EFFECTS OF EXERCISE TRAINING ON

GENERALIZED ANXIETY DISORDER AND MEDICAL PATIENTS

by

MATTHEW PAYTON HERRING

(Under the Direction of Patrick J. O'Connor)

ABSTRACT

This dissertation investigated the effects of exercise training on anxiety symptoms among patients with a chronic illness and symptoms among generalized anxiety disorder (GAD) patients. A systematic review of randomized controlled trials (RCT) of exercise training effects on anxiety symptoms among medical patients showed that, compared with no treatment conditions, exercise training significantly reduced anxiety symptoms by a mean effect Δ of 0.29 (95% confidence interval, 0.23-0.36). Exercise training programs of no more than 12 weeks, using session durations greater than 30 minutes and an anxiety report time frame greater than the past week resulted in the largest anxiety reductions. The findings of the systematic review highlighted the need for well-designed RCTs that use understudied types of exercise, such as resistance exercise training (RET), to investigate exercise training effects on understudied patient groups, particularly anxiety disorder patients.

A RCT quantified the effects of six weeks of RET and aerobic exercise training (AET) on remission and worry symptoms among sedentary women with GAD and compared the effects of RET and AET, matched on the body area exercised (legs), total positive work, total time actively engaged in exercise, and weekly progression in load, on other symptoms and signs characteristic

of GAD patients. Remission rates were higher among exercise conditions and significantly better in the RET condition compared with a wait list control. Six weeks of exercise training for the RET and AET groups combined significantly reduced worry symptoms, and RET and AET resulted in moderate-to-large improvements in symptoms associated with GAD. Well-designed investigations are needed that: (1) use large sample sizes to compare the effects of exercise training alone to empirically-supported treatments for GAD; (2) compare exercise modes that use different training intensities and durations matched on perceptual responses during exercise to better understand the minimal and optimal dose necessary to improve symptoms; and (3) block randomize patients based upon potential confounding variables including comorbid psychiatric diagnoses.

The findings of this dissertation support the efficacy of exercise training as a potential treatment both for (1) GAD and its related symptoms and (2) for anxiety symptoms among patients with a chronic illness.

INDEX WORDS: Aerobic exercise training, Anxiety, Exercise, Exercise training, Generalized Anxiety Disorder, Meta-analysis, Mood, Patients, Randomized controlled trial, Resistance exercise, Systematic review, Weight lifting

EFFECTS OF EXERCISE TRAINING ON GENERALIZED ANXIETY DISORDER AND MEDICAL PATIENTS

by

MATTHEW PAYTON HERRING

B.S., The University of Georgia, 2002

M.Ed., The University of Georgia, 2005

M.S., The University of Georgia, 2007

A Dissertation Submitted to the Graduate Faculty of the University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2010

EFFECTS OF EXERCISE TRAINING ON

GENERALIZED ANXIETY DISORDER AND MEDICAL PATIENTS

by

MATTHEW PAYTON HERRING

Major Professor:	Patrick J. O'Connor
Committee:	Rodney K. Dishman
	Cynthia Suveg

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
July 2010

DEDICATION

"*Be who you are and say what you feel because those who mind don't matter and those who matter don't mind.*"

- Dr. Seuss

It's a bit of a strange irony that a writer so often considered a master of silly, joy-provoking humor would also so poignantly characterize a bit of what my family means to me. Standing at the end of this intense process I would be remiss to allow myself or anyone else to think, "wow, Matt, that's a great job. . .," and to leave it there, for there are far more important details of this story than this 250 to 300 page beast. This process and this aspect of the man that I continue to become is dedicated to my consistently random but always unique and unfaltering family, including those that have gone on before us. To my dad's parents, a sharecropper and his resilient wife, in whose eyes I could have done no wrong – how amazing it is the myriad of things I, this supposedly well-educated man, still can learn from the lives of two people with an 8th and a 4th grade education. To my mom's mom, a beacon of goodness who was taken far too early in my life, for instilling in me the standards of a good man and the importance of pressing your luck. To Daddy (apparently pronounced "deddy" by yours truly) for his love, patience, discipline, and example, for teaching me that tears out of sadness, joy, pain and anger are okay, for consistently reiterating how important loyalty is, and for teaching me that, while others may not always like me, I can at least make sure people respect me for my work ethic. To Mama, for her love, sacrifices, tenacity, and relentless pursuit of happiness for her children, for illustrating

what strength really is, for challenging and expecting me to always do more, and for making sure I remember from where all of this comes. To my siblings, Josh and Anna, for years of laughs, for their support, and for loving the weird one. Last, but most certainly not least, to Lisa, my soon-to-be wife, for her commitment to our purpose, her patience, her diligence, her adventurous spirit, and her unyielding genuineness, for her uncanny ability to put it all in perspective simply with her beautiful smile, and most importantly, for loving me for who I am as well as who I am becoming.

ACKNOWLEDGEMENTS

"*When you get to the end of your rope, tie a knot and hang on*."

- Franklin D. Roosevelt

Not surprisingly, one of the most admirable and forthright presidents coined one of my favorite quotes. In the struggle that this academic effort often has been over the past few years, there have been a number of influential parties that have contributed to the binding of the knot onto which I could steadfastly cling when I have come to the end of that proverbial rope. These individuals have afforded me the support and stability to muster the strength to continue to compete, to mount counterattacks, and to avoid the embarrassment of failing, or worse yet, giving up. It is to them that I owe any and all academic successes and to them who I humbly offer my gratitude.

To my family, the Herrings, the Brakes and the Fields, there is no measure of gratitude that can express how thankful I am for the role that you all play in my life. Work has always been work, but our family is our way of life. You all have breathed into me a passion to work to succeed no matter the task and to persevere in the face of far greater adversity. This document and any other professional successes that I am fortunate to enjoy are testaments to your sacrifices, your patience, your understanding, and your love. Thank you for consistently facilitating my realization that this is but one aspect of a very fulfilling life. You have all of my love and thanks.

To my Ex Psych crew (formerly known as the Ex Psyc Boyz until Cherie came along and left her mark), Timmy P, Pasley, the greek, Nate, Cherie the VIP, our quasi-ex psych boy Chris

Black, and the newest member, baby Derek, all of you deserve some type of award comparable to an Oscar for best supporting cast in this crazy screenplay that has been and is my professional life. I can only hope that I have positively shaped some aspect of your experiences as well, particularly in helping you all to realize that professionalism can and must have a sense of humor and very few things in this life are above ridicule. To Timmy P in particular, I will forever be grateful for your service to our country, your guidance, your patience, your contributions, and for your friendship.

To Pat, the road certainly has been long on this road trip through PhD-land. I have enjoyed the sights and sounds, however, and I am tremendously grateful to have had you as the GPS guiding this crazy academic Winnebago. Thank you for your candor, your guidance and your patience, for constantly reiterating that less is more, and for believing that I can be good at this. I cannot thank you enough for the opportunities you have helped me to see to fruition and, ultimately, for your friendship. Mojitos all around.

To Dish, thank you for helping me see that my personality can find a niche in this frequently political, murky milieu of research. Thank you for challenging me to exceed expectations and for never kicking me out of your office (sort of). There is not a whiskey top-shelf enough to thank you for your impact. . . but the next one is on me.

To Cindy Suveg, Tompo, Steve Olejnik, and the remainder of the extremely talented faculty at the University of Georgia that I have been fortunate enough to work with over the years, thank you for your invaluable contributions to my academic progress. To Marni Jacob and all of my Ex Psych lab assistants, thank you for all that you have done to ensure the completion of this overall project. I could not have done this without your vital role.

Finally, to God through whom all of this and all I am is possible. Thank you for placing on my heart a desire to succeed and to utilize the abilities you so graciously bestowed on me. Thank you for keeping on my heart the strength that is in your Word, especially in the difficult times (1 Corinthians 15:10; 2 Timothy 1:7), and for teaching me to be content in this and all circumstances (Philippians 4).

And to you reading these pages, keep your head up and keep truckin'.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

This dissertation seeks to better understand the effects of exercise training on anxiety symptoms among medical and Generalized Anxiety Disorder (GAD) patients. Anxiety, an unpleasant mood characterized by feelings of apprehension and thoughts of worry, is an adaptive response to perceived threats that can develop into a maladaptive anxiety disorder if symptoms become severe and chronic (Barlow, 2002). Anxiety is a major public health burden. Approximately 28.8% of the US population meets diagnostic criteria for at least one anxiety disorder, with estimated 12-month prevalence rates among individuals aged 18 years or older of 18.1% (Kessler, Berglund, Demler et al., 2005). Reviewers have concluded that exercise training, a healthful, inexpensive, accessible potential therapy, is associated with reductions in anxiety symptoms among healthy adults (Long & van Stavel, 1995; McDonald & Hodgdon, 1991; Morgan, 1985; O'Connor, Raglin & Martinsen, 2000; Wipfli, Rethorst & Landers, 2008). However, limited evidence exists regarding the effects of exercise training on anxiety among individuals with anxiety symptoms, including individuals suffering from a chronic illness and individuals with a clinical anxiety disorder. A better understanding of the effects of exercise training on anxiety among these individuals plausibly could enhance quality of life, reduce disability and impairment, and improve the treatment of both anxiety and other chronic illnesses.

Statement of the Problem:

Epidemiological and experimental evidence suggests that regular physical activity and exercise training can attenuate anxiety symptoms among healthy individuals. However, little

empirical attention has been focused on the investigation of the effects of exercise training as an intervention to improve anxiety symptoms among patient groups.

Compared to healthy adults, anxiety disorders are more common among persons with a myriad of chronic illnesses, including those with asthma (Kuehn, 2008), cancers (Dahl, Haaland, Myletun et al., 2005), cardiovascular diseases (Fan, Strine, Jiles & Mokdad, 2006), lung diseases (Kunik, Roundy, Veazey et al., 2005), multiple sclerosis (Korostil & Feinstein, 2007) psychological disorders (Moffitt, Harrington, Caspi et al., 2007) and pain-related disorders (Roy-Byrne, Davidson, Kessler et al., 2008). Anxiety symptoms can negatively impact treatment outcomes (Tohen, Calabrese, Vieta et al., 2007) and result in a patient non-adherence to prescribed treatments (Sherbourne, Hays, Ordway, DiMatteo & Kravitz, 1992). Although exercise training has been suggested as a plausibly effective and practical tool for attenuating anxiety among patients with a chronic illness (Physical Activity Guidelines Advisory Committee, 2008; Stewart, Hays, Rogers, Spritzer & Greenfield, 1994), no systematic review has been published to evaluate the available evidence of the anxiolytic effects of exercise training on chronically ill patients.

There is substantial epidemiological and experimental evidence for an association between physical inactivity and anxiety. There is less evidence, however, available regarding the effects of exercise training on anxiety disorders and many of these investigations suffer from research design and methodological limitations (Brown et al., 2007; Diaz & Motta, 2008; Manger & Motta, 2005; Newman & Motta, 2007). Only one well designed randomized, controlled trial has demonstrated that exercise training improves symptoms of an anxiety (panic) disorder (Broocks et al., 1998). Thus, there is strong need for additional randomized, controlled trials investigating whether exercise training can improve other types of anxiety disorders. For

example, exercise training may be especially likely to benefit individuals with GAD because of the nature of GAD symptoms. Exercise is thought to have positive effects on problems associated with GAD, including concentration (Colcombe & Kramer, 2003), fatigue (Puetz, O'Connor & Dishman, 2006), insomnia (King, Oman, Brassington, Bliwise & Haskell, 1997; King, Baumann, O'Sullivan, Wilcox & Castro, 2002; Singh, Clements & Fiatarone, 2001; Singh, Stavrinos, Scarbek, Galambos, Liber & Fiatarone Singh, 2005), and muscle tension (Smith, O'Connor, Crabbe & Dishman, 2002).

One proposed investigation in this dissertation will focus on resistance exercise training as an intervention. The influence of resistance exercise training on mental health outcomes is poorly understood compared to the effects of aerobic exercise training. No study has focused on the effects of resistance exercise training on anxiety symptoms among people with an anxiety disorder. In adults without a clinical anxiety disorder, self-reported anxiety symptoms are attenuated following resistance exercise training (Cassilhas et al., 2007; Tsutsumi et al., 1998). It seems noteworthy that resistance exercise training effects on depression and fatigue outcomes have exceeded those for aerobic exercise training, especially given that depression and fatigue are often comorbid with anxiety disorders such as GAD (Katon et al., 2007; Kurtze et al., 2001; Puetz, Beasman & O'Connor, 2006). However, no published randomized, controlled trial has compared the effects of resistance exercise training with the effects of aerobic exercise training on anxiety outcomes. Thus, there is a clear need to learn whether resistance exercise training can improve anxiety symptoms and to learn how well resistance exercise training compares to aerobic exercise training and current therapies for anxiety.

Subproblems:

Subproblem 1: A systematic review and meta-regression analysis is needed to quantify the magnitude and variability of the population effect of exercise training on anxiety symptoms among individuals with a chronic illness and to learn whether variables of theoretical or practical importance, such as features of the exercise stimulus and the method for measuring anxiety, account for variation in the estimated population effect.

Subproblem 2: Findings from a systematic review of the literature need to be applied in designing a randomized, controlled trial to experimentally manipulate exercise training among individuals with anxiety problems, such as women with GAD, to gain a better understanding of the effect of exercise training on anxiety and related symptoms (e.g., mood, concentration, motor tension).

Subproblem 3: Information gained from a review of the extant literature needs to be applied in designing the most appropriately matched comparison between the effects of a resistance exercise training program and the effects of an aerobic exercise training program on anxiety and related symptoms. There is a clear need to know how the effects of resistance exercise training on anxiety symptoms compare to the effects of aerobic exercise training and current therapies for anxiety.

Hypotheses:

Hypothesis 1: A systematic review and meta-regression analysis assessing the effect of exercise training on anxiety symptoms among individuals with a chronic illness will reveal a statistically significant, moderate-sized reduction in anxiety symptoms in response to exercise training. Moderator analyses will show that the effect is moderated by key features of the exercise stimulus and the method by which anxiety is measured.

Hypothesis 2: A randomized, controlled trial of the effect of exercise training on symptoms among sedentary women with generalized anxiety disorder will show significant improvements among women who complete a resistance exercise training program or an aerobic exercise training program compared to a wait list control condition in which women maintain their current lifestyle.

Hypothesis 3: A randomized, controlled trial of the effect of exercise training on symptoms among sedentary women with generalized anxiety disorder will show no differences between women who complete a resistance exercise training program and women who complete an aerobic exercise training program.

Statistical Analysis:

Meta-analytic procedures will be used to estimate the population effect size for anxiety outcomes among medical patients in response to exercise training. A meta-regression analysis will be used in moderator analyses to learn whether variables of theoretical or practical importance account for variation in the estimated population effect. The extant literature can be further elucidated by utilizing the strengths of meta-analysis, including (i) stringent criteria for study selection, (ii) consistency in summarizing research, (iii) quantitative precision, (iv) avoidance of small sample bias, and (v) consideration of between-studies heterogeneity associated with both sampling error and random effects population variance. A macro (SPSS, Chicago IL, Version 16.0) will be used for the calculation of the aggregated mean effect size delta and the associated 95% confidence interval (95%CI) according to a random effects model (Lipsey & Wilson, 2001). Moderator variables will be entered into mixed-effects multiple linear regression analysis with maximum likelihood estimation to determine their independent effects on variation in the magnitude of the effect (Hedges & Olkin, 1985; Lipsey & Wilson, 2001).

Significant moderators in the regression analysis will be decomposed using a random effects model to compute mean effect sizes (Δ) and 95% confidence intervals (Lipsey & Wilson, 2001).

The results of the randomized, controlled trial will be analyzed using SPSS 16.0. Remission will be analyzed using the number needed to treat (NNT) and associated 95% confidence interval (95%CI). A 3 (condition: resistance exercise training, aerobic exercise training, wait list control) X 3 (time: week two, week four, week six) mixed-model ANCOVA using the baseline score as a covariate with repeated measures on the time factor will be used to examine the condition, time and interaction effects on worry symptoms. The assumption of sphericity will be tested by examining Mauchly's W and epsilon values. If the assumption is violated, the Huynh-Feldt adjustment will be used. The Bonferroni correction will be used to adjust for family-wise error rate for pairwise comparisons. For all outcomes (e.g., anxiety symptoms, depression symptoms, mood, difficulty concentrating, irritability and muscle tension), Hedge's d effect sizes and associated 95%CIs will be calculated to evaluate the magnitude of treatment effects for the resistance exercise training and aerobic exercise training conditions compared with the wait list condition at each time point (week two, week four and week six).

Delimitations:

First delimitation: This research will not investigate the effects of exercise training on anxiety among individuals without elevated anxiety symptoms.

Second delimitation: The randomized, controlled trial will be limited to experimentally investigating the effects of exercise training on anxiety and related symptoms among sedentary women aged 18-39 with a primary *DSM-IV* diagnosis of GAD.

Third delimitation: The randomized, controlled trial will not exclude individuals with comorbid psychiatric diagnoses provided that GAD is the principal diagnosis.

Fourth delimitation: The randomized, controlled trial will compare the effects of a resistance exercise training program on anxiety and related symptoms with the effects of an aerobic exercise training program that will be matched to the resistance exercise training program on: (i) the total amount of time spent actively engaged in exercise, (ii) the total amount of positive work completed during the time actively engaged in exercise, (iii) a five percent progression in load (intensity) each week, and (iv) the body region exercised (legs).

Overview and Organization:

The remaining sections of this dissertation will compose four chapters that will: (i) provide a comprehensive review of the extant literature to aid understanding and a rationale for investigating the relation between exercise training and anxiety; (ii) provide a systematic review of randomized, controlled trials of the effects of exercise training on anxiety symptoms among medical patients that both quanitifies the magnitude of the estimated population effect and determines the extent to which variables of theoretical or practical importance account for variation in the estimated population effect; (iii) experimentally investigate the effects of exercise training on symptoms among sedentary women with generalized anxiety disorder and differences between the magnitude of effects for resistance exercise and aerobic exercise training; and, (iv) provide a concluding discussion of the effects of exercise training on generalized anxiety disorder and medical patients.

References

Barlow, D. H. (2002). *Anxiety and its disorders*. New York: Guilford Press.

Broocks, A., Bandelow, B., Pekrun, G., George, A., Meyer, T., Bartmann, U., Hillmer-Vogel, U., & Ruther, E. (1998). Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder *American Journal of Psychiatry,155*, 603-609.

Brown, R. A., Abrantes, A. M., Strong, D. R., Mancebo, M. C., Menard, J., Rasmussen, S. A. et al. (2007). A pilot study of moderate-intensity aerobic exercise for Obsessive Compulsive Disorder. *The Journal of Nervous and Mental Disease*, *195*(6), 514-520.

Brown, T., Di Nardo, P., & Barlow, D. H. (1994). *Anxiety disorders interview schedule adult version (ADIS-IV): Client interview schedule*. Albany, New York: Graywind Publications.

Cassilhas, R. C., Viana, V., Grassman, V., Santos, R., Santos R., Tufik, S. et al. (2007). The impact of resistance exercise on the cognitive function of the elderly. *Medicine & Science in Sports & Exercise*, *39*(8), 1401-1407.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science*, *14*(2), 125-130.

Dahl, A. A., Haaland, C. F., Mykletun, A., Bremnes, R., Dahl, O., Klepp, O. et al. (2005). Study of anxiety disorder and depression in long-term survivors of testicular cancer. *Journal of Clinical Oncology*, *23*(10), 2389-2395.

Diaz, A. B., & Motta, R. (2008). The effects of an aerobic exercise program on posttraumatic stress disorder symptom severity in adolescents. *International Journal of Emergency Mental Health*, *10*(1), 49-59.

Fan, A. Z., Strine, T. W., Jiles, R., & Mokdad, A. H. (2008). Depression and anxiety associated with cardiovascular disease among persons aged 45 years and older in 38 states of the United States, 2006. *Preventive Medicine*, *46*(5), 445-450.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. New York: Academic Press.

Katon, W., Lin, E. H. B., & Kroenke, K. (2007). The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *General Hospital Psychiatry*, *29*(2), 147-155.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593-602.

King, A. C., Baumann, K., O'Sullivan, P., Wilcox, S., & Castro, C. (2002). Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: A randomized controlled trial. *Journals of Gerontology Series A: Biological and Medical Sciences*, *57*(1), 26-36.

Korostil, M., & Feinstein, A. (2007). Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Multiple Sclerosis*, *13*(1), 67-72.

Kuehn, B. M. (2008). Asthma linked to psychiatric disorders. *JAMA*, *299*(2), 158-160.

Kurtze, N., & Svebak, S. (2001). Fatigue and patterns of pain in fibromyalgia: Correlations with anxiety, depression and co-morbidity in a female county sample. *British Journal of Medical Psychology*, *74*, 523-537.

Lipsey, M. W., & Wilson, D. B. (2001). *Practical meta-analysis*. Newbury Park, CA: Sage.

Long, B. C., & van Stavel, R. (1995). Effects of exercise training on anxiety: A meta-analysis. *Journal of Applied Sport Psychology*, *7*(2), 167-189.

Manger, T. A., & Motta, R. W. (2005). The impact of an exercise program on posttraumatic stress disorder, anxiety, and depression. *International Journal of Emergency Mental Health*, *7*(1), 49-57.

McDonald, D. G., & Hodgdon, J. A. (1991). *The Psychological Effects of Aerobic Fitness Training: Research and Theory*. New York: Springer-Verlag.

Moffitt, T. E., Harrington, H. L., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M., et al. (2007). Depression and generalized anxiety disorder: Cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of General Psychiatry*, *64*(6), 651-660.

Morgan, W. P. (1985). Affective beneficence of vigorous physical activity. *Medicine & Science in Sports & Exercise*, *17*(1), 94-100.

Newman, C. L., & Motta, R. W. (2007). The effects of aerobic exercise on childhood PTSD, anxiety, and depression. *International Journal of Emergency Mental Health*, *9*(2), 133-158.

O Connor, P. J., Raglin, J. S., & Martinsen, E. W. (2000). Physical activity, anxiety and anxiety disorders. *International Journal of Sport Psychology*, *31*(2), 136-155.

Oman, R. F., & King, A. C. (2000). The effect of life events and exercise program format on the adoption and maintenance of exercise behavior. *Health Psychology*, *19*(6), 605-612.

Puetz, T. W., Beasman, K. M., & O'Connor, P. J. (2006). The effect of cardiac rehabilitation exercise programs on feelings of energy and fatigue: A meta-analysis of research from 1945 to 2005. *European Journal of Cardiovascular Prevention & Rehabilitation*, *13*(6), 886-893.

Puetz, T. W., O Connor, P. J., & Dishman, R. K. (2006). Effects of chronic exercise on feelings of energy and fatigue: a quantitative synthesis. *Psychological Bulletin*, *132*(6), 866-876.

Roundy, K., Cully, J. A., Stanley, M. A., Veazey, C., Souchek, J., Wray, N. P., et al. (2005). Are anxiety and depression addressed in primary care patients with chronic obstructive pulmonary disease? A chart review. *Primary Care Companion to the Journal of Clinical Psychiatry*, *7*(5), 213-218.

Roy-Byrne, P. P., Davidson, K. W., Kessler, R. C., Asmundson, G. J. G., Goodwin, R. D., Kubzansky, L., et al. (2008). Anxiety disorders and comorbid medical illness. *Focus*, *6*(4), 467-485.

Sherbourne, C. D., Hays, R. D., Ordway, L., DiMatteo, M. R., & Kravitz, R. L. (1992). Antecedents of adherence to medical recommendations: results from the Medical Outcomes Study. *Journal of Behavioral Medicine*, *15*(5), 447-468.

Singh, N. A., Clements, K. M., & Singh, M. A. F. (2001). The efficacy of exercise as a long-term antidepressant in elderly subjects: A randomized, controlled trial. *Journals of Gerontology Series A: Biological and Medical Sciences*, *56*(8), 497-504.

Singh, N. A., Stavrinos, T. M., Scarbek, Y., Galambos, G., Liber, C., & Fiatarone Singh, M. A. (2005). A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *Journals of Gerontology Series A: Biological and Medical Sciences*, *60*(6), 768-776.

Smith, J. C., O'Connor, P., Crabbe, J., & Dishman, R. (2002). Emotional responsiveness after low- and moderate-intensity exercise and seated rest. *Medicine & Science in Sports & Exercise*, *34*(7), 1158-1167.

Stewart, A. L., Hays, R. D., Wells, K. B., Rogers, W. H., Spritzer, K. L., & Greenfield, S. (1994). Long-term functioning and well-being outcomes associated with physical activity and exercise in patients with chronic conditions in the Medical Outcomes Study. *Journal of Clinical Epidemiology*, *47*(7), 719-730.

Tsutsumi, T., Don, B. M., Zaichkowsky, L. D., Takenaka, K., & Oka, K. (1998). Comparison of high and moderate intensity of strength training on mood and anxiety in older adults. *Perceptual and motor skills*, *87*(3), 1003-1011.

Wipfli, B. M., Rethorst, C. D., & Landers, D. M. (2008). The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose-response analysis. *Journal of Sport & Exercise Psychology*, *30*(4), 392-410.

CHAPTER 2

REVIEW OF LITERATURE

What is Anxiety?

Anxiety refers to unpleasant feelings of apprehension and thoughts of worry. It is an adaptive response to an objective or perceived threat but can be maladaptive if the anxiety becomes severe and chronic (Barlow, 2002). Anxiety frequently is accompanied by behavioral changes (e.g., agitation, flight, freezing) and autonomic nervous system (ANS) activation.

Theories of Anxiety

A number of theoretical models have been proposed to explain the etiology and expression of anxiety and anxiety disorders. The preponderance of theoretical models can be classified according to cognitive models, integrative and hierarchical models, and neurobiological models. Although no single theory has yet proven adequate, some key theoretical underpinnings are discussed in the following section.

Cognitive Models

Cognitive models of anxiety focus on the roles of biases in attention, interpretation, memory and judgment in the etiology and maintenance of anxiety (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg & IJzendoorn, 2007). The primary feature of cognitive models of anxiety is the assumption that anxiety is in large part caused and maintained by biases in the processing of emotion-congruent information (Mogg & Bradley, 2005). Evidence has suggested that biases reflective of anxious apprehension can occur both explicitly and implicitly among individuals that experience elevated anxiety (Barlow, 2002; Eysenck, 1992; Mathews, 1997;

Mathew & MacLeod, 1994). Cognitive biases have been subdivided into three distinctive categories within the following discussion: attentional bias, memory bias, and interpretative bias.

Attentional Bias

Beck's Cognitive Schemata

One of the earliest cognitive models postulated that anxiety is characterized by a processing bias toward threat-related information such that information about one's self, the world, and the future are consistently processed in a distorted fashion as dangerous (Barlow, 2002; Beck & Emery, 1985; Beck, Rush, Shaw & Emery, 1979). Therefore, threat-related material would be preferentially processed at both early (e.g., attention and stimulus encoding) and late (e.g., memory and interpretation) processing stages (Bar-Haim et al., 2007), resulting in inaccurate processing of information rather than a rational perception of threat (Barlow, 2002).

That contention was extended and it was proposed that threat-related attentional bias plays a critical role in an individual's underlying vulnerability to anxiety, but that biases existed at specific stages of information processing (Williams, Watts, MacLeod & Matthews, 1997). Specifically, anxious individuals focus attention toward threat during early processing stages but divert attention away from threat during later, more strategic stages (Williams et al., 1997). This process would more likely function to preserve enhanced anxiety rather than diminish the threatening value of the stimulus through continued evaluation.

According to Barlow (2002), attentional bias and hypervigilance for threat-related cues among individuals with anxiety has been supported by research with a variety of paradigms, including the Stroop test (Williams, Mathews & MacLeod, 1996) among individuals with rape-induced posttraumatic stress disorder (Foa, Feske, Murdock, Kozak & McCarthy, 1991), socially anxious individuals (Mattia, Heimberg & Hope, 1993; McNeil, Ries, Taylor et al., 1995),

individuals with panic disorder (Hope, Rapee, Heimberg & Dombeck, 1990), and GAD patients (Mogg, Bradley, Williams, & Mathews, 1993), as well as the dot probe detection task with panic disorder patients (Asmundson, Sandler, Wilson & Walker, 1992; McNally, Hornig, Otto & Pollack, 1997) and individuals with obsessive-compulsive disorder (Tata, Leibowitz, Prunty, Cameron & Pickering, 1996).

It also has been postulated that biases in the evaluation of environmental stimuli may plausibly play a more salient role compared with attentional biases in anxiety vulnerability (Mogg & Bradley, 1998). Thus, pathological anxiety may result, in part, from cognitive appraisal errors like overestimating the intensity of a feared event, underestimating one's ability to cope, or catastrophically misinterpreting physiological symptoms associated with anxiety (O'Connor, Martinsen & Raglin, 2000).

