CHAPTER 23

Building a Science of Personalized Interventions for PTSD

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This chapter is dedicated to exploring "next steps" in improving treatment outcomes for people with posttraumatic stress disorder (PTSD). Over the past decade, there has been growing attention to the development of *personalized interventions* to improve treatment response rates. Personalized interventions consider at least three factors for the refinement and tailoring of treatment: the individual patient, his or her specific problem, and the particular set of circumstances under which the individual is treated. This idea was proposed by psychotherapy researchers over a half-century ago (e.g., Luborsky, Cris-Christoph, Mintz, & Auerbach, 1988; Paul, 1967), but the methodological and statistical means by which to reach this goal were lacking. More recently, there have been advances in the conceptualization of personalized interventions along with advances in research and analytic methods that are likely to allow this goal to be realized.

This chapter reviews several evolving strategies for personalizing mental health interventions that are relevant to the treatment of PTSD. These include adaptation of treatments for specific populations and environments, modular therapies, sequential multiple assignment randomized trials (SMART), and individualized metrics. We also report on the literature regarding personalized treatments in the context of neurobiological findings.

Therapies Adapted for Specific Populations and Environments

The most common example of adaptations of evidence-based therapies (EBTs) lies in their application to different cultures. Because most EBTs have been developed and tested mainly with Caucasian and Western samples,

the concepts and examples used in the treatments may not be relevant to and are potentially discordant with other cultures. Adaptations may involve not only a translation to a different language but also reformulation of the treatment to attend to culturally relevant trauma-related experiences and concepts as well as reformulation of the interventions themselves so that the treatment is consistent with the patient's experience and perspective (Bernal, Jimenez-Chafey, & Rodriguez, 2009; Hinton, Field, Nickerson, Bryant, & Simon, 2013).

To date, most adaptations have been developed for culturally distinct subgroups of a population of interest. The process by which adaptations are made typically involves collaboration with providers, patients, and community stakeholders to assess the content validity of the treatment, to revise the treatment, and to engage in iterative modifications throughout the initial delivery of the protocol (Dixon, Ahles, & Marques, 2016; Hinton, Rivera, Hofmann, Barlow, & Otto, 2012).

The most conservative study design assesses whether the cultural adaptation of the protocol confers added benefit relative to the standard approach. Evaluations using this type of design with regard to adaptations of cognitive-behavioral therapy (CBT) for Latino populations in the United States have found mixed results, with benefit associated only with some adaptations depending on the specific treatment, type of problem, and strength of identification with the subculture (Ng & Weisz, 2016). The results thus far suggest that culturally sensitive perceptions of mental health disturbances as well as their solutions vary from subgroup to subgroup and from culture to culture, indicating the importance of utilizing qualitative data derived from multiple sources to formulate adaptations and of developing reliable means by which to make generalizations (see Riggs et al., Chapter 24, this volume, on implementation science).

Several recent studies of traumatized populations have described collaborative processes between researchers and stakeholders who represent minority populations or cultures different from the researchers to develop more appropriate and effective engagement strategies, assessment measures, and therapies (e.g., Kaysen et al., 2013; Tay & Silove, 2017; Valentine, Dixon, Borba, Shtasel, & Marques, 2016), providing good examples of implementation science principles. Clinical trials have evaluated the feasibility and efficacy of adapted cognitive-behavioral therapies relative to wait list or treatment as usual in several non-Western cultures. Probably the most well-studied intervention used in non-Western settings is narrative exposure therapy (NET). NET was initially developed by Western clinician-researchers mainly using "Western" cognitive-behavioral concepts to address PTSD in African refugees. A number of randomized controlled trials (RCTs) have successfully been conducted in a variety of cultural settings, demonstrating NET's effectiveness in both Western and non-Western countries (e.g., Hijazi et al., 2014; Neuner, Schauer, Klaschik, Karunakara, & Elbert, 2004; Neuner et al., 2008).

