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Psychobiological Approaches for Anxiety Disorders

Treatment Combination Strategies

Edited by Stefan G. Hofmann

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A John Wiley & Sons, Ltd., Publication

This edition first published 2012

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered Office
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Offices
350 Main Street, Malden, MA 02148-5020, USA
9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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Library of Congress Cataloging-in-Publication Data

Psychobiological approaches for anxiety disorders : treatment combination strategies / edited by Stefan G. Hofmann.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-97181-9 (cloth) – ISBN 978-0-470-97180-2 (pbk.)
I. Hofmann, Stefan G.
[DNLM: 1. Anxiety Disorders–therapy. 2. Combined Modality Therapy–methods. WM 172]

616.85′22–dc23

2011043015

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Set in 10/12pt Palatino by Thomson Digital, Noida, India

1 2012

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ABOUT THE CONTRIBUTORS

Gail Alvares is a PhD student at the Brain and Mind Research Institute, University of Sydney, working in the field of social anxiety and decision making. Her research explores some of the fundamental ways in which stress and anxiety influences learning and habit formation.

Dr Borwin Bandelow is Professor at the Department of Psychiatry and Psychotherapy at the University of Göttingen, Germany. He is the Managing Director of the clinic and head of the Anxiety Disorders Unit. As a psychiatry and neurology specialist, a psychologist, and a psychotherapist, Borwin Bandelow specializes in anxiety disorders (panic disorder, generalized anxiety disorder, and social phobia), schizophrenia, depression, psychotherapy, and psychopharmacology. He has authored or co-authored over 200 publications internationally in both books and scientific journals. Borwin Bandelow is President of the German Society for Anxiety Research. He is Editor-in-Chief of the German Journal of Psychiatry, one of the first on-line psychiatric journals.

Frances S. Chen, PhD, is a postdoctoral fellow at the University of Freiburg, Germany. She completed her PhD in psychology at Stanford University. From 2009 to 2010, she was a Visiting Professor of Psychology at Deep Springs College in California. She currently conducts research at the University of Freiburg as a Fulbright Scholar and Alexander von Humboldt Postdoctoral Fellow. Her research focuses on neurobiological and psychological factors influencing social relationships, in particular attachment behavior and behavior within negotiation and conflict settings.

Michelle L. Davis is a research assistant for the Anxiety Research and Treatment Program at Southern Methodist University. She received a BSc in Biology at Texas Tech University. She is currently a project coordinator for a study funded by the National Institute of Drug Abuse examining exercise as an augment to cognitive behavioral treatment for smoking cessation.

Lindsey B. DeBoer is a clinical psychology doctoral candidate at Southern Methodist University. She received a BA in Psychology and in Child Development at The University of Texas at Dallas and an MA in clinical psychology at SMU. Ms. DeBoer is currently a research assistant for the

Anxiety Research and Treatment Program at SMU. Her research focuses on the interplay between anxiety and health behaviors including eating behavior, exercise, and substance use, as well as augmenting empirically supported psychotherapy with exercise and dietary interventions.

Dr Dominique de Quervain is a full professor at the Faculty of Medicine and Faculty of Psychology and Director of the Division of Cognitive Neuroscience, University of Basel, Switzerland. He studied medicine at the University of Berne, Switzerland, and was a Postdoctoral Fellow at the University of California Irvine, USA, and at the universities of Basel and Zurich, Switzerland. He is interested in the effects of stress hormones on memory in health and disease and in the identification of memory-related genes in humans using behavioral genetics approaches together with neuroimaging techniques.

Dr Gregor Domes completed his PhD in psychology at the University of Tübingen, Germany, and his postdoctoral research at the University of Rostock, Germany and the University of Zurich, Switzerland. Currently, he is an assistant professor at the University of Freiburg, Germany and a member of the Freiburg Brain Imaging Center. His research focuses on the behavioral and neural effects of steroid hormones and neuropeptides in health and mental disorders.