Memory Bias

Inconsistent evidence has been reported concerning the role of memory biases in the etiology of anxiety (Mineka, Watson & Clark, 1998). A small body of literature has suggested an autobiographical memory bias in anxiety (Burke & Mathews, 1992; Richards & Whitaker, 1990), while other investigations have found no significant evidence for such a bias (Levy & Mineka, 1997). Results from separate studies suggested an implicit memory bias for threatening information among individuals with anxiety (Mathews, Richards & Eysenck, 1989), but this finding was not replicated in subsequent investigations (Bradley, Mogg & Williams, 1995; Mathews, Mogg, Kentish & Eysenck, 1995; Nugent & Mineka, 1994).

Interpretative

Judgmental and interpretative biases also have been suggested in the etiology of anxiety. Interpretative bias paradigms assess the tendency of anxious individuals to interpret ambiguous

material as threatening (Barlow, 2002). Anxious individuals have shown a heightened expectation of future negative events compared with controls (MacLeod & Byrne, 1996). Also, anxious individuals have shown the propensity to interpret ambiguous homophones (Mathews et al., 1989) and ambiguous sentences (Eysenck, Mogg, May, Richards & Mathews, 1991) in a negative manner. Patients with panic disorder were shown to be more prone to interpret ambiguous situations in which there was a sudden noticeable increase in some physiological function (i.e., breathing or heart rate) as threatening compared to individuals with other anxiety disorders (Clark, Salkovskis, Ost et al., 1997). However, judgmental and interpretive biases have received the least empirical attention among cognitive biases (Mineka, Watson & Clark, 1998).

Empirical Evidence

Meta-analytic evidence supports the role of cognitive biases in the etiology of anxiety. A recent meta-analytic review of 172 studies examining threat-related biases among anxious and non-anxious individuals concluded that threat-related attentional bias is robust among anxious individuals but does not exist in the non-anxious (Bar-Haim et al., 2007). A limited number of studies have shown that successful treatment in anxious patients leads to attenuation of the observed threat-related bias (Lundh & Oest, 2001; Mathews, Mogg, Kentish & Eysenck, 1995). More recently, event-related potentials (ERP) were used to examine attention deployment in response to different emotional facial expressions among high-anxious and low-anxious individuals. Results indicated that threat-related faces evoked faster latencies and larger amplitudes of early ERP components among high-anxious individuals compared to low anxious (Bar-Haim, Lamy & Glickman, 2005). In summary, clear evidence exists for a role of cognitive factors in the etiology of anxiety and its disorders.

Integrative and Hierarchical Models

A number of theoretical models have expounded on and extended the seminal two-factor affective model of Tellegen (1985), which emphasized the role of basic dimensions of positive and negative affect, to consider anxiety from a dimensional point of view. Most notably, the "tripartite" model (Clark & Watson, 1991), Barlow's three-factor model (Barlow, 1988; 1991), Barlow's hierarchical model of the anxiety disorders (Barlow, 1991; Brown & Barlow, 1992; Zinbarg & Barlow, 1996) and the more recent "quadripartite" model (Watson, 2009) have sought to more comprehensively elucidate the nature of anxiety and other closely related affective states.

Tripartite Model

The tripartite model extended the two-factor affective model (Tellegen, 1985) by postulating a second specific factor, physiological hyperarousal, which is posited as anxiety-specific (Clark & Watson, 1991; Mineka, Watson & Clark, 1998). According to the model, anxiety and depressive symptoms can be classified relative to three factors such that many symptoms are indicators of a significant component of generalized distress considered as "negative affect," including both anxious and depressed mood as well as several additional symptoms (e.g., sleep disturbance, difficulty concentrating, irritability) that are particularly prevalent in both types of disorder (Barlow, 2002; Clark & Watson, 1991; Mineka, Watson & Clark, 1998). The related component of "positive affect" appears relatively specific to depression in that depression is characterized by low positive affect, anhedonia, and cognitive and motor slowing, but does not appear to contribute a significant proportion of variance to anxiety (Barlow, 2002). Symptoms associated with the third specific factor, physiological hyperarousal, are thought to most accurately represent the discriminative aspects of each type of

disorder (Mineka et al., 1998; Watson, 2009). Symptoms associated with somatic tension and hyperarousal, including shortness of breath, dizziness, and dry mouth, are purported to be more closely related to anxiety, while anhedonia and low positive mood are relatively specific to depression (Mineka et al., 1998; Watson, 2009). These models imply that the processes of assessment and differential diagnosis may be improved by a stronger focus on symptom clusters specific to each disorder type rather than placing emphasis on nonspecific manifestations of negative affect (Watson, 2000; Watson, 2005; Watson, 2009). Nonetheless, a substantial body of evidence supports the general structure of the tripartite model and it is clear that negative affect may be a crucial factor to the understanding of both anxiety and depressive disorders as well as the relation among those disorders (Barlow, 2002; Joiner, 1996; Joiner, Catanzaro & Laurent, 1996; Joiner, Steer, Beck, Schmidt, Rudd & Catanzaro, 1999; Watson, Clark, Weber, Assenheimer, Strauss & McCormick, 1995).

Barlow's Three-Factor Model

A similar three-factor model has been articulated that emphasizes that mood and anxiety are fundamentally emotional disorders (Barlow, 1988; 1991; Barlow, Chorpita & Turovsky, 1996; Chorpita, Albano, & Barlow, 1998). Thus, the model relates these disorders to processes associated with anxiety, fear, and depression. The model contends that, while generalized distress and negative affect are primary manifestations of anxiety, autonomic arousal is predominantely an expression of fear or panic, and anhedonia and hopelessness are pertinent indicators of depression (Barlow et al., 1996; Chorpita et al., 1998; Mineka et al., 1998). The model essentially parallels the tripartite model (Clark & Watson, 1991) in that anhedonia and low positive affect are considered unique symptom clusters associated with mood disorders (Mineka et al., 1998).

Barlow's Hierarchical Model of the Anxiety Disorders

Increasing evidence has shown that the Diagnostic and Statistical Manual anxiety disorders are quite heterogeneous, subsuming a myriad of symptoms (Mineka et al., 1998; Watson, 2009; Zinbarg & Barlow, 1996). Specifically, evidence has suggested that a single specific factor (i.e., anxious arousal or somatic tension/hyperarousal) is unlikely to entirely account for the variability in symptoms among all anxiety disorders (Mineka et al., 1998). For example, anxious arousal was found to represent a more specific element of panic disorder as opposed to a general characteristic of the anxiety disorders (Brown, Chorpita & Barlow, 1998). Thus, a hierarchical model of the anxiety disorders, which postulated that each of the anxiety disorders possesses a shared component thought to correspond to the higher-order factor of generalized distress or negative affectivity in a two-factor hierarchical model, was proposed to address the heterogeneity of disorders (Barlow, 1991; Brown & Barlow, 1992; Watson, 2009; Zinbarg & Barlow, 1996). The higher-order factor is contended to be common across anxiety disorders but also shared with depression. The factor is thought to be responsible in large part for the overlap both among anxiety disorders and between depression and anxiety (Brown & Barlow, 1992; Mineka et al., 1998; Watson, 2009; Zinbarg & Barlow, 1996). However, each individual anxiety disorder also is thought to contain a unique, discriminative component that sets each disorder apart from others. A number of structural analyses employing both self-report and interview data have rendered support for the hierarchical model of anxiety disorders (Brown et al., 1998; Spence, 1997; Zinbarg & Barlow, 1996).

Integrative Hierarchical Model of Anxiety and Depression

The integrative hierarchical model of anxiety and depression incorporates key elements from both the tripartite model and Barlow's hierarchical model of the anxiety disorders. In point

of fact, the authors reported that a more accurate and comprehensive model is one that integrates key components of the tripartite model with Barlow's hierarchical model of the anxiety disorders (Mineka et al., 1998). Within the integrative model, each individual disorder is considered as possessing both a common and a unique component such that the shared component is a higher-order factor that is common to both anxiety and mood disorders and to which the overlap between them can be attributed (Mineka et al., 1998; Watson, 2009). The marked difference is that each disorder includes unique components that distinguish it from each other disorder (Mineka et al., 1998; Watson, 2009). For example, anxious arousal is no longer considered a ubiquitous characteristic of anxiety disorders, but is specific to panic disorder (Brown et al., 1998; Mineka et al., 1998). The authors also employed a quantitative component into the model to summarize a substantial amount of evidence relative to the size of the common and unique components. Results indicated significant differences across disorders (Mineka et al., 1998). For example, with the exception of GAD which is a distress-based disorder that possesses a substantial amount of the common factor variance, particularly with MDD, other anxiety disorders contain a reduced component of nonspecific general distress (Mineka et al., 1998; Watson, 2009).

Quadripartite Model

More recent attention has been placed on the inability of hierarchical models, particulary a single general factor, to adequately capture comorbidities among unipolar mood and anxiety disorders (Watson, 2009). The integrative hierarchical model has received substantial support in the literature for the prediction of a high level of comorbidity between disorders that have strong negative affectivity (Watson, 2009). However, much less support has been provided for the postulation of weaker overlap between disorders that contain less general factor variance given

high comorbidity between disorders such as specific and simple phobia which contain a lesser amount of nonspecific variance (Watson, 2005; Watson, 2009). Several limitations have been noted regarding the use of disorder-based analyses in previous models, including: (i) low base rates, (ii) changing diagnostic criteria, (iii) diagnostic inconsistencies across studies, (iv) diagnostic unreliability, and (v) diagnostic heterogeneity (Watson, 2009). To address these limitations, Watson (2009) proposed a model that represents a synthesis of the earlier tripartite and integrative hierarchical models in which two quantitative elements, the level of specificity (symptoms classified at varying levels of specificity of anxiety versus depression) and the magnitude of the general distress variance, are considered when assessing symptom properties. The quadripartite model uses level of specificity and the magnitude of the general distress variance to organize relevant symptoms into four groups that reflect a range of combinations of distress and specificity (Watson, 2009). The defining feature which extends this model beyond the tripartite model is a symptom group characterized by low distress symptoms with limited specificity based on the premise that even symptoms that exhibit a seemingly weak distress component can also illustrate little or no specificity (Watson, 2009). Watson (2009) presents some compelling data from initial analyses of PTSD, OCD and MDD using the symptoms-based approach. Nonetheless, further research is necessary to more comprehensively elucidate the merits and limitations of the quadripartite theoretical approach.

Neurobiological Models

A number of theorists have focused on the neurobiological basis of anxiety. The focus appears to have shifted from a neuroanatomical perspective to a perspective that considers both neuroanatomy and receptor physiology, biochemistry, and brain function (Barlow, 2002).

Gray's Behavioral Inhibition System

Well-known personality theorist Hans Eysenck (1967; 1981) theorized that personality and emotion largely resulted from the interaction of individual traits of cortical arousal and autonomic nervous system reactivity with limbic system influence. On the other hand, Jeffrey Gray, a prominent theorist of the neurobiological basis of anxiety, proposed that personality and emotions, and therefore anxiety, are not primarily determined by differential arousal intensity but by three affective-motivational systems (Barlow, 2002; Gray, 1982; Gray & McNaughton, 1996). The primary system in Gray's model (1982; Gray & McNaughton, 1996) is the behavioral inhibition system (BIS), consisting of the septal area, the hippocampus, and the circuit of Papez. The system incorporates ascending and descending cholinergic, dopaminergic and noradrenergic inputs in the septo-hippocampal and hypothalamic brain regions (Gray, 1982; Gray & McNaughton, 1996). According to this model, an active and sensitive BIS that presents an exaggerated inhibitory reaction to signals of novelty or punishment is the biological basis of anxiety (Barlow, 2002; Gray, 1982; Gray & McNaughton, 1996). A second, complimentary system, the behavioral approach system (BAS) involves the medial forebrain bundle and responds to signals of rewards and nonpunishment by facilitating approach (Barlow, 2002; Gray, 1982; Gray & McNaughton, 1996). Accordingly, anxious individuals, characterized by an active BIS, reflect a combination of Eysenck's introversion and neuroticism. Conversely, individuals with an active BAS reflect a combination of Eysenck's extroversion and stability (Barlow, 2002; Gray, 1982; 1985). Gray (1991) also posited a role of a third system, the fight-flight system (FFS), in fear and/or panic responses to unconditioned punishment and unconditioned frustrative nonreward stimuli (Gray & McNaughton, 1996).

Kagan's Behavioral Inhibition

After noting two distinct, stable behavioral profiles characterized by either withdrawal or approach among children, Kagan (1989; 1994) distinguished these profiles as "temperaments" which reflected the conclusion that behavioral clusters result from a relatively stable biological base in an organism's genotype. It also was noted that the environment is capable of modulating biologically based tendencies based upon observations of a number of physiological correlates of behavioral inhibition, including increased salivary cortisol levels, muscle tension, high heart rates, enhanced pupilary dilation, and elevated urinary catecholamine levels (Barlow, 2002; Kagan, 1989; 1994). These variations in temperament have been attributed to biological predispositions, namely the reactivity of several amygdalar brain circuits (Barlow, 2002).

A number of investigations have shown an association between Kagan's inhibited temperament and the development of anxiety disorders (Barlow, 2002). A review of the extant literature concluded that behavioral inhibition can be construed as a risk factor for the development of anxiety disorders in children (Turner, Biedel & Wolf, 1996). Children characterized by an inhibited temperament show increased risk for anxiety disorder development later in childhood (Biederman, Rosenbaum, Bolduc-Murphy et al., 1993; Hirshfeld, Rosenbaum, Biederman, 1992). First-degree relatives of children characterized by a behaviorally inhibited temperament also show a higher prevalence of anxiety disorders compared to the relatives of uninhibited children (Rosenbaum, Biederman, Hirshfeld, Bolduc & Chaloff, 1991). Nonetheless, some evidence has suggested that only a small to moderate percentage (~30%) of children who clearly met criteria for behavioral inhibition early in life developed an anxiety disorder (Biederman, Rosenbaum, Hirshfeld et al., 1990).

State Anxiety Versus Trait Anxiety

Anxiety is commonly conceptualized as entailing two distinct dimensions (Spielberger, 1966). State anxiety refers to transient feelings of tension and worry that can vary in intensity from moment-to-moment. Personal experience along with a large body of research demonstrates that anxiety may fluctuate from moment to moment. Anxiety symptoms can be transiently increased in response to certain drugs, such as amphetamine (Biala & Kruk, 2009), caffeine (Alsene, Deckert, Sand & de Wit, 2003), and procedures such as CO_2 inhalation (Coryell, Pine, Fyer & Klein, 2006) and lactate infusion (Pitts & McClure, 1967), as well as in anticipation of a wide variety of objective or perceived threats such as occurs prior to surgery (Perks, Chakravarti & Manninen, 2009), athletic competition (Sanchez, Boschker & Llewellyn, 2009) and social interaction (Tillfors, Furmack, Marteinsdottir et al., 2001). Symptoms of anxiety also can be transiently reduced with drugs, such as benzodiazepines and pregabalin (Nutt, Mandel & Baldinetti, 2008), as well as in response to social or behavioral interventions including meditation and progressive muscle relaxation (Rausch, Gramling & Auerbach, 2006), massage (Imanishi, Kuriyama, Shigemori et al., 2007), music (Cooke, Chaboyer, Schluter & Hiratos, 2005), acute bright light exposure (Youngstedt & Kripke, 2007) and acute bouts of exercise (Breus & O'Connor, 1998; Youngstedt, O'Connor, Crabbe & Dishman, 1998; O'Connor & Cook, 1998).

Several widely used instruments have been developed to assess state anxiety and related symptoms including visual analog scales (Hornblow & Kidson, 1976), the Beck Anxiety Inventory (Beck & Steer, 1990), Spielberger's State Anxiety Inventory (Spielberger et al., 1983), the Multiple Affect Adjective Checklist (Zuckerman & Lubin, 1985), the Anxiety Sensitivity Index (Peterson & Reiss, 1987), the Symptom Checklist-90 (Derogatis, 1992), and the tension

subscale of the Profile of Mood States (POMS; McNair, Lorr & Droppleman, 1992). Scores are thought to reflect state anxiety level when a participant is instructed to indicate how he/she feels "right now." Some measurement instruments, such as the POMS, use instructions that have a longer time frame (i.e., indicate how you have been feeling during the past week including today) that may yield results that differ from "right now" results but are interpreted as reflecting state anxiety. Scores that are derived from instructions using an even longer time frame, such as asking a participant to indicate how he/she usually, generally or typically feel, are regarded as representations of trait anxiety levels.

Trait anxiety refers to an individual's predisposition and/or proneness to appraise an event or stimulus as threatening. Some research has suggested that an individual's level of trait anxiety is fairly consistent over the lifespan (Kagan & Snidman, 1999; Schwartz, Snidman & Kagan, 1999; Van Ameringen, Mancini & Oakman, 1998). However, there is substantial evidence that trait anxiety scores are nonetheless sensitive to change. Interventions designed to reduce trait anxiety symptoms, including cognitive and behavioral therapies (Jorm, 1989; Mitte, 2005), chronic massage (Moyer, Rounds & Hannum, 2004) and relaxation training (Manzoni, Pagnini, Castelnuovo & Molinari, 2008), produce moderate-to-large reductions in anxiety scores.

A number of psychometric measurement instruments have been developed to assess trait anxiety, or the severity of general anxiety symptoms. Some of the most widely used scales include the trait anxiety scale of Spielberger's State-Trait Anxiety Inventory (Spielberger et al., 1983), the Beck Anxiety Inventory (Beck & Steer, 1990), the Hamilton Rating Scale for Anxiety (Hamilton, 1969), and the anxiety scale (HADS-A) of the Hospital Anxiety and Depression Scales (Zigmond & Snaith, 1983). The instructional set for these instruments prompt a participant to indicate his/her general level of anxiety across time frames greater than a week.

State and trait anxiety interact in predictable ways. Individuals with high levels of trait anxiety have a stronger predisposition to perceive a greater number of situations as threatening, more frequently experience periods of elevated state anxiety, and have a stronger anxiety reaction to a given stimulus than those with low or average trait anxiety (Speilberger et al., 1983).

Spielberger (1985), among others (e.g. Taylor, 1953), considers state and trait anxiety to be unidimensional constructs. Other researchers have conceptualized both state and trait anxiety as multidimensional constructs (e.g., Endler, 1997; Endler, Edwards & Vitelli, 1991; Endler, Parker, Bagby & Cox, 1991; Endler, Edwards, Vitelli & Parker, 1989), contending that there are two facets of state anxiety (cognitive-worry and autonomic-emotional) and four facets of trait anxiety (social evaluation, physical danger, ambiguous, and daily routines) (Endler & Kocovski, 2001).

Relation of Anxiety to Other Emotions and Mood States

Differentiating anxiety from related concepts such as the emotion of fear is important (Smith & Crabbe, 2000). While fear is a brief emotional reaction to a threatening stimulus, anxiety is a longer lasting, more abstract reaction to a larger range of stimuli than those that induce fear (O'Connor et al., 2000). Nomologically, fear and stress are closely related to anxiety because fear, stress, and anxiety responses are regulated by similar brain structures including the basolateral and central nuclei of the amygdala, the bed nucleus of the stria terminalis, and hippocampal regions (Deacon, Bannerman & Rawlins, 2002; Tuvnes, Steffenach, Murison, Moser & Moser, 2003; Walker, Toufexis & Davis, 2003).

A number of models have postulated positive relations between anxiety and depressive mood states. Clark and Watson (1991) proposed a tripartite model which postulated that anxiety

and depression shared non-specific features of distress or negative affect, such as neuroticism. Within this model anxiety is distinguished from depression by physiological arousal (Brown et al., 1998; Watson et al., 1995). Anxiety also is plausibly positively related to depression as indicated by serotonergic involvement in the etiology of anxiety and depression. Recent association studies in humans found correlations between a single functional polymorphism in the promoter of the 5-HT1A receptor and both trait anxiety and depression (Lemonde, Du, Bakish et al., 2004; Strobel, Gutknecht, Rothe et al., 2003). A positive relation between anxiety, depression and fatigue mood states also is indicated by reductions in symptoms of these mood states in response to similar treatments (i.e., exercise training). For example, a recent meta-analytic review of the effects of cardiac rehabilitation programs on feelings of energy and fatigue found similar mean effect sizes for feelings of energy and fatigue ($\Delta = 0.59$), anxiety ($\Delta = 0.40$), and depression ($\Delta = 0.35$) (Puetz, Beasman & O'Connor, 2006). Similarly, 24 weeks of cycling exercise training at 55% of VO_2 max resulted in similar reductions in state (ES = 1.02) and trait anxiety (ES = 1.13), depression (ES = 0.98), and feelings of fatigue (0.86) in older men (Antunes, Stella, Santos, Bueno & deMello, 2005).

Anxiety Disorders

Frequent or intense anxiety symptoms can suggest an anxiety disorder; however, there are qualitative differences between anxiety disorders and nonpathologic levels of anxiety symptoms. Anxiety disorders are a group of disabling conditions characterized by excessive, chronic maladaptive anxiety symptoms that are usually accompanied by a strong autonomic nervous system activation, altered anxiety-related cognitions, and altered behavior (usually avoidance) which can contribute to increased personal distress and impaired function. The differentiation between anxiety disorder patients and healthy individuals is usually based on the

intensity and number of symptoms, the degree of personal suffering, and the extent to which normal functioning is impaired.

Pathological anxiety has been classified into six disorders by the American Psychiatric Association: specific phobia, social phobia, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and post-traumatic stress disorder (American Psychiatric Association, 2000). Specific phobia is characterized by an irrational fear and avoidance of specific objects, places, or situations that actually pose little or no danger. Social phobia, also referred to as social anxiety disorder (SAD), is an intense fear of being judged, criticized, and evaluated by others. Panic disorder (PD) involves repeated episodes of intense fear that strike without warning and without obvious cause or source, which frequently produce the fear of being alone or going to public places (Agoraphobia) and persistent fear of the next attack. Individuals diagnosed with obsessive-compulsive disorder (OCD) experience repeated, unwanted thoughts or compulsive behaviors that seem impossible to stop which are usually associated with repetitive acts or rituals to attenuate the anxiety. Post-traumatic stress disorder (PTSD) involves a delayed, often prolonged response, which frequently includes flashbacks, dreams, insomnia, and hypervigilance, to a stressful event (either short or long-lasting) that was substantially threatening or catastrophic. Generalized anxiety disorder (GAD) is characterized by persistent excessive or pathologic worry about multiple concerns (e.g., everyday life events and activities) for at least 6 months with at least 3 of the following symptoms: restlessness or feeling on edge, being easily fatigued, difficulty concentrating, irritability, muscle tension, or sleep disturbance. The anxiety must not be caused by another disorder and the individual experiences significant distress or functional impairment related to the symptoms (American

Psychiatric Association, 2000). One of the primary investigations of this dissertation will examine the effects of exercise training among individuals with GAD.

Prevalence

Anxiety disorders are the most prevalent mental health disorders in the United States. The National Comorbidity Survey-Replication (NCS-R) found that 28.8% of the US population meets diagnostic criteria for at least one anxiety disorder, with estimated 12-month prevalence rates among individuals aged 18 years or older of 18.1% (Kessler, Berglund, Demler et al., 2005).

Higher Prevalence Among Women

Approximately 30 million people in the US will develop an anxiety disorder in their lifetime, with a lifetime prevalence higher among women (~31%) compared with men (19%) (Lepine, 2002). More recent evidence indicates that females have both higher 12-month prevalence rates and lifetime risk of GAD, SAD, PTSD, and PD compared with males (Himle, Baser, Taylor, Campbell & Jackson, 2009).

Differences Across Race/Ethnicity

There is a limited amount of research regarding the prevalence of anxiety disorders among racial and ethnic subpopulations. An investigation of the NCS-R sample showed significantly greater rates of GAD in non-Hispanic whites compared to non-Hispanic blacks and Hispanics, higher rates of PD compared to non-Hispanic blacks, and increased rates of SAD compared to Hispanic individuals (Breslau, Aguilar-Gaxiola, Kendler, Su, Williams & Kessler, 2005). Results of a more recent examination of 12-month prevalence and lifetime risk of anxiety disorders among non-Hispanic white Americans, African Americans, and American Blacks of Caribbean descent indicated both elevated 12-month prevalence of all anxiety disorders except

PTSD among non-Hispanic whites and higher immediate and cumulative risk for development of GAD and SAD at any given age compared with African Americans and Caribbean Blacks (Himle et al., 2009).

Differences Across Age Groups

The median age of onset of anxiety disorders ranges from the mid-teens to the early twenties, while people aged 15-24 years experience episodes of anxiety 40% more often than people aged 25-54 years (Kessler, Amminger, Aguilar-Gaxiola, Alonso, Lee & Ustun, 2007). Although evidence suggests that people experience the greatest risk for developing most anxiety disorders in their teens and early twenties regardless of race, non-Hispanic whites have shown a greater risk to experience the onset of some anxiety disorders (GAD, SAD, PD) after the age of 60 years (Himle et al., 2009).

Prevalence of Comorbid Anxiety and Depressive Disorders

There has been increasing interest in both the comorbidity of anxiety with other mood disorders, particularly depressive disorders, and the relation of these comorbid conditions with other chronic medical illnesses. Social phobia, PTSD, PD and OCD frequently appear comorbidly with other mood disorders, most frequently with major depressive disorder (Ohayon, Shapiro & Kennedy, 2000). Recent results from the World Mental Health surveys indicated that, among approximately 85,000 people from 17 developing and western countries, individuals with comorbid depressive-anxiety disorder (e.g. GAD, PD and/or agoraphobia, PTSD, or SAD along with dysthymia or major depressive disorder) were more likely to suffer from several chronic medical illnesses including hypertension, heart disease, and pain-related medical illnesses compared to individuals with either a single anxiety or single depressive disorder (Scott, Bruffaerts, Tsang et al., 2007).

Personal and Economic Costs

While less than a third of individuals with anxiety disorders seek treatment, there still is a substantial economic burden associated with anxiety disorders. An estimated 44 billion dollars is attributed to anxiety disorders annually because of direct psychiatric and nonpsychiatric costs as well as indirect costs from reduced work productivity (DuPont, Rice, Miller, Shiraki, Rowland & Harwood, 1996; Greenberg, Sisitsky, Kessler et al., 1999).

Anxiety disorders also are strongly and independently associated with reduced health-related quality of life (Harter, Conway & Merikangas, 2003; Sareen, Jacobi, Cox, Belik, Clara & Stein, 2006), increased disability (Kroenke, Spitzer, Williams, Monahan & Lowe, 2007; Ludman, Katon, Russo et al., 2006; Sareen, Cox, Clara & Asmundson, 2005), increased absenteeism from work (Stein, Roy-Byrne, Craske et al., 2005), and increased use of healthcare resources (Katon & Walker, 1998; Marciniak, Lage Dunayevich et al., 2005; McLaughlin, Khandler, Kruzikas & Tummala, 2006; Simon & Von Korff, 1991; Walker, Katon, Russo, Ciechanowski, Newman & Wagner, 2003). Several large population-based and primary care investigations also have demonstrated that individuals with a DSM-IV anxiety disorder report significantly more medically unexplained physical symptoms compared to individuals without an anxiety disorder (Katon, Lin & Kroenke, 2007; Katon, Sullivan & Walker, 2001; Kroenke & Price, 1993; Kroenke, Spitzer, Williams et al., 1994; Simon, Gater, Kisely & Piccinelli, 1996).

Risk Factors for Anxiety Disorders

Genetics

Twin and family studies have often been used to assess the influence of genetic factors on anxiety. Familial aggregation largely resulting from genetic risk factors has been documented for all major anxiety disorders (Hettema, Neale & Kendler, 2001). Twin studies of the estimated

variance attributable to genetic effects on development of anxiety disorders have reported ranges of 25-65%. Also, twin studies of trait anxiety indicate that approximately 30% of the overall variance can be attributed to genetic factors (Eley & Gregory, 2004). Analyses of the incidence of anxiety disorders among monozygotic and dizygotic twins have shown that approximately 30-40% of the variance between individuals is attributable to genetic variation (Hettema et al., 2001; Sullivan, Neale & Kendler, 2000). Association and linkage studies among humans have aimed at the identification of specific genes or chromosomal regions thought to be important to particular anxiety traits and disorders, but have reported inconsistent findings (Finn, Rutledge-Gorman & Crabbe, 2003). In sum, there is clear evidence that genetic factors impact an individual's susceptibility to anxiety.

Disease Comorbidity

The potential contributing role of health status in the development of maladaptive anxiety is of interest. Anxiety is strongly and independently associated with chronic medical illnesses (Roy-Byrne, Davidson, Kessler et al., 2008), reduced health-related quality of life (HRQOL) and disability (Kroenke et al., 2007; Sareen et al., 2006; Ludman et al., 2006; Sareen et al., 2005; Harter et al., 2003). Although anxiety is not uncommon among healthy individuals, compared to healthy adults anxiety disorders are more common among persons with a variety of chronic medical illnesses, including those with asthma (Kuehn, 2008), cancers (Dahl, Haaland, Myletun et al., 2005), cardiovascular diseases (Fan, Strine, Jiles & Mokdad, 2008), depression (Moffitt, Harrington, Caspi et al., 2007), gastrointestinal diseases (Addolorato, Mirijello, D'Angelo et al., 2008), lung diseases (Kunik, Roundy, Veazey et al., 2005), multiple sclerosis (Korostil & Feinstein, 2007) and pain-related disorders (Roy-Byrne et al., 2008). For example, 11 prospective studies indicated an increased risk of cardiovascular disease (RR: 1.5-8) associated

with increased chronic anxiety (Kubzansky, Davidson & Rozanski, 2005). It is uncertain the degree to which anxiety contributes to these conditions or whether anxiety is entirely a response to the presence of these diseases.