At least three adaptations of cognitive processing therapy (CPT) have been tested in RCT designs (Bass et al., 2013; Bolton et al., 2014; Weiss et al.,

2015). As an example of the adaptation of CPT for the Kurdish population in Iraq, initial review indicated that two traditional CPT themes considered related to trauma, impact on *self-esteem* and *intimacy*, did not have a direct translation in the Kurdish language, so alternative themes of *respect* and *caring* were identified and used in the treatment. The adapted version of CPT was found to show moderate to strong effect sizes relative to wait list on depression, posttraumatic stress symptoms, and dysfunction (Bolton et al., 2014). A similar process of adaptation has been applied to trauma-focused cognitive-behavioral therapy (TF-CBT) for delivery to Congolese female adolescent victims of sexual violence. Adaptations included the use of familiar games and songs to convey concepts and visits to the girls' guardians, with the goal of reducing the family's perception of stigma and fostering family acceptance of and reconnection with the victim. Results of an RCT comparing TF-CBT to wait list found that the treatment group reported significant reductions in trauma symptoms and increased prosocial behavior (O'Callaghan, McMullen, Shannon, Rafferty, & Black, 2013). Both of these studies indicate that an evidence-based treatment can successfully be adapted to very different cultures. There have been several other evidence-based interventions that demonstrated successful adaptation to other cultures, including an open trial of eye movement desensitization and reprocessing (EMDR) therapy in the Congo (Allon, 2015) and behavioral activation treatment for depression among Kurds in Northern Iraq (Bolton et al., 2014).

Several questions can be posed when considering the adaptation of evidence-based treatments across different environments. With regard to any treatment, one might ask how much a specific therapy can be adapted and still be considered the same treatment, or how many changes can be made to a protocol before it becomes unrecognizable and evolves into another treatment. These types of questions highlight the need for caution regarding assumptions that the benefits in an adapted version will be similar to those of the established protocol. If an established treatment is substantially changed, the empirical evidence that provided the rationale for the application of the treatment to the new population may no longer provide a credible basis for predictions of beneficial outcomes. An alternative approach may be to identify the key common elements of effective trauma treatments (see Schnyder et al., 2015) and to develop treatments based on general principles of recovery instantiated in the language, idioms, beliefs, and behaviors of the specific culture or population.

Modular Therapies

Modular therapies describe psychotherapies in which evidence-based modules known to address and resolve specific problems are selected and organized to create a treatment plan tailored to a particular patient's most significant symptoms and concerns. This approach reduces the risk of including interventions and concepts that are not particularly relevant to the individual

patient, potentially leading to greater willingness to engage in treatment, better treatment attendance, increased use of interventions, and ultimately better outcomes. The approach is particularly attractive considering the potential heterogeneity of the symptom profiles of patients diagnosed with DSM-5 PTSD or alternatively diagnosed with either PTSD or complex PTSD (CPTSD) as delineated in the 11th revision of the *International Classification of Diseases and Related Health Problems* (ICD-11). Moreover, it could be helpful in creating a streamlined treatment plan that is inclusive of the common comorbid symptoms and disorders, such as depression, chronic pain, and substance use. Thus, a modular therapy is an approach that can be conceptualized as an efficient and effective way to address all and only the problems presented by a particular patient.

Current treatment protocols offer a standardized sequence of interventions, with treatment generally focusing on processing of the trauma memory (e.g., CPT, NET, prolonged exposure [PE], cognitive therapy for PTSD [CT-PTSD]). Other therapies present or include resource-building interventions, such as social support enhancements, relationship strengthening, and emotion regulation interventions (e.g., brief eclectic psychotherapy for PTSD [BEPP], EMDR therapy, interpersonal therapy [IPT], skills training in affective and interpersonal regulation [STAIR] narrative therapy), and still others that have been identified as relevant to commonly occurring comorbidities, such as behavioral activation for depression, biofeedback for chronic pain, and relapse prevention for substance use. In addition, the introduction or integration of other types of interventions like medication, mindfulness, or psychodynamic interventions can be considered. The specific interventions or series of interventions to be selected for investigating a modular therapy approach remain to be considered and may vary as different researchers use protocols with which they are experienced as the reference or standard treatment to which the modularized treatment will be compared.