Samantha G. Farris is a clinical psychology doctoral student at the University of Houston. She received her Bachelor's degree in psychology from Rutgers University, while working at the Center of Alcohol Studies. After completing her degree, Ms Farris worked as a research coordinator at the Center for the Treatment and Study of Anxiety, at the University of Pennsylvania. Her current research interests include the relationship between anxiety and substance use disorders, and dissemination of empirically-supported treatments.

Keith Ganasen, MD, is a resident in psychiatry. He has, during his training in psychiatry, embarked on research in the anxiety disorders, and is planning a career in academic psychiatry.

Dr Adam Guastella is Associate Professor, a clinical psychologist, and principal research fellow at the Brain and Mind Research Institute, University of Sydney. He manages the youth anxiety services at the institute. His research focuses on using translational models to improve social function in disorders of social deficit and to develop novel methods to reduce anxiety.

Bridget A. Hearon, MA, is a doctoral student in the Clinical Psychology Program at Boston University. Her research interests include the treatment

of anxiety and substance use disorders as well as factors which influence health behaviors.

Dr Markus Heinrichs is a full Professor at the Faculty of Economics and Behavioral Sciences and at the Faculty of Medicine, Director of the Laboratory for Biological and Personality Psychology, and Director of the Outpatient Clinic for Stress-Related Disorders at the University of Freiburg, Germany. He received his PhD from the University of Trier, Germany, where he began his studies on oxytocin and social behavior. Prior to his position at the University of Freiburg, he spent 10 years at the University of Zurich, Switzerland, where he was a professor of clinical psychology and psychobiology from 2007 to 2009. His research topics include experimental therapy research on mental disorders with social deficits, neurobiology of social interaction, and stress- and anxiety-protective factors.

Michael W. Otto, PhD, is Professor of Psychology at Boston University. Michael Otto specializes in the cognitive-behavioral treatment of anxiety, mood, and substance use disorders. An enduring theme across these disorders is the role of exposure-based emotional tolerance/acceptance strategies in improving mental health and activity levels. His research focuses on difficult-to-treat populations, including interventions for patients who have failed to respond to previous treatments. He also focuses on health behavior promotion ranging from medication adherence to engagement in exercise, and has published over 300 articles, chapters, and books spanning his research interests.

Mark B. Powers, PhD, is Assistant Professor and Co-Director of the Anxiety Research and Treatment Program at Southern Methodist University. He received a BA at the University of California at Santa Barbara, an MA at Pepperdine University, and a PhD from the University of Texas at Austin. He also completed a pre-doctoral fellowship at Boston and Harvard universities and a residency at the University of Washington. He has over 70 publications and his current research focuses on mechanisms of change in anxiety disorders.

Markus Reitt is a clinical psychologist at the Department of Psychiatry and Psychotherapy at the University of Göttingen. He is trained in Cognitive Behavioral Therapy. In his research, he cooperates with the East China Normal University, Shanghai, China. He is currently working with the Task Force for Germany National Guidelines for Anxiety Disorders.

Franklin R. Schneier, MD, is Professor of Clinical Psychiatry at the Department of Psychiatry at Columbia University in New York and

Research Psychiatrist in the Anxiety Disorders Clinic of New York State Psychiatric Institute. His research has focused on psychobiology, and cognitive-behavioral and pharmacological treatments for anxiety and mood disorders.

Jasper J. A. Smits, PhD, is Associate Professor and Co-director of the Anxiety Research and Treatment Program at Southern Methodist University. He is a federally funded investigator of intervention strategies to improve outcomes for adults suffering from anxiety and related disorders.