Neurobiological Aspects of Anxiety

Key Neuroanatomical Structures

The neural circuits involved in anxiety include afferent nerve fibers that allow the sensing of potentially threatening stimuli, brain areas that appraise afferent sensations and integrate them with memories of prior experience, and efferent nerves that generate a coordinated endocrine, autonomic, and muscular response (O'Connor et al., 2000). Neuroimaging data indicate that several brain areas are consistently involved in the expression of anxiety including midbrain structures, thalamus, right hippocampus, anterior cingulate cortex (ACC), insular cortex, and the right prefrontal cortex (Reiman, 1997). The neural circuitry of anxiety is thought to involve the amygdala, hippocampus, striatum, basal ganglia, thalamus, hypothalamus and pituitary, anterior paralimbic structures (ACC, ventral/medial prefrontal cortex, orbital frontal cortex, subcallosal cortex and insular cortex), periacqueductal gray, parabrachial nucleus, and locus coeruleus (Cannistraro & Rauch, 2003). While evidence is the strongest for the role of the amygdala, the insular cortex also appears to play a key role in the pathophysiology of anxiety (Damsa, Kosel & Moussally, 2009).

Amygdala

The amygdala appears to be crucial in the neural assessment of and response to threat (LeDoux, 1998). It both coordinates the automatic threat response and integrates sensory features of the stimulus into context and relevant memories through cortical and subcortical inputs (Damsa et al., 2008). Anatomically, the amygdala appears to be a central structure in the

coordination of cognitive, affective, neuroendocrine, cardiovascular, respiratory, and musculoskeletal components of fear and anxiety responses (Goddard and Charney, 1997). The amygdala has rapid and direct access to anxiety-related sensations via projections to structures such as the thalamus and the locus coeruleus (O'Connor et al., 2000).

Lateral Amygdala

Specifically, sensory information from visual, auditory, olfactory, nociceptive, and visceral pathways project through the anterior thalamus to the lateral nucleus of the amygdala, which transmits stimulus-related signals to the central nucleus of the amygdala (Cannistraro & Rauch, 2003). Particular attention has been focused on the basolateral nucleus of the amygdala in large part because it has a high concentration of benzodiazepine receptors (Niehoff & Kuhar, 1983). Inhibition of the basolateral nucleus of the amygdala decreases and excitation increases anxiety-like behaviors (Sajdyk & Shekhar, 1997). Benzodiazepines have elicited anxiolytic effects when directly injected into the basolateral amygdala, while blocking the benzodiazepine site on the $GABA_A$ receptor impedes this effect (Sanders & Shekhar, 1995). Moreover, recent evidence indicated that lesioning interneurons which preferentially express neurokinin1 receptors in the basolateral nucleus of the amygdala resulted in anxiety-like behavior (Truitt, Johnson, Dietrich, Fitz & Shekhar, 2009; Truitt, Sajdyk, Dietrich, Oberlin, McDougle & Shekhar, 2007).

Central Amygdala

The central nucleus of the amygdala has been implicated as the point at which information is integrated and autonomic and behavioral responses are executed (Cannistraro & Rauch, 2003; Davis, 1992; LeDoux, Iwata, Cicchetti & Reis, 1988). Efferents projecting from the central nucleus of the amygdala are responsible for common physiological and behavioral anxiety responses. For example, efferents projecting to the lateral hypothalamus initiate a

sympathetic response (Price & Amaral, 1981), while efferents projecting to the locus coeruleus result in increases in blood pressure and heart rate (Cedarbaum & Aghajanian, 1978). In response to threatening stimuli, the amygdala also is thought to regulate behavioral outcomes in conjunction with other structures such as the paraventricular nucleus of the hypothalamus (Cannistraro & Rauch, 2003).

Evidence also suggests that reciprocal projections between the amygdala and the hippocampus play a role in anxiety. The hippocampus is involved with declarative memory storage, processing the context of the mood or emotional response (LeDoux, 1998). Hippocampal dysfunction may play an important role in the etiology of anxiety as a result of deficiencies in the recognition of potentially threatening stimuli (Cannistraro & Rauch, 2003). For example, a review of the available neuroimaging data concluded that there was evidence for abnormal basal hippocampal activity among PD patients, as well as reduced hippocampal volume among PTSD patients (Rauch, Shin & Wright, 2003).

Insular Cortex

Although research into the neuroanatomical basis of anxiety has primarily focused on the amygdala, the insular cortex also may play a vital role. The insular cortex has bidirectional projections to the amygdala, the nucleus accumbens, and the orbitofrontal cortex (Ongur & Price, 2000; Reynolds & Zahm, 2005). Based on these projections, the location of the insular cortex in the neural network appears to be central to the reception of information about the salience and value of a stimulus (Paulus & Stein, 2006). Insular activation also is thought to play a role in the differential processing of positive versus negative emotions (Buchel, Morris, Dolan & Friston, 1998). Connections between the insular cortex and important limbic and executive functioning

brain regions suggest that the insula may be a focal point for augmented physiological sensations and enhanced cognitive engagement often associated with anxiety (Paulus & Stein, 2006).

The insular cortex, particularly the anterior insula, is thought to play a critical role in interoception, the sense of the physiological condition of the body (Craig, 2002), by integrating information about the relevance and value of a stimulus with the effect that the stimulus has on body state (Paulus & Stein, 2006). Anterior insular cortex dysfunction may contribute to the etiology of anxiety via an altered interoceptive prediction signal. That is, anxiety-prone individuals experience an altered signal of the difference between expected and observed body state (Paulus & Stein, 2006).

Several lines of evidence suggest that insular cortex activity is altered in relation to anxiety, particularly among anxiety-prone individuals and those with anxiety disorders. For example, an investigation using fMRI showed significantly greater bilateral insula activation in response to emotional faces among anxiety-prone healthy adults (i.e., upper 15^{th} percentile on STAI trait scale) compared to individuals with normal anxiety scores (Stein, Simmons, Feinstein & Paulus, 2007). Associations between symptom provocation and increased cerebral blood flow in the bilateral insular cortex have also been shown among anxiety disorder patients (Rauch, Savage, Apert, Fischman & Jenike, 1997). A down-regulation of $GABA_A$ receptors in the right insular cortex among PD patients has been shown, while enhanced right insular activation also has been reported in response to fearful faces among individuals with a specific phobia (Malizia, Cunningham, Bell, Liddle, Jones & Nutt, 1998; Wright, Martis, McCullin, Shin & Rauch, 2003). Regional cerebral blood flow was significantly increased in the insular cortex following intravenous infusion of yohimbine, a noradrenergic antagonist known to produce anxiogenic

responses (Cameron, Zubieta, Grunhaus & Minoshima, 2000). Thus, both the amygdala and the insular cortex appear to be involved in anxiety.

Key Neurotransmitter Systems

Although some evidence has supported a role of neuropeptides, such as cholecystokinin (see van Megen, Westenberg, den Boer & Kahn, 1996 for review), and neuromodulators, such as adenosine (Alsene et al., 2003; Childs, Hohoff, Deckert, Xu, Badner & de Wit, 2008) and endocannabinoids (see Viveros, Marco & File, 2005 for review), in the etiology of anxiety, the most compelling evidence has focused on the role of major neurotransmitters including γ-aminobutyric acid (GABA), norepinephrine (NE), serotonin (5-HT) and glutamate.

GABA-ergic

GABA receptors are widespread throughout areas thought to be involved in anxiety responses including the amygdala, hippocampus, hypothalamus, PAG, and the lateral septum (Cherubini & Conti, 2001; Millan, 2003; Mody, 2001; Sanger, 1985). Both chloride-permeable, ionotropic $GABA_A$ and metabotropic $GABA_B$ receptors are implicated in the genesis and expression of anxious behavior (Barnard, Skolnick, Olsen et al., 1998; Bowery & Enna, 2000; Millan, 2003). GABAergic pathways are thought to primarily exert an inhibitory influence on the release and action of other biochemicals thought to influence the etiology of anxiety, including 5-HT, NE, dopamine (DA), glutamate, CRF and cholecystokinin (CCK) (Millan, 2003).

Animal models have provided the most comprehensive evidence of the potential role of GABA in the etiology of anxiety. For example, mice deficient in GAD65, one of the two isoforms of glutamic acid decarboxylase from which GABA is synthesized, have exhibited approximately 50% reduced time in the open arm of the elevated zero maze and significantly

lower center time in the open field, suggesting that a reduced ability to synthesize GABA may be responsible for increased anxiety-like behavior (Kash, Tecott, Hodge & Baekkeskov, 1999). Neurochemical studies involving GABA also have demonstrated that interruption of GABAergic transmission can elicit anxiety-like responses (Martijena, Manzanares, Lacerra & Molina, 2002; Stork, Ji & Obata, 2002).

$GABA_A$ receptors have received the most attention in relation to anxiety. Neuroimaging studies have indicated specific associations between alterations in the density and binding properties of $GABA_A$ receptors, particularly with radioligands of benzodiazepine sites (Millan, 2003), and anxiety disorders (Kaschka, Feistel & Ebert, 1995; Tiihonen, Kuikka, Rasanen et al., 1997). For example, a single photon emission computed tomography (SPECT) study of panic-related abnormalities of the benzodiazepine receptor complex among nine patients with PD revealed a significant decrease in the regional activity index in multiple brain regions, leading the authors to suggest that findings could be attributed to benzodiazepine receptor effects (Kaschka et al., 1995).

Substantial attention has been paid to the receptor distribution and the pharmacological actions of benzodiazepines (BZD). Single photon emission tomography studies have shown diminished benzodiazepine receptor binding in the hippocampus and temporal lobe and reduced uptake of Iiomazenil in frontal, temporal and occipital cortices among PD patients (Kaschka, Feistel & Ebert, 1995; Schlegel, Steinert, Bockisch, Hahn, Schloesser & Benkert, 1994).

Benzodiazepines have been shown to reduce anxiety levels in most animal models of anxiety (Borsini, Podhorna & Marazziti, 2002; File & Seth, 2003). For example, increased exploratory behavior in a novel environment in rats following BZD administration into the dorsal hippocampus has been reported (Stefanski, Palejko, Bidzinski, Kostowski & Plaznik, 1993).

In humans, the anxiolytic effects of BZD agonists are clinically and experimentally well-established. BZD agonists have been shown to be effective in the treatment of anxiety disorders, whereas BZD inverse agonists (e.g., β-carboline) inhibit the function of the ion channel and exhibit anxiogenic properties (Cole, Hillman, Seidelman, Klewer & Jones, 1995; Dorow, Duka, Holler & Sauerbrey, 1987; Dorow, Horowski, Paschelke, Amin & Braestrup, 1983; Sarter, Bruno & Berntson, 2001). BZD agonists also inhibit cholinergic neurons in the basal forebrain (Sarter & Bruno, 1999). Cholinergic neuronal function in the basal forebrain provides a link between anxiety and ANS responses associated with anxiety because cholinergic activity modifies both the expression of anxiety and cardiovascular reactivity (Sarter & Bruno, 1999).

Metabotropic, G protein-coupled $GABA_B$ receptors function in the slower component of neural inhibition (Millan, 2003). Although comparatively less evidence is available regarding the anxiolytic/anxiogenic functions of $GABA_B$ receptors, some, albeit inconsistent, data from pharmacological interventions and animal models suggest an anxiolytic role of $GABA_B$ receptor agonists. $GABA_B$ receptor deficient mice have demonstrated no meaningful perturbations in anxiety-like behaviors (Schuler, Luscher, Blanchet, et al., 2001). However, baclofen, a $GABA_B$ receptor agonist has been shown to attenuate anxiety elicited by stress and to reduce state anxiety scores in substance-abuse patients (Addolorato, Caputo, Capristo, et al., 2002; Dalvi & Rodgers, 1996). Similarly, acute and chronic administration of a novel $GABA_B$ receptor positive modulator decreased anxiety-like behavior in the light/dark and elevated zero maze tests (Mombereau, Kaupmann, Froestl, Sansig, van der Putten & Cryan, 2004). More recently, the $GABA_B$ receptor positive allosteric modulator CGP7930 and the $GABA_B$ receptor antagonist SCH 50911 elicited significantly increased time spent in the open areas of the elevated zero maze (Frankowska, Filip & Przegalinski, 2007). Thus, although the available body of literature

is smaller than that available for $GABA_A$, there is some evidence to suggest the role of $GABA_B$ receptors in the etiology of anxiety.

Noradrenergic

Several lines of evidence have implicated norepinephrine (NE), or noradrenergic activity, in anxiety responses. Proponents of the etiological role of NE have contended that increased noradrenergic release results in anxiety due in large part to excessive, dysfunctional arousal (Charney & Bremner, 1999; Sandford, Argyropoulous & Nutt, 2000). The locus coeruleus (LC) is thought to be a focal point of noradrenergic activity because it integrates distinct, convergent inputs which facilitate the processing of and response to anxiogenic stimuli (Aston-Jones, Akaoka, Charlety & Chouvet, 1991; Lapiz, Mateo, Durkin, Parker & Marsden, 2001; Kawahara, Kawahara & Westerink, 2000; Singewald & Sharp, 2000). Specifically, the LC predominantly receives input from ascending noradrenergic projections that innervate the hippocampus, amygdala, PAG, cortex and hypothalamus (Millan, 2003; Tanaka, Yoshida, Emoto & Ishii, 2000; Valentino and Aston-Jones, 1995).

Results from pharmacological interventions and animal studies point toward the etiological role of NE. Activation of the LC via electrical stimulation or pharmacological agents evokes anxiety-like behavior in primates, and fear-related behaviors to threatening situations are decreased following bilaterial lesions of the LC (Charney, Deutch, Southwick & Krystal, 1995). Much attention has been focused on α2-adrenoreceptor agonists, such as clonidine, which decreases LC activity and has been shown to both attenuate preoperative anxiety in humans (Ahmed & Takeshita, 1996; Bitsios, Szabadi & Bradshaw, 1998; Millan, Maiofiss, Cussac, Audinot, Boutin & Tancredi, 2002; Thomson, Peterson & Hudson, 1998) and to reduce panic responses elicited by sodium lactate (Coplan, Liebowitz, Gorman et al., 1992). Conversely, α_2-

adrenoreceptor antagonists, such as yohimbine, increase LC activity and have been shown to elicit anxiety in high trait anxious individuals and individuals particularly susceptible to experience panic attacks (Bremner, Krystal, Southwick & Charney, 1996a;b; Charney, Woods, Krystal, Nagy & Heninger, 1992; Krystal, McDougle, Woods, Price, Heninger & Charney, 1992). Clonidine also has been shown to significantly attenuate yohimbine-induced increases in plasma 3-methoxy-4-hydroxy-phenylethyleneglycol (MHPG), blood pressure and autonomic responses, suggesting both that noradrenergic hyperactivity contributes to anxiety and that the anxiolytic effects of clonidine likely result from effects on receptors that reduce noradrenergic activity (Charney, Heninger & Redmond, 1983).

Although conflicting evidence exists, β-adrenergic blockers have been shown to be effective in treatment of social anxiety. Propranolol is a non-selective β-adrenergic antagonist that has been used to treat social phobia (Southwick, Bremner, Rasmusson, Morgan, Arnsten & Charney, 1999). Propranolol administration following a traumatic event has shown efficacy in mitigating and potentially preventing subsequent onset of PTSD (Piman, Sanders, Zusman et al., 2002; Vaiva, Ducrocq, Jezequel, et al., 2003).

Animal models of anxiety have provided additional supportive evidence of the etiological role of the noradrenergic system in anxiety. The α2A-adrenoreceptor subtype (Adra2a), thought to mediate several physiological actions of NE (Finn et al., 2003), has been isolated and deleted in mice and anxiety-related behaviors have been tested (Altman, Trendelenburg, MacMillan et al., 1999; Schramm, McDonald & Limbird, 2001). Following saline injection Adra2a knockout mice illustrated a significantly decreased number of rearings and a significantly increased amount of time spent in the dark side of the light/dark test, suggesting that increases in anxiety-like behavior were a result of the inability of Adra2a knockout mice to regulate the release of NE

(Schramm et al., 2001). In a separate investigation, Adra2a knockout mice demonstrated reduced open arm time and exploratory head dips in the elevated plus maze and decreased rearing and activity upon subsequent exposure to a novel open field (Lahdesmaki, Sallinen, MacDonald, Kobilka, Fagerholm & Scheinin, 2002). Thus, although some inconsistency exists among the available evidence, the extant literature supports a contributory role of noradrenergic activity in the etiology of anxiety.

Serotonergic (5-HT)

Dysregulation of the serotonergic system has been implicated in the etiology of anxiety. Significant attention has been focused on the role of the 5-HT transporter (5-HTT), which is central to both serotonergic neurotransmission and peripheral actions in large part due to its role in the regulation of the magnitude and duration of serotonergic responses (Lesch, Bengel, Heils, et al., 1996). Lesch and colleagues (1996) reported that individuals with diminished 5-HTT function have greater anxiety-related personality characteristics, particularly neuroticism. However, meta-analytic reviews of the evidence since the seminal work by Lesch and colleagues (1996) have revealed conflicting evidence regarding the relation between the 5-HTT promoter polymorphism and anxiety-related personality traits (Munafo, Clark & Flint, 2005; Schinka, Busch & Robichaux-Keene, 2004; Sen, Burmeister & Ghosh, 2004).

Animal studies have provided substantial evidence of the role of serotonin in the etiology and expression of anxiety-like behavior. Animal models have elucidated two potential anxiogenic and anxiolytic serotonergic pathways within the brain. Serotonergic innervation of the amygdala and hippocampus through the dorsal raphe is purported to mediate anxiety-like behavior via action at 5-HT2 receptors (Graeff, Silviera, Nogueira, Audi & Oliviera 1993). Conversely, hippocampal 5-HT1A receptor innervation via the median raphe plausibly enhances

resilience to anxiogenic events (Grove, Coplan & Hollander, 1997). For example, an investigation of the contribution of serotonin receptors to anxiety-like behaviors using 5-HT1A knockout mice demonstrated the involvement of 5-HT1A receptors in the modulation of anxiety-like (i.e., exploratory) behaviors, suggesting that reduced 5-HT1A receptor density may increase anxiety (Ramboz, Oosting, Amara et al., 1998). Human studies have corroborated these findings, showing elevated anxiety among individuals with a low density of central 5-HT1A receptors (Condren, Dinan & Thakore, 2002; Tauscher, Bagby, Javanmard, Christensen, Kasper & Kapur, 2001).

Recent association studies in humans found correlations between a single functional polymorphism in the promoter of the 5-HT1A receptor and trait anxiety (Lemonde et al., 2004; Strobel et al., 2003). An examination of the ability of a temporary reduction in central 5-HT transmission through acute tryptophan depletion to reverse the efficacy of selective serotonin reuptake inhibitors (SSRI) in social anxiety disorder patients showed that tryptophan depletion induced significant increases in anxiety (Argyropoulos, Hood, Adrover et al., 2004).

Pharmacological interventions also provide evidence for a role of serotonin in the etiology of anxiety. A comparison of the efficacy of sertraline, a SSRI, or cognitive-behavioral therapy (CBT) compared with a waiting list control among anxiety disorder patients aged 60 years and older revealed a more robust effect for sertraline than CBT (Schuurmans, Comijs, Emmelkamp, et al., 2006). Similar investigations have shown that the SSRI fluoxetine is effective in treating several anxiety disorders (Goddard & Charney, 1997). Methyl-Chlorophenylpiperazine (m-CPP), a 5-HT agonist, elicits anxiety reactions in the majority of PD patients but in a minority of controls (Charney, Woods, Goodman & Heninger, 1987). Moreover, investigations in animals and humans have shown that the 5-HT releaser

methylenedioxymethylamphetamine (Ecstasy) can modify anxiety and anxiety-like behavior in a dose-dependent fashion (Parrot, 2000; Liechti & Vollenweider, 2001; Fone, Beckett, Topham, Swettenham, Ball & Maddocks, 2002; Green & McGregor, 2002; Navaro & Maldanado, 2002).

Glutamatergic

Although the association between glutamate neurotransmission and anxiety disorders has received less empirical attention, dysregulation of the glutamatergic system is thought to play an important role in the pathogenesis of anxiety, anxiety disorders, including GAD and OCD, and fear conditioning (Bergink, van Megen & Westenberg, 2004; Pittenger, Coric, Banasr, Krystal & Sanacora, 2008; Simon & Gorman, 2006). The excitation spectrum for glutamate ranges from normal neurotransmission, dysregulated excess neurotransmission resulting in pathological symptoms such as mania or panic, to excitotoxicity causing dendritic damage (Berginik et al., 2004).

Evidence linking glutamatergic activity to anxiety and anxiety-like behavior has been provided by animal studies and pharmacological interventions. Glutamate receptor ligands have shown anxiolytic effects in conditioned behavior animal models using conflict tests and unconditioned behavior models including the social interaction paradigm, the elevated plus maze, the ultrasonic vocalization paradigm and the acoustic startle paradigm (Berginik et al., 2004). Specifically, preclinical studies have suggested that compounds which activate *N*-methyl-*D*-aspartate (NMDA), amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate, and metabotropic receptors might have anxiolytic properties (Bergink et al., 2004). For example, NMDA receptor antagonists have elicited decreased anxiety-like behaviors in the conflict test (Corbett & Dunn, 1991; Xie & Commissaris, 1992) and in social interaction paradigms (Corbett & Dunn, 1991), and increased open field locomotion (Jessa, Nazar, Bidzinsky & Plaznik, 1996;

Kotlinska & Liljequist, 1998). Competitive NMDA receptor antagonists have consistently shown decreased anxiety-like behavior in the conflict test (Corbett & Dunn, 1991; Willetts, Clissold, Hartmann et al., 1994) and in the acoustic startle paradigm (Anthony & Nevins, 1993). Similarly, NMDA receptor antagonists that bind to the glycine site have consistently produced decreased anxiety-like behavior in the acoustic startle paradigm (Anthony & Nevins, 1993; Karcz, Jessa, Nazar et al., 1997; Koek & Colpaert, 1991) and in the conflict test (Anthony & Nevins, 1993; Kehne, Baron, Harrison et al., 1995; Kotlinska & Liljequist, 1998). Although less evidence is available regarding the effects of AMPA receptor antagonists and metabotropic receptor agonists and antagonists, AMPA receptor agonists have demonstrated anxiolytic properties in the conflict test (Karcz, Kubich & Liljequist, 1995; Benvenga, Leander & Ornstein, 1993). Metabotropic agonists have reduced anxiety-like behavior across multiple paradigms, including the acoustic startle paradigm (Helton, Tizzano, Monn et al., 1997), the conflict test (Klodzinska, Chojnacka-Wojcik, Palucha et al., 1999), and the social interaction paradigm (Shekhar & Keim, 2000). Nonetheless, one limitation is that the majority of the compounds used in previous studies possess muscle relaxant properties that can confound the accurate interpretation of some anxiolytic responses such as increased locomotion (Bergink et al., 2004).

Treatments that are known to decrease the excitatory output of basolateral neurons of the amygdala through decreased excitatory glutamatergic transmission also reduce anxiety (LeDoux, 1994; Maren & Fanselow, 1996). For example, riluzole monotherapy, which attenuates glutamatergic overstimulation, has demonstrated efficacy for reducing anxiety ratings among patients with treatment-resistant major depressive disorder (Zarate, Payne, Quiroz et al., 2004). Anxiety also was attenuated among treatment-resistant MDD patients following the addition of riluzole to their ongoing medication treatment (Sanacora, Kendell, Levin et al., 2007). Among

18 GAD patients, a fixed dosage of 100 mg of riluzole per day for 8 weeks resulted in a 62% reduction in Hamilton Anxiety Rating Scale (HAM-A) scores, with 8 participants achieving scores indicative of remission (Mathew, Amiel, Coplan et al., 2005). Similarly, statistically significant improvements in HAM-A scores were reported following 6-12 weeks of riluzole augmentation therapy at a twice daily dose of 50 mg among 13 patients with treatment-resistant OCD (Coric, Taskiran, Pittenger et al., 2005). Thus, the available evidence suggests that dysregulation of the glutamatergic system, particularly glutamatergic overstimulation, plausibly plays a role in the genesis and expression of anxiety and anxiety disorders.

Hypothalamic-Pituitary-Adrenal axis (HPA)

The HPA axis has been implicated in the etiology of anxiety (Arborelius, Owens, Plotsky & Nemeroff, 1999). Corticotrophin-releasing hormone (CRH), the primary mediator of HPA activity, modulates anxiety when injected into the brain (Dunn & Swiergiel, 1999; Martins, Marras & Guimaraes, 1997). For example, intraventricular injection of CRF has resulted in anxiety-like behaviors among rats during the conflict test (Britton, Morgan, Rivier, Vale & Koob, 1985; Britton, Lee, Dana, Risch & Koob, 1986), social interaction (Dunn & File, 1987), acoustic startle (Swerdlow, Geyer, Vale & Koob, 1986) and elevated plus maze (File & Baldwin, 1988). Similarly, infusion of CRF into the locus coeruleus significantly decreased open-field behavior in rats (Butler, Weiss, Stout & Nemeroff, 1990).

Studies of anxiety using knockout mice have investigated the potential mediating role of two CRH receptors which mediate the actions of CRH: CRH-R1 and CRH-R2 (Holsboer, 2000; Keck, Holsboer & Muller, 2004; Muller, Zimmermann, Sillaber et al., 2003). Results have shown that mice that lack the CRH-R1 gene exhibit reduced anxiety-like behaviors during conflict-based anxiety animal models such as the elevated plus maze and light/dark transition test

(Smith, Aubry, Dellu et al., 1998; Timpl, Spanagel, Sillaber et al., 1998). Data regarding anxiety-like behavior in CRH-R2 knockout mice have been inconsistent (Leonardo & Hen, 2005). Research also has involved a transgenic mouse line characterized by central overproduction of CRH, which consistently exhibit heightened anxiety during open field, elevated plus maze, and light/dark transition tests (Stenzel-Poore, Duncan, Rittenberg, Bakke & Heinrichs, 1996; Stenzel-Poore, Heinrichs, Rivest, Koob & Vale, 1994). Open field activity, open arm time on the elevated plus maze, and the number of light/dark transitions consistently have been decreased in CRH transgenic mice compared to wildtype mice (Stenzel-Poore et al., 1996; Stenzel-Poore et al., 1994; Heinrichs, Stenzel-Poore, Gold et al., 1996; Heinrichs, Min, Tamraz, Carmouche, Boehme & Vale, 1997). Cumulatively these results suggest that elevated levels of CRH plausibly contribute to the etiology of anxiety.

Measurement of Anxiety Symptoms

Self-report Questionnaires

General, non-pathological levels of anxiety are most often measured with self-report, self-rating questionnaires. A number of widely used instruments have been developed to assess state anxiety, including visual analog scales (Hornblow & Kidson, 1976), the Beck Anxiety Inventory (Beck & Steer, 1990), the state scale of the State-Trait Anxiety Inventory (Spielberger et al., 1983), the Multiple Affect Adjective Checklist (Zuckerman & Lubin, 1985), the Anxiety Sensitivity Index (Peterson & Reiss, 1987), the Symptom Checklist-90 (Derogatis, 1992), and the tension subscale of the Profile of Mood States (POMS; McNair, Lorr & Droppleman, 1992), and trait anxiety, including the trait anxiety scale Spielberger's State-Trait Anxiety Inventory (Spielberger et al., 1983), the Beck Anxiety Inventory (Beck & Steer, 1990), and the anxiety scale (HADS-A) of the Hospital Anxiety and Depression Scales (Zigmond & Snaith, 1983).

State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg & Jacobs, 1983) is the most widely-used and well-validated self-report or self-rating questionnaire of anxiety in the world (O'Connor, Raglin & Martinsen, 2000). As of 1989, Spielberger reported that the STAI had appeared in over 3,000 studies across multiple scientific and medical disciplines. A simple *Google Scholar* search using the phrase "State-Trait Anxiety Inventory" yielded in excess of 150 additional studies since 1990 in which the phrase appeared in the article title.

The STAI (Form Y) was designed to be self-administered either individually or to groups with no time limits. Form Y was developed for use with high school students, college students and adults (Spielberger et al., 1983). The questionnaire is composed of 2 scales, each comprised of twenty Likert type, forced choice items. The S-Anxiety scale consists of twenty forced choice items to which an examinee responds to the item-statement that best describes the **intensity** of his/her feelings based upon a four-point scale: (1) not at all; (2) somewhat; (3) moderately so; (4) very much so (Spielberger et al., 1983, p. 11). The T-Anxiety scale also consists of twenty forced choice items. An examinee is instructed to indicate how he/she **generally** feels by rating the **frequency** of his/her feelings of anxiety according to a four-point scale: (1) almost never; (2) sometimes; (3) often; (4) almost always (Spielberger et al., 1983, p. 11).

