The Cutting Edge

TRANSDIAGNOSTIC TREATMENT FOR ANXIETY AND DEPRESSION

Michelle G. Craske Ph.D., is Professor of Psychology and of Psychiatry and Biobehavioral Sciences, and Director of the Anxiety Disorders Research Center, at UCLA. She has published extensively in the area of fear and anxiety disorders, including over 300 scientific articles, four books on the topics of the etiology and treatment of anxiety disorders, gender differences in anxiety, translation from the basic science of fear learning to treating phobias and anxiety disorders, and principles and practice of cognitive behavioral therapy, as well as several self-help books and therapist guides. In addition, she has been the recipient of National Institute of Mental Health funding for research projects pertaining to risk factors for anxiety disorders and depression among children and adolescents, the cognitive and physiological aspects of anxiety and panic attacks, neural mediators of behavioral treatments for anxiety disorders, fear extinction mechanisms of exposure therapy, and the development and dissemination of treatments for anxiety and related disorders. She is presently Associate Editor for *Behaviour Research and Therapy* a scientific board member for the Anxiety Disorders Association of America a member of the DSM-5 Anxiety, Obsessive Compulsive Spectrum, Posttraumatic, and Dissociative Disorders Work Group, and Chair of the Anxiety Disorders Subworkgroup. She is also a member of the APA Clinical Treatment Guidelines Advisory Steering Committee for the development of practice guidelines.

INTRODUCTION

Recent interest in transdiagnostic therapies that transcend DSM diagnostic boundaries represents an important paradigmatic shift in evidence-based treatments. The evolution from behavioral therapies delivered in accordance with careful functional analyses of presenting problems to cognitive behavioral therapies (CBT) tied to specific diagnoses led to a proliferation of treatment manuals for different anxiety disorders. On the one hand, these manuals were essential for promoting independently conducted randomized controlled trials that significantly advanced our knowledge of treatment outcome and process. On the other hand, the sheer number of treatment manuals for different disorders is a major barrier to the implementation of evidence-based practice in service settings.

Transdiagnostic approaches retain empirical science but are more easily implemented. Furthermore, they accord with accruing evidence for commonalities in areas of cognitive, behavioral, and neural dysregulation across anxiety and related disorders. Transdiagnostic models are expected to improve therapeutic outcomes, especially for patients with comorbidity, although initial evidence would suggest otherwise.

Future directions for transdiagnostic models include greater attention to the differences as well as the commonalities across groups of disorders that are highly comorbid, such as anxiety and depression, while maintaining a transdiagnostic (i.e., single manual) treatment model. This can be achieved by matching of specific treatment strategies (from a larger pool within a transdiagnostic model) to emotional, behavioral, neural, cognitive, and other domains that are most dysregulated for a given patient. A personalized transdiagnostic approach satisfies the needs of implementation in service settings and additionally may improve outcomes.

RATIONALE FOR A TRANSDIAGNOSTIC APPROACH

A primary motivation for the transdiagnostic approach is the proliferation of treatment manuals for different disorders, sometimes with multiple versions for the same disorder (e.g., panic disorder), that are unwieldy and therefore prohibitive in service settings.[1] The need for evidence-based practices in real-world settings is very apparent.[2] Furthermore, the high rate of comorbidity among anxiety disorders and between anxiety and depression[3] renders specific manuals for specific disorders very inefficient, since most patients present with more than one disorder. Implementation will be greatly facilitated by a single treatment model for all anxiety disorders as well as unipolar depression. Even though

*Correspondence to: Michelle G. Craske, Ph.D., Department of Psychology, University of California at Los Angeles, California. E-mail: craske@psych.ucla.edu

DOI 10.1002/da.21992
Published online in Wiley Online Library (wileyonlinelibrary.com).

anxiety disorder specific CBT (targeting the most severe, distressing, or disabling disorder) positively influences comorbid conditions including depression,[4] full remission of comorbidity is uncommon, comorbidity may resurge over time,[5] and simultaneous application of more than one disorder-specific CBT does not enhance outcomes.[6] Therefore, in addition to facilitating implementation, transdiagnostic approaches are expected to improve upon therapeutic outcomes for the full range of disorders in a given patient.[7]