Dr Leila Maria Soravia is a Postdoctoral Fellow at the Department of Psychiatric Neurophysiology of the University Hospital of Psychiatry, University of Berne, Switzerland. She studied Psychology at the University of Berne, and obtained her PhD at the Department of Clinical Psychology and Psychotherapy of the University of Zürich, Switzerland. She has focused on the investigation of the neuroendocrinological mechanisms of anxiety disorders and the development of new treatment approaches, especially for social phobia and spider phobia. Her main interest is in the exploration of the HPA-axis, the glucocorticoid cortisol, and its influence on fear memory in phobic patients.

Dan J. Stein's MD, PhD, is Professor and Chairman of the Department of Psychiatry at the University of Cape Town in South Africa. His research focuses on the psychobiology of anxiety disorders, ranging from animal models, through clinical research, and on to epidemiological work.

Dr Dirk Wedekind is a senior consultant psychiatrist at the Department of Psychiatry at the University of Göttingen, Germany. He attended medical school in Göttingen, Germany and studied affective neuroscience in Maastricht, The Netherlands. His scientific work has focused on the neurobiology and neuropharmacology of anxiety disorders. He also worked on clinical and biological aspects of addiction disorders and did research on personality- and somatoform disorders. He has authored and co-authored more than 60 articles in scientific journals and books and is a frequent national speaker on pharmacological and clinical topics.

ABOUT THE EDITOR

Stefan G. Hofmann, PhD, is Professor of Psychology at Boston University and the Director of the Psychotherapy and Emotion Research Laboratory. He is president-elect of the Association for Behavioral and Cognitive Therapies and president-elect of the International Association for Cognitive Psychotherapy. He is also a Board Member of the Academy of Cognitive Therapy and of the Anxiety Disorders Association of America. He is an advisor to the DSM-V Development Process. He is widely published with more than 200 peer-reviewed journal articles and book chapters, and 10 books, including "An Introduction to Modern CBT" (Wiley-Blackwell, 2012). His primary research interests center on treatment of anxiety disorders for which he has received many research awards. Weblink: http://www.bostonanxiety.org/

INTRODUCTION

Stefan G. Hofmann

Department of Psychology, Boston University, Boston, MA, USA

Individuals with anxiety disorders show excessive fear when confronted with specific objects, situations, physical sensations, or other external or internal cues in the absence of any actual danger. As a consequence, people with these debilitating conditions often avoid these cues or endure their anxiety under great distress. This often leads to great personal suffering, diminished quality of life, and high economic cost to society (Olatunji *et al*. 2007).

Epidemiological studies indicate that the group of anxiety disorders, which includes specific phobias, social anxiety disorder, generalized anxiety, obsessive compulsive disorder, panic disorder, agoraphobia, and post-traumatic stress disorder, are the most prevalent class of mental disorders, with 12-month and lifetime prevalence rates of 18.1 and 28.8%, respectively (Kessler *et al*. 2005a; b).

A large body of work supports the efficacy of cognitive behavioral therapy (CBT) (Hofmann and Smits 2008) and anxiolytic medication for treating anxiety disorders (Roy-Byrne and Cowley 2002). CBT combines cognitive strategies to target maladaptive beliefs about the fear-eliciting cues and exposure techniques aimed at helping patients reacquire a sense of safety around cues associated with anxiety disorders. In contrast to CBT, pharmacological interventions aim to directly target biochemical pathways underlying the anxiety elicited by disorder-specific cues (Bourine and Lambert 2002). Pharmacological agents that have demonstrated efficacy for a variety of anxiety disorders include benzodiazepines, tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), reversible inhibitors of monoamine oxidase-A (RIMA), and buspirone (Baldwin *et al*. 2005; Bourine and Lambert 2002). There is some evidence to suggest that CBT may be more tolerable and

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more cost-effective, especially in the long-term, than some of these traditional anxiolytic agents (Otto *et al*. 2006). Although both treatment modalities are efficacious, there is clearly room for improvement (Hofmann and Smits 2008; Roy-Byrne and Cowley 2002).