The S-Anxiety scale is used to evaluate respondents' present feelings of apprehension, tension, nervousness, and worry. The scale additionally may be used both to assess how a respondent felt at a specific time in the recent past and to evaluate how a respondent anticipates feeling in response to either a specific situation likely to be encountered in the future or in various hypothetical situations (Spielberger et al., 1983).

The T-anxiety scale was developed to assess the general predisposition toward feelings of anxiety, or "differences between people in the tendency to perceive stressful situations as dangerous or threatening" (Spielberger et al., 1983, p. 5) and the intensity of responses to such situations. The T-Anxiety scale is used (i) in "assessing clinical anxiety" in various health care patient populations, (ii) as a screening tool both for anxiety problems and to select psychological research subjects based upon differing motivation and drive levels, and (iii) as an evaluation method for the efficacy of psychological, behavioral modification, and substance-abuse treatment protocols (Spielberger et al., 1983).

Reliability

Barnes and colleagues (2002) used reliability generalization, a meta-analytic method proposed by Vacha-Haase (1998), to study the score reliability of the state and trait scales of the STAI (Barnes, Harp & Jung, 2002). Mean coefficient alpha (α) values were examined across 52 independent investigations for the S-Anxiety scale and 51 independent investigations for the T-Anxiety scale. Articles included in the investigation were classified into three categories: (i) articles in which no mention of reliability was made; (ii) articles in which authors acknowledged reliability of STAI scores; and, (iii) articles in which reliability coefficients were computed on the study data analyzed (Barnes et al., 2002). Moderator analyses examined study characteristics (i.e., anxiety-eliciting context versus not, experimental design, medical or non-medical), sample characteristics (i.e., age, sample size) and type of reliability coefficients (i.e., internal consistency, test-retest). The authors hypothesized that state anxiety would be more reliably measured in contexts in which increased anxiety would be expected (i.e, surveying mothers of hospitalized children during hospitalization). Trait anxiety would be expected to be less affected by context given its non-transient conceptualization.

A mean coefficient alpha value of 0.91 was reported for the S-Anxiety scale and a value of 0.89 for the T-Anxiety scale (Barnes et al., 2002). Internal consistency values were reported to be stable across studies for both scales, while the stability, as expected, was lower for the more transient state anxiety dimension. Moderator analyses indicated that the use of Form Y compared to other forms of the STAI resulted in somewhat higher internal consistency (Barnes et al., 2002). Studies with higher state score reliabilities tended to have somewhat higher state score standard deviations, tended to use participants greater than 16 years of age, tended to be psychometric in nature, and tended to use Form Y (mean $\alpha = 0.89$; $d = 0.60$). These results suggest generally satisfactory internal consistency values for both scales across a broad range of studies involving various samples.

Similarly, an examination of the psychometric properties of the STAI with 217 older adult psychiatric outpatients reported coefficient alpha values of 0.92 for the S-Anxiety scale and 0.90 for the T-Anxiety scale (Kabacoff, Segal, Hersen & Van Hasselt, 1997). A separate examination of the STAI using 50 clinically-diagnosed GAD patients and 94 normal controls reported S-Anxiety coefficient alpha values of 0.94 for patients and .85 for controls and T-Anxiety coefficient alpha values of 0.88 for patients and 0.79 for controls (Stanley, Beck & Zebb, 1996).

There is a diverse literature reporting test-retest reliability data for the STAI. An investigation of the psychometric properties of the STAI in older adults yielded test-retest coefficients of 0.62 for the S-Anxiety scale and 0.84 for the T-Anxiety scale using retest intervals of 2 – 4 weeks (Stanley et al., 1996). A separate review of the available evidence of investigations utilizing the STAI reported a mean test-retest reliability coefficient (calculated across 7 independent investigations) of 0.70 and a median value of 0.68 for the S-Anxiety scale,

while the mean and median test-retest reliability coefficients for the T-Anxiety scale were larger at values of 0.88 (Barnes et al., 2002).

The use of the STAI in Exercise Research

In the past 15 years as few as 13 randomized, controlled trials (RCTs) have utilized the state and trait scales of the STAI to assess changes in anxiety responses to exercise training (Antunes, Stella, Santos, Bueno & de Mello, 2005; Blumenthal, Babyak & Moore et al., 1999; Blumenthal, Sherwood, Babyak et al., 2005; DiLorenzo, Bargman, Stucky-Ropp et al., 1999; Courneya, Friedenreich, Quinney et al., 2003; Kulcu, Kurtais, Tur, Gulec & Seckin, 2007; Oken, Kishiyama, Zajdel et al., 2004; Paz-Diaz, de Oca, Lopez & Celli, 2007; Rippe, Price, Hess et al., 1998; Seki, Watanabe, Sunayama et al., 2003; Tsai, Wang, Chan et al., 2003; Tsutsumi, Don, Zaichkowsky et al., 1998; Wand, Bird, McAuley et al., 2004). The STAI was administered prior to and following exercise training programs of 1 – 5 sessions per week of 20 – 90 minutes per session ranging from 2 – 26 weeks in length. A diverse range of population samples were tested across these 13 investigations including both healthy adults and adults with a chronic medical illness.

However, only 1 of 13 exercise training investigations (Tsai et al., 2003) reported any information regarding the reliability and validity of the instrument. Among a sample of hypertensive adults, the authors reported coefficient alpha values of 0.89 and 0.84 for the S-Anxiety and T-Anxiety scales, respectively (Tsai et al., 2003). Despite the relative lack of information regarding the psychometric properties of the STAI in recent studies of exercise, a large body of past exercise research generally provides compelling evidence that STAI scores are reliable, valid self-report measures of anxiety (O'Connor et al., 2000).

Validity

Strong support exists for the construct validity of the STAI through evidence of discriminant, convergent, and concurrent validity of the S-Anxiety and T-Anxiety scales. These types of evidence have been established through known groups, correlational, and experimental investigations.

Statistically significant intercorrelations of the expected direction and of moderate magnitude have been reported for S-Anxiety scale scores and total scores on both the Worry Scale (0.41) and the Padua Inventory (0.48), which is a 60-item inventory that assesses common obsessive and compulsive behaviors in 94 normal controls (Stanley et al., 1996). Significant intercorrelations of the expected direction and of moderate magnitude were reported for T-Anxiety scale scores and total scores on both the Worry Scale (0.57) and the Padua Inventory (0.57; 1996). The significant correlations demonstrate convergent evidence between measures of the related constructs of state and trait anxiety, worries, and obsessive-compulsive symptoms. Additional convergent evidence was provided by statistically significant correlations among T-Anxiety scores and total scores on both the Worry Scale (0.40) and the Padua Inventory (0.44) in a sample (n = 50) of Generalized Anxiety Disorder (GAD) patients (Stanley et al., 1996). A separate investigation demonstrated additional convergent evidence via statistically significant correlations found between S-Anxiety scores and total scores on both the Penn State Worry Questionnaire (PSWQ; 0.36) and the Worry Scale (0.33) among 57 older adults clinically-diagnosed with GAD (Stanley et al., 2001). Statistically significant correlations also were shown between T-Anxiety scores and total scores on both the PSWQ (0.45) and Worry Scale (0.55). Discriminant evidence is provided in the same investigation by lack of statistically significant

correlations between S-Anxiety scores and scores on two versions of the Fear Questionnaire (FQ-A, 0.23; FQ-F, 0.15).

Compelling evidence within exercise research has been demonstrated by contrasted groups research. Because exercise has well-established anxiolytic effects, the ability of the STAI to assess changes in anxiety scores between patients with clinically-diagnosed anxiety disorders and healthy controls following exercise provides discriminant validity evidence. For example, STAI scores were significantly reduced following 20 minutes of treadmill walking in 15 clinically-diagnosed panic patients compared to normal controls (O'Connor & Davis, 1992). The STAI-Y1 also was found to accurately reflect both the expected elevations following the ingestion of 800 mg of caffeine and the expected reductions following 60 minutes of moderate-intensity cycling (Youngstedt, O'Connor, Crabbe & Dishman, 1998). Additional experimental evidence is provided by results of RCTs of anxiogenic manipulations showing the sensitivity of the STAI. For example, in an examination of the anxiety responses following CO_2 inhalation in subjects at high-risk for panic disorder (e.g., at least one first degree relative diagnosed), results indicated that STAI scores were significantly greater in high risk individuals compared to low-risk subjects (Coryell et al., 2006). Similarly, an examination of the ability of a temporary reduction in central 5-HT transmission through acute tryptophan depletion to reverse the efficacy of selective serotonin reuptake inhibitors in social anxiety disorder patients showed that tryptophan depletion induced significant increases in anxiety, as measured both by the STAI and visual analogue scales, which were more prominent during the recital of an autobiographical script stressor (Argyropoulos et al., 2004). In sum, the available evidence supports the psychometric properties of both the state and trait scale of the STAI.

Physical Activity and Anxiety

Physical activity is defined as bodily movement produced by skeletal muscle resulting in energy expenditure (Casperson, Powell & Christenson, 1985). Exercise training refers to cumulative, acute bouts of physical activity that are planned, structured and repeated, and result in improvement or maintenance of one or more components of physical fitness (Casperson et al., 1985).

Population-based Evidence

Although the 1996 US Surgeon General's report on physical activity and health reported that regular physical activity reduces anxiety, there has been a lack of compelling population-based evidence of the effect of physical activity on anxiety symptoms. One early notable exception to the limited amount of epidemiological evidence is the Canada Fitness Survey in which approximately 22,000 Canadians, aged 10 years and older, were asked questions about anxiety and physical activity (Stephens, 1988). The results indicated that anxiety was more likely among those individuals reporting little or no physical activity compared to those reporting moderate and very active lifestyles.

More recently, a limited amount of evidence from nationally representative and population-based cross-sectional and prospective cohort design studies supports that regular physical activity protects against anxiety disorders and anxiety symptoms. The National Co-Morbidity study examined physical activity and anxiety in approximately 5876 Americans and reported crude odds reductions of 43% among active individuals compared to those reporting little or no physical activity (Goodwin, 2003). After adjustments were made for sociodemographic and illness variables, odds reductions were 28% among active individuals compared to those reporting little or no physical activity (Goodwin, 2003). Similarly, data from

7000 individuals aged 18-79 who took part in the German National Health Interview and Examination Survey (GHS) indicated that 63% of the 573 individuals diagnosed with an anxiety disorder reported a physically inactive lifestyle (Schmitz, Kruse & Kugler, 2004). More recently, four cross-sectional studies have indicated that regular physical activity is associated with reduced odds of anxiety (DeMoor, Beem, Stubbe, Boomsma & de Gues, 2006; Strine, Chapman, Kobau & Balluz, 2005; Taylor, Cable, Faulkner, Hillsdon, Narici & van der Bij, 2004; Thorsen, Nystad, Stigum et al., 2005). However, these are merely cross-sectional data which provide no conclusive evidence of the temporal nature of the relationship between physical activity and anxiety.

At least 2 studies have used prospective cohort designs which reduce the likelihood that the association between physical activity and anxiety is explainable by people becoming less physically active after experiencing anxiety symptoms. The Northern Rivers Mental Health Study examined the relationship between physical activity and the onset of anxiety disorders in approximately 1407 Australians over a 2-year time period (Beard, Dietrich, Brooks, Brooks, Heathcote & Kelly, 2006). The results indicated that odds were reduced 53% for individuals reporting at least 3 hours of vigorous activity per week (Beard et al., 2006). This reduction was not statistically significant, however, most likely due to the small number of individuals in the sample who developed an anxiety disorder (n = 67 of 1407).

The Early Developmental State of Psychopathology Study (Munich Cohort) examined the association between physical activity and the development of an anxiety disorder over 12 months among approximately 2548 German young adults (Strohle, Hofler, Pfister et al., 2007). Of the 2548 participants, 228 developed an anxiety disorder over the course of the study. After adjusting for age and sex, the odds of developing an anxiety disorder were significantly reduced

by an average 48% in regularly physically active young adults compared to those who were physically inactive.

Regarding the consistency of the relationship between physical activity and anxiety, reviews of the available evidence suggest that age is not a significant moderator. For example, a large cross-sectional study of 42,000 individuals reported that physical activity was protective across all age categories, but physically inactive young adults were 20% more likely to report anxiety than physically inactive middle-aged and older adults (Taylor et al., 2004). Another cross-sectional study of approximately 19,000 twins and families reported nonsignificant interactions between exercise and age, exercise and gender, and exercise, age, and gender (DeMoor et al., 2006). There has been a lack of compelling evidence regarding the relation between physical activity and decreased risk of anxiety among children and adolescents. The available evidence has largely resulted from cross-sectional comparisons using small samples and psychometrically poor measurement instruments. Temporally-appropriate prospective cohort studies and well-designed randomized controlled trials which utilize well-validated measures of both physical activity and anxiety with large samples of children and adolescents are needed to draw stronger conclusions.

At present very few studies have provided adequate information about the racial or ethnic composition or the health status of population samples. Thus, there is inadequate evidence to suggest that race/ethnicity or medical condition moderates the relation between physical activity and anxiety.

There also has been limited population-based evidence suggesting that the odds of an anxiety disorder may be modified by variations in the weekly frequency of exercise bouts. One cross-sectional study reported a dose-response relationship between physical activity and lower

prevalence of anxiety disorders (Goodwin, 2003). The percentage of adults with anxiety disorders was highest among those reporting physical inactivity and was reduced in a step-wise fashion among those who reported rare, occasional, and regular physical activity (Goodwin, 2003). However, there is not enough consistent evidence from prospective cohort and randomized controlled trials to make a strong conclusion regarding a dose-response relationship. For example, some investigations show a protective effect of physical activity (Wyshak, 2001), while others show no protection (Backmand, Kaprio, Kujula & Sarna, 2003; Binsinger, Laure & Ambard, 2006).

In summary, the limited amount of population-based evidence shows that anxiety disorder odds reductions associated with physical activity on average range from 30 – 55% in physically active individuals compared to those reporting little or no physical activity (Goodwin, 2003; Beard et al., 2007; Strohle et al., 2007). There is inconsistent evidence concerning both the role of potential moderator variables (e.g., age, sex, race/ethnicity, and physical activity characteristics) and the potential for a dose-response relationship. More evidence from temporally appropriate prospective cohort studies and well-designed experimental studies is necessary to draw strong conclusions regarding the specific relation of physical activity and anxiety.

Experimental Evidence

Because the available evidence suggests that a positive association between regular physical activity and anxiety odds reduction exists, there has been interest in ascertaining a better understanding of the relation between exercise training and both non-pathological and pathological anxiety. Relevant literature reviews, most focused on anxiety symptoms among healthy adults, have often concluded that acute bouts of exercise and/or exercise training are

associated with a reduction in anxiety symptoms (Byrne & Byrne, 1993; Fox, 1999; Long & van Stavel, 1995; McDonald & Hodgdon, 1991; Morgan, 1985; O'Connor et al., 2000; Petruzzello, Landers, Hatfield, Kubitz & Salazar, 1991; Raglin, 1997; Wipfli, Rethorst & Landers, 2008). Others have concluded there is a lack of methodologically sound evidence for the claim of exercise training induced reductions in anxiety symptoms in the general population (De Moor, Boomsma, Stubbe, Willemsen & de Geus, 2008; Dunn, Trivedi & O'Neal, 2001). The extant evidence is reviewed in more detail in the following section.

Exercise Training

Since 1990, there have been 6 quantitative reviews of the available evidence of the effects of exercise training on anxiety (Kugler, Seelbach & Kruskemper, 1994; Long and van Stavel, 1995; McDonald & Hodgdon, 1991; Petruzzello et al., 1991; Schlicht, 1994; Wipfli et al., 2008).

Petruzzello et al., 1991

In the earliest review, Petruzzello and colleagues (1991) examined 104 studies (57 of trait anxiety) of the effect of acute and chronic exercise on state and/or trait anxiety in individuals without a clinical anxiety disorder. Results indicated significant reductions in state (ES = 0.24) and trait anxiety (ES = 0.34) as well as what the authors deemed "commonly assessed physiological correlates of anxiety" (e.g., blood pressure) following exercise training (Petruzzello et al., 1991). Several independent moderators of the overall mean effect were reported. Larger reductions in anxiety symptoms appeared following exercise session durations of 20-30 minutes (ES = 0.41). There appeared to be no apparent dose-response regarding intensity. However, larger effects following exercise training were reported for individuals with elevated trait anxiety levels. Exercise training effects were similar to other active treatments and

larger than control conditions. Moderator analyses also indicated that the length of exercise training was significantly related to the overall mean effect size. Program lengths > 9 weeks elicited significantly larger anxiety reductions, and program lengths greater than 15 weeks had the same mean anxiolytic effect as psychotherapy (ES = 0.90). The moderator analyses should be cautiously interpreted because of the small number of studies included. Also, most of the analyzed studies were not experiments and only 13 of 104 studies were randomized, controlled trials.

McDonald and Hodgdon, 1991

In another early meta-analytic review, the authors derived 33 effect sizes, 13 for state anxiety and 20 for trait anxiety, from 22 investigations of the effect of regular physical activity on anxiety among individuals without a medical diagnosis (McDonald & Hodgdon, 1991). An overall mean effect size of -0.04 was reported. Moderator analyses indicated that regular physical activity could reduce anxiety as measured by trait anxiety scores.

Schlicht, 1994

In contrast to previous results, a meta-analysis examining 20 studies (22 effects) of physical activity and anxiety found nonsignificant mean effect sizes for investigations of the effect of acute exercise and exercise training on anxiety (Schlicht, 1994). This discrepancy likely is due in large part to a number of potential methodological issues associated with both the sample of studies and the meta-analytic techniques used in the review. The author's description of the meta-analytic methods used both to calculate and to aggregate effect sizes is unclear. Based on the author's description that the Schmidt-Hunter method was used, it appears that Meta 5.0 software (Schwarzer, 1989) was used to estimate correlations from test statistics presented in the included studies, which reduces the statistical precision compared to calculating effect sizes

from original means and either standard deviations or standard errors (see Hedges & Olkin, 1985; Rosenthal, 1991). The average effect size was then calculated based upon a fixed effects model using sample size as a weight which fails to account for random effects population variance. Moreover, effect sizes derived from multiple measures used within the same experiment were averaged to yield one effect size per investigation, precluding the meaningful examination of both the influence of different psychometric measurement instruments and the influence of multiple effects per study. Also, the inclusion criteria yielded a smaller sample of studies than included in previous meta-analytic reviews.

Kugler et al., 1994

Kugler and colleagues (1994) conducted a meta-analytic review of 13 studies, four lacking a control group, which examined the effect of rehabilitation exercise programs on anxiety among patients with coronary heart disease. A mean anxiety reduction of 0.31 standard deviations was found, suggesting that exercise training is as effective for the attenuation of anxiety in persons with a chronic, non-psychiatric medical illness as it is in healthy adults. However, as with the prior meta-analyses, because the review did not focus on randomized, controlled trials that compared exercise training to a control condition, meaningful interpretation of the effects derived is precluded.

Long and van Stavel, 1995

As a partial replication of an earlier meta-analytic review completed by Petruzzello and colleagues (1991), a meta-analysis was conducted with an expanded, updated study sample. Seventy-six effects were derived from 40 studies using either a within-subjects design or a between-subjects design to examine the effects of exercise training on anxiety symptoms in adults without a medical or psychiatric condition (Long & van Stavel, 1995). Overall mean

effects of 0.45 and 0.36 were found for 26 effects derived from within-subjects design and 50 effects derived from between-subjects designs, respectively (Long & van Stavel, 1995). Moderator analyses showed significantly larger improvements among samples of men only and mixed samples of men and women compared to sample of women only, but showed no significant effects for program length, session duration, or frequency (Long & van Stavel, 1995).

A number of methodological limitations diminish the meaningfulness of these findings. The inclusion criteria used required studies of aerobic exercise training to meet minimal requirements of at least 20 minutes per session for a least 3 sessions per week for a program length of no less than 6 weeks, while "nonaerobic" training programs were required to involve exercise of at least 20 minutes per session for at least 2 sessions per week for a program length of no less than 6 weeks. These exclusion criteria preclude the examination of the minimal dose (exercise frequency, session duration and program length) necessary to elicit anxiety reductions. Also, studies of psychiatric samples (n=4) were excluded although individuals with elevated levels of anxiety would likely experience greater psychological benefits from exercise training compared to individuals with normal baseline anxiety levels. Regarding the meta-analytic techniques used in the review, the authors also did not consider both sampling error and the random effects (population) variance that should be considered when assessing the effects of different exercise training paradigms on anxiety symptoms.

Methodological limitations also are present in the design characteristics and methodology of the included studies. Studies were included that lacked randomization (n=25) and compared exercise to only another active treatment such as counseling or stress management.

Wipfli, Rethorst & Landers, 2008

Because previous meta-analytic reviews by Petruzzello and colleagues (1991) and Long and van Stavel (1995) included only 13 and 15 randomized, controlled trials of the effects of exercise on anxiety symptoms, respectively, Wipfli and colleagues (2008) conducted a meta-analysis of 49 randomized, controlled trials. The results showed an overall weighted effect size of 0.48 (0.33 to 0.63). Moderator analyses showed significantly larger effect sizes for participants 31-45 years of age compared to participants aged 45 years or older and for an exercise frequency of 3-4 times per week compared to 1-2 times or 5+ times per week (Wipfli et al., 2008). It should be noted, however, that the contrast results for frequency likely achieved significance because 32 of the 40 effect sizes included in the moderator analysis were in the 3-4 times per week category.

Limitations of Previous Meta-analytic Reviews

Results from previous meta-analytic reviews of the effects of exercise training on anxiety symptoms have been characterized by a number of key methodological limitations. Previous reviews have calculated an aggregated mean effect size across effects derived from investigations that have used within- and between-subjects designs (Kugler et al., 1994; Long & van Stavel, 1995; Petruzzello et al., 1991; Wipfli et al., 2008). Aggregating effects from fundamentally different research designs is contraindicated because effect sizes calculated from a within-subjects designs use the standard deviation of the change score, whereas the pooled baseline standard deviation is used in a between-subjects design.

Previous meta-analytic reviews have included effect sizes derived from examinations of both acute exercise and exercise training protocols in the calculation of the overall mean effect

size (Petruzzello et al., 1991; Schlicht, 1994; Wipfli et al., 2008). This confounds the transient and persistent effects of exercise.

A number of fundamental issues regarding the measurement of anxiety also are present in previous reviews. For example, using anxiety outcome measures that prompt a participant to rate a current ("right now") or recent ("during the past week") level of anxiety potentially confound the accurate measurement of persistent changes in anxiety in response to cumulative bouts of exercise training. Because state anxiety is known to fluctuate in response to a number of variables that may be present at only pre- or post-training, results could be biased (Long & van Stavel, 1995; Petruzzello et al., 1991; Schlicht, 1994; Wipfli et al., 2008). Psychosocial stressors, circadian variation (Monteleone & Maj, 2008), and physical factors including caffeine (Alsene et al., 2003) and bright light exposure (Youngstedt & Kripke, 2008) are examples of potential biasing variables. Additionally, one previous review reports recoding STAI trait anxiety scale scores as a state anxiety measure for moderator analyses if the score was obtained immediately following exercise (Petruzzello et al., 1991). Because the trait anxiety scale is not designed to assess transient fluctuations in anxiety, the recoded results are likely biased. Furthermore, calculating a single average effect for studies using multiple anxiety measures precludes the meaningful examination of the potentially important moderating factor of time frame of anxiety recall (Schlicht, 1994; Wipfli et al., 2008).

Although evidence has demonstrated both that anxiety is more common among individuals with a variety of chronic medical illnesses (Roy-Byrne et al., 2008) and that anxiety is strongly and independently associated with reduced health-related quality of life (HRQOL) and disability (Kroenke et al., 2007; Sareen et al., 2006; Ludman et al., 2006; Sareen et al., 2005; Harter et al., 2003) among patients with a chronic medical illness, most reviews have not focused

on summarizing the effects of exercise training on anxiety among individuals with a chronic medical illness. Although meta-analytic reviews have summarized evidence from exercise training studies of fibromyalgia (Rossy, Buckelew, Dorr et al., 1999) and cardiovascular patients (Kugler et al., 1994; Puetz et al., 2006), these analyses failed to focus on the best available evidence.

Summary

The available evidence from previous reviews, mostly focused on healthy adults, suggests that exercise training plausibly is an effective and practical treatment for attenuating anxiety symptoms. While it seems plausible that exercise training could be especially beneficial for individuals likely to experience elevated anxiety, including those coping with a chronic illness, the influence of exercise training on anxiety among patients with a chronic illness is poorly understood. Because there is a need for a well-designed systematic review to summarize randomized, controlled trials of exercise training on anxiety among patients with a chronic illness, one goal of this dissertation will be to conduct a systematic review of exercise training effects on anxiety among individuals with a chronic illness. The systematic review also will address limitations from previous reviews by: (i) focusing on studies which randomized participants to either an exercise training intervention or a comparison condition that lacked exercise training, (ii) accounting for variation due both to sampling error and population variance, and (iii) examining the potential moderating role of the time frame of anxiety report used.

Exercise Training Among Anxiety Disorder Patients

There have been a limited number of investigations of the effect of exercise training on anxiety among populations with clinical anxiety since 1989. Findings suggest that exercise

training may plausibly attenuate anxiety symptoms among individuals with an anxiety disorder. However, methodological limitations preclude meaningful conclusions.

Martinsen, Sandvik & Kolbjornsrud, 1989

In one of the first studies, 44 inpatients with a DSM-III anxiety disorder (agoraphobia without panic attacks: n=2; social phobia: n=6; GAD: n=8; and, agoraphobia with panic attacks: n=28) completed aerobic exercise, usually walking or jogging, for one hour, five sessions per week for eight weeks (Martinsen, Sandvik & Kolbjornsrud, 1989). All patients exhibited improvements except those diagnosed with social phobia. Patients with GAD and agoraphobia without panic attacks maintained improvements at a 1-year follow-up (Martinsen et al., 1989). However, a key limitation of this study is the lack of a control comparison.

Martinsen, Hoffart & Solberg, 1989

A second study examined the effects of aerobic and nonaerobic exercise among 79 inpatients with various DSM-III-R anxiety disorders (Martinsen, Hoffart & Solberg, 1989). Fifty-six inpatients had a diagnosis of panic disorder with agoraphobia, 13 were diagnosed with social phobia, and 10 were diagnosed with GAD. Patients were randomly assigned to aerobic or non-aerobic exercise of one hour, three sessions per week for eight weeks. Following the eight weeks of training, patients in both exercise groups showed similar and significant reductions in anxiety independent of changes in aerobic capacity (Martinsen et al., 1989). These results suggested that increases in aerobic fitness are not necessary to elicit reductions in anxiety symptoms. Limitations included the absence of a control group and that treatments were administered concomitantly.

Sexton, Maere & Dahl, 1989

Walking was compared to jogging in 52 inpatients over an eight week exercise training protocol and at a six month follow-up. The authors reported persistence in anxiety reductions 6 months after 8 weeks of aerobic exercise training. Psychological improvements were not significantly different between jogging and walking (Sexton et al., 1989). However, the absence of a control group prevents the ability to draw any conclusion about training effects on anxiety.

Brown, Abrantes, Strong et al., 2007

A 12-week pilot study examined the effect of the addition of aerobic exercise training to regular care on obsessive compulsive disorder (OCD) symptoms (Brown et al., 2007). Fifteen patients diagnosed with OCD who had received pharmacotherapy or CBT for OCD treatment for at least 3 months completed moderate-intensity aerobic exercise training for 20 to 40 minutes, three to four sessions per week for 12 weeks. Following exercise training, OCD symptom severity was significantly reduced (ES = 1.69) and clinically meaningful reductions were demonstrated for 69% and 50% of patients at posttreatment and at a 6-month follow-up, respectively (Brown et al., 2007). Although the preliminary study lacked a true control condition, results suggested both the potential efficacy of exercise training and the need for well-designed randomized, controlled trials.

Merom, Phongsavan, Wagner et al., 2008

The effect of adding a moderate intensity home-based exercise program to 8-10 weeks of group cognitive-behavioral therapy (GCBT) was examined in a randomized, controlled trial of 74 patients with social phobia, GAD, or panic disorder (Merom et al., 2008). The authors reported that the addition of exercise to GCBT resulted in large reductions (ES=1.36) in anxiety compared to the GCBT control condition (Merom et al., 2008).

Broocks, Bandelow, Pekrun et al., 1998

A randomized, placebo-controlled investigation examined the efficacy of 10 weeks of aerobic exercise training in the treatment of panic disorder (Broocks et al., 1998). Forty-six outpatients diagnosed with moderate to severe panic disorder with or without agoraphobia (DSM-III-R) were randomly assigned to either 10 weeks of walking/running a four-mile route three to four times per week, clomipramine (112.5 mg/day) or placebo. Both exercise and medication resulted in significant decreases in anxiety symptoms compared to the placebo condition, suggesting that exercise training is as effective as pharmacotherapy. Moreover, outpatients who completed the exercise program reported large reductions in anxiety (ES = 1.10) compared to those who took daily placebo pills. The clomipramine treatment group had lower attrition and resulted in both earlier and larger reductions in anxiety symptoms (Broocks et al., 1998). Because of the strong research design, this experiment provides the strongest evidence that exercise training can attenuate anxiety symptoms among anxiety disorder patients.

