ELSEVIER

Advancing Personalized Medicine: Application of a Novel Statistical Method to Identify Treatment Moderators in the Coordinated Anxiety Learning and Management Study

Andrea N. Niles
Amanda G. Loerinc
Jennifer L. Krull

University of California, Los Angeles

Peter Roy-Byrne

University of Washington at Harborview Medical Center, Center for Healthcare

Greer Sullivan

University of Arkansas for Medical Sciences

Cathy D. Sherbourne

RAND Corporation, Santa Monica, CA

Alexander Bystritsky
Michelle G. Craske

University of California, Los Angeles

There has been increasing recognition of the value of personalized medicine where the most effective treatment is selected based on individual characteristics. This study used a new method to identify a composite moderator of response to evidence-based anxiety treatment (CALM) compared to Usual Care.

Eight hundred seventy-six patients diagnosed with one or multiple anxiety disorders were assigned to CALM or Usual Care. Using the method proposed by Kraemer (2013), 35 possible moderators were examined for individual effect sizes then entered into a forward-stepwise regression model predicting differential treatment response. *K*-fold cross validation was used to identify the number of variables to include in the final moderator.

Ten variables were selected for a final composite moderator. The composite moderator effect size ($r = .20$) was twice as large as the strongest individual moderator effect size ($r = .10$). Although on average patients benefitted more from CALM, 19% of patients had equal or greater treatment response in Usual Care. The effect size for the CALM intervention increased from $d = .34$ to $d = .54$ when accounting for the moderator.

Findings support the utility of composite moderators. Results were used to develop a program that allows mental health professionals to prescribe treatment for anxiety based on baseline characteristics (http://anxiety.psych.ucla.edu/treatmatch.html).

Keywords: anxiety disorders; CBT; primary care; moderators; model selection; personalized medicine; precision medicine

ALTHOUGH COGNITIVE BEHAVIORAL THERAPIES are effective for the treatment of anxiety disorders (Hofmann & Smits, 2008; Norton & Price, 2007), response rates range from 38% to 77% depending on disorder, indicating that many patients do not respond (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012). The need for personalized medicine, where the most effective treatment is selected based on individual characteristics (i.e., treatment moderators), has received increasing attention (Simon & Perlis, 2010) as evidenced by the $215 million Precision Medicine Initiative (National Institute of Health, 2016). However, the research on moderators for anxiety disorder treatment is severely lacking due to insufficient sample sizes and underpowered statistical methods (Schneider, Arch, & Wolitzky-Taylor, 2015). Prior moderation analyses typically have compared response to two evidence-based treatments. This is a valuable question given that multiple therapeutic approaches may be effective. At the same time, many patients do not have access to evidence-based treatment (Stein et al., 2011; Weisberg, Dyck, Culpepper, & Keller, 2007). As reviewed by Kazdin (2015), a more basic question, and one that may inform the current treatment climate, is whether there is additional benefit for a patient in receiving specialized anxiety treatment compared to what is already in use—i.e., who benefits from additional treatment beyond usual care.

Kraemer (2008, 2013) discusses problems with existing research on treatment moderation, including disagreement over the definition of moderators and a failure to define a moderator effect size. Consequently, it is not possible to determine which moderators have the largest effect on the likelihood of benefiting from a treatment. The addition of effect sizes to moderator studies allows comparison of moderator effect size for the same treatment choice and outcome (Kraemer, 2013). Another limitation with existing approaches is that researchers typically examine one moderator per statistical model (Schneider et al., 2015). Because moderators tend to have modest effect sizes (Kraemer, 2013), combining multiple moderators into one model should produce larger effects and ultimately greater precision when assigning patients to treatments. Kraemer's approach uses effect size rather than statistical significance to directly compare moderator importance. In addition, her approach combines individual moderators into a composite, which results in greater power to predict which treatment will be most effective.

In this study, we evaluated moderators of response to an intervention comprised of computer-assisted CBT or psychotropic medications, jointly termed the Coordinated Anxiety Learning and Management program (CALM), or treatment as usual in primary care (Craske et al., 2011; Roy-Byrne et al., 2010). In this study, a moderator is defined as a baseline variable that helps identify on whom or under what conditions treatment has a causal effect on outcome (2013). CALM was more effective overall than Usual Care (UC) in reducing symptoms of anxiety and depression and improving functioning (Craske et al., 2011; Roy-Byrne et al., 2010). Although patients assigned to CALM showed superior outcomes than patients in UC, CALM was not effective for all patients. Furthermore, some patients assigned to UC improved. These patterns of response highlight the need to identify moderators of response to CALM versus UC. Because CBT can be expensive and time-intensive (Barlow, Levitt, & Bufka, 1999) and medications can have side effects, identifying characteristics that help primary care providers determine whether to refer patients to an anxiety specialist or to continue with treatment as usual is critical.

In a recent review, Schneider et al. (2015) identified 24 studies that examined moderators of treatment for anxiety. Of those studies, 4 had a large sample size, 15 used high-quality statistics, and only 1 had both. The studies compared a variety of treatments including CBT, mindfulness-based treatments, psychodynamic psychotherapy, pharmacotherapy, and capnometry-assisted respiratory training. The results were variable across studies, and the authors state that few conclusions can be drawn given the paucity of research, the limited sample sizes, and the high variability in terms of treatments compared and moderators assessed. The authors conclude that if our goal is to inform clinicians about how to match patients to treatments, the methodological quality and consistency across studies needs improvement.

To our knowledge, no prior studies have examined moderators of response to evidence-based treatment versus usual care. Thus we briefly review existing literature on predictors of response to CBT and medication for anxiety disorders. Prior studies have shown that race, ethnicity, gender, and socio-economic status (Piacentini, Bergman, Jacobs, McCracken, & Kretchman, 2002; Schuurmans et al., 2009; Watanabe et al., 2010; Wolitzky-Taylor, Arch, Rosenfield, & Craske, 2012) are unrelated to treatment outcome, with one exception for gender (Craske et al., 2014): we found that women with social phobia had better outcomes than men from acceptance and commitment therapy and CBT (regardless of treatment condition). In terms of clinical variables, findings for the effect of baseline disorder severity on outcome are mixed with some studies showing that higher baseline scores predict poorer