Transdiagnostic approaches accord with accruing evidence for commonalities in cognitive, behavioral, emotional, and other areas of dysregulation across anxiety disorders and unipolar depression. Commonalities occur in the latent structure of DSM symptomatology, with anxiety and unipolar depressive disorders each loading on a broad general negative affect factor.[8]† The personality trait of neuroticism is a common correlate and predictor of most if not all anxiety disorders as well as depression.[9] The genetic risk factors for anxiety and depression appear largely nonspecific, although likely comprised of more than one factor.[10] Preliminary data indicate similarities in amygdala hyperactivity to threat cues across anxiety and depression.[11] Other indices of threat sensitivity that are shared across the anxiety disorders include attentional bias to threat, interpretation bias toward threat, physiological anticipation of threat, deficits in extinction of threat learning, and avoidance of threat.[11] Certain features of attentional bias and interpretation bias are shared with depression as well.[11]

EXISTING TRANSDIAGNOSTIC THERAPIES

Existing transdiagnostic approaches take two forms. The first is applicable to specific disorders within a category of diagnosis, such as anxiety disorders and eating disorders, and is comprised mostly of generic reformatting of CBT strategies. The second transcends all diagnostic boundaries and involves acceptance-based therapeutic strategies.

Generic CBT. Generic CBT group treatments for heterogeneous anxiety disorders and mixed samples of anxiety and depression have yielded promising outcomes in an open trial[12] ($N = 52$) and a benchmarking comparison against disorder-specific CBT[13] ($N = 143$). Internet transdiagnostic programs for anxiety and depression have been shown to be more effective than waitlist comparisons in larger but undiagnosed samples.[14]

The Coordinated Anxiety Learning and Management (CALM) Tools for Living program is a transdiagnostic CBT model applicable to multiple anxiety disorders, that is partially automated to guide novice therapists (and patients) in service settings. In contrast to other transdiagnostic programs, some CBT strategies are generic (e.g., breathing retraining), whereas branching mechanisms tailor other CBT strategies to the "object of threat" that is most distressing or disabling for a given individual (e.g., in vivo exposure to social situations versus to trauma reminders for posttraumatic stress). A newer version, CALM Tools for Living-II, is applicable to multiple anxiety disorders as well as unipolar depression. The CALM CBT program (sometimes combined with expert recommendations for psychotropic medications) was more effective than treatment as usual (often involving pharmacotherapy and psychotherapy) in a large primary care sample ($N = 1004$) with panic disorder, social anxiety disorder, generalized anxiety disorder, or posttraumatic stress disorder, the majority of whom were also depressed.[16,17] Nonautomated versions of this transdiagnostic CBT program have been tested in comparison to acceptance-based approaches, described below.

Barlow's Unified Protocol uses generic CBT for anxiety disorders combined with emphasis upon response to emotions more generally.[1] It includes motivational enhancement, psychoeducation, emotion awareness training (i.e., self monitoring and mindfulness exercises), cognitive reappraisal, emotion driven behaviors and emotional avoidance (identify and modify behaviors that prevent full exposure to strong emotions), awareness and tolerance of physical sensations (in general), interoceptive and situational exposure (to specific feared cues), and relapse prevention. The Unified Protocol has been shown to be more effective than the passage of time alone[18] in a small sample ($N = 37$) of individuals with a principal anxiety disorder diagnosis.

Acceptance Based. Transdiagnostic approaches that transcend all diagnostic boundaries and have been applied to anxious samples include mindfulness-based stress reduction (MBSR)[19] and Acceptance and Commitment Therapy (ACT).[20] ACT is a behavioral therapy that cultivates mindfulness, acceptance, cognitive diffusion (flexible distancing from the literal meaning of cognitions), and other strategies to increase psychological flexibility and promote behavior change consistent with personal values. These approaches emphasize experiential avoidance as a common factor that underlies various forms of emotional disturbance.[20] Randomized controlled trials of ACT,[21] albeit limited in number, have yielded promising effects in comparison to waitlist and CBT. We demonstrated comparable effects between ACT and transdiagnostic CBT (structured in the same format as the CALM Tools for Living program but without the automated feature) for heterogeneous anxiety disorders ($N = 128$).[22] Whereas moderate levels of anxiety sensitivity and absence of comorbid mood disorder predicted better anxiety outcomes from CBT than ACT, comorbid mood disorders predicted better anxiety outcomes from ACT than CBT.[23] Similarly, we found generally comparable effects between MBSR (combined with psychoeducation and ACT-based values) and transdiagnostic CBT, both delivered in group formats for heterogeneous anxiety disorders, with each treatment showing an advantage on

†Although, the structure of symptoms is influenced by age range and inclusion of a wider array of DSM symptoms beyond internalizing disorders.[15]

a different anxiety outcome ($N = 105$).[24] Combined, these data suggest few differences between CBT-based and acceptance-based transdiagnostic approaches.