Although only two RCTs have been conducted to examine the effects of exercise training on anxiety symptoms among anxiety disorder patients, the findings suggest that exercise training can attenuate anxiety symptoms among anxiety disorder patients. However, methodological limitations of these studies, including no standardization of the exercise stimulus or intensity (Broocks et al., 1998; Merom et al., 2008) and a sample that included individuals with various anxiety disorders (i.e., 35% diagnosed with GAD) (Merom et al., 2008), diminish the ability to draw meaningful conclusions relative to exercise training dose effects on specific anxiety disorders.

Hesitancy to Examine Effects of Exercise in Anxiety Disorder Patients

This limited amount of evidence regarding the effects of exercise training among anxiety disorder patients may be in part the result of hesitancy to pursue research on the effects of exercise in anxiety disorder patients. This negative attitude toward exercise as a potential treatment for anxiety may stem from one influential study showing increased anxiety symptoms following the infusion of lactate. Pitts and McClure (1967) measured the anxiety response to intravenous infusion of sodium DL-lactate with calcium and a placebo (glucose) in 10 controls and 14 anxiety neurotic patients. The authors reported increased anxiety responses in patients after infusion of the sodium DL-lactate that raised blood levels of lactate to about 40 mg/dl. All but one of the patients experienced a panic attack and in a small number of cases the anxiety persisted for 2-5 days. Most controls reported little anxiety in response to lactate infusion. It was inferred that physical activity could cause anxiety symptoms since intense exercise increases muscle and blood lactate, while maximal exercise typically increases blood levels of lactate 2 -3 times more than sodium DL-lactate infusion.

Subsequently some researchers presented numerous reasons why infused lactate *would* induce anxiety symptoms and increased lactate from exercise *would not* induce anxiety symptoms (Grosz & Farmer, 1972). Infused lactate is quickly converted to bicarbonate and carbon dioxide, which has been shown to be associated with panic attacks as a function of metabolic alkalosis and subsequent hyperventilation. Exercise induced elevations in lactate result in metabolic acidosis and consequently would not induce hyperventilation. Moreover, one review revealed that only 5 panic attacks were reported during exercise involving 444 exercise bouts performed by 420 panic disorder patients (O'Connor et al., 2000). Research also has shown that lactate accumulations resulting from exercise are not related to post-exercise anxiety

in individuals without clinical disorders (Gauvin et al., 1997), and that state anxiety is reduced following intense exercise performed by panic disorder patients (O'Connor, Smith & Morgan, 2005).

Summary

There is substantial epidemiological and experimental evidence for an association between physical inactivity and anxiety. There is less evidence, however, available regarding the effects of exercise training on anxiety disorders and many of these investigations suffer from weak research design and methodological limitations (Brown et al., 2007; Diaz & Motta, 2008; Manger & Motta, 2005; Newman & Motta, 2007). Only one well designed randomized, controlled trial has demonstrated that exercise training improves symptoms of an anxiety (panic) disorder (Broocks et al., 1998). Thus, there is a strong need for additional randomized, controlled trials investigating whether exercise training can improve other types of anxiety disorders. For example, exercise training may be especially likely to benefit individuals with GAD because of the nature of GAD symptoms. Exercise training is thought to have positive effects on problems associated with GAD including fatigue (Puetz, O'Connor & Dishman, 2006), and insomnia and other sleep disturbances (King, Oman, Brassington, Bliwise & Haskell, 1997; King, Baumann, O'Sullivan, Wilcox & Castro, 2002; Singh, Clements & Fiatarone, 1997; Singh, Stavrinos, Scarbek, Galambos, Liber & Fiatarone Singh, 2005).

Generalized Anxiety Disorder

Diagnostic criteria

Diagnostic criteria for GAD have evolved over time and across revisions to diagnostic classification systems. Originally considered a subsidiary of anxiety neurosis, a disorder first

described by Freud (1924), GAD was not classified as an independent disorder until Klein (1964) identified PD.

The DSM-III diagnostic criteria for GAD involved four major symptom groups: (i) motor tension; (ii) autonomic hyperactivity; (iii) apprehensive expectation; and, (iv) vigilance and scanning. According to this original classification scheme, anxiety had to be continuously experienced for at least 1 month (American Psychiatric Association, 1980).

In the first revision to the DSM (DSM-III-R), the duration of excessive anxiety and worry had to persist for at least 6 months (American Psychiatric Association, 1987). This change in the symptom duration necessary for diagnosis recognized the chronic status of GAD, though it has been suggested that there is little difference between patients with symptom durations of between 1 to 6 months (Tyrer & Baldwin, 2006).

The DSM-IV criteria for GAD reduced the number of symptoms associated with anxiety from the 18 previously considered by the DSM-III-R to 6 symptoms discussed below. The nine DSM-III-R autonomic hyperactivity symptoms were entirely eliminated. According to the DSM-IV, GAD is characterized by persistent excessive or pathologic anxiety and worry on most days for at least 6 months about activities of daily life (e.g. work, school performance) that an individual finds difficult to control that is associated with at least 3 of the following symptoms: (i) restlessness or feeling on edge, (ii) being easily fatigued, (iii) difficulty concentrating, (iv) irritability, (v) muscle tension, and (vi) sleep disturbance. The symptoms and focus of the anxiety are not caused by another substance or disorder and the individual experiences significant distress or functional impairment related to symptoms (American Psychiatric Association, 2000).

The World Health Organization's (WHO) International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) criteria has minor differences compared with DSM-IV criteria for GAD. The primary, general, and mental state symptoms are comparable, but the ICD-10 criteria require the presentation of at least 4 symptoms, including one autonomic arousal symptom (i.e., palpitations, sweating, trembling, dry mouth), and sleep disturbance symptoms are omitted (World Health Organization, 1994).

Conceptualizations

The past two decades have been marked with controversy concerning the most appropriate diagnostic classification scheme for GAD. The primary focus of this issue is whether or not GAD is an autonomous syndrome or merely a clinical manifestation of major depressive disorder (MDD) or another mood disorder. Because chronic worry and negative affect are two primary features of GAD that appear in several DSM-IV disorders (Brown et al., 1998), GAD has been described in various ways. Researchers have conceptualized GAD as: (i) "the basic emotional disorder" (Finn et al., 2003), (ii) a nonspecific cluster of residual anxiety symptoms (Breier, Charney & Heninger, 1985), and (iii) as an anxious temperament type (Akiskal, 1998). High correlations between GAD and neuroticism suggest overlap between the factors that influence variation in neuroticism and increase liability for GAD (Hettema, Prescott & Kendler, 2004).

Neuroticism, as well as negative emotionality, is common to both GAD and MDD (Hettema, Neale, Myers, Prescott & Kendler, 2006; Moffit, Caspi, Harrington et al., 2007). Such similarities along with additional evidence have resulted in the contention that GAD might be better conceptualized as a prodrome, residual, or severity marker of MDD or another comorbid mood disorder (Kessler, DuPont, Berglund & Wittchen, 1999). The deletion of the nine DSM-

III-R autonomic hyperactivity symptoms, intended to improve the differential diagnosis between GAD and panic disorder, resulted in the inadvertent effect of strengthening the general distress/negative affectivity component of GAD which increased its comorbidity with MDD (Brown, DiNardo, Lehman & Campbell, 2001; Mineka et al., 1998; Watson, 2009). Results of the National Comorbidity study indicated that approximately 84% of adults diagnosed with GAD also were diagnosed with a comorbid mood disorder (Judd, Kessler, Paulus, Zeller, Wittchen & Kunovac, 1998). More recent evidence from a large clinical sample indicated that two thirds of patients with a primary MDD diagnosis had a comorbid GAD diagnosis, while a third of those with a primary GAD diagnosis had comorbid MDD (Brown, Campbell, Lehman, Grisham & Mancill, 2001).

Comorbidity with MDD

Family, twin and high-risk transmission studies conducted to examine a genetic basis for the similarities between MDD and GAD have shown that GAD and MDD share a majority of genetic risk factors (Goldberg, 2008; Kendler, Neale, Kessler, Heath & Eaves, 1992; Roy, Neale, Pedersen, Mathe & Kendler, 1995). Meta-analytic evidence indicates a modest familial aggregation (MDD: OR = 2.8; GAD: OR = 6.1) and heritability (MDD: 37%; GAD: 32%) for MDD and GAD (Hettema, 2008; Hettema, Neale & Kendler, 2001; Sullivan, Neale & Kendler, 2000). After adjusting for demographic covariates and comorbidity, significant familial aggregation for MDD and GAD among both probands and parents suggested partially overlapping familial risk (Kendler, Davis & Kessler, 1997). Results also have shown common genetic and environmental factors among MDD, GAD, PD and specific phobias among men and women (Kendler, Prescott, Myers & Neale, 2003).

A more recent examination conducted by Watson (2009) of the comorbidity of GAD with both unipolar mood disorders and the other anxiety disorders calculated weighted mean tetrachoric correlations among DSM mood and anxiety disorders across four national epidemiological studies: (i) the National Comorbidity Study (Krueger, 1999; N=8098), (ii) the National Comorbidity Study Replication (Kessler et al., 2005; N=3199), (iii) Wave 1 of the Netherlands Mental Health Survey and Incidence Study (Vollebergh, 2003; N=7076), and (iv) the Australian National Survey of Mental Health and Well-Being (Slade & Watson, 2006; N=10, 641). GAD showed correlations ranging from r = 0.42 to 0.58 with the other DSM anxiety disorders. However, the strongest comorbidity was shown for the unipolar mood disorders with weighted mean tetrachoric correlations of 0.64 and 0.66 with MDD and dysthymic disorder, respectively (Watson, 2009).

Some evidence has suggested that prior GAD diagnosis increases risk for MDD. Among 8068 adult twins, prior GAD diagnosis was shown to increase the risk of MDD (Hettema, Kuhn, Prescott & Kendler, 2006). However, Moffitt and colleagues (2006) have reported that MDD preceded GAD almost as frequently as GAD preceded MDD.

Generalized anxiety disorder and MDD also share common descriptive features. Evidence suggests a higher prevalence of both GAD and MDD in women, especially in middle age, and among those that are separated or divorced, have low income, or are unemployed (Hettema, 2008). Data from the National Comorbidity Survey (NCS-R) also showed that the cumulative age-of-onset curves for GAD and MDD were nearly identical (Kessler, Gruber, Hettema, Hwang, Sampson & Yonkers, 2007).

Nonetheless, a wealth of evidence argues against a potential unifying conceptualization of GAD and MDD. Some authors have contended that the most pronounced differences between

anxiety and depression are differences relative to the underlying biology. For example, depression is characterized by activation of the dorsal insular cortex and anterior cingulate cortex (ACC), and basal over-activation of the amygdala (Goldberg, 2008). In contrast, anxiety is characterized by ventral insular cortex activation, deactivation in the posterior cingulate cortex, and autonomic arousal (Goldberg, 2008). Longitudinal analyses have revealed significant divergence between GAD and MDD regarding both risk factors (Moffitt et al., 2007) and illness course (Fergusson, Horwood & Boden, 2006). Moreover, meaningful variation in the strength and consistency of associations between risk factors (e.g., time decay in odds ratios linking onset of temporally primary disorders with subsequent onset of secondary disorders) for GAD and MDD was found in the National Comorbidity Survey Follow-up (Kessler et al., 2008). These differences in risk factors cast doubt on the view that GAD and MDD are simply different manifestations of the same underlying internalizing disorder. The results also potentially discredit the contention that GAD may simply be a prodome, residual or severity marker of MDD (Kessler et al., 2008).

Nonpsychiatric Comorbidity

While evidence has suggested that lifetime comorbidity with another Axis I psychiatric disorder occurs in approximately 90% of individuals with GAD (Wittchen, Zhao, Kessler & Eaton, 1994), anxiety disorders, including GAD, also are strongly and independently associated with non-psychiatric chronic medical illnesses (Harter et al., 2003; Sareen et al., 2006). For example, high rates of GAD have been shown among individuals with a chronic illness, including irritable bowel syndrome (Hazlett-Stevens, Craske, Mayer, Chang & Naliboff, 2003), asthma (Nascimento, Nardi, Valenca et al., 2002; Valenca, Falcao, Freire et al., 2006; Vila, Nollet-Clemencon, Vera et al., 1999), and chronic pain (Atkinson, Slater, Patterson, Grant &

Garfin, 1991; McWilliams, Goodwin & Cox, 2004). Although there is limited evidence for cancer, one investigation of 367 men diagnosed with prostate cancer showed a 13% prevalence rate for GAD (Roth, Nelson, Rosenfeld et al., 2006).

Prevalence

GAD is among the most common anxiety disorders, being present in 22% of primary care patients complaining of anxiety problems (Wittchen, 2002). The lifetime prevalence of GAD has been estimated at approximately 4%, ranging from 2.0%-6.6% (Davidson, Zhang, Connor et al., 2010; Grant, Hasin, Stinson et al., 2005; Vesga-Lopez, Schneier, Wang et al., 2008). GAD is at least twice as prevalent as panic disorder (Kessler & Wittchen, 2002) and has comorbidity rates that equal or exceed those of other anxiety disorders (Noyes, 2001).

Differences Across Age

Population-based research has suggested that there are age-related differences associated with GAD. Results of the NCS-R revealed that lifetime prevalence of GAD increases from young adulthood (~4.1%) to middle adulthood (6.8-7.7%), but declines after the age of 60 years to approximately 3.6% (Kessler et al., 2005). Similarly, Brenes and colleagues (2008) showed a 50% lower prevalence of GAD among older adults compared to young and middle-aged adults (Brenes, Knudson, McCall, Willamson, Miller & Stanley, 2008). However, compared to other anxiety disorders, previous reports have indicated that the prevalence of GAD is higher among older adults, showing rates as high as 10.2% (Beekman, Bremmer, Deeg et al., 1998; Copeland, Dewey, Wood, Searle, Davidson & McWilliam, 1987; Flint, 1994). Also, younger adults have shown a greater propensity to report cognitive symptoms compared to older adults (Brenes et al., 2008).

Differences Across Race/Ethnicity

Very little attention has been devoted to the study of racial differences in the presentation of GAD. No significant racial differences were reported regarding number and type of symptoms among primary care patients diagnosed with GAD (Brown, Shear, Schulberg & Madonia, 1999). However, in an examination of cross cultural differences among older adults with GAD, African-Americans reported a greater number of general and somatic symptoms compared to whites (Kraus, Kunik, Rhoades, et al., 2005).

Personal and Economic Costs of GAD

There is a considerable economic burden associated with GAD primarily due to reduced work productivity and overuse of health services particularly primary care and emergency room visits, diagnostic and laboratory procedures, pharmacy costs and hospitalizations (Davidson et al., 2010). Recent estimates suggest that the annual health care cost for an individual diagnosed with GAD is approximately $7500 (Zhu, Zhao, Ye, Marciniak & Swindle, 2009). Compared with patients solely diagnosed with GAD, estimated annual total health care costs are approximately $700 higher for GAD patients with comorbid depression, approximately $3000 higher for GAD patients with pain, and approximately $6000 higher for GAD patients with comorbid depression and pain (Zhu et al., 2009). Moreover, GAD patients with comorbidity have significantly higher direct costs compared to GAD patients without comorbidity across a number of domains, including hosptilizations, psychiatry, internal medicine, diagnostic procedures, medications and work absenteeism (Lothgren, 2004).

Women are more frequently affected by GAD than men and this disparity increases with age (Vesga-Lopez et al., 2008, Wittchen, 2002). The chronic, debilitating nature of GAD also results in significant impairment and disability. While functional impairments and comorbid

conditions are present across gender, disability and rates of comorbid mood disorders are significantly higher among women (Vesga-Lopez et al., 2008).

Role and quality of life impairments of GAD are comparable, if not greater, in magnitude to other disabling chronic physical and mental disorders including other anxiety disorders, somatoform disorders, physical conditions, and MDD (Hoffman, Dukes & Wittchen, 2008; Kessler, Keller & Wittchen, 2001). After adjusting for the presence of other mental disorders and sociodemographic variables, individuals with pure GAD experienced an average of 1.5-5.4 impairment days in the prior month (Kessler et al., 2002). These values are comparable to past-month role impairment values previously observed among individuals with ulcers, arthritis, diabetes, and autoimmune disease (Kessler, Greenberg, Mickelson, Meneades & Wang, 2001).

Risk Factors for GAD

Genetic Factors

Genetic factors plausibly play a role in the etiology of GAD. Familial aggregation has been reported, with a particularly high prevalence of GAD among first-degree relatives of GAD probands (19.5%) compared to relatives of controls (3.5%; Noyes, Clarkson, Crowe, Yates & McChesney, 1987). Mendelwicz and colleagues (1993) reported similar results for relatives of GAD probands compared to controls (morbidity risk: 8.9% vs. 1.9%). More recently, a large familial study reported statistically significant odds ratios among first degree relatives of GAD probands ranging from 1.4 to 1.8 compared to controls (Newman & Bland, 2006). Meta-analytic results have primarily attributed this familial risk for GAD to genetic factors (Hettema et al., 2001). Twin studies specifically focused on GAD potentially provide more compelling evidence compared to familial studies. With heritability ranging from 15-40%, results suggest that

genetics plays a significant role in the etiology of GAD (Hettema, Prescott & Kendler, 2001; Kendler et al., 1992; Scherrer, True, Xian et al., 2000).

Environmental Factors

A myriad of environmental variables have been examined in association with the development of GAD. In contrast to MDD, there is a limited amount of available evidence concerning the effects of parental loss or separation in GAD. Nevertheless, analysis of data from the Early Developmental Stages of Psychopathology Study (EDSP) revealed that early parental separation increased the risk for the majority of anxiety disorders including GAD (Wittchen, Kessler, Pfister & Lieb, 2000). A similar investigation showed that parental separation predicted GAD (OR = 1.4-1.8), with a greater impact resulting from maternal compared to paternal separation (Kendler et al., 1992).

Parental style also has been examined as a risk factor for GAD. Parental attachment was less stable among undergraduate students meeting DSM-IV criteria for GAD compared to controls (Eng & Heimberg, 2006). Also, in a comparison of the dimensions of the Parental Bonding Instrument (PBI), GAD patients rated parents as less caring and more overprotective compared with controls (Silove, Parker, Hadzi-Pavlovic, Manicavasagar & Blaszczynski, 1991). However, caution has been suggested against over-interpretation of environmental effects of single adversities (Hettema, 2008).

Inconsistent results have been reported regarding the etiological role of stressful life events (SLE) in GAD. Adolescent SLEs have significantly predicted adult MDD onset, but not GAD (Pine, Cohen, Johnson & Brook, 2002). Schoevers and colleagues (2005) showed that earlier history of depression or anxiety predicted GAD onset, but showed no effects of SLE (Schoevers, Deeg, van Tilburg & Beekman, 2005). When high-contextual threat SLEs rated on

humiliation, entrapment, loss, and danger were assessed as potential predictors of GAD, SLEs characterized by loss or danger predicted GAD (Kendler, Silberg, Neale, Kessler, Heath & Eaves, 1991).

Cognitive Factors

Attentional biases have been purported to play a primary role in the etiology of GAD (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg & van IJzendoorn, 2007; Mogg & Bradley, 2005; Williams, Watts, MacLeod & Matthews, 1997). Threat-related attentional biases consistently have been shown in anxiety disorder patients, including those with GAD (Bar-Haim et al., 2007; Hettema, 2008). In a recent review of attentional bias in GAD versus MDD, results indicated an attentional bias for several minor emotional cues, including negative or threatening words, pictures of angry faces, and a limited number of positive cues, among individuals with GAD that was not shown for non-anxious individuals (Mogg & Bradley, 2005). An attentional bias to external threat-related cues may be important both for its role as an index for judging the motivational salience of external cues and for its potential role in exacerbating anxiety disorders (Mogg & Bradley, 2005). For example, an attentional bias for external threat-related cues may result in GAD patients focusing on a wider range of minor negative environmental cues, potentially contributing to an increase in anxious thoughts and worries (Mogg & Bradley, 2005).

Neuroanatomical Factors

Given the controversy surrounding the sensitivity and specificity of the diagnosis of GAD it is not surprising that there have been inconsistent results regarding the underlying neuroanatomic basis of GAD. Early PET studies pointed to the occipital lobe, cortex, limbic regions, and basal ganglia as potentially important brain regions in GAD (Buchsbaum, Wu, Haier et al., 1987; Wu, Buchsbaum, Hershey, Hazlett, Sicotte & Johnson, 1991). More recent

work has suggested that activation and co-activation in the amygdala, anterior cingulate cortex (ACC), insula, and prefrontal cortex plausibly play a role in the etiology of GAD.

Amygdala

Substantial evidence has indicated that the amygdala plays an essential role in the etiology of anxiety and its disorders. For example, significantly larger right and total amygdala volumes have been found among individuals with GAD compared to age-, weight-, height- and handedness-matched controls (De Bellis, Casey, Dahl et al., 2000). A more recent fMRI investigation showed significantly greater anticipatory responses (i.e., anticipation of adverse outcomes) in the amygdala among individuals with GAD compared to healthy controls (Nitschke, Sarinopoulos, Oathes et al., 2009). GAD participants showed significantly greater anticipatory activation, or hyperresponsivity, in the bilateral dorsal amygdala preceding aversive and neutral pictures (Nitschke et al., 2009). These findings support evidence suggesting that individuals with GAD exhibit hyperresponsivity to pathology-specific and non-specific cues (Hoehn-Saric, Schlund & Wong, 2004). Carter and Krug (2009) postulated that these findings also plausibly reflect enhanced anticipatory emotional responsiveness associated with GAD, suggesting that GAD is associated with overresponsiveness in an amygdala-based anticipatory arousal system.

Anterior Cingulate Cortex

Several lines of evidence link the ACC to the etiology of anxiety. A number of studies have shown increased activation of the ACC during the anticipation of aversive stimuli (Butler, Pan, Epstein et al., 2005; Nitschke et al., 2006; Straube, Schmidt, Weiss, Mentzel & Miltner, 2007). For example, a PET study showed a positive association between regional cerebral blood

flow in the ACC and anticipatory anxiety such that the least anxious subjects experienced the largest magnitude blood flow reductions (Simpson, Drevets, Snyder, Gusnard & Raichle, 2001).

The available literature suggests that the ACC is part of a neural circuit that can exert regulatory control over the amygdala (Ochsner, Ray, Cooper et al., 2004; Quirk, Likhtik, Pelletier & Pare, 2003; Phelps, Delgado, Nearing & LeDoux, 2004). A recent investigation of the predictive ability of pretreatment amygdala and rostral ACC reactivity to facial expressions for treatment outcomes in GAD patients showed that greater rostral ACC and lesser amygdala responsivity to fearful faces predicted larger decreases in anxiety following 8 weeks of Venlafaxine treatment (Whalen, Johnstone, Somerville et al., 2008). The authors suggested that it is plausible that activation of the rostral ACC in response to fearful faces regulates the amygdala, resulting in reduced amygdala activation and subsequent anxiolytic treatment effects (Whalen et al., 2008). In a similar investigation (Nitschke et al., 2009), anticipatory ACC activity was shown to be independently associated with decreases in worry and other anxiety symptoms as measured by the the Hamilton Rating Scale for Anxety (HAM-A; Hamilton, 1969) and the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger & Borkovec, 1990).

Insular Cortex

Although there has been less focus on the role of the insular cortex in the etiology of anxiety, the limited amount of evidence, along with reciprocal connections between the amygdala and insular cortex, suggests that insular activity is involved in the etiology of GAD. For example, GAD patients have shown reduced insular activation following anxiety symptom reduction with Citalopram treatment (Hoehn-Saric et al., 2004).

Prefrontal Cortex

Consistent with evidence implicating the ACC in the etiology of GAD, the prefrontal cortex has received substantial attention as a brain region plausibly involved in the etiology of GAD. An early PET study reported hypermetabolism in the prefrontal cortical regions of GAD patients (Wu et al., 1991). In a more recent proton magnetic resonance spectroscopy (MRS) study, GAD patients had a 16.5% higher N-acetylaspartate (NAA)/creatine ratio in the right dorsolateral prefrontal cortex compared to age- and sex-matched controls (Mathew, Mao, Coplan et al., 2004). Also, given the role of the amygdala in the genesis of GAD, it is important that a recent fMRI study showed that the right amygdala and right ventrolateral prefrontal cortex showed strong negative coupling in response to masked angry faces (Telzer, Mogg, Bradley et al., 2008).

Other Brain Regions

A number of neuroimaging investigations have implicated additional brain structures that are potentially relevant in the etiology of GAD, though the evidence has not been as consistent or strong as the aforementioned structures. Decreased concentrations of choline and creatine in the bilateral centrum semiovale have been reported among GAD patients compared to controls (Coplan, Mathew, Mao et al., 2006). Similarly, a recent proton MRS study revealed a strong relationship between anxiety symptom changes and hippocampal NAA among GAD patients treated with riluzole for 8 weeks (Mathew, Price, Mao et al., 2008). At present, additional neuroimaging research is needed to better elucidate the specific neural circuitry that underlies GAD.

Neurobiological Factors

Serotonergic

Pharmacological interventions provide evidence for a role of the serotonergic system in the etiology of GAD. For example, 5HT-1A receptor pharmacological agents, such as buspirone and gepirone, have shown efficacy in the treatment of GAD (Mitte, Noack, Steil & Hautzinger, 2005). Level 1 evidence, which is established by results of more than one placebo-controlled trial having total sample sizes over 30 (see Davidson et al., 2010, Table 2, p. 7), supports the efficacy of several SSRI drugs in GAD treatment including escitalopram (Davidson, Bose, Korotzer & Zheng, 2004), paroxetine-immediate release (Pollack, Zaninelli, Goddard et al., 2001; Rickels, Zaninelli, McCafferty, Bellew, Iyengar & Sheehan, 2003), and sertraline (Allgulander, Dahl, Austin, et al., 2004; Morris, Dahl, Kutcher, Sogaard, Allgulander & Burt, 2003).

Venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has shown efficacy as a treatment for GAD (Whalen et al., 2008). Results of a quantitative synthesis of studies examining outcome predictors following venlafaxine treatment of GAD showed that approximately 56% of individuals with GAD included in the analyzed studies showed considerable (>50% symptom reduction) improvement following treatment (Pollack, Meoni, Otto & Hackett, 2003).

Noradrenergic

Although there is a limited amount of compelling evidence, results from pharmacological interventions, animal models and studies in humans suggest a role of noradrenergic dysregulation in the etiology of GAD. Results from an early investigation of noradrenergic function in GAD patients indicated increased plasma NE and MHPG levels along with a

decreased number of α2-adrenoreceptors, suggesting noradrenergic hyperactivity in GAD patients (Sevy, Papadimitriou, Surmont, Goldman & Mendlewicz, 1989). Administration of clonidine, an α2-adrenoreceptor agonist which results in anxiolytic effects, has resulted in blunted GH response in individuals with GAD (Ableson, Glitz, Cameron et al., 1991). Given that noradrenergic activity regulates autonomic responses, evidence that females with GAD have an attenuated skin conductance response to stress and slower post-stress recovery also suggests a hyporesponsive and prolonged autonomic response among individuals with GAD (Hoehn-Saric, McLeod & Zimmerli, 1989; Sullivan, Coplan, Kent & Gorman, 1999).

Stronger evidence has been provided more recently by investigations of selective serotonin and norepinephrine reuptake inhibitors (SNRI) such as venlafaxine and duloxetine. At least 5 studies have indicated the efficacy of venlafaxine for treatment of GAD. Preclinical studies using the mouse zero maze model of anxiety have demonstrated significant anxiolytic effects of duloxetine as indicated by reductions in several anxiety-like animal behaviors (Troelsen, Nielsen & Mirza, 2005). More recently, a 10-week, double-blind, progressive-titration, flexible-dose trial involving 327 adult outpatients with GAD showed significantly greater improvements among patients who received duloxetine compared to patients who received placebo (Rynn, Russell, Erickson, et al., 2008).

GABA

Similar to evidence of the role of GABA in non-pathological anxiety states, the majority of empirical attention regarding the role of GABA in the etiology of GAD has been focused on the pharmacological properties of benzodiazepines (BZD) and their receptors. A CO_2-induced anxiety model has been developed that is postulated to model GAD in which 7.5% CO_2 is inhaled for 20 consecutive minutes (Bailey, Papadopoulos, Seddon & Nutt, 2009). In a double-

blind, placebo-controlled, three-way crossover study in 12 healthy volunteers, the BZD receptor agonists alprazolam and zolpidem both were shown to attenuate CO_2-induced anxiety (Bailey et al., 2009). Similarly, an acute dose of lorazepam, a BZD receptor agonist, has demonstrated efficacy in the reduction of CO_2-induced subjective anxiety symptoms (Bailey, Kendrick, Diaper, Potokar & Nutt, 2007). BZD receptor sensitivity also has been examined through the measurement of saccadic eye velocity. BZD receptors in the superior coliculus/pons area are thought to partially control saccadic eye velocity, which is slowed in response to BZD challenge (Nutt, 2001). Using this model, Kroboth and colleagues (1998) reported that GAD patients demonstrated a reduced sensitivity to alprazolam, suggesting that GAD patients plausibly have reduced sensitivity of central BZD receptors.