The infrastructure supporting the implementation of flexible modular therapies typically includes assessment measures and decision-making flowcharts (Chorpita & Weisz, 2009). The therapist and patient collaborate to review the initial assessment results and to identify the primary problem; this information is used, in turn, to select a module or series of modules for the treatment plan. A critical aspect of the work is regular symptom assessment, identifying progress made on target symptoms. The results of these assessments guide next-step decision making about whether to repeat the module, go on to the next planned module, or revise plans for the next module if the secondary symptoms have resolved or new symptoms or problems have emerged.

Relevant to this discussion is consideration of the potential benefits of the flexible multimodular treatment approach broadly conceived and evidence for its success. In studies of child and adolescent mental health programming, the flexible sequencing of self-contained modules has been demonstrated to be more effective compared to the use of full protocols for a single disorder (Daleiden, Chorpita, Donkervoet, Arensdorf, & Brogan,

2006) or to the sequencing of full protocols for different disorders (Weisz et al., 2012). There are no published data regarding patient preferences or administrator preferences between protocol-driven versus modular selection in PTSD. However, treatment duration for modular as compared to standard protocols tends to be shorter, suggesting greater benefit for the patient with regard to time commitment and potentially for the health care system in terms of staff resources and clinician time (Weisz et al., 2012). Lastly, clinicians report more positive attitudes about adopting modular therapies compared to standard protocol therapies (Borntrager, Chorpita, Higa-McMillan, & Weisz, 2009; Chorpita et al., 2015), suggesting the potential for greater ease of adoption and dissemination and uptake of these evidence-based interventions. Demonstration of the feasibility, effectiveness, and satisfaction associated with the flexible modular approach suggests its potential for PTSD patients and value in future research.

Sequential Multiple Assignment Randomized Trial Designs

Research to date on modular therapies has been structured so that the formulation of the treatment to be implemented is generally made at the initial assessment following a flowchart, with the selection of the modules and their sequence having been predetermined. The assessment of interest occurs at the end of the trial (posttreatment and at follow-up) to determine if the modular treatment outcome is superior to a standard treatment. An alternative approach is a sequential multiple assignment randomized trial (SMART; Collins, Murphy, & Strecher, 2007; Lei, Nahum-Shani, Lynch, Oslin, & Murphy, 2012; Murphy, 2005). In SMART designs, assessments critical to the process and outcome of a study are conducted at several points across the treatment, there are repeated randomizations into alternative interventions based on the periodic assessment results, and the comparator treatment is not an established standard but another multiple randomization sequence. SMART designs are useful when no established standard treatment exists and empirical and/or theoretical guides are not available to create hypotheses about a preferred treatment approach. SMART designs are not tests of adapted treatments but are used to inform the development of adaptive treatments, which then can be compared to standard treatments.

To provide a relevant example from the PTSD literature, it is known that Web-based PTSD programs have better outcomes when there is some level of therapist involvement, but studies had varied widely regarding the number of sessions and amount of time that therapists have engaged with patients (Olthuis et al., 2016). To gather information about the relative benefits of differing amounts of therapist support, a SMART trial could be designed such that the amount of therapist involvement is adjusted systematically from lower to higher amounts contingent on the results of periodic assessments. This approach would provide answers to many more questions