Most recently, we completed the first RCT of a transdiagnostic model (ACT) and a disorder-specific CBT, in this case for social anxiety disorder ($n = 87$).[25] Both treatments were substantially more effective than a waitlist comparison, but there was no evidence that one treatment approach was more efficacious than the other for either social anxiety or comorbid conditions. Thus, the assumption that transdiagnostic approaches will improve outcomes, especially for comorbidity, relative to disorder-specific approaches may not prove to be the case, at least with existing transdiagnostic treatments.

NEW DIRECTIONS FOR TRANSDIAGNOSTIC APPROACHES

Extant transdiagnostic approaches, whether CBT-based or acceptance-based, have been delivered via standardized sets of therapeutic strategies for individuals with mixed presentations of anxiety and depression. They emphasize the commonalities that underlie varying manifestations of psychopathology, consistent with the evidence reviewed above. However, there are differences as well as commonalities across anxiety and depression. For example, differences exist across anxiety disorders in terms of acute fear versus more diffuse anxious responding to personally relevant threats.[26] Physiological profiles for blood-injection phobias distinctly differ from other phobias and attentional biases are not entirely consistent across different anxiety disorders.[27] Also whereas commonalities exist between generalized anxiety disorder and major depression in familial transmission, genetic risk, neuroticism, and childhood risk factors such as abuse and parental divorce, there are also differences in terms of neuroimaging and neuroendocrinology: with more dorsal insular cortex and anterior cingulate cortex activation associated with depression, and more ventral insular cortex and less posterior cingulate cortex activation associated with anxiety; and with more evidence for hypothalamic–pituitary–adrenal and hypothalamic–pituitary–thyroid dysregulation in depression than in anxiety.[28] Also, whereas negative affect and elements of threat processing are shared between anxiety and depression, deficits in positive affect and in neural (striatal) reward processing appear more relevant to depression.[29] Differences exist in cognitive biases as well; depression is associated with selective attention to negative cues at long durations of 1 s or more, indicative of strategic processing, whereas attentional bias in anxiety occurs more automatically.[30] Also, appraisal biases to interpret ambiguous information in a negative fashion are more threat-laden in anxiety disorders and entail more negative self-evaluation in depression.[30] The ultimate goal is for transdiagnostic models that are applicable to anxiety disorders as well as unipolar depression. By failing to address the sources of dysregulation that differ across anxiety and depression, existing transdiagnostic models ignore important treatment targets.

Furthermore, existing transdiagnostic models fail to consider individual differences that are likely to occur across the various cognitive, behavioral, neural, emotional, and other domains of dysfunction that are targeted in treatment. For example, attentional bias to threat is stronger on average in anxious groups relative to healthy controls, but large individual differences exist within anxious groups in terms of attentional bias toward or away from threat.[31] Similarly, whereas anxious individuals on average display deficits in extinction relative to healthy controls,[32] effect sizes from studies using identical procedures (i.e., $d = 0.54$, range = 0.23–0.99) suggest that some anxious individuals do not differ from healthy controls. Thus, outcomes may be improved by personalizing treatment to the areas of cognitive, behavioral, emotional, or other functioning that are most dysregulated for a given patient, akin to the biomarkers and biosignature approach recommended by NIMH.[33]

A final limitation of existing models is that they do not capitalize on exciting translational research. For example, great strides are being made in translating the latest basic science of fear learning and extinction to enhance exposure therapy using behavioral and pharmacological aids that optimize inhibitory learning and its retrieval,[34] such as d-cycloserine.[35] Other examples include cognitive bias modification training[36] and positive interpretation training.[37]