Regarding BZD receptor distribution, neuroimaging studies have shown potential distribution dysfunction in brain areas among GAD patients. For example, a functional brain imaging study using magnetic resonance imaging and single photon emission tomography showed significantly decreased BZD receptor binding in the left temporal lobe, significantly higher left hemispheric BZD binding, and a more homogeneous central BZD density distribution among GAD patients compared with age- and sex-matched controls (Tiihonen, Kuikka, Rasanen et al., 1997).

HPA Axis Functioning

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has been implicated in the etiology of anxiety (Leonardo & Hen, 2006). Over-expression of corticotrophin-releasing factor (CRF), the primary mediator of HPA axis functioning, has been implicated in increased anxiety-like behavior in animal models of anxiety (Arborelius et al., 1999). However, to this point, there has been a lack of compelling evidence to confirm a similar role in humans. Of the very few

studies that have explicitly studied HPA axis functioning among GAD patients, no specific abnormalities have been reported (Hoehn-Saric, McLeod, Lee & Zimmerli, 1991; Pomara, Willoughby, Sidtis, Cooper & Greenblatt, 2005). For example, examinations of cerebrospinal fluid levels of CRF among GAD patients have shown no differences compared with healthy controls (Banki, Karmacsi, Bissette & Nemeroff, 1992; Fossey, Lydiard, Ballenger, Laraia, Bissett & Nemeroff, 1996).

Measurement of GAD

Diagnostic Interviews

Diagnostic interviews are characterized by structured or semi-structured interviews that assess psychopathology according to diagnostic criteria set forth by psychiatric classification systems such as the DSM-IV (American Psychiatric Association, 2000). The use of a diagnostic interview permits formal, careful, and thorough assessment of psychopathology.

The Anxiety Disorders Interview Schedule for DSM-IV – Adult and Lifetime Version (ADIS-IV; Brown, DiNardo, & Barlow, 1994) is one such diagnostic interview used to assess for the presence of psychopathology. The ADIS-IV is a structured diagnostic interview schedule that examines current episodes of anxiety disorders and is designed to allow for differential diagnosis among the anxiety disorders (Brown, Dinardo & Barlow, 1994). The interview also has sections designed to screen for related disorders including mood disorder, somatoform disorders, substance abuse disorders, psychotic disorders and medical illnesses according to DSM-IV diagnostic criteria (Brown, Dinardo & Barlow, 1994). Each diagnostic section of the ADIS-IV contains questions designed to determine if a patient meets diagnostic criteria for a specific disorder, the focal concern associated with individual symptoms, and the relation of each symptom to symptoms previously reported in other sections (Brown, DiNardo & Barlow, 1994).

Following initial screening questions linked to the key feature of the disorder which are dichotomously rated (i.e., yes/no), clinicians assign symptom severity ratings to each disorder. For example, the symptom severity of GAD is assessed using a nine-point (0-8) Likert-type scale. These severity ratings allow discrimination between principal diagnoses.

The psychometric properties of the ADIS-IV are well established. Previous editions of the ADIS have demonstrated sufficient reliability for most of the anxiety disorders covered (DiNardo, O'Brien, Barlow, Waddell & Blanchard, 1983). For example, the test-retest reliability for the DSM-III-R anxiety disorders ranged from 0.57 to 0.82 (DiNardo, Moras, Barlow, Rapee & Brown, 1993). The lower limit coefficients can be attributed in part to changing diagnostic criteria for certain disorders, particularly GAD. The reliability of the ADIS-IV: Lifetime version was examined using a sample of 362 outpatients who underwent 2 independent administrations (Brown, Lehman, Campbell & DiNardo, 2001). Kappa coefficients demonstrated adequate inter-rater agreement for overall diagnosis ranging from 0.61 to 0.81 (Brown et al., 2001). More specifically, the inter-rater reliability for dimensional ratings of GAD ranged from $r = 0.72$ to $r = 0.83$ (Brown et al., 2001).

The validity of the ADIS has been illustrated through a substantial body of experimental research in which the ADIS exhibits expected changes in symptom severity in response to treatments known to be efficacious among anxiety disorder patients. For example, cognitive-behavioral therapy (CBT), the most frequently employed psychosocial treatment for GAD, has been classified as a well-established empirically supported treatment approach for GAD by multiple work groups targeting the elucidation of effective practice-based treatment approaches (Chambless, Baker, Baucom et al., 1998; Kendall & Chambless, 1998; Nathan & Gorman, 1998; Roth & Fonagy, 1996). Across two clinical trials of approximately 112 clinically diagnosed

GAD patients, the ADIS showed an approximately 3 point mean reduction in symptom severity ratings in response to CBT (Borkovec & Costello, 1993; Wetherell, Gatz & Craske, 2003). These findings indicate the ADIS can be used to validly assess anxiety symptom severity among individuals with GAD.

Questionnaires

Several questionnaires are available for assessing clinically important anxiety symptoms. One of the most widely used is the Hamilton Rating Scale for Anxiety (HAM-A) while other scales, such as the Penn State Worry Questionnaire (PSWQ), focus on symptoms that are especially pertinent to GAD.

The Hamilton Anxiety Rating Scale

The Hamilton Anxiety Rating Scale (HAM-A) is a clinician-administered rating scale used to assess the severity of anxiety symptoms, anxiety symptom improvement in response to treatment, and the timing of anxiety improvements (Hamilton, 1959; Riskind, Beck, Brown & Steer, 1987). The scale is comprised of 14 items which provide a measure of general anxiety including psychic (cognitive) anxiety and somatic anxiety. Table 2.1 presents the 14 items that comprise the HAM-A. By summing items 1-6 and item 14, the HAM-A psychic factor can be computed, while the HAM-A somatic factor is obtained by summing items 7-13 (Hamilton, 1959). Each item is rated on a 5-point scale from 0 (not at all present) to 4 (very severe/severely disabling). The total score is the sum of the 14 item scores and ranges from 0 to 56. Higher scores indicate a greater degree of symptom severity, distress and potential impairment.

Table 2.1. Hamilton Anxiety Rating Scale Items

Item Number	Item Content
1	Anxious mood
2	Tension
3	Fears
4	Insomnia
5	Concentration
6	Depressed mood
7	General somatic symptoms (muscular)
8	General somatic symptoms (sensory)
9	Cardiovascular symptoms
10	Respiratory symptoms
11	Gastrointestinal symptoms
12	Genito-urinary symptoms
13	Autonomic symptoms
14	Behavior at interview

Evidence has suggested that the psychometric properties of the HAM-A are sufficient. Beck and colleagues (1988) reported appropriate internal consistency values ($\alpha = 0.83$) for the HAM-A in an investigation of 160 psychiatric patients, 18 of whom were diagnosed with GAD (Beck, Epstein, Brown & Steer, 1988). Because the HAM-A is a clinician-administered rating scale that has predominantly been used as a test-retest measure for evaluating the efficacy of anxiolytic medications, inter-rater reliability is imperative for the appropriate use of the scale (Bruss, Gruenberg, Goldstein & Barber, 1994). Among 97 anxiety disorder patients, intraclass correlation coefficients (ICC) illustrated sufficient inter-rater reliability with values of 0.74 for HAM-A total score, 0.73 for HAM-A psychic anxiety total score and 0.70 for HAM-A somatic anxiety total score (Maier, Buller, Philipp & Heuser, 1988). Similary, an examination of joint interview and test-retest methods reported ICCs ranging from 0.74 to 0.96 (Bruss et al., 1994).

Although the HAM-A is the most widely used psychometric indicator of the anxiolytic efficacy of potential anxiolytic drugs, some authors have contended that only limited support has been provided for the validity of the scale (Maier et al., 1988; Riskind et al., 1987). However, a

review of the extant literature produced several lines of evidence supporting the psychometric properties and use of the HAM-A. For example, a discriminant function analysis conducted using the HAM-A alone among 44 individuals diagnosed with GAD and 44 normal controls demonstrated that 95.5% of the two samples could be classified correctly (Stanley, Beck & Zebb, 1996).

The majority of the available validity evidence for the Hamilton Anxiety Rating Scale is provided by its extensive use and sensitivity as a measure of the well-established treatment response of GAD patients to pharmacotherapy. Effect sizes from 21 double-blind placebo-controlled clinical trials that used changes in HAM-A (Hamilton, 1959) scores from baseline to endpoint as the primary measure of efficacy for commonly used medications for the treatment of GAD were reviewed by Hidalgo and colleagues (2007). Results demonstrated that the HAM-A was sensitive enough to detect treatment changes for all classes of drugs. For example, an 8-week randomized, double-blind, placebo-controlled investigation of the efficacy of daily flexible (20-50 mg) dosages of paroxetine in the treatment of symptoms among 324 outpatients with GAD revealed significantly greater reduction of GAD symptoms as measured by the HAM-A and the HADS-A compared to placebo controls (Pollack, Zaninelli, Goddard et al., 2001).

Evidence from investigations of the efficacy of pharmacotherapy for GAD also suggests that certain HAM-A cut-scores both corrorborate clinical diagnosis of GAD via diagnostic interview and demonstrate remission. A cut-score of ≥20 on the HAM-A is considered indicative of GAD, particularly when responses to items 1 and 2 are ≥ 2 (Hoffman & Mathew, 2008). For example, in a large clinical trial of the efficacy of venlafaxine XR, mean baseline HAM-A scores for 529 patients meeting DSM-IV diagnostic criteria for GAD were ≥ 26 with a range of 20-52 (Allgulander, Hackett & Salinas, 2001). Moreover, HAM-A scores were

sensitive to treatment changes in response to venlafaxine XR as indicated by mean score reductions ranging from 13.8 to 16.4 for treatment groups across the 24 week trial.

HAM-A score change from baseline to endpoint also has been used to represent response rates in a number of pharmacological studies. For example, 3 multi-center, randomized, placebo-controlled trials recently showed response rates of 42-58%, defined as a 50% or greater change from baseline to endpoint on the HAM-A (Koponen et al., 2007; Rynn et al., 2007; Hartford et al., 2007).

Clinical guidelines have been set forth for the establishment of remission among anxiety disorder patients according to HAM-A score at endpoint. Ballenger (1987) suggested that a score of ≤ 7 on the HAM-A at endpoint established remission. A number of pharamacological investigations have provided support for this guideline. For example, an 8-week examination of the efficacy of two fixed doses of paroxetine (20 or 40 mg daily) in the treatment of symptoms among 566 outpatients with GAD showed significantly greater reductions in total HAM-A score compared to placebo (Rickels, Zaninelli, McCafferty, Bellew, Iyengar & Sheehan, 2003). Remission, defined as a HAM-A score ≤ 7, was realized in 30% and 36% of outpatients in the treatment groups, demonstrating the ability of the HAM-A to detect response to paroxetine treatment for GAD (Rickels et al., 2003).

Some authors have contended that the use of the original HAM-A scale is contraindicated due to its lack of instructions for administration and scoring and lack of scripted questions to guide interviewers during administration (Shear, Vander Bilt, Rucci et al., 2001). These potential deficiencies led to the development of the Hamilton Anxiety Rating Scale Interveiw Guide (HARS-IG) and Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A) to standardize clinical probe questions and to reduce potential interrater variance

(Bruss et al., 1994; Shear et al., 2001). For the HARS-IG, ICCs revealed improved interrater agreement compared to the original HAM-A (Bruss et al., 1994). Similarly, two-way random effects model ICCs showed stronger test-retest reliability for the SIGH-A (0.89, 95% CI: 0.83 to 0.93) compared to the original HAM-A (0.86; 0.78 to 0.91), although the difference was not statistically significant (Shear et al., 2001). Although these studies illustrate some discrepancies between the original HAM-A and newer structure interview guides, the differences do not appear to significantly reduce the utility of the HAM-A.

Thus, the available evidence supports the utility of the HAM-A and suggests that: (i) a cut point of ≥ 20 can be used to screen individuals with GAD; (ii) an approximately 50% reduction in total score from baseline to endpoint is representative of treatment response; and, (iii) a score of ≤ 7 at endpoint can be used to establish remission.

The Penn State Worry Questionnaire

The Penn State Worry Questionnaire (PSWQ) is a 16-item self-report questionnaire that measures symptoms of pathological worry (Molina & Borkovec, 1994). The PSWQ appears to be GAD specific, because individuals diagnosed with GAD who experience excessive and uncontrollable worry score significantly higher on the PSWQ compared to both individuals who meet some, but not all, criteria (Meyer, Miller, Metzger & Borkovec, 1990) and individuals meeting diagnostic criteria for other anxiety disorders (Brown, Anthony & Barlow, 1992).

Several sources were used for the initial item development including daily diary entries by GAD patients involved in a therapy outcome study that detailed symptom experience (Borkovec & Mathews, 1988), items from a pre-existing cognitive/somatic anxiety inventory (Borkovec & Mathews, 1988) and generation of novel items based on theoretical views of worry (Meyer et al., 1990). Resulting items were administered rated on a 1 to 5 scale (1 = “not at all

typical of me"; 5 = "very typical of me") by 337 college students. Principal components factor analysis was applied to resulting data and, on a repeated cycle of deletion, 16 items were retained with an internal consistency of 0.93 (Meyer et al., 1990). Table 2.2 presents the 16 items.

Table 2.2. Penn State Worry Questionnaire Items

Item Number	Item Content
1	If I do not have enough time to do everything, I do not worry about it*
2	My worries overwhelm me
3	I do not tend to worry about things*
4	Many situations make me worry
5	I know I should not worry about things, but I just cannot help it
6	When I am under pressure I worry a lot
7	I am always worrying about something
8	I find it eay to dismiss worrisome thoughts*
9	As soon as I finish one task, I start to worry about everything else I have to do
10	I never worry about anything*
11	When there is nothing more I can do about a concern, I do not worry about it any more*
12	I have been a worrier all my life
13	I notice that I have been worrying about thing
14	Once I start worrying, I cannot stop
15	I worry all the time
16	I worry about projects until they are all done

* denotes a reverse-scored item (modified from Meyer et al., 1990)

The psychometric properties have been extensively investigated since the inventory was developed. The PSWQ has demonstrated adequate reliability with internal consistency values ranging from 0.83 to 0.95 (Brown, Antony & Barlow, 1992; Fresco, Mennin, Heimberg & Turk, 2003; Meyer et al., 1990; Molina & Borkovec, 1994; Stanley et al., 2001). Meyer and colleagues (1990) reported results from a total of 8 investigations of the psychometric properties of the PSWQ. Results indicated strong internal consistency values, ranging from 0.91 to 0.95. In two investigations of test-retest reliability, the PSWQ was found to be stable over periods of 2 weeks ($r = 0.75$), 1 month ($r = 0.93$), and 8-10 weeks (0.92). A separate analysis revealed that PSWQ

scores were significantly higher among 48 individuals (26 females) who met diagnostic criteria for GAD compared with scores for both individuals who met diagnostic criteria for PTSD and normal controls. In summary, investigations by Meyer and colleagues provided evidence that individuals with GAD present high scores on the PSWQ, that gender differences are negligible, and that the PSWQ illustrates independence from other common measures of anxiety and depression based upon its focus on pathological worry.

The predictive validity of the PSWQ also has received attention. An examination of the characteristics of GAD among older adults demonstrated nearly perfect classification accuracy using the PSWQ when self-report measures were subjected to discriminant function analysis (Beck, Stanley & Zebb, 1996). More stringent analysis of the screening utility, or predictive validity, of the PSWQ has been conducted via receiver operating characteristic analysis (Behar, Alcaine, Zuellig & Borkovec, 2003; Fresco, Mennin, Heimberg & Turk, 2003). A particular strength of ROC analysis is the robustness of the test even when cases and controls are unequally represented in a sample (Rice & Harris, 1995). ROC analyses have sought to determine (i) sensitivity: the percentage of individuals with a positive diagnosis of GAD that are identified by the PSWQ as having GAD; (ii) positive predictive power: the percentage of individuals classified as having GAD by the PSWQ who actually had GAD; (iii) specificity: the percentage of individuals without GAD that the PSWQ correctly identified as not having GAD; and, (iv) negative predictive power: the percentage of individuals classified by the PSWQ as not having GAD who actually did not have GAD.

Results from an examination of the specificity and sensitivity of certain cut point scores on the PSWQ among 159 individuals with GAD and 113 normal controls revealed that a PSWQ cut point of 45 maximized sensitivity (0.99) and specificity (0.98) (Behar et al., 2003). The

results of a second study by these authors, however, yielded different results. Among 2449 students a PSWQ cut point score of 62 demonstrated high specificity (0.86), suggesting that a score of 62 could accurately detect 86% of non-GAD participants. The authors reported that the PSWQ also showed strong negative predictive power (0.98), a low false negative rate (0.25) and a low false positive rate (0.14) (Behar et al., 2003). However, a very low positive predictive power (0.27) was found, suggesting that, although a cut point score of 62 can identify 75% of individuals with GAD in a sample, only 27% of those will actually be correctly diagnosed with GAD using a diagnostic inventory or interview (Behar et al., 2003).

Convergent and discriminate validity evidence also has been provided by correlational research. The PSWQ has been shown to only moderately correlate with common measures of general anxiety symptoms such as the trait scale of the STAI ($r = 0.45$) and the Beck Anxiety Inventory (BAI) ($r = 0.32$) and has shown small correlations with the HAM-A ($r = 0.15$) among both younger adults with GAD (Brown et al., 1992) and older adults (Stanley et al., 2001; Wetherall, Gatz & Craske, 2003). These correlational results suggest that screening procedures utilizing the PSWQ to assess pathological worry along with the HAM-A to assess symptom severity may be more appropriate than relying simply on a clinician-rated scale such as the HAM-A. This contention is supported by more recent evidence from a meta-analytic review of the efficacy of CBT for the treatment of GAD suggested that the PSWQ should be preferentially considered as an outcome measure in examinations of treatment efficacy for GAD because of its focus on pathological worry, the cardinal symptom of GAD (Covin, Oiumet, Seeds & Dozois, 2008).

This evidence suggests that (i) the PSWQ is a useful tool for correctly identifying individuals that do not meet criteria for GAD, (ii) additional diagnostic evidence is likely

necessary to most accurately screen individuals thought to meet criteria for GAD, and (iii) a cut point score of 45 possesses sufficient sensitivity and specificity to screen individuals when recruiting/advertising for participants characterized by elevated worry symptoms, but higher cut point scores may be necessary for screening among general student populations.

Related Symptoms

Muscle Tension – Tremor

Increased muscle tension is a common symptom of GAD and has been suggested to be the most discriminative somatic symptom among GAD patients (Hoehn-Saric, 2007; Pluess, Conrad & Wilhelm, 2009). General muscle tension may be a peripheral manifestation of CNS arousal that can focus on specific muscle groups and contribute to problems such as writer's cramp and tension headaches (Hoehn-Saric, 2007). Despite conflicting evidence about the relation between anxiety and muscle tension, muscle relaxation therapies have been as effective as cognitive interventions in addressing worry - the defining symptom of GAD (Pluess et al., 2009).

Physiological Tremor

Other variables related to muscle tension such as physiological hand tremor have been found to be enhanced among anxiety disorder patients (Graham, 1945) and reduced with common pharamacological treatments (i.e., propranolol & alprazolam) (Milanov, 2007). Physiological tremor is a normal, involuntary rhythmic oscillation with variable amplitude and a usual mean frequency range of 4 – 12 Hz (Gandevia, 2001). Classified as a postural, or resting, tremor on the basis that it occurs when a limb is positioned against gravity (Charles, Esper, Davis, Maciunas & Robertson, 1999; Morgan & Sethi, 2005), physiological tremor is often most noticeable when the outstretched hand is held constant (Hallett, 1998). Although numerous

central and peripheral factors are thought to contribute to tremor, the causes of physiological tremor are incompletely understood. It has been suggested that the causes of tremor can be reduced to a limited number of factors, including peripheral mechanical factors, peripheral and central reflex loop feedback, and activity (i.e. central oscillations) in regions of the CNS (Deuschl, Raethjen, Lindemann & Krack, 2001; Elble, 1996; Hallett, 1998)

Peripheral Factor Involvement in Tremor

Peripheral mechanical factors are thought to be dominant influences on the generation and alterations of tremor (Hallett, 1998). The resonant frequency of an extremity is a key peripheral factor which is primarily determined by the inertia of the limb and joint stiffness (Elble, 1996; Hallett, 1998). This is to say that the joint system of the extremity, comprised of the joint and its associated muscles, has mechanical properties analogous to a spring-mass system (Hallett, 1998). The frequency at which this system oscillates is a function of the inertia of the limb, or mass in the system, and the stiffness of the muscle, or spring (Deuschl et al., 2001; Hallett, 1998). For example, during exercise, muscle contraction would increase tremor through increases in the frequency of oscillations resulting from increased stiffness about the joint. Other key peripheral mechanisms for alterations in tremor include "changes in muscle contraction dynamics, proprioceptive reflexes, and muscle receptor properties" (Gandevia, 2001, p.1769). Changes in muscle contraction dynamics and muscle receptor properties (e.g. contributions of muscle spindles to the stretch reflex) play a critical role in exercise-induced alterations of tremor. During exercise, once firing rates of motor units become unduly low compared to the constant speed of muscle contraction, the stabilizing effect of the stretch reflex declines and tremor develops (Gandevia, 2001, Matthews, 1997).

Reflex loop feedback also contributes to tremor as muscle activity is relayed to the CNS via reflex loops. The simplest peripheral reflex loop involves feedback of a movement through activation of the muscle spindle, transmission of the signal through the Ia afferent monosynaptically onto the motoneuron, and through the motor axon to stimulate the extrafusal muscle fibers (Hallett, 1998). Central reflex loop feedback, the most basic central factor, relays muscle activity from the periphery to the CNS (Hallett, 1998). The most salient example of a central reflex loop is one that regulates targeted movements. As a function of the cerebellum, the progress of a movement is relayed via feedback to a module which compares the motor command with the actual position of the extremity. The signal from the comparator drives the motor apparatus and contributes to changes in tremor (Hallett, 1998).

Central Nervous System Involvement in Tremor

Although peripheral mechanical factors are thought to be the dominant influences on tremor (Hallett, 1998), CNS involvement in tremor has been well-established. Central oscillations occur when brain neurons produce rhythmic activity. When this activity is related to motor commands and the frequency is 8 – 12 Hz (Hallett, 1998), the oscillations may be a mechanism for the generation of and/or alterations in tremor (Deuschl et al., 2001). Such central oscillators, which are independent of peripheral input (Hallett, 1998), plausibly arise from rhythmic activity of a group of neurons within a nucleus (Deuschl et al., 2001). A number of animal experiments have indicated such activity to be present within cells in the inferior olive and the thalamus (Llinas, 1984; Llinas & Yarom, 1981).

CNS involvement in tremor also stems from variations in efferent activity from the motor cortex (Koster, Lauk, Timmer et al., 1998). In an investigation of the central mechanisms in human enhanced physiologic tremor, individuals with persistent mirror movement syndrome and

controls were compared using transcranial magnetic stimulation, long-latency reflexes, and cross-spectral analysis of electromyography time series recorded from the wrist extensors (Koster et al., 1998). The authors concluded that the 8 to 12 Hz component of enhanced physiologic tremor is transmitted transcortically, originating from two separate generators from both sides of the motor cortex (Koster et al., 1998).

CNS involvement in tremor also stems from variations in central afferent feedback to the motor cortex (Elble, 1996). Specifically, physiologic tremor is affected both by oscillations in sensorimotor loops and by oscillations of central neuronal networks (Elble, 1996). Variations in motor-related cortico-cortical interactions also play a role in tremor (Raethjen, Lindemann, Morsnowski et al., 2004). Raethjen and colleagues (2004) used epicortical recordings from the M1 and supplementary motor areas of the brain along with surface electromyographic recordings to examine synchronized activity as an indicator of the involvement of physiologic tremor in cortico-cortical interactions. The authors concluded that the cortical correlates of physiologic tremor may be involved in linking different cortical motor centers (Raethjen et al., 2004).

Tremor and Mood

There is an emerging body of evidence that links the cerebellum, basal ganglia, and related thalamic structures involved in the control of tremor to mood states of fatigue (Herring & O'Connor, In Review) and anxiety (Demyttenaere et al., 2004; Nutt, 2001). Brain-imaging studies have indicated the importance of the cerebellum and cerebellar activity in both anxiety and tremor. An examination of regional cerebral metabolism among 18 GAD patients during a passive viewing task showed higher metabolic rates in the cerebellum and thalamus relative to healthy controls (Wu, Buchsbaum, Hershey et al., 1991). Results also showed that during vigilance tasks, GAD patients also showed increased activity in the basal ganglia (Wu et al.,

1991). These data suggest that GAD may be characterized by hyperactivity in some brain regions, particularly the thalamus (Nutt, 2001). Given evidence of the role of the thalamus in attentional processing (Coull, Buchel, Friston et al., 1999), increased thalamic metabolic activity may help to explain the hypervigilance often seen in GAD patients (Nutt, 2001). Moreover, in a model depicting the relation between brain circuits and GAD symptoms, hypervigilance is thought to be modulated by thalamic activity, worry is modulated by activity in the cingulate cortex, autonomic changes are modulated by the temporal lobe insula, and, more importantly, activity in the basal ganglia modulates motor tension (Nutt, 2001).

Pharmacological evidence corroborates brain-imaging evidence suggestive of a link between physiological tremor and anxiety. Tremor found in GAD patients has been classified as an enhanced physiological tremor (Milanov, 2007). A recent investigation of the clinical and electromyographic pattern of tremor among 120 GAD patients compared the effects of propranolol and alprazolam to no treatment (Milanov, 2007). Results indicated that GAD patients presented a postural and kinetic hand tremor that was characterized as enhanced physiological tremor that was attenuated by both propranolol and alprazolam (Milanov, 2007).

There also is evidence that pharmacological agents known to produce (caffeine and β-adrenergic agonists) or attenuate (β-adrenergic antagonists) stimulant effects, affect both anxiety and physiological tremor (Morgan & Sethi, 2005). Propranolol, a β-adrenergic antagonist has shown efficacy as an anxiolytic (Glannon, 2008) and is the most effective β-adrenergic antagonist for attenuation of drug-induced tremors (Morgan & Sethi, 2005). Hand tremor has been studied in relation to smoking habits and the consumption of caffeine among 49 smokers/snuffers and 49 non-smokers/non-snuffers (Ellingsen, Bast-Pettersen, Efskind et al., 2006). Results indicated increased hand tremor in response to caffeine and nicotine among

smokers/snuffers (Ellingsen et al., 2006). Oral ingestion of a single dose of caffeine at typical consumptive levels (~ 3mg/kg body weight) results in significant increases in physiologic tremor (Miller, Lombardo & Fowler, 1998). However, a meta-analytic review of the available evidence on methylxanthine use for exacerbations of chronic obstructive pulmonary disease showed that methylxanthine use resulted in non-significant increases in tremor (Barr, Rowe & Camrgo, 2003). Also, a non-significant increase in hand tremor in response to 200 mg of caffeine was found among surgeons (Humayun, Rader, Pieramici, Awh & de Juan, 1997). The effects of caffeine on anxiety are well-documented and as little as 150 mg of caffeine can reliably elevate anxiety (Monteleone & Maj, 2008; Vanderveen et al., 2001). In summary, evidence suggests an overlap in the CNS neurology that underlies both physiological tremor and GAD symptoms.

Sleep

Sleep disturbance is one criterion for the diagnosis of GAD according to the DSM-IV. Insomnia was first included in the vigilance and scanning symptom group of the DSM-III (American Psychiatric Association, 1980). Subsequent revisions integrated "trouble falling asleep" and "trouble staying asleep" into the vigilance and scanning symptom group as well (American Psychiatric Association, 1987). In the most recent revision, the DSM-IV recognizes sleep disturbance as one of the 6 independent, specific symptoms of GAD (American Psychiatric Association, 2000).

Adjusted odds ratios from the German Health Survey (GHS) indicated that social phobia (OR: 3.95, 95%CI: 1.73 to 9.04) and GAD (OR: 3.94, 95%CI: 1.66-9.34) had the strongest relationships with global Pittsburgh Sleep Quality Inventory scores (PSQI; Buysse, Reynolds, Monk, Berman & Kupfer, 1989) and that GAD was most strongly associated with elevated daytime dysfunction subscale scores (Ramsawh, Stein, Belik, Jacobi & Sareen, 2009). Monti

and Monti (2000) reviewed 6 studies that examined all-night sleep with polysomnography in insomniac GAD patients compared with normal controls. The cumulative results of these studies indicated that GAD patients with mild-to-moderate intensity symptoms often experience increased sleep latency and reduced total sleep time and sleep efficiency (Monti and Monti, 2000). At present there is inconsistent evidence regarding non-REM sleep structure, REM sleep features, and the intensity of sleep disturbances among patients with severe GAD.