and much more quickly compared to RCTs, which are highly controlled and do not propose contingency-based changes for individual participants across the course of treatment. In SMART designs, there are typically at least two stages, each with its own randomization procedure, hypotheses, and outcome evaluation. In this investigation, for example, Stage 1 participants are randomized into either a no-therapist Web-based treatment condition (nWBT) or a biweekly therapist-supported (bWBT) condition. After 6 weeks, each participant is classified as a responder or nonresponder (e.g., someone who has experienced less than a 10-point drop in his or her PTSD score). Stage 2 is the initiation phase where responders continue in their assigned condition while the nonresponders in each condition are rerandomized. In the nWBT condition, nonresponders are randomly assigned to either biweekly or weekly Web-based treatment (bWBT or wWBT). In the original bWBT, nonreponders are assigned to weekly WBT or weekly WBT with an additional phone call as needed (wWBT or w + WBT). The trial is completed at the end of a second 6 weeks.

This design allows comparison of the two first-stage treatments, nWBT and bWBT, with regard to their nonresponse rates at the 6th week as well as the differential benefit observed among the responders at both the 6th and 12th weeks. It also tests four adaptive interventions in the second stage (or randomization) of the trial. Determination of the relative benefits of one adaptation over another can be assessed by comparing outcomes of the pair of adaptations to which nonresponders have been randomized (bWBT vs. wWBT, wWBT and w + WBT) and as relative to the initial responders.

This type of design can be applied to explore several other types of treatment questions. For example, the first phase of a SMART RCT might compare a trauma-focused (TF) versus non-trauma-focused (NTF) treatment. At the end of this phase, nonresponders in each condition would be randomized again, where, for example, nonresponders to TF receive either more TF or switch to an NTF, while nonresponders to NTF might either obtain more NTF or switch to TF. Similarly, two different medications might be tested in the first randomization phase, and in the second phase, nonresponders could be randomized to an increased dose of the same medication or a switch to another drug. In both of these examples, the relative efficacy of two treatments is being assessed in the first randomization, the relative proportion of nonresponders is being identified, and preliminary data regarding options for nonresponders are being obtained.

Treatment Selection

One of the most common approaches to personalized mental health is treatment selection, defined as using patient factors to identify the optimal intervention for an individual among a set of available treatments (see Cohen & DeRubeis, 2018, for an extensive review).

Historically, treatment selection in mental health and in medicine more broadly has been practiced through the use of diagnoses. Patients are given a diagnosis to identify an appropriate and effective treatment. The strategy of identifying which treatments are helpful for specific disorders has been formalized in several ways, including efforts to define empirically supported treatments (ESTs) (Chambless & Hollon, 1998). However, for most mental health disorders, multiple evidence-based treatments exist, and there are relatively few contexts in which a single specific treatment has been identified as superior to all others and other factors have been investigated.

Patient preference is one. This is appropriate, not only because it respects the patient's autonomy and dignity, but also due to the assumed relationship between a patient's preference and his or her willingness to initiate and engage with (or adhere to) a preferred treatment relative to a nonpreferred treatment. To date, the relationship between patient preference and actual treatment outcomes is unclear, and it likely varies as a function of myriad contextual factors (e.g., patient's understanding of or exposure to the options; the necessity of the patient's active participation and commitment). In the clinical trials that have examined this association, researchers have reported results that are positive, negative, and equivocal (Cohen & DeRubeis, 2018). Regardless, practice guidelines are clear that respecting patient preference is an essential part of ethical clinical practice.

Clinician judgment also plays a significant role in treatment selection (Cohen & DeRubeis, 2018). Clinicians who attend to information about a specific patient's presentation can generate hypotheses about the patient's expected response to a given treatment (Lorenzo-Luaces, DeRubeis, & Bennett, 2015). For example, Raza and Holohan (2015) surveyed Veterans Affairs clinicians in the United States who had been trained in both CPT and prolonged exposure (PE) with regard to patient variables that they believed might inform the decision between CPT, PE, or alternative treatments. CPT was selected over PE for patients with strong guilt, strong shame, acts of perpetration, and dissociation history, whereas PE was preferred to CPT for patients with low literacy, low cognitive functioning, and moderate/severe traumatic brain injury. However, it should be noted that there is not an evidence base to support these selection criteria to date, and it is uncertain whether these are factors to which clinicians and patients should attend. Additionally, the complexity of the decision-making process in the context of numerous distinct factors suggests that there are opportunities for data-driven, multivariable prediction models to help inform the treatment selection process.