NEW DIRECTIONS: PERSONALIZED TRANSDIAGNOSTIC APPROACH

Transdiagnostic approaches that target both anxiety and depression will possess greater utility than existing approaches as they will be applicable to a larger target population. In addition, by targeting both commonalities and differences, the treatment is likely to cover the major areas of emotional, cognitive, behavioral, and other domains of dysregulation relevant to anxious or depressed patients, which in turn may improve outcomes. The incorporation of strategies guided by the latest translational findings has the potential to improve outcomes even further. The expansion of therapeutic strategies to cover both commonalities and differences across anxiety and depression will result in a large treatment manual. However, a personalized medicine approach[33] can guide selection of specific strategies from a larger set to match each individual patient's profile of dysregulation, as is the case with our CALM Tools for Living-II program.

CONCLUSION

Transdiagnostic approaches are an exciting development in evidence-based treatments, driven by the need for approaches that are more easily implemented in practice settings. Although they clearly will facilitate

implementation, existing transdiagnostic models may not improve outcomes beyond disorder-specific CBT. New directions are proposed by which transdiagnostic models are expanded to cover commonalities as well as differences across anxiety and depression combined with translational research to guide treatments and a personalized medicine approach to selecting the right strategies for each patient. Whether or not such steps improve therapeutic outcomes relative to disorder-specific approaches, the value of transdiagnsotic approaches for implementation cannot be underestimated given the dire need for evidence-based practice in service settings.