Pain

Substantial evidence has indicated an association between pain and psychiatric disorders. Chronic pain and pain-related symptoms have been shown to be associated with mood, anxiety, somatoform, substance abuse and personality disorders (Dersh, Polatin & Gatchel, 2002). Primary care patients with anxiety disorders frequently report chest pain, abdominal pain, headache, or joint and limb pain (Kroenke, Spitzer, Williams et al., 1994). Although the association between chronic pain and depression has received the most research attention, a number of studies have shown stronger associations between pain conditions and anxiety disorders compared to depression (Breslau & Davis, 1991; McWilliams, Cox & Enns, 2003; Merikangas, Angst & Isler, 1990).

The association between GAD and pain is important because of the increased prevalence of pain among individuals with GAD, the associated increased health care costs, and because GAD patients reporting high pain interference have more severe anxiety, greater functional limitations and greater work absenteeism (Teh, Morone, Karp et al., 2009). Primary care patients with GAD often report pain as the initial reason for seeking help from their general practitioner (Wittchen, Kessler, Beesdo, Krause, Hofler & Hoyer, 2002). Data from the National Comorbidity Survey revealed a significantly higher prevalence of GAD among individuals with

chronic pain (7.3%) compared to individuals without chronic pain (2.6%) (McWilliams, Cox & Enns, 2003). In a sample of 1029 primary care patients, patients with GAD (n=110) had significantly higher medical care costs and pain interference ratings compared to patients without GAD (Olfson & Gameroff, 2007). The largest healthcare costs were found for those individuals with GAD reporting high pain interference (Olfson & Gameroff, 2007).

There is substantial evidence for the relationship between GAD and pain. After adjusting for age, gender, income and race, a significant positive association (OR=2.30) was found for the association between chronic pain and past-year GAD diagnosis among 382 individuals meeting diagnostic criteria for chronic pain (McWilliams, Cox & Enns, 2003). In a nationally representative sample of 3032 individuals, odds ratios for GAD were significantly larger for individuals with arthritis (OR=2.17), migraine headaches (OR=3.86), and back pain (OR=2.54) compared to those individuals who did not report a pain condition (McWilliams, Goodwin & Cox, 2004). More recently, the association between pain and GAD was compared to the association between pain and other anxiety disorders in a community sample of 4181 individuals (Beesdo, Hoyer, Jacobi, Low, Hofler & Wittchen, 2009). The association between pain and GAD (OR=5.8 for pain symptoms; OR=16.0 for pain disorder) was shown to be stronger than the association between pain and other anxiety disorders (OR=2.4 for pain symptoms; OR=4.0 for pain disorder). More importantly, primary care patients reporting symptoms of GAD were shown to be 2.5 times more likely to report muscle pain (Mean-Christensen, Roy-Byrne, Sherbourne, Craske & Stein, 2008).

Treatments with known efficacy for reducing GAD symptoms also have been shown to reduce clinically significant pain among GAD patients. For example, duloxetine, a serotonin-norepinephrine reuptake inhibitor, was shown to improve anxiety symptoms and clinically

significant pain among 840 GAD patients (Hartford, Endicott, Kornstein et al., 2008). Thus, the evidence suggests that there is an important association between pain and GAD that warrants further empirical attention.

Treatments of GAD

The evidence base for pharmacological and psychosocial therapies for GAD treatment has continued to grow in recent years (Davidson et al., 2010). Based on the results of a comprehensive multidimensional meta-analysis of GAD treatments, Westen and Morrison (2001) suggested that available treatments for GAD can produce impressive short-term effects, but that most patients in treatment fail to maintain improvements at clinically meaningful follow-ups. Presently there is a myriad of drug and psychosocial treatments for GAD, but there is a lack of compelling evidence that the combination of the two different treatment modalities conveys any additional benefit compared to the efficacy of each individual therapy (Davidson et al., 2010). Therefore, each type of treatment is independently addressed in the following sections.

Pharmacological

A substantial amount of evidence supports the use of pharmacological treatment for GAD (Allgulander et al., 2004; Hidalgo, Tupler & Davidson, 2007; Rickels et al., 2003). The evidence base for the efficacy of pharmacotherapy has continuously grown over the past 50 years and a plethora of drug choices now exist for GAD treatment. For many years the primary focus of pharmacotherapy for GAD was relegated to BZD treatment until expansion to serotonergic agents and a more recent focus on the development of pharmacological agents with novel mechanisms (Davidson et al., 2010).

There have been a number of reviews within the past decade of the available evidence concerning the pharmacological treatment of GAD. One notable meta-analytic review used a

random-effects model to examine the aggregated Hedges *g* effect size for 72 effects derived from 48 investigations of the efficacy of pharmacological treatments in GAD (Mitte, Noack, Steil & Hautzinger, 2005). The most frequently investigated drugs were BZDs, including diazepam (k=12), alprazolam (k=6), and lorazepam (k=6), and azapirones (i.e., buspirone, k=12), but a number of effects were derived from studies of antihistamines and SSRIs (Mitte et al., 2005). Mean effect sizes of 0.32 for BZDs and 0.30 for azapirones were reported, and the authors reported that all categories of pharmacotherapy were superior to placebo (Mitte et al., 2005). However, there are methological limitations that potentially preclude the meaningful interpretation of the results including the use of broad diagnostic criteria (i.e., including earlier DSM-II and DSM-III diagnoses), the inclusion of investigations that evaluated the treatment of comorbid anxiety and depression, and a seemingly narrow focus on BZDs and azapirones.

A more recent quantitative review extended beyond previous reviews by addressing the above-mentioned limitations. Effect sizes from 21 double-blind placebo-controlled trials of medications used for treating clinically diagnosed GAD using changes in HAM-A (Hamilton, 1959) scores from baseline to endpoint as the primary measure of efficacy were reviewed (Hidalgo et al., 2007). Compared to placebo, significant mean effect sizes were reported for all medication categories, except complimentary/alternative medicine, as follows: pregabalin (n=2; Pande, Crockatt, Feltner et al., 2003; Feltner, Crockatt, Dubovsky et al., 2003): ES = 0.50; antihistamines (hydroxyzine [n=3; Darcis, Ferreri, Natens, Burtin & Deram, 1995; Lader & Scotto, 1998; Llorca, Spadone, Sol et al., 2002]): ES = 0.45; SNRI (venlafaxine, n=5; Davidson, DuPont, Hedges & Haskins, 1999; Rickels, Pollack, Sheehan & Haskins, 2000; Gelenberg, Lydiard, Rudolph, Aguiar, Haskins & Salinas, 2000; Allgulander, Hackett & Salinas, 2001; Hackett, Haudiquet & Salinas, 2003): ES = 0.42; BZD (alprazolam [n=1; Moller, Volz, Reimann

& Stoll, 2001], diazepam [n=1; Hackett et al., 2003] and lorazepam [n=2; Feltner et al., 2003; Pande et al., 2003]): ES = 0.38; SSRI (paroxetine [n=2; Pollack et al., 2001; Rickels et al., 2003], sertraline [n=2; Rynn et al., 2001; Allgulander et al., 2004], fluvoxamine [n=1; Walkup, Labellarte, Riddle et al., 2001], and escitalopram [n=3; Davidson, Bose, Korotzer & Zheng, 2004; Goodman, Bose & Wang, 2005 and unpublished data from Forest laboratories): ES = 0.36; and, azapirones (buspirone, n=1; Davidson et al., 1999): ES = 0.17 (Hidalgo et al., 2007). These data suggest a moderate overall effect for drug therapy in the treatment of GAD. However, compared to other anxiety disorders, GAD was found to have a lower response to treatment (Hidalgo et al., 2007). For example, larger mean effect sizes have been reported for the use of pharmacotherapy among OCD (ES = 0.45-1.48, Greist, Jefferson, Kobak, Katzelnick & Serlin, 1995) and PD patients (ES = 0.55, Otto, Tuby, Gould, McLean & Pollack, 2001).

Antidepressants

Antidepressants, particularly SSRIs and more recently serotonin norepinephrine reuptake inhibitors (SNRI), have been recommended as first line medications for the treatment of GAD both because of extensive evidence regarding the potential efficacy of those drugs and because of the relatively positive side-effect profile. Relevant evidence regarding the efficacy of the most frequently utilized pharmacological therapies is presented below.

SSRIs

SSRIs have been recommended as first line medications for the treatment of GAD due in large part to a more favorable side-effect profile compared with some other drug classes (Davidson et al., 2010; Hoffman & Mathew, 2008). Although paroxetine and escitalopram are two of the only FDA approved SSRIs for the treatment of GAD (Hoffman & Mathew, 2008), level 1 evidence, which is established by results of more than one placebo-controlled trial having

total sample sizes over 30 (see Davidson et al., 2010), exists for and supports the efficacy of several SSRI drugs in GAD treatment including escitalopram (Davidson et al., 2004), paroxetine-immediate release (Pollack et al., 2001; Rickels et al., 2003), and sertraline (Allgulander et al., 2004; Morris, Dahl, Kutcher, Sogaard, Allgulander & Burt, 2003). For example, an 8-week randomized, double-blind, placebo-controlled investigation of the efficacy of daily flexible (20-50 mg) dosages of paroxetine in the treatment of symptoms among 324 outpatients with GAD revealed significantly greater reduction of GAD symptoms as measured by the HAM-A and the anxiety scale of the Hospital Anxiety and Depression Scales compared to placebo controls (Pollack et al., 2001). Similar evidence is provided by an 8-week examination of the efficacy of two fixed doses of paroxetine (20 or 40 mg daily) in the treatment of symptoms among 566 outpatients with GAD that showed significantly greater reductions in total HAM-A score compared to placebo (Rickels, Zaninelli, McCafferty, Bellew, Iyengar & Sheehan, 2003). Remission, defined as a HAM-A score ≤7, was realized in 30% and 36% of outpatients in the treatment groups, demonstrating the efficacy of paroxetine as a treatment for GAD (Rickels et al., 2003).

SNRIs

Serotonin and norepinephrine reuptake inhibitors, particularly FDA approved venlafaxine and duloxetine, are a novel class of antidepressants that have received empirical attention in the past decade and are emerging as first line medications in the treatment of GAD (Hoffman & Mathew, 2008). Meta-analytic evidence has demonstrated the efficacy of venlafaxine, showing that, among 5 clinical trials, 56% of individuals with GAD showed at least a 50% decrease in symptoms following 8 weeks of venlafaxine treatment (Pollack, Meoni, Otto & Hackett, 2003). Davidson and colleagues (2010) more recently reported that level 1 evidence supporting the use

of SNRI drugs in patients meeting DSM-IV criteria for GAD (i.e., Allgulander et al., 2001; Davidson et al., 1999; Hartford et al., 2007; Koponen et al., 2007; Rickels et al., 2000; Rynn et al., 2008). For example, a 24-week, double-blind, placebo-controlled investigation of three fixed doses (37.5, 75 and 150 mg daily) of venlafaxine extended release (XR) among 541 outpatients with GAD demonstrated that all doses of venlafaxine XR significantly reduced anxiety symptoms compared to placebo (Allgulander et al., 2001). Similarly, a flexible daily dose of venlafaxine XR (75-225 mg) significantly reduced HAM-A total scores ≥40% beginning during week 1 (Gelenberg et al., 2000). However, conflicting evidence has been provided by an 8-week study that noted no significant differences in HAM-A total scores between a fixed daily dosage of venlafaxine XR, diazepam, or placebo (Hackett et al., 2003). Regarding adverse events, although venalafaxine XR and paroxetine both significantly reduced HAM-A total scores among GAD patients in an 8-week open-label investigation, paroxetine led to significant weight gain while venlafaxine XR elicited significant increases in both systolic and diastolic blood pressure (Kim, Pae, Yoon et al., 2006).

The efficacy of duloxetine has been demonstrated via results of a pooled analysis of three clinical trials (Allgulander, Hartford, Russell et al., 2007). Results from three double-blind, placebo-controlled trials, two of which were 10-week flexible dose (60-120 mg/day) and one which was a 9-week fixed dose (60 or 120 mg/day), demonstrated significantly improved HAM-A total scores in duloxetine-treated patients compared to placebo controls (Allgulander et al., 2007). However, although a comparable 9-week investigation of 513 GAD patients showed significantly reduced HAM-A scores for both a 60 mg/day dose and a 120 mg/day dose compared to placebo, the rate of discontinuation due to adverse events was 11.3% for the 60 mg dose and 15.3% for the 120 mg dose (Koponen et al., 2007).

A smaller amount of evidence exists regarding the efficacy of other antidepressant treatments. One placebo-controlled investigation of the efficacy of imipramine, trazodone and diazepam demonstrated greater efficacy of imipramine and trazodone in attenuating anxiety symptoms among patients meeting DSM-III criteria for GAD compared to placebo (Rickels, Downing, Schweizer & Hassman, 1993). However, caution has been suggested in recommending such drugs as first line treatments due in large part to poorer tolerability and a higher risk of adverse side effects (Davidson et al., 2010).

Antidepressant Treatment Nonadherence

Treatment non-adherence to antidepressants is a fundamental issue regarding pharmacotherapy for GAD primarily because higher relapse rates are associated with early discontinuation of drug therapy (Davidson et al., 2010). Non-adherence rates among individuals with GAD mimic those of MDD and have been reported to be as high as 50% within the first 3 months of treatment (Davidson et al., 2010; Lin, Von Korff, Katon et al., 1995; Lin, Von Korff, Ludman et al., 2003). There is a plethora of reasons for non-adherence, including adverse side effects (e.g., weight gain), perceived lack of efficacy, symptom improvement, ambivalence regarding treatment, and the stigma associated with the use of psychoactive medication (Davidson et al., 2010). Moreover, evidence has suggested that individuals with GAD who are characterized by impulsiveness, novelty seeking traits, and illustrate a disdain for regimentation appear to be at higher risk for treatment non-adherence (Wingerson, Sullivan, Dager, Flick, Dunner & Roy-Byrne, 1993). Also, GAD patients, who often present with cardiovascular and gastrointestinal symptoms, may be highly sensitive to some of the side effects of antidepressant drug therapies (Davidson et al., 2010).

Azapirones

Azapirones, such as buspirone, are partial 5-HT1A agonists that have increasingly received attention as pharmacological treatment options for GAD because some have contended that azapirones have sustained tolerability and reduced addictive potential (Hoffman & Mathew, 2008). A meta-analytic review of the efficacy of various classes of drug treatment for GAD showed an aggregated effect size of $g = 0.30$ for 10 studies that examined the efficacy of azapirones (mostly buspirone) among individuals meeting DSM-III or DSM-IIIR criteria for GAD (Mitte et al., 2005). Based on the results, the authors suggested that azapirones were as effective as benzodiazepines in the reduction of anxiety symptoms among individuals with GAD. However, Davidson and colleagues (2010) do not recommend azapirones as first line treatments because of delayed onset of action, variable tolerability, and lack of efficacy in recent BZD users.

Benzodiazepines

Benzodiazepines have been the most frequently examined pharamacological treatment for GAD and have shown adequate efficacy, a rapid onset of action, an acceptable side-effect profile and good tolerability (Davidson et al., 2010; Rickels & Rynn, 2002). Results from a meta-analytic review of 48 studies which examined the efficacy of pharmacological treatment in GAD revealed a mean effect size of $g = 0.32$ for 37 effects derived from studies of benzodiazepines (Mitte et al., 2005). The use of BZDs in GAD treatment also has been particularly appealing due to the propensity of BZDs to preferentially affect somatic symptoms which frequently cause significant impairment (Rickels et al., 1993). Moreover, because insomnia is a frequently presented symptom among individuals with GAD, BZDs may also be

appealing based on evidence indicating BZDs are better for sleep than SSRIs and can be used as hypnotics (Davidson et al., 2010).

Although meta-analytic results seemingly provide a substantial body of supportive evidence for the short-term efficacy of BZDs (Davidson et al., 2010), a more recent meta-analytic review did not find compelling evidence for the short-term effectiveness of BZDs (Martin, Sainz-Pardo, Furukawa, Martin-Sanchez, Seoane & Galan, 2007). Concern also has been expressed about the potential risk for abuse and physiological dependence associated with long-term BZD use (O'Brien, 2005). BZD use also has been contradicted in patients characterized by hostility, impatience, irritability and impulsivity (Rosenbaum, Woods, Groves & Klerman, 1984).

Psychosocial

Several psychosocial therapies effectively treat GAD and do so without the adverse side effects often encountered with pharmacotherapy. Tyrer and Baldwin (2006) reported that the most commonly utilized psychosocial treatments have been cognitive and behavioral treatments including cognitive behavioral therapy (CBT), dynamic psychotherapy, and anxiety-management training. Additional empirical attention has been focused on applied relaxation (Borkovec & Costello, 1993), worry exposure (Hoyer, Beesdo, Gloster, Runge, Hofler & Becker, 2009), metacognitive therapy (Wells & King, 2006) and integrative therapy (Newman, Castonguay, Borkovec, Fisher & Nordberg, 2008). However, because CBT has been the predominant focus of empirical investigations of the efficacy of psychosocial treatments, the extant evidence of the efficacy of CBT in the treatment of GAD will be highlighted in the following section.

Cognitive-Behavioral Therapy (CBT)

Cognitive-behavioral therapy (CBT), the most frequently employed psychosocial treatment for GAD, has been classified as a well-established empirically supported treatment (EST) approach for GAD by multiple work groups targeting the elucidation of effective practice-based treatment approaches (Chambless, Baker, Baucom et al., 1998; Kendall & Chambless, 1998; Nathan & Gorman, 1998; Roth & Fonagy, 1996). CBT primarily involves cognitive restructuring, relaxation, worry exposure, behavior modification, and problem solving (Hoehn-Saric, 2007; Lang, 2004). A review of the extant literature has shown that CBT significantly improves symptoms among individuals with GAD compared with no treatment, analytic psychotherapy, non-directive therapy, pill placebos and other placebos (Borkovec & Ruscio, 2001). For example, an examination of the effect of CBT, analytical psychotherapy, and anxiety-management training indicated that CBT resulted in significantly better symptom improvement at both the endpoint of treatment and at a 6 month follow-up compared to both analytical psychotherapy and anxiety-management training (Durham, Murphy, Allan, Richard, Treliving & Fenton, 1994). More recently, a randomized clinical trial examined the efficacy of 12 weeks of CBT in GAD symptom reduction compared to enhanced usual care in 134 older adults with GAD in primary care (Stanley, Wilson, Novy et al., 2009). Results indicated that CBT elicited significantly larger improvements in worry severity, as measured by the PSWQ, and depressive symptoms, as measured by the BDI-II, compared to enhanced usual care (Stanley et al., 2009).

Meta-analytic evidence has supported the efficacy of CBT in the treatment of GAD compared to both placebo and other well-established treatments. For example, a meta-analytic review of randomized, placebo-controlled trials of the efficacy of CBT for anxiety disorders

among adults reported an aggregated effect size for studies of GAD patients of $g = 0.51$ (95% CI, 0.05 to 0.97) compared with placebo conditions (Hofmann & Smits, 2008). Meta-analytic evidence also has shown comparable efficacy for CBT when compared with pharmacotherapy. In a quantitative review of 35 studies, CBT was shown to be the most effective psychosocial treatment with a mean effect size (0.70) similar to pharmacological treatment (0.60) (Gould, Otto, Pollack & Yap, 1997). The authors updated that meta-analysis and concluded that CBT is efficacious for GAD symptom reduction in the short- and long-term (Gould, Safren, Washington & Otto, 2004). A number of salient results were reported in a more recent meta-analytic review of the available evidence from investigations of CBT and pharmacotherapy (Mitte, 2005). Compared to no treatment control conditions, CBT resulted in a mean effect size of 0.82 (95% CI, 0.62 to 1.01), while comparison with placebo control conditions resulted in an aggregated effect size of 0.57 (95% CI, 0.30 to 0.85) (Mitte, 2005). More importantly, effect sizes computed from studies directly comparing CBT and pharmacotherapy revealed no significant differences in the efficacy of the two therapy approaches, suggesting that CBT may be as effective in the treatment of GAD as drug therapy (Mitte, 2005).

Some controversy has emerged from separate meta-analytic reviews regarding both the long-term efficacy of GAD and the focus of previous meta-analyses on outcome measures that assessed general anxiety and therefore lacked sufficient GAD symptom specificity. Westen and Morrison (2001) conducted a meta-analytic review of the effectiveness of ESTs for GAD that comprised a cognitive or behavioral component. Based on a small number of results, the authors concluded that, although CBT produced significant, meaningful symptom reductions initially, the available evidence failed to support the long-term efficacy of CBT (Westen & Morrison, 2001). However, this conclusion was in stark contrast to previous meta-analytic reviews that

provided support for the short- and long-term efficacy of CBT (Gould et al., 2004). Westen and Morrison's contentions stimulated some researchers to argue that the outcome measures used within their meta-analysis did not adequately assess the fundamental component of GAD, pathological worry (Aikins, Hazlett-Stevens & Craske, 2001). To address these issues, Covin and colleagues (2008) conducted a meta-analysis of the efficacy of CBT in reducing pathological worry, the cardinal symptom of GAD, to estimate the mean effect for studies using the PSWQ as the primary outcome measure (Covin, Ouimet, Seeds & Dozois, 2008). The overall effect size (-1.15) was moderated by age and treatment modality such that larger reductions in pathological worry were found among younger adults and for individual treatment (Covin et al., 2008). To address the issue concerning the long-term efficacy of CBT, a subanalysis revealed maintenance of symptom reduction at 6- and 12-month follow-up (Covin et al., 2008).

The extant evidence suggests that CBT is more effective than other empirically-examined psychosocial therapies and has comparable efficacy to pharmacotherapy. However, less favorable outcomes have been reported for CBT when clinical, as opposed to statistical, significance is used as the outcome criterion (Borkovec, Newman, Pincus & Lytle, 2002). Thus, there is a need for continued empirical research into the efficacy of psychosocial treatments.

Physical Activity and GAD

Population-based

The extant literature regarding the effects of physical activity on GAD has been limited. Nonetheless, at least three large population-based studies have shown an approximately 23%-53% reduced odds of GAD among individuals who reported regular physical activity compared to individuals reporting non-regular or no physical activity. Using data from the National Comorbidity Study, regular physical activity was associated with a significantly decreased

likelihood of GAD (OR = 0.61; 95%CI: 0.42 to 0.88) among 8098 Americans aged 15-54 reporting regular physical activity compared to no activity after adjusting for sociodemographic variables and physical illnesses (Goodwin, 2003). A separate 4-year prospective longitudinal study of 2548 German nationals aged 14-24 at the outset of the study showed that subjects reporting regular physical activity had 23% reduced odds (OR=0.77; 95%CI: 0.30 to 2.01) of experiencing GAD during the course of the study (Strohle et al., 2007). After adjusting for sociodemographic variables, certain chronic diseases and stressful life events, findings from the first Israeli National Health Interview Survey (N=2082) similarly indicated an approximately 53% reduction (OR=0.47; 95%CI: 0.2 to 1.14) in the odds of GAD among individuals who reported regular physical activity compared to individuals reporting no regular physical activity (Muhsen, Lipsitz, Garty-Sandalon, Gross & Green, 2008). Although limited, the available evidence suggests that regular physical activity can reduce the likelihood of GAD.

Experimental

There is a paucity of compelling evidence of the effects of exercise training on GAD in large part because of the extremely limited number of exercise training interventions that have been conducted with individuals diagnosed with GAD. Randomized controlled trial (RCT) research designs are necessary to draw the most definitive conclusions regarding the effect of physical activity on GAD. No RCT that has focused on individuals with GAD has been conducted. However, the effect of adding a moderate intensity home-based exercise program to 8-10 weeks of group cognitive-behavioral therapy (GCBT) was examined in a randomized, controlled trial of 74 patients with social phobia, GAD, or panic disorder (Merom et al., 2008). The authors reported that the addition of exercise to GCBT resulted in large reductions (ES=1.36) in anxiety compared to the GCBT control condition (Merom et al., 2008).

Methodological limitations of this study, including no standardization of the exercise stimulus or intensity and a sample that included individuals with various anxiety disorders (i.e., 35% diagnosed with GAD), diminish the ability to draw meaningful conclusions relative to exercise training dose effects on GAD. Given the lack of compelling evidence, there is a clear, strong need for RCTs of the effect of exercise training among individuals with GAD. Thus, one primary goal of this dissertation is to conduct an RCT of the effects of resistance exercise training or aerobic exercise training compared to a wait list control among sedentary women diagnosed with GAD.

Plausible Mechanisms for the Anxiolytic Effects of Exercise

There have been a number of putative mechanisms suggested to underlie the anxiolytic effects of exercise. Although there have been some minimally invasive studies in humans, a preponderance of the information regarding plausible mechanisms for the anxiolytic effects of exercise has been derived from studies of animals. The different mechanisms can be broadly categorized in two groups: cognitive/psychological mechanisms and physiological/neurobiological mechanisms.

Cognitive/Psychological

Distraction/Time-out Hypothesis

Bahrke and Morgan (1978) postulated that exercise can distract attention from anxiety-provoking thoughts and thereby produce a "time-out" from daily cares and worries. The distraction hypothesis has been tested for a single bout of exercise. State anxiety (STAI; Speilberger et al., 1983) was measured in 18 high trait-anxious college females before and after exercise at moderate (40% aerobic capacity) intensity, exercise while studying, studying only, and quiet rest (Breus & O'Connor, 1998). No significant decrease in anxiety was reported for

exercise while studying, studying only, or quiet rest. There was a significant anxiety reduction after the exercise-only condition (d = 0.52), providing support for the distraction hypothesis. Other psychological mechanisms have been proposed for the effects of exercise on anxiety reductions including an increase in competence, social interaction associated with exercise programs, expectancy effects (e.g., expecting a gain in psychological benefits from exercise; Berger, Owen, Motl & Parks, 1998), and enjoyment (Motl, Berger & Leuschen, 2000).

Exposure

Some researchers have posited that exercise may exert anxiolytic effects through the modification of self-perpetuating patterns of avoidance by teaching persistence in the presence of negative somatic challenges (Smits, Berry, Powers, Greer & Otto, 2008; Stathopoulou, Powers, Berry, Smits, & Otto, 2006). That is, exercise can be viewed as an adaptive activity that may facilitate the pursuit of goals in the presence of aversive thoughts or feelings of apprehension. Exercise also may function as a form of interoceptive exposure because it increases arousal, essentially providing exposure to the somatic symptoms of anxiety within a controlled environment (Smits et al., 2008). However, this hypothesis has not yet been adequately tested.

Physiological/Neurobiological

Exercise also may improve brain health, and therefore plausibly exert anxiolytic effects, by directly acting on the neurobiological system including neural tissue, neuromodulators and neurotransmitters. Most of the understanding of neurobiological mechanisms has built upon studies of animal behavior. Several behaviors have been considered reflective of anxiety-like responses in rats. Increased locomotion in rats usually reflects an adaptive motivational state of low behavioral inhibition (e.g. less freezing), especially in purposeful locomotion, and animals also exhibit other behaviors such as approaching the center of an open-field. Low levels of

locomotion, freezing, few approaches to center of open-field, defecation, urination, and shivering are regarded as responses comparable to human anxiety. For example, the limbic-motor integration model, expounded upon by Mogenson (1987) has been shown relevant for the study of physical activity and anxiety behaviors (Dishman, 1997). According to this model, fearful locomotion is controlled by limbic system modulation of the tegmental pedunculopontine nucleus of the mesencephalic locomotor system by reciprocal inhibition between GABA and DA transmission within the corpus striatum. GABA efferents from the nucleus accumbens to the ventral pallidum are thought to inhibit locomotion (Dishman, 1997).

In animals, exercise has been shown to affect: (i) anxiety-like behavior as measured with acoustic startle, stress-induced hyperthermia, social interaction, light-enhanced startle, and some, but not all, measures in the open field (Salam, Fox, DeTroy, Guignon, Wohl & Falls, 2009), (ii) neurogenesis and neuronal survival (van Praag, Christie Sejnowski & Gage, 1999; van Praag, Chunm & Gage, 2005; van Praag, Kempermann & Gage, 1999; van Praag, Kempermann & Gage, 2000), (iii) angiogenesis (Swain, Harris, Wiener et al., 2003), (iv) the expression of neurotrophic factors (Duman, Schlesinger, Russel & Duman, 2008; Gomez-Pinilla, Ying, Roy, Molteni & Edgerton, 2002; Neeper, Gomez-Pinilla, Choi & Cotman, 1995; Neeper, Gomez-Pinilla, Choi & Cotman, 1996; Vaynman, Ying & Gomez-Pinilla, 2004; Vaynman, Ying & Gomez-Pinilla, 2004), and (v) serotonergic (Chen, Lin, Yu et al., 2008; Greenwood, Foley, Day et al., 2005; Greenwood, Foley, Day et al., 2003; Greenwood, Strong, Brooks & Fleshner,2008), noradrenergic (Dishman, Hong, Soares et al., 2000; Dunn, Reigle, Youngstedt, Armstrong & Dishman, 1996; Soares, Holmes, Renner, Edwards, Bunnell & Dishman, 1999) and GABAergic (Dishman, Dunn, Youngstedt et al., 1996) neurotransmitter systems. Because the wealth of mechanistic investigations of the anxiolytic effects of exercise have focused on neurotransmitters

and neuromodulators, the following sections focus on the effects of exercise on the serotonergic, noradrenergic, and GABAergic systems.