Individualized Metrics

Early research efforts to discover what works for whom largely revolved around subgroup analyses, in which differences between distinct subgroups

(e.g., men vs. women, older vs. younger individuals, presence or absence of a history of childhood abuse) were examined. When these differences were detected and determined to be statistically significant, researchers would claim they had identified a potential moderator, meaning that a variable had been identified that was associated with differential response across different treatments. These factors have been labeled "prescriptive" variables. Statistically, this relationship was often detected[1] when predicting treatment response in the form of an interaction between a predictor variable and the treatment term (sometimes described as an "aptitude-by-treatment" interaction). These interactions could be "ordinal," which in subgroup analyses implies that the difference between expected treatment response exists in one subgroup but not the other (e.g., Treatment A is better than Treatment B for men, but no difference is expected between the two treatments for women). They could also be "disordinal," involving a full crossover effect (e.g., Treatment A is better than Treatment B for older individuals, and Treatment B is better than Treatment A for younger individuals). For example, Rizvi and colleagues (2009) identified age as a disordinal prescriptive factor in an RCT comparing PE to CPT: older women had better outcomes in PE versus CPT and younger women had better outcomes in CPT relative to PE.

The more common and easily detected effects are prognostic. Prognostic variables are those for which associations with outcome exist either irrespective of treatment or for which the relationship is only known for a single treatment.[2] A prognostic relationship can be identified if a variable has been shown to predict treatment response in the same way across multiple treatments; for example, in an RCT comparing PE and CPT, Rizvi and colleagues (2009) found that, regardless of the treatment to which the women were randomized, those with higher pretreatment depression and guilt experienced larger improvements in PTSD symptoms than those with lower depression and guilt. Alternatively, when a predictive relationship is identified through the investigation of data from a sample of individuals in which everyone was provided with the same treatment, that relationship is also said to be prognostic. Importantly, prognostic relationships of this final type should not be *assumed* to provide information about what treatment an individual ought to

[1]It is important to note that prescriptive interaction effects can only be truly detected when data from two or more treatments are examined (Cohen & DeRubeis, 2018).

[2]It should be noted that although variables are often described as "being" prescriptive or prognostic, a given factor can have a prognostic relationship with outcome in one context and a prescriptive relationship in another. For example, if a study comparing Treatment A versus Treatment B found that individuals' levels on factor X had the same association with posttreatment outcome across both treatments, it would be accurate to describe factor X as prognostic in that study. However, an analysis of a separate study comparing Treatment A versus Treatment C might find that factor X predicted a differential response between those two treatments, and those authors would be justified in concluding that factor X was a prescriptive variable in their data. Both sets of authors would be correct.

receive. It is tempting to infer that a patient with a poor prognosis in a given treatment should be directed to seek an alternative. However, a patient who has a poor predicted outcome for a given treatment based on a prognostic model might be expected to have an equally poor or even worse response to an alternative treatment.

Despite the multitude of studies examining patient-specific characteristics of treatment outcomes in depression, anxiety, and to some extent PTSD, the uptake by clinicians has been minimal at best, due in part to the paucity of successful replications of the findings. For example, individual variables such as childhood abuse, depression, dissociation, and severity of symptoms that have been found to predict outcomes in some studies have been tested and not found predictive in others (see Cloitre, Petkova, Su, & Weiss, 2016, for a review). These conflicting results likely have many sources, including small sample sizes, inconsistent statistical methodology, treatment and sample heterogeneity, and weak effects of individual predictor variables (Cohen & DeRubeis, 2018).