Because these treatment modalities are less than perfect when administered as monotherapies, investigators have examined whether combining pharmacotherapy and psychotherapy is more effective than either of the monotherapies for reducing anxiety symptoms. Many of these studies show that combination strategies are not substantially more effective than monotherapies in the short term and may even be worse in the long term for some anxiety disorders. Thus some cases, adding conventional pharmacotherapy can even be detrimental to the success of psychological treatments, such as when using benzodiazepines in combination with exposure therapy for panic disorder (see Otto *et al*., 2006, for a review).

A more recent approach toward combination therapy is to enhance the mechanism of CBT using pharmacological agents. Some of these approaches are highly promising and support such augmentation strategies to further enhance the efficacy of CBT. Examples of those agents include D-cycloserine, yohimbine, cortisol, oxytocin, propranolol, and various nutritional supplements. Some of these agents appear to act as cognitive enhancers based on the mechanism through which they augment CBT (Hofmann *et al*. 2011).

The goal of this book is to discuss the evidence from the existing literature on conventional and novel combination therapies for anxiety disorders. For this purpose, a number of leading investigators were invited to present the evidence of combination strategies for treating anxiety disorders. The first chapter gives an overview of the biology and efficacy of combination strategies, which points to some of the limitations of the contemporary literature and recommends that future research should embrace a translational research approach. The following chapters 2, 3, and 4 discuss traditional combination strategies using benzodiazepines, tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs, RIMA, and buspirone. Chapter 5 discusses the evidence of D-cycloserine as a cognitive enhancer of CBT. Similarly, yohimbine (Chapter 6), cortisol (Chapter 7), and oxytocin (Chapter 8) offer new combination strategies born out of a translational research approach. Chapter 9 discusses dietary supplements, which offer promising options that are worthy of further investigation. Chapter 10 provides a general roadmap for future research in combination treatments for anxiety disorders and recommends that the field of psychiatry and pharmacology should:

- move beyond the traditional horse race comparison of clinical trials and toward translational research from 'bench to bedside;'
- move closer toward understanding the mechanism of treatment change; and

- move closer toward personalized medicine by tailoring the treatment to the client based on certain biomarkers.

I hope that this volume will inspire researchers, clinicians, policy makers, funding agencies, and the pharma industry to move beyond conventional paradigms of combination therapies for anxiety disorders.

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Chapter 1

THE BIOLOGY AND EFFICACY OF COMBINATION STRATEGIES FOR ANXIETY DISORDERS

Keith A. Ganasen and Dan J. Stein

Department of Psychiatry, University of Cape Town, Cape Town, South Africa

INTRODUCTION

Optimal treatment of anxiety disorders is important as they are the most prevalent psychiatric disorders in community studies, and generalized anxiety disorder is the most prevalent psychiatric disorder in primary care (Kessler *et al*. 2010). In addition, anxiety disorders begin early in life, and predispose to the development of comorbid disorders such as depression and substance use disorders; early and robust treatment may therefore be important in secondary prevention (Goodwin and Gorman 2002). Anxiety disorders are not only associated with significant suffering in affected individuals and families, but also contribute enormously to the societal burden of disease; a number are among the most disabling of all medical conditions (Lopez *et al*. 2006).

Fortunately, there have been significant advances in the treatment of anxiety disorders. A range of medications have been approved in the past few decades for the major anxiety disorders on the basis of randomized controlled trials showing efficacy and safety. Similarly, during the same period, a number of psychotherapies have been rigorously studied, and shown to have both short-term and longer-term efficacy. Expert guidelines, often incorporating systematic meta-analyses of the research literature, have been developed, and highlight the evidence base for first-line interventions, such as selective serotonin uptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) (Ipser and Stein 2009). The majority of patients with anxiety disorders can be expected to respond to such first-line interventions.