REFERENCES

1. Wilamowska ZA, Thompson-Hollands J, Fairholme CP, Ellard KK, Farchione TJ, Barlow DH. Conceptual background, development, and preliminary data from the unified protocol for transdiagnostic treatment of emotional disorders. Depress Anxiety 2010;27(10):882–890.
2. Shafran R, Clark DM, Fairburn CG, et al. Mind the gap: improving the dissemination of CBT. Behav Res Ther 2009;47(1):902–909.
3. Kessler RC, Berglund P, Demier O, et al. The epidemiology of major depressive disorder: results from the Nationa Comorbidity Survey Replication (NCS-R). J Am Med Assoc 2003;289(23):3095–3105.
4. Tsao JCI, Mystkowski JL, Zucker BG, Craske MG. Effects of cognitive- behavioral therapy for panic disorder on comorbid conditions: replication and extension. Behav Ther 2002;33(4):493–509.
5. Brown TA, Antony MM, Barlow DH. Diagnostic comorbidity in panic disorder: effect on treatment outcome and course of comorbid diagnoses following treatment. J Consult Clin Psychol 1995;63(3):408–418.
6. Craske MG, Farchione TJ, Allen LB, Barrios V, Stoyanova M, Rose R. Cognitive behavioral therapy for panic disorder and comorbidity: more of the same or less of more? Behav Res Ther 2007;45(6):1095–1109.
7. McManus, F., Shafran R, Cooper Z. What does a transdiagnostic approach have to offer the treatment of anxiety disorders? Br J Clin Psychol 2010;49(4):491–505.
8. Brown TA, Chorpita BF, Barlow DH. Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. J Abnorm Psychol 1998;107(2):179–192.
9. Zinbarg RE, Mineka S, Craske MG, et al. (in submission). Prospective associations of personality traits and cognitive vulnerabilities with diagnoses of internalizing disorders over three years in adolescents.
10. Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am J Psychiatry 2001;158(10):1568–1578.
11. Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. What is an anxiety disorder? Depress Anxiety 2009;26(12):1066–1085.
12. Norton PJ. An open trial of a transdiagnostic cognitive-behavioral group therapy for anxiety disorder. Behav Ther 2008;39(3):242–250.
13. McEvoy, PM. Nathan P. Effectiveness of cognitive behavior therapy of diagnostically heterogeneous groups: a benchmarking study. J Consult Clin Psychol 2007;75(2):344–350.
14. Titov N, Dear BF, Schwencke G, et al. Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. Behav Res Ther 2011;49(8):441–452.
15. Wittchen HU, Beesdo K, Gloster AT. The position of anxiety disorders in structural models of mental disorders. Psychiatr Clin North Am 2009;32(3):465–81.
16. Roy-Byrne P, Craske MG, Sullivan G, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized control trial. J Am Med Assoc 2010;303(19):1921–1928.
17. Craske MG, Stein MB, Sullivan G, et al. Disorder-specific impact of coordinated anxiety learning and management treatment for anxiety disorders in primary care. Arch Gen Psychiatry 2011;68(4):378–388.
18. Farchione TJ, Fairholme CP, Ellard KK, et al. Unified protocol for transdiagnostic treatment of emotional disorders: a randomized controlled trial. Behav Ther 2012;43(3):666–678.
19. Kabat-Zinn J, Massion AO, Kristeller J, et al. Effectiveness of a meditation based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry 1992;149:936–943.
20. Hayes SC, Strosahl K, Wilson K. Acceptance and Commitment Therapy: Understanding and Treating Human Suffering. New York: Guilford Press; 1999.
21. Twohig MP, Hayes SC, Plumb JC, et al. A randomized clinical trial of acceptance and commitment therapy versus progressive relaxation training for obsessive-compulsive disorder. J Consult Clin Psychol 2010;78(5):705–716.
22. Arch JJ, Eifert GH, Davies C, Plumb JC, Rose RD, Craske MG (in press). Randomized trial of cognitive behavioral therapy versus acceptance and commitment therapy for the treatment of mixed anxiety disorders. J Consult Clin Psychol.
23. Wolitzky-Taylor KB., Arch JJ, Rosenfield D, Craske MG. (in press). Prognostic and prescriptive moderators of treatment outcome for anxiety disorders: a comparison of cognitive behavioral therapy to acceptance and commitment therapy. J Consult Clin Psychol.
24. Arch JJ, Ayers CR, Baker A, Almklov E, Dean D, Craske MG. (in submission). Randomized clinical trial of Mindfulness Based Stress Reduction (MBSR) versus Group Cognitive Behavioral Therapy (CBT) for mixed anxiety disorders.
25. Craske MG., Niles A, Burklund, L, Wolitzky-Taylor K, Plumb J, Saxbe D, Taylor S, Lieberman M (in preparation). Cognitive behavioral therapy versus acceptance and commitment therapy for social anxiety disorder: outcomes and moderators.
26. McTeague L, Lang PJ. The anxiety spectrum and the reflex physiology of defense: from circumscribed fear to broad distress. Depression and Anxiety 2012;29:264–281.
27. Craske MG, Waters A. Panic disorder, phobias and generalized anxiety disorder. Annual Review of Clinical Psychology 2005;1:197–226.
28. Martin EJ, Nemeroff CB. The biology of generalized anxiety disorder and major depressive disorder. In: DP Goldberg, KS Kendler, PJ Sirovatka, editors, Diagnostic Issues in Depression and Generalized Anxiety Disorder: Refining the Research Agenda for the DSM-V. Arlington, VA: American Psychiatric Association; 2010:45–70.
29. Hardin MG, Schroth E, Pine DS, Ernst M. Incentive-related modulation of cognitive control in healthy, anxious, and depressed adolescents: development and psychopathology related differences. J Child Psychol Psychiatry 2007;48(5):446–454.
30. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. Annu Rev Clin Psychol 2005;1:167–195.
31. Shechner T, Britton JC, Perez-Edgar K, et al. Attention biases, anxiety and development: toward or away from threats or rewards. Depress Anxiety 2012;29:282–294.

32. Lissek S, Powers AS, McClure, EB, et al. Classical fear conditioning in the anxiety disorders: a meta-analysis. Behav Res Ther 2005;43(11):1391–1424.
33. National Institute of Mental Health. From Discovery to Cure: Accelerating the Development of New and Personalized Interventions for Mental Illnesses. Washington, DC: Government Printing Office; 2010.
34. Craske MG, Liao B, Brown L, Vervliet B. Role of inhibition in exposure therapy. Journal of Experimental Psychopathology 2012;3:322–345.
35. Bontempo A, Panza KE, Bloch MH. D-cycloserine augmentation of behavioral therapy for the treatment of anxiety disorders: a meta-analysis. J Clin Psychiatry 2012;73(4):533–537.
36. Hakamata Y, Lissek S, Barh-Haim Y, et al. Attention bias modification treatment: a meta-analysis toward the establishment of novel treatment for anxiety. Biol Psychiatry 2010;68:982–990.
37. Holmes EA, Mathews A, Dalgleish T, Mackintosh B. Positive interpretation training: effects of mental imagery versus verbal training on positive mood. Behav Ther 2006;37(3):237–247.