Multivariable Prediction Models

Over the last decade, several different solutions for data-driven, evidence-based treatment selection have been described, including Kraemer's (2013) "M*" approach, Petkova, Tarpey, Su, and Ogden's (2016) composite moderator approach, and DeRubeis and colleagues' (2014) Personalized Advantage Index (PAI) approach. What these approaches have in common is their application of statistical modeling in longitudinal treatment datasets (that comprise pretreatment or baseline variables and posttreatment outcome data) to capture simultaneously the predictive signal from multiple prescriptive variables. By aggregating the effects of many small but reliable moderators, these approaches generate recommendations that could lead to clinically significant differences in patient outcomes.

The composite moderator approach has been used to assess treatment outcome in PTSD. Through this data-driven approach, Cloitre and colleagues (2016) identified patient characteristics that predicted differential outcome in three multi-modular treatment conditions depending on the interventions included in the sequence. The three conditions included STAIR Narrative Therapy, a two module treatment in which a skills module was followed by a trauma-focused module (the test condition) and two comparator treatments in which the content of each module was replaced by a nonspecific active comparator, present-centered therapy (PCT; called "supportive counseling" in the study). The two comparators resulted in delivery of a predominantly trauma-focused therapy (PCT plus Narrative Therapy) therapy and a predominantly skills focused therapy (STAIR plus PCT). The moderator that most strongly differentiated outcomes was a ratio of patient burden (PTSD, depression, dissociation, interpersonal problems, and anger) relative to a patient strength (emotion regulation capacity). The participants in the STAIR narrative therapy condition

showed the best outcomes regardless of ratio. However, participants with a low ratio of symptom severity relative to emotion regulation had better outcomes in the trauma-focused therapy than in the skills-focused treatment, whereas those with a high ratio of symptom severity relative to emotion regulation had better outcomes in the skills-focused treatment. If replicated, these results could be used to match patients with treatments whereby some patients would receive a trauma-focused treatment and others a skills-based or non-trauma-focused treatment based on a ratio identifying their symptom burden relative to strengths. This variable (a ratio of symptom burden to patient strengths) is an example of a prescriptive variable.

Another treatment selection approach that has been applied to PTSD is DeRubeis and colleagues' (2014) PAI approach. Using data from a study comparing CPT to PE in women with rape trauma PTSD, Keefe and colleagues (2018) identified four moderators that predicted differential risk of dropout between the two treatments: childhood physical abuse, current relationship conflict, anger, and race. All individuals in the study were randomized to either CPT or PE, which did not differ in their dropout rates. After creating a logistic regression model that tracked the interactions between all four variables and treatment, the risk of dropout for each individual in both conditions could be predicted, and the treatment associated with the highest likelihood of treatment completion identified. Patients who received their PAI-indicated treatment had a significantly lower dropout rate (19.7%) compared to those who received their nonindicated treatment (40.5%). If replicated, these findings combined with models designed to maximize symptom reduction could be used to minimize treatment dropout by helping match patients to the treatment most likely to result in treatment completion.

Prognostic models have also demonstrated potential utility for treatment selection when deciding between treatments that are not equivalent in their average treatment effect. Following the approach described by Lorenzo-Luaces, DeRubeis, van Straten, and Tiemens (2017), Wiltsey Stirman and colleagues (2020) constructed a single prognostic model for a combined sample of individuals with PTSD treated with either PE or PCT. They found that the patients with good prognoses who were randomized to receive PE experienced significantly more improvement than patients with good prognoses who received PCT, whereas patients with poor prognoses showed little to no advantage when receiving PE versus PCT. The patients predicted to have poor prognoses were those with higher symptom severity or case complexity, including worse mental and physical functioning, the presence of military sexual trauma, longer time since the trauma, and lower endorsement of treatment credibility. If replicated, these and other models could be used to inform the collaborative decision-making processing by which clinicians and patients determine the best path toward recovery from PTSD.