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At the same time, underdiagnosis and undertreatment of, and resistance to treatment in, anxiety disorders remain significant problems. Underdiagnosis and undertreatment may reflect a range of structural and attitudinal barriers, including insufficient numbers of well-trained therapists and insufficient mental health literacy in both the general population and primary care practitioners. First-line treatments may work in the majority of cases, but even when appropriately diagnosed and treated, 40% or more of patients may fail to respond (Pallanti *et al*. 2002; Bandelow and Ruther 2004). There is a relative lack of effectiveness trials in anxiety disorders, but in real-world settings, where patients may have increased comorbidity, and where clinicians are required to be generalists rather than specialists, treatment response rates may be lower, and tolerability concerns more obvious, particularly over the longer term.

Combination treatment is an important consideration in attempts to improve the efficacy and effectiveness of intervention in anxiety disorders. Given the multiple factors, including neurobiological and psychological variables, involved in anxiety disorder pathogenesis, there is a prima facie case for a comprehensive treatment approach including pharmacotherapy and psychotherapy. Indeed, early thinking suggested pharmacotherapy was useful for a rapid treatment response, while psychotherapy was valuable for a maintained response, even after discontinuation of short-term intervention (Riba and Ballon 2005). It has therefore been surprising to see a growing evidence base suggesting relatively little advantage in combining pharmacotherapy and psychotherapy for anxiety disorders (Foa *et al*. 2002; Otto *et al*. 2005; Black 2006; Bandelow *et al*. 2007; Hofmann *et al*. 2009).

Perhaps one of the most exciting developments in combination treatment of anxiety disorders, if not in all of medicine, has been the adoption of a rigorous translational neuroscience approach (Davis *et al*. 2006; Otto *et al*. 2007; Hofmann *et al*. 2011; Kaplan and Moore 2011). Advances in a range of basic neuroscience areas, including animal models of anxiety disorders, have allowed combination interventions to be studied in the laboratory. Rather than relying on standard first-line pharmacotherapies, such work has focused on targets (e.g. in glutamatergic systems) that may be specifically relevant to enhancing cognitive-behavioral interventions. Such work provides a rigorous foundation for moving findings through to the bedside, in the form of proof-of-principle clinical studies. This approach appears to have significant potential and has therefore attracted considerable interest from researchers, making this book extremely timely.

This chapter will briefly focus on a number of background issues relevant to combination treatment in anxiety disorders. First, we will review some of the psychobiology relevant to an understanding of how combined treatments work. Second, we will review some of the findings addressing, and issues concerning, the efficacy of such combined treatments.

PSYCHOBIOLOGY OF COMBINATION TREATMENTS

There is a growing understanding of the neurocircuitry underlying the fear response in animals and anxiety disorders in humans. Advances in structural and functional neuro-imaging have been key in developing our understanding of such circuitry in clinical conditions (Shin and Liberzon 2010). Thus, a growing body of evidence suggests that anxiety disorders are characterized by abnormalities in both prefrontal and subcortical (e.g. amygdala, hippocampus) circuitry (Grillon 2002; Anderson and Insel 2006). Neurotransmitters involved in such pathways include serotonergic, noradrenergic, glutamatergic, gamma-aminobutyric acid (GABA)ergic, and neuropeptide systems, and many available pharmacotherapies act on such systems (Charney 2003).

One approach to understanding the psychobiology of combined pharmacotherapy and psychotherapy is to argue that pharmacotherapy acts predominantly on bottom-up neurotransmitter-mediated mechanisms, while psychotherapy acts mainly on top-down cognitive-affective processes. Medications, such as SSRIs, may act on the amygdala and its efferent pathways (e.g. to hypothalamus and brainstem) to reduce panic attacks, which in turn leads to reduced anticipatory anxiety and phobic avoidance (Gorman *et al*. 2000). However, interventions such as CBT, may act upstream of the amgydala, strengthening the ability of medial prefrontal areas to inhibit sub-cortically mediated processes, by decreasing cognitive misattributions and deconditioning the fear response (Mayberg 2002).

