mHealth (Nahum-Shani, Hekler, & Spruijt-Metz, 2015; Nahum-Shani et al., 2014; Spruijt-Metz & Nilsen, 2014). A JITAI is an emerging, mobile health intervention design in which *real-time* information on the dynamics of an individual's emotional, social, physical and contextual state is used to individualize the type and delivery, or timing, of interventions. JITAIs can be designed to prevent negative health outcomes, promote the adoption of healthy behaviors and/or help a person maintain healthy behaviors. Often, JITAIs are delivered via smartphone applications (Klasnja, 2015). However, given our evolution toward ubiquitous computing, they can be delivered anyplace and via any number of devices (Intille, 2004). Potentially, they could also be used to intervene or guide in-the-moment clinical decision making in CAMH as part of technology-assisted clinical decision support systems. Interest in JITAIs has led to the development of micro-randomized trials (Klasnja et al., 2015; Liao, Klasnja, Tewari, & Murphy, 2015), a novel kind of multi-stage randomized trial design which can be used to answer open scientific questions to build high-quality JITAIs.

Conclusions

By defining which treatment is best, and when, for an individual child, based on his/her current or evolving status, adaptive interventions hold the promise of improving health outcomes for greater numbers of children with (or at risk for) CAMH disorders.

The primary goal of this special issue is to introduce the readership to adaptive interventions in CAMH, as well as to survey (a subset of) current and ongoing work on adaptive interventions in CAMH. The various articles in this special issue demonstrate the diversity of data collection and data analysis methods being used to evaluate and develop better adaptive interventions in CAMH.

While the field of adaptive interventions is still in its infancy (especially the use of SMART studies for developing high-quality adaptive interventions), this special issue also demonstrates that there is quite a bit of momentum in this area of CAMH research. This is not surprising given that CAMH has now established the efficacy for a wide variety of interventions across a number of CAMH disorders, and researchers are now turning toward addressing new questions such as those listed in Table 1. Similarly, both data collection and data analysis methodology related to the development and evaluation of adaptive interventions have advanced significantly over the past decade—and will continue to advance—as evidenced by a boom in interest on this topic in the quantitative, methodological or statistical literatures.

A secondary goal is that this special issue inspires others to consider research on adaptive interventions and improve on this emerging area of science. There is much work ahead on the development and evaluation of adaptive interventions in CAMH (which many of the manuscripts in this paper touch on), but also on how existing conceptual, behavioral or developmental theories can be, or ought to be, adapted to inform the development of adaptive interventions and vice-versa.

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Table 1

Example scientific questions for the development of adaptive interventions in child and adolescent mental health.

| Example questions | Special issue papers that focus on such question(s) |
|---|--|
| Which is the best treatment to start with in the context of an adaptive intervention or sequence of treatments? ^a | Naar-King et al. (2015) Pelham et al. (2015) |
| What next treatment (strategy or tactic) is best among children identified as partial responders or non-responders to initial treatment? ^a | Naar-King et al. (2015) Pelham et al. (2015) |
| How should non-response (or non-engagement or non-adherence) during initial treatment be defined for purposes of deciding whether to transition to a subsequent treatment (or engagement or adherence) strategy? ^b | Shih et al. (2014) Pettit et al. (2015) |
| How does a set of pre-specific adaptive interventions compare on longitudinal or end of study psychological outcomes? ^a | Almirall et al. (2015) Pelham et al. (2015) |
| How do different adaptive interventions or sequences of treatments compare on cost of benefit-cost? | Page et al. (2015) |
| What are the challenges or barriers—i.e., in terms of acceptability and feasibility from the perspective of youth, parents or clinicians—to implementing an adaptive intervention or sequence of treatments in actual clinical practice? | August et al. (2014) Chronis-Tuscano et al. (2015) Gunlicks-Stoessel et al. (2015) |
| Does providing a behavioral intervention first enhance response to subsequent augmentation with medication, should medication be needed? Conversely, does providing medication first enhance the likelihood of adherence to subsequent augmentation with behavioral intervention, should behavioral intervention be needed? (Murphy, et al. 2007) | Pelham et al. (2015) |
| Does a particular initial treatment—which, in the short-term does not improve outcomes—elicit information about the youth that could be used to tailor subsequent treatments and, thereby, improve outcomes longer-term? ^a (Murphy, et al. 2007) | |
| Does determining the best adaptive intervention (among a set) differ depending on the research outcome used? If so, how can this information be used to decide which adaptive intervention is best for which individual? ^a (Lizotte et al. 2012) | |
| How long should we provide initial treatment before declaring an individual child in need of additional treatment? Similarly, at what time point should non-responders (or responders) be transitioned to subsequent treatment? ^b | |
| What baseline variables are important in deciding for whom we should begin with one treatment approach over another? ^a | |
| What baseline variables are important in deciding for whom we should provide longer- versus shorter-duration initial treatment? ^b | |
| How often should children be monitored for response/non-response? | |
| How should we re-engage children who are non-adherent or likely to drop-out of treatment? | |
| Should non-adhering non-responders be treated differently from adhering non-responders? ^a | |
| What continuation or maintenance treatment is best among children identified as early responders? | |
| What parent, school or contextual factors are important in making initial and subsequent treatment decisions? ^a | |
| What is the best way to prioritize or combine multiple tailoring variables (including from different informants, e.g., parents, children, teachers or clinicians) to make initial and subsequent treatment decisions? ^a | |
| If different informants (e.g. parents, children, teachers or clinicians) differ substantively in their assessment of child progress during treatment, then is this information useful in making subsequent treatment decisions? ^a (De Los Reyes, et al. 2013) | |
| How effective is a particular adaptive intervention relative to a suitable control, such as treatment as usual? | |

Notes.

^aThe full-scale SMART designs described in this special issue (Almirall et al. 2015; Naar-King et al. 2015; Pelham-Jr, et al. 2015), could also be used to address many of these questions.

^bThe initial randomization in the study by Gunlicks-Stoessel et al. (2015) is motivated, in part, by questions such as this.

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