Nevertheless, one important criticism of these efforts is that the sample sizes available in the RCT datasets that have been used have been insufficient

for the purpose of modeling interaction effects (Luedtke, Sadikova, & Kessler, 2019). This has led to recent proposals of alternative modeling approaches for informing treatment selection, including the use of prognostic models.

One solution proposed by Kessler, Bossarte, Luedtke, Zaslavsky, and Zubizarreta (2019) allows for researchers to move iteratively between more exploratory analyses using larger, inexpensive archival datasets and more controlled tests of precision medicine models in smaller clinical trial datasets that can accommodate more extensive measurement. A second solution (Kessler et al., 2017) is to construct independent prognostic models within each condition, and to then infer treatment recommendations by comparing the predictions for each treatment generated by the separate models. Deisenhofer and colleagues (2018) demonstrated this approach in a sample of individuals receiving TF-CBT or EMDR therapy for PTSD. Age, employment status, gender, and functional impairment were identified as predicting treatment response among the people receiving TF-CBT, and those four variables were used to construct a prognostic model for TF-CBT. A separate prognostic model that relied on only baseline depression and antidepressant prescription was constructed using data from the subset of the sample who received EMDR therapy. A new individual's values on the relevant factors would be fed into each prognostic model, thus generating separate predictions of treatment response from the two prognostic models (TF-CBT or EMDR therapy), and the recommended treatment would be identified by whichever treatment was predicted to lead to a better outcome.

Neurobiological Findings

Since the Institute of Medicine (2011) call for precision medicine specified for the development of personalized treatment strategies for mental disorders, research methodologies have been suggested to promote such development (Leon, 2011; Soliman, Aboharb, Zeltner, & Studer, 2017), with genetics (Smoller, 2014; Sullivan et al., 2018) and neuroimaging (Etkin, 2014) at the forefront. Genetic and epigenetic factors, and neuroimaging as well as neuroimmunological findings have made substantial contributions to the development of therapeutic algorithms that identify treatments likely to provide good outcome depending on patient characteristics. This approach has been applied successfully in various medical disciplines for a number of years, for example, in areas such as oncology (Bristow et al., 2018; Janiaud, Serghiou, & Ioannidis, 2019), guiding the therapeutic decision making of surgeons, medical oncologists, and radio-oncologists.

In mental health, personalized medicine appears to be in its infancy (Cohen & DeRubeis 2018; Ng & Weisz, 2016). The search for endophenotypes for major depression has long been suggested (Hasler, Drevets, Manji, & Charney, 2004). However, as Hellhammer, Meinlschmidt, and Pruessner (2018) pointed out in a recent review, "Psychobiological research has

generated a tremendous amount of findings on the psychological, neuroendocrine, molecular and environmental processes that are directly relevant for mental and physical health, but have overwhelmed our capacity to meaningfully absorb, integrate, and utilize this knowledge base" (p. 147).

In mood disorders, some progress has been made with regard to psychosocial risk factors as well as genetic and epigenetic factors, and neuroimaging findings (Prendes-Alvarez & Nemeroff, 2018). For instance, increased gray matter density in the right inferior frontal gyrus (rIFG) was identified as a potential biomarker of bipolar disorder (Alda & Manchia, 2018). Furthermore, greater pretreatment ventral and pregenual anterior cingulate cortex (ACC) activation may predict better antidepressant medication outcome but poorer psychotherapy outcome (Ball, Stein, & Paulus, 2014). In the field of anxiety disorders, only a few biological moderators of treatment outcome across disorders were identified (Schneider, Arch, & Wolitzky-Taylor, 2015). Again, genetics and neuroimaging seem to emerge as the most promising areas of research (Casey & Lee, 2015). As in depression, the ACC appears to play an important role (Ball et al., 2014).