While such an approach may be heuristically useful, it may entail some over-simplification. First, neurocircuitry alterations following psychotherapy are not limited to prefrontal areas; instead they may be widespread (Roffman *et al*. 2005; Frewen *et al*. 2008). Conversely, the effects of pharmacotherapy are unlikely to be limited to sub-cortical neurotransmitter activity; rather they may lead to significant changes in high-level cognitive and affective processing. Furthermore, such an approach does not explain why certain combinations of pharmacotherapy and psychotherapy appear ineffective or even contra-indicated (Otto *et al*. 2005). Indeed, both pharmacotherapy and psychotherapy are interventions that have complex and interactive effects on the brain-mind.

Another question that requires a more complex approach is whether combination strategies are likely to be similar across different anxiety disorders, or whether specific combined treatment approaches will be needed for each disorder. On the one hand, imaging studies suggest that there are a number of overlapping mechanisms that cut across different anxiety disorders. A recent meta-analysis of brain imaging studies in anxiety disorders, for example, found an increase in the activity of the amygdala and insula in participants with post-traumatic stress disorder (PTSD), social anxiety disorder, and with specific phobia, relative to healthy control subjects (Etkin and Wager 2007). Thus, it may be predicted

that SSRIs act to decrease insula activity, while CBT acts to decrease amygdala activity, in a number of these conditions (Furmark *et al*. 2002; Carey *et al*. 2004). On the other hand, there is also involvement of distinctive neurocircuitry in different anxiety disorders (Etkin and Wager 2007). Furthermore, within a particular disorder, different neuronal circuitry may be involved in different symptom presentations (Lueken *et al*. 2011). Thus, it is possible that different forms of combined treatment may be effective, not only for different anxiety disorders, but also for different subtypes of particular anxiety disorders.

Imaging studies in humans will no doubt continue to be important in answering such questions. For example, particular neurocircuitry findings predict response to pharmacotherapy, while others predict response to psychotherapy, or to combined treatment (Brody *et al*. 1998; Furmark *et al*. 2002; 2005). Data from studies that address the impact of particular gene variants on neuro-imaging findings are also likely to be important in developing more integrative models. Also, in order to develop more complex models of combined treatments, it would be helpful to have good laboratory models of anxiety disorders and interventions. Fortunately, there is a range of ongoing work in this area. We briefly review some of the relevant work targeting neurotransmitter systems (e.g. glutamatergic, noradrenergic, and adenosine systems), neuroendocrine systems (e.g. glucorticorticoids), and social neuropeptides (e.g. oxytocin (OT)).

Neurotransmitter Systems

Laboratory research has suggested the glutamatergic system as a target for combined pharmacotherapy and psychotherapy; this research demonstrated that the *N*-methyl-D-aspartate (NMDA)-glutamate receptor of the lateral and basolateral amygdaloid nuclei was involved in fear conditioning and fear extinction in rodents (Davis *et al*. 1993). Given that antagonists of the NMDA receptor prevented both the acquisition and extinction of fear (Lee and Kim 1998), the question arose of whether an NMDA agonist would facilitate the extinction of conditioned fear (Walker *et al*. 2002). Indeed, rats that received the partial NMDA agonist D-cycloserine (DCS), in combination with repeated exposure to the conditioned stimulus, had enhanced extinction of their fear as compared to the rats that received DCS alone (Walker *et al*. 2002). The work provided a solid foundation for clinical trials of combined DCS and CBT; the first of these seminal proof-of-principle clinical studies was undertaken in acrophobia (Ressler *et al*. 2004), and several others soon followed.

Animal research has also questioned the extent to which the effects of DCS on fear extinction are generalized. Rats given DCS and fear extinction training to one stimulus, also exhibited reduced fear to another stimulus (Ledgerwood *et al*. 2005). Furthermore, some animal work has indicated that DCS may prevent the relapse of learned fear (Ledgerwood *et al*. 2004).