In the area of trauma-related disorders, specifically PTSD, the literature to date on biological moderators of treatment outcome is even more scarce, and the majority of studies appear to suffer from methodological limitations (Schneider et al., 2015). Smoller (2016) emphasized the role of gene–environment interactions and the fact that stress-related disorders are polygenic. Moreover, there appears to be genetic overlap among stress-related disorders including PTSD, major depressive disorder, and anxiety disorders.

Large-scale genome-wide association studies, epigenome-wide association studies, and other genomic analyses have demonstrated that the development of PTSD is strongly influenced by genetic and epigenetic factors. The Psychiatric Genomics Consortium PTSD Workgroup led by Karestan Koenen (Nievergelt et al., 2018) took a systematic approach to developing new knowledge about the genetic underpinnings of PTSD, using large datasets, up-to-date technologies, and novel analytic methodologies. For example, the consortium found that childhood trauma exposure and lifetime PTSD severity are associated with accelerated DNA methylation age (Wolf et al., 2018). However, studies looking into genetic or epigenetic predictors of treatment outcome are still scarce. In a small pilot study of PE therapy with combat veterans suffering from PTSD, methylation of the GR gene (*NR3C1*) exon 1F promoter assessed at pretreatment predicted treatment outcome (Yehuda et al., 2013). More recently, Pape and colleagues (2018) identified pretreatment *NR3C1* methylation levels as a potential marker to predict PTSD treatment outcome, independent of the type of therapy.

With regard to neuroimaging markers, the subgenual anterior cingulate cortex (sgACC), default mode network, and salience network seem to play an important role as outcome predictors of transcranial magnetic stimulation for PTSD (Philip et al., 2018).

Shvil, Rusch, Sullivan, and Neria (2013) reviewed neural, psychophysiological, and behavioral markers of fear processing in PTSD. It remains to be studied, however, to what degree markers of fear processing, such as hyperactivation of the amygdala, dorsal ACC, and insula, and hypoactivation in other brain areas, turn out to be sufficiently robust treatment outcome markers as well. The same applies to psychophysiological variables such as startle response, heart rate variability, or skin conductance response. In a recent small psychotherapy outcome study of a combination of CBT for substance use disorder with CPT for PTSD, Soder and colleagues (2019) identified baseline resting heart rate variability as a possible biomarker predicting PTSD treatment outcomes in adults with co-occurring substance use disorder and PTSD. The authors concluded that patients with poorer autonomic emotional regulation, as reflected by low heart rate variability, may not respond as well to psychotherapy in general.

Taken together, there is an emerging body of literature on putative biomarkers that might be used as predictors of PTSD treatment outcome. It can be expected that in the future, such biomarkers will be used to develop personalized treatment strategies for people with PTSD, and to inform collaborative processes of joint decision making among therapists and their patients. At this point in time, however, the development of therapeutic algorithms to optimize clinical outcomes of empirically supported therapies has a limited evidence base.

Conclusions

The goal of personalized therapy research is to generate a body of knowledge that will translate to clinical services such that therapists will be able to provide the most effective treatment in the most efficient manner to every patient based on their individual symptoms, characteristics, and preferences. This chapter has identified some of the conceptual and methodological building blocks that are contributing to the development of a science of personalized intervention. These include study designs that involve the systematic adaptation of treatments for specific populations, evaluation of flexible sequencing of modular interventions, and SMART designs that allow for the rapid testing and identification of adaptations likely to succeed. The building blocks also include statistical strategies and computer power that can analyze vast amounts of data to provide reliable information about which psychological, social, or genetic and other neurobiological characteristics are associated with what types of outcomes in which treatments, facilitating a match of patient to treatment to optimize outcome. Hopefully, these building blocks of treatment designs and statistical analyses can be productively stacked together to advance science and provide answers to the question that has long been asked: *What works for whom?* If successful, personalized

intervention science will provide a research and treatment pathway that will markedly alter the nature of mental health care services.

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