Serotonergic

Serotonergic function, particularly dysregulation of the serotonergic system, has been linked to the pathogenesis of anxiety. Substantial evidence from investigations of humans and animals suggests a plausible mitigating role of serotonergic function underlying the anxiolytic effects of exercise. In humans, evidence has largely focused on the ability of exercise to alter the release and metabolism of 5-hydroxytryptamine (5-HT) in the brain (Chaouloff, 1997). Exercise induces the breakdown of triglycerides into free fatty acids (FFA), which subsequently are used to fuel increased levels of muscular contraction (Davis, Bailey, Woods, Galiano, Hamilton & Bartoli, 1992). Increased serum levels of FFA compete with tryptophan to bind with albumin, leading to increases in unbound tryptophan due to FFA preferential binding affinity (Blomstrand, Celsing & Newsholme, 1988; Chaouloff, Laude & Elghozi, 1989). The increased unbound tryptophan stimulates an influx of tryptophan into the brain and thus the potential for increased synthesis of 5-HT (Chaouloff, 1997).

Two studies in humans have used meta-chlorophenyl-piperazine (m-CPP), a well-established probe of serotonergic function with the highest affinity to 5-HT_{2C} receptors (Hoyer & Schoeffter, 1991) which elicits anxiety reactions in the majority of PD patients but in a minority of controls (Charney, Woods, Goodman & Heninger, 1987). One study comparing marathon runners to healthy controls showed that m-CPP was associated with a significantly reduced cortisol response and a blunted prolactin response among marathon runners, whereas ipsapirone administration resulted in a significant cortisol increase among both groups (Broocks, Meyer, George et al., 1999). The authors interpreted these findings as a selective downregulation of 5-

HT_{2C} receptors by exercise (Broocks et al., 1999). A second double-blind randomized trial showed a blunted cortisol response to m-CPP among 12 untrained volunteers following 10 weeks of 3 sessions per week of moderate-intensity aerobic exercise (Broocks, Meyer, Gleiter et al., 2001). Again, these authors suggested that the findings might reflect a downregulation of central 5-HT_{2C} receptors (Broocks et al., 2001).

Several animal studies also have shown altered serotonergic function in response to exercise. Increased 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) have been shown in the rat hippocampus following acute intense exercise (Gomez-Merino, Bequet, Berthelot, Chennaoui & Guezennec, 2001). A more recent investigation of four weeks of treadmill exercise training among rats showed reduced 5-HT levels in the hippocampus and diminished 5-HT_{1A} receptor expression in the amygdala (Chen, Lin, Yu et al., 2008). A number of additional investigations have used acute administration of a selective 5-HT reuptake inhibitor (SSRI), which has been shown to elicit anxiety-like behavior in rodent models of anxiety (Bagdy, Graf, Anheuer, Modos & Kantor, 2001; Belzung, Le Guisquet, Barreau & Calatayud, 2001; Burghardt, Bush, McEwen & LeDoux, 2007) to assess behavioral responses among rats allowed access to running wheels compared to sedentary rats. For example, rats allowed 6 weeks of access to running wheels showed reductions in dorsal raphe nucleus hyperactivity and anxiety-like behavioral responses including exaggerated shock-elicited freezing and shuttle box escape deficits in response to acute SSRI administration (Greenwood, Foley, Day et al., 2005; Greenwood, Foley, Day et al., 2003). Similarly, results of a more recent investigation showed that rats given access to running wheels for 6 weeks were protected againsts anxiety-like behavioral responses elicited by an 10 mg/kg injection of fluoxetine (Greenwood, Strong, Brooks

& Fleshner, 2008). Thus, there is clear evidence for a plausible role of serotonergic function in the anxiolytic effects of exercise.

Noradrenergic

Human and animal studies have suggested the role of noradrenergic modulation of the anxiolytic effects of exercise. Exercise-induced increases in the release of norepinephrine (NE) have been associated with decreased anxiety (Pagliari & Peyrin, 1995). Evidence has indicated that endurance-trained athletes have a higher than normal β-adrenoreceptor density on lymphocytes and that a session of prolonged high intensity physical activity is accompanied by increased β-adrenoreceptor density on lymphocytes (Schaller, Mechau, Scharmann, Weiss, Baum & Liesen, 1999). However, while lymphocyte β-adrenoreceptors may provide a peripheral index of noradrenergic activity, they do not provide a measure of brain noradrenergic activity. Additionally, given that growth hormone is increased in response to resistance exercise training exercise, it is particularly salient that the α2-adrenoreceptor agonist clonidine has reliably resulted in altered growth hormone (GH) responses among panic disorder patients (Abelson, Glitz, Cameron, Lee, Bronzo & Curtis, 1992; Brambilla, Bellodi, Arancio, Nobile & Perna, 1995; Coplan, Papp, Martinez et al., 1995) and among individuals with GAD (Abelson et al., 1991).

Changes in brain noradrenergic activity have been estimated via measurements of 3-methoxy-4-hydroxyphenylglycol (MHPG; NE metabolite) levels in the urine, plasma, or cerebrospinal fluid (CSF). Although investigations of urinary MHPG after a single session of physical activity have shown increased MHPG excretion or no change, the fact that increases in plasma levels of norepinephrine during exercise result mainly from sympathetic nerves

innervating the heart with some contribution from exercising skeletal muscles makes the relevance of increased plasma MHPG following exercise unclear for anxiety (Dishman, 1998).

A number of investigations using rats have shown effects of exercise on noradrenergic activity in brain regions thought to be important to anxiety-like behavior. For example, exercise training has been shown to increase levels of norepinephrine in the locus coeruleus (LC), amygala, hippocampus, and hypothalamus (Dishman, Hong, Soares et al., 2000). One investigation examined norepinephrine, MHPG and 3,4 dihydroxyphenylglycol (DHPG) in the frontal cortex, hippocampus, pons-medulla and spinal cord among 36 rats randomly assigned to 24-hour access to a running wheel, treadmill running for 1 hour per day or sedentary control for 8 weeks (Dunn, Reigle, Youngstedt, Armstrong & Dishman, 1996). The findings suggested that treadmill training is associated with increased noradrenergic metabolism in areas containing noradrenergic cell bodies and ascending terminals (Dunn et al., 1996). Results also indicated that treadmill training and wheel running are accompanied by increases in norepinephrine levels in areas containing noradrenergic cell bodies and in the spinal cord (Dunn et al., 1996). A separate investigation showed that norepinephrine levels in the frontal cortex of rats randomly assigned to shoebox cages with 24-hour access to activity wheels for 4-5 weeks were significantly lower during and following footshock compared to sedentary rats (Soares, Holmes, Renner, Edwards, Bunnell & Dishman, 1999). Although some inconsistencies are present, the wealth of the available evidence suggests that noradrenergic function is a plausible mechanism of the anxiolytic effects of exercise.

GABA/BZD

A limited amount of evidence supports GABA/BZD as a mechanism underlying the anxiolytic effects of exercise. In an investigation of chronic activity-wheel running and treadmill

training effects on the central nervous system neurotransmitter system in rats, the activity-wheel running condition showed increased levels of GABA and a decreased number of $GABA_A$ in the corpus striatum and increased open-field locomotion (Dishman et al., 1998). These findings are consistent with an anxiolytic effect according to the limbic-motor integration model of locomotor behavior proposed by Mogensen (1987).

References

Abelson, J. L., Glitz, D., Cameron, O. G., Lee, M. A., Bronzo, M., & Curtis, G. C. (1991). Blunted growth hormone response to clonidine in patients with generalized anxiety disorder. *Archives of General Psychiatry*, *48*(2), 157-162.

Addolorato, G., Caputo, F., Capristo, E., Domenicali, M., Bernardi, M., Janiri, L. et al. (2002). Baclofen efficacy in reducing alcohol craving and intake: A preliminary double-blind randomized controlled study. *Alcohol and Alcoholism, 37*, 504-508.

Addolorato, G., Mirijello, A., D'Angelo, C., Leggio, L., Ferrulli, A., Abenavoli, L. et al. (2008). State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting. *International Journal of Clinical Practice*, *62*(7), 1063-1069.

Ahmed, I., & Takeshita, J. (1996). Clonidine: A critical review of its role in the treatment of psychiatric disorders. *CNS DRUGS*, *6*, 53-70.

Aikins, D. E., Hazlett-Stevens, H., & Craske, M. G. (2001). Issues of measurement and mechanism in meta-analyses: Comment on Westen and Morrison (2001). *Journal of Consulting and Clinical Psychology*, *69*(6), 904-907.

Akiskal, H. S. (1998). Toward a definition of generalized anxiety disorder as an anxious temperament type. *Acta Psychiatrica Scandinavica*, *98*, 66-73.

Allgulander, C., Dahl, A. A., Austin, C., Morris, P. L. P., Sogaard, J. A., Fayyad, R. et al. (2004). Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *American Journal of Psychiatry*, *161*(9), 1642-1649.

Allgulander, C., Hackett, D., & Salinas, E. (2001). Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: Twenty-four-week placebo-controlled dose-ranging study. *The British Journal of Psychiatry*, *179*(1), 15-22.

Allgulander, C., Hartford, J., Russell, J., Ball, S., Erickson, J., Raskin, J. et al. (2007). Pharmacotherapy of generalized anxiety disorder: results of duloxetine treatment from a pooled analysis of three clinical trials. *Current Medical Research and Opinion*, *23*(6), 1245-1252.

Alsene, K., Deckert, J., Sand, P., & de Wit, H. (2003). Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology*, *28*(9), 1694-1702.

Altman, J. D., Trendelenburg, A. U., MacMillan, L., Bernstein, D., Limbird, L., Starke, K. et al. (1999). Abnormal regulation of the sympathetic nervous system in a2A-adrenergic receptor knockout mice. *Molecular Pharmacology*, *56*(1), 154-161.

American Psychiatric Association (1980). *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*. Washington, DC: American Psychiatric Association.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)*. Washington, DC: American Psychiatric Association.

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington, DC: American Psychiatric Association.

Anthony, E. W., & Nevins, M. E. (1993). Anxiolytic-like effects of N-methyl-D-aspartate-associated glycine receptor ligands in the rat potentiated startle test. *European Journal of Pharmacology*, *250*(2), 317-324.

Antunes, H. K. M., Stella, S. G., Santos, R. F., Bueno, O. F. A., & Mello, M. T. (2005). Depression, anxiety and quality of life scores in seniors after an endurance exercise program. *Revista Brasileira de Psiquiatria*, *27*, 266-271.

Arborelius, L., Owens, M. J., Plotsky, P. M., & Nemeroff, C. B. (1999). The role of corticotropin-releasing factor in depression and anxiety disorders. *Journal of Endocrinology*, *160*(1), 1-12.

Argyropoulos, S. V., Hood, S. D., Adrover, M., Bell, C. J., Rich, A. S., Nash, J. R. et al. (2004). Tryptophan depletion reverses the therapeutic effect of selective serotonin reuptake inhibitors in social anxiety disorder. *Biological Psychiatry*, *56*(7), 503-509.

Asmundson, G. J. G., Sandler, L. S., Wilson, K. G., & Walker, J. R. (1992). Selective attention toward physical threat in patients with panic disorder. *Journal of Anxiety Disorders*, *6*(4), 295-303.

Aston-Jones, G., Akaoka, H., Charlety, P., & Chouvet, G. (1991). Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus coeruleus neurons. *Journal of Neuroscience*, *11*(3), 760-769.

Atkinson, J. H., Slater, M. A., Patterson, T. L., Grant, I., & Garfin, S. R. (1991). Prevalence, onset, and risk of psychiatric disorders in men with chronic low back pain: a controlled study. *Pain*, *45*(2), 111-121.

Bäckmand, H., Kaprio, J., Kujala, U., & Sarna, S. (2003). Influence of physical activity on depression and anxiety of former elite athletes. *International Journal of Sports Medicine*, *24*(8), 609-619.

Bagdy, G., Graf, M., Anheuer, Z. E., Modos, E. A., & Kantor, S. (2002). Anxiety-like effects induced by acute fluoxetine, sertraline or m-CPP treatment are reversed by pretreatment with the 5-HT2C receptor antagonist SB-242084 but not the 5-HT1A receptor antagonist WAY-100635. *The International Journal of Neuropsychopharmacology*, *4*(04), 399-408.

Bahrke, M., & Morgan, W. P. (1978). Axniety reduction following exercise and meditation. *Cognitive Therapy and Research, 2*(4), 323-333.

Bailey, J. E., Kendrick, A., Diaper, A., Potokar, J. P., & Nutt, D. J. (2007). A validation of the 7.5% CO2 model of GAD using paroxetine and lorazepam in healthy volunteers. *Journal of Psychopharmacology*, *21*(1), 42-49.

Bailey, J. E., Papadopoulos, A., Seddon, K., & Nutt, D. J. (2009). A comparison of the effects of a subtype selective and non-selective benzodiazepine receptor agonist in two CO2 models of experimental human anxiety. *Journal of Psychopharmacology*, *23*(2), 117-122.

Baldwin, H. A., & File, S. E. (1988). Reversal of increased anxiety during benzodiazepine withdrawal: evidence for an anxiogenic endogenous ligand for the benzodiazepine receptor. *Brain Research Bulletin*, *20*(5), 603-606.

Ballenger, J. C. (1999). Clinical guidelines for establishing remission in patients with depression and anxiety. *The Journal of Clinical Psychiatry*, *60*, 29-34.

Banki, C. M., Karmacsi, L., Bissette, G., & Nemeroff, C. B. (1992). CSF corticotropin-releasing hormone and somatostatin in major depression: response to antidepressant treatment and relapse. *European Neuropsychopharmacology*, *2*(2), 107-113.

Bar-Haim, L., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M., & van IJzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychological Bulletin*, *133*, 1–24.

Bar-Haim, Y., Lamy, D., & Glickman, S. (2005). Attentional bias in anxiety: A behavioral and ERP study. *Brain and Cognition*, *59*(1), 11-22.

Barlow, D. H. (1988). *Anxiety and its disorders: the nature and treatment of anxiety and panic*. New York: Guilford Press.

Barlow, D. H. (1991). The nature of anxiety: Anxiety, depression, and emotional disorders. In RM Rapee & DH Barlow (Eds.) *Chronic anxiety: Generalized anxiety disorder and mixed anxiety-depression* (pp. 1-28). New York: Guilford.

Barlow, D. H. (2002). *Anxiety and its disorders*. New York: Guilford Press.

Barlow, D. H., Chorpita, B. F., & Turovsky, J. (1996). Fear, panic, anxiety, and disorders of emotion. In D.A. Hope (Ed.), *Nebraska Symposium on Motivation: Vol. 43. Perspectives on anxiety, panic, and fear.* Lincoln: University of Nebraska Press.

Barnard, E. A., Skolnick, P., Olsen, R. W., Mohler, H., Sieghart, W., Biggio, G. et al. (1998). International Union of Pharmacology. XV. Subtypes of γ-aminobutyric $acid_A$ receptors: Classification on the basis of subunit structure and receptor function. *Pharmacological Reviews*, *50*(2), 291-314.

Barnes, L. L. B., Harp, D., & Jung, W. S. (2002). Reliability generalization of scores on the Spielberger state-trait anxiety inventory. *Educational and Psychological Measurement*, *62*(4), 603-618.

Barr, R. G., Rowe, B. H., & Camargo, C. A. (2003). Methylxanthines for exacerbations of chronic obstructive pulmonary disease: Meta-analysis of randomised trials. *British Medical Journal*, *327*(7416), 643-645.

Beard, J. R., Dietrich, U. C., Brooks, L. O., Brooks, R. T., Heathcote, K., & Kelly, B. (2006). Incidence and outcomes of mental disorders in a regional population: the Northern Rivers Mental Health Study. *Australian and New Zealand Journal of Psychiatry*, *40*(8), 674-682.

Beck, A. T., & Emery, G. (1985). *Anxiety disorders and phobias: A cognitive perspective*. New York: Basic Books.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893-897.

Beck, A. T., Rush, A. J., Shaw, B. F., & Emery, G. (1979). *Cognitive theory of depression*. New York: Guilford.

Beck, A. T., & Steer, R. A. (1990). *Manual for the Beck Anxiety Inventory*. San Antonio, TX: Psychological Corporation.

Beck, J. G., Stanley, M. A., & Zebb, B. J. (1996). Characteristics of generalized anxiety disorder in older adults: A descriptive study. *Behaviour Research and Therapy*, *34*(3), 225-234.

Beekman, A. T. F., Bremmer, M. A., Deeg, D. J. H., Van Balkom, A., Smit, J. H., De Beurs, E. et al. (1998). Anxiety disorders in later life: A report from the Longitudinal Aging Study Amsterdam. *International Journal of Geriatric Psychiatry*, *13*(10), 717-726.

Beesdo, K., Hoyer, J., Jacobi, F., Low, N. C. P., Höfler, M., & Wittchen, H. U. (2009). Association between generalized anxiety levels and pain in a community sample: Evidence for diagnostic specificity. *Journal of Anxiety Disorders, 23*(5), 684-693.

Behar, E., Alcaine, O., Zuellig, A. R., & Borkovec, T. D. (2003). Screening for generalized anxiety disorder using the Penn State Worry Questionnaire: A receiver operating characteristic analysis. *Journal of Behavior Therapy and Experimental Psychiatry*, *34*(1), 25-43.

Belzung, C., Le Guisquet, A. M., Barreau, S., & Calatayud, F. (2001). An investigation of the mechanisms responsible for acute fluoxetine-induced anxiogenic-like effects in mice. *Behavioural Pharmacology*, *12*(3), 151-162.

Benvenga, M. J., Leander, J. D., & Ornstein, P. L. (1993). Anxiolytic effect of the competitive AMPA antagonist LY215490 in a pigeon punished responding model. *Social Neuroscience Abstracts, 19*, 293.

Berger, B. G., Owen, D. R., Motl, R. W., & Parks, L. (1998). Relationship between expectancy of psychological benefits and mood alteration in joggers. *International Journal of Sport Psychology*, *29*, 1-16.

Bergink, V., van Megen and, H., & Westenberg, H. G. M. (2004). Glutamate and anxiety. *European Neuropsychopharmacology*, *14*(3), 175-183.

Biala, G., & Kruk, M. (2009). Effects of co-administration of bupropion and nicotine or D-amphetamine on the elevated plus maze test in mice. *The Journal of Pharmacy and Pharmacology*, *61*(4), 493-502.

Biederman, J., Rosenbaum, J. F., Bolduc-Murphy, E. A., Faraone, S. V., Chaloff, J., Hirshfeld, D. R. et al. (1993). A 3-year follow-up of children with and without behavioral inhibition. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*, 814-821.

Biederman, J., Rosenbaum, J. F., Hirshfeld, D. R., Faraone, S. V., Bolduc, E. A., Gersten, M. et al. (1991). Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. *Annual Progress in Child Psychiatry and Child Development*, 269-284.

Binsinger, C., Laure, P., & Ambard, M. F. (2006). Regular extra curricular sports practice does not prevent moderate or severe variations in self-esteem or trait anxiety in early adolescents. *Journal of Sports Science and Medicine*, *5*, 123-129.

Bitsios, P., Szabadi, E., & Bradshaw, C. M. (1998). The effects of clonidine on the fear-inhibited light reflex. *Journal of Psychopharmacology*, *12*(2), 137-145.

Blomstrand, E., Celsing, F., & Newsholme, E. A. (1988). Changes in plasma concentrations of aromatic and branched-chain amino acids during sustained exercise in man and their possible role in fatigue. *Acta Physiologica Scandinavica*, *133*(1), 115-121.

Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, W. E., Herman, S., Khatri, P. et al. (1999). Effects of exercise training on older patients with major depression. *Archives of Internal Medicine, 159*, 2349-2356.

Blumenthal, J. A., Sherwood, A., Babyak, M. A., Watkins, L. L., Waugh, R., Georgiades, A., et al. (2005). Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: A randomized controlled trial. *JAMA,* 293, 1626-1634.

Borkovec, T. D., & Costello, E. (1993). Efficacy of applied relaxation and cognitive-behavioral therapy in the treatment of generalized anxiety disorder. *Journal of Consulting and Clinical Psychology*, *61*, 611-619.

Borkovec, T. D., & Mathews, A. M. (1988). Treatment of nonphobic anxiety disorders: A comparison of nondirective, cognitive, and coping desensitization therapy. *Journal of Consulting and Clinical Psychology*, *56*(6), 877-884.

Borkovec, T. D., Newman, M. G., Pincus, A. L., & Lytle, R. (2002). A component analysis of cognitive-behavioral therapy for generalized anxiety disorder and the role of interpersonal problems. *Journal of Consulting and Clinical Psychology*, *70*(2), 288-297.

Borkovec, T. D., & Ruscio, A. M. (2001). Psychotherapy for generalized anxiety disorder. Discussion. *The Journal of Clinical Psychiatry. Supplement*, *62*(11), 37-45.

Borsini, F., Podhorna, J., & Marazziti, D. (2002). Do animal models of anxiety predict anxiolytic-like effects of antidepressants? *Psychopharmacology*, *163*(2), 121-141.

Bowery, N. G., & Enna, S. J. (2000). γ-Aminobutyric $acid_B$ receptors: first of the functional metabotropic heterodimers. *Journal of Pharmacology and Experimental Therapeutics*, *292*(1), 2-7.

Bradley, B. P., Mogg, K., & Williams, R. (1995). Implicit and explicit memory for emotion-congruent information in clinical depression and anxiety. *Behaviour Research and Therapy*, *33*(7), 755-770.

Brambilla, F., Bellodi, L., Arancio, C., Nobile, P., & Perna, G. (1995). a2-Adrenergic receptor sensitivity in panic disorder: II Cortisol response to clonidine stimulation in panic disorder. *Psychoneuroendocrinology*, *20*(1), 11-19.

Breier, A., Charney, D. S., & Heninger, G. R. (1985). The diagnostic validity of anxiety disorders and their relationship to depressive illness. *American Journal of Psychiatry, 142*, 787-797.

Bremner, J. D., Krystal, J. H., Charney, D. S., & Southwick, S. M. (1996). Neural Mechanisms in dissociative amnesia for childhood abuse: relevance to the current controversy surrounding the" false memory syndrome." *American Journal of Psychiatry, 153*, 71-82.

Bremner, J. D., Krystal, J. H., Southwick, S. M., & Charney, D. S. (1996). Noradrenergic mechanisms in stress and anxiety: II. Clinical studies. *Synapse*, *23*(1), 39-51.

Brenes, G. A., Penninx, B. W., Judd, P. H., Rockwell, E., Sewell, D. D., & Wetherell, J. L. (2008). Anxiety, depression and disability across the lifespan. *Aging & Mental Health*, *12*(1), 158-163.

Breslau, J., Aguilar-Gaxiola, S., Kendler, K. S., Su, M., Williams, D., & Kessler, R. C. (2005). Specifying race-ethnic differences in risk for psychiatric disorder in a USA national sample. *Psychological Medicine*, *36*(01), 57-68.

Breslau, N., Davis, G. C., Andreski, P., & Peterson, E. (1991). Traumatic events and posttraumatic stress disorder in an urban population of young adults. *Archives of General Psychiatry*, *48*(3), 216-222.

Breus, M., & O'Connor, P. (1998). Exercise-induced anxiolysis: A test of the" time out" hypothesis in high anxious females. *Medicine & Science in Sports & Exercise*, *30*(7), 1107-1112.

Britton, K., Morgan, J., Rivier, J., Vale, W., & Koob, G. F. (1985). Chlordiazepoxide attenuates CRF-induced response suppression in the conflict test. *Psychopharmacology*, *86*, 170-174.

Britton, K. T., Lee, G., Dana, R., Risch, S. C., & Koob, G. F. (1986). Activating and anxiogenic effects of corticotropin releasing factor are not inhibited by blockade of the pituitary-adrenal system with dexamethasone. *Life Sciences*, *39*(14), 1281-1286.

Broocks, A., Bandelow, B., Pekrun, G., George, A., Meyer, T., Bartmann, U., et al. (1998). Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder. *American Journal of Psychiatry, 155*, 603-609.

Broocks, A., Meyer, T., George, A., Hillmer-Vogel, U., Meyer, D., Bandelow, B., et al. (1999). Decreased neuroendocrine responses to metachlorophenylpiperazine(m-CPP) but normal responses to ipsapirone in marathon runners. *Neuropsychopharmacology*, *20*(2), 150-161.

Broocks, A., Meyer, T., Gleiter, C. H., Hillmer-Vogel, U., George, A., Bartmann, U. et al. (2001). Effect of aerobic exercise on behavioral and neuroendocrine responses to meta-chlorophenylpiperazine and to ipsapirone in untrained healthy subjects. *Psychopharmacology*, *155*(3), 234-241.

Brown, R. A., Abrantes, A. M., Strong, D. R., Mancebo, M. C., Menard, J., Rasmussen, S. A. et al. (2007). A pilot study of moderate-intensity aerobic exercise for Obsessive Compulsive Disorder. *The Journal of Nervous and Mental Disease*, *195*(6), 514-520.

Brown, T., Di Nardo, P., & Barlow, D. H. (1994). *Anxiety disorders interview schedule adult version (ADIS-IV): Client interview schedule*. Albany, NY: Graywind Publications.

Brown, T. A., Antony, M. M., & Barlow, D. H. (1992). Psychometric properties of the Penn State Worry Questionnaire in a clinical anxiety disorders sample. *Behaviour Research and Therapy*, *30*(1), 33-37.

Brown, T. A., & Barlow, D. H. (1992). Comorbidity among anxiety disorders: Implications for treatment and DSM-IV. *Journal of Consulting and Clinical Psychology*, *60*(6), 835-844.

Brown, T. A., Campbell, L. A., Lehman, C. L., Grisham, J. R., & Mancill, R. B. (2001). Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology*, *110*(4), 585-599.

Brown, T. A., Chorpita, B. F., & Barlow, D. H. (1998). Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology*, *107*(2), 179-192.

Brown, T. A., Di Nardo, P. A., Lehman, C. L., & Campbell, L. A. (2001). Reliability of DSM-IV anxiety and mood disorders: Implications for the classification of emotional disorders. *Journal of Abnormal Psychology*, *110*(1), 49-58.

Bruss, G. S., Gruenberg, A. M., Goldstein, R. D., & Barber, J. P. (1994). Hamilton Anxiety Rating Scale Interview guide: Joint interview and test-retest methods for interrater reliability. *Psychiatry Research*, *53*(2), 191-202.

Büchel, C., Morris, J., Dolan, R. J., & Friston, K. J. (1998). Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron*, *20*, 947-957.

Buchsbaum, M. S., Wu, J., Haier, R., Hazlett, E., Ball, R., Katz, M. et al. (1987). Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. *Life Sciences*, *40*(25), 2393-2400.

Burghardt, N. S., Bush, D. E. A., McEwen, B. S., & LeDoux, J. E. (2007). Acute selective serotonin reuptake inhibitors increase conditioned fear expression: blockade with a 5-HT2C receptor antagonist. *Biological Psychiatry*, *62*(10), 1111-1118.

Burke, M., & Mathews, A. (1992). Autobiographical memory and clinical anxiety. *Cognition & Emotion*, *6*(1), 23-35.

Burton, D. (1998). Measuring competitive state anxiety. *Advances in Sport and Exercise Psychology Measurement*, *7*, 129-148.

Butler, P. D., Weiss, J. M., Stout, J. C., & Nemeroff, C. B. (1990). Corticotropin-releasing factor produces fear-enhancing and behavioral activating effects following infusion into the locus coeruleus. *Journal of Neuroscience*, *10*(1), 176-183.

Butler, T., Pan, H., Epstein, J., Protopopescu, X., Tuescher, O., Goldstein, M., et al. (2005). Fear-related activity in subgenual anterior cingulate differs between men and women. *Neuroreport*, *16*(11), 1233-1236.

Buysse, D. J., Reynolds 3rd, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193-213.

Byrne, A., & Byrne, D. G. (1993). The effect of exercise on depression, anxiety and other mood states: A review. *Journal of Psychosomatic Research*, *37*(6), 565-574.

Cameron, O. G., Zubieta, J. K., Grunhaus, L., & Minoshima, S. (2000). Effects of yohimbine on cerebral blood flow, symptoms, and physiological functions in humans. *Psychosomatic Medicine, 62*, 549-559.

Cannistraro, P. A., & Rauch, S. L. (2003). Neural circuitry of anxiety: Evidence from structural and functional neuroimaging studies. *Psychopharmacology Bulletin*, *37*(4), 8-25.

Carter, C. S., & Krug, M. K. (2009). The Functional neuroanatomy of dread: Functional magnetic resonance imaging insights into Generalized Anxiety Disorder and its treatment. *American Journal of Psychiatry*, *166*(3), 263-265.

Casperson, C. J., Powell, K. E., & Christenson, G. M. (1985). Physical activity, exercise and fitness. *Public Health Report*, *100*, 125–31.

Cedarbaum, J. M., & Aghajanian, G. K. (1978). Activation of locus coeruleus neurons by peripheral stimuli: modulation by a collateral inhibitory mechanism. *Life Sciences*, *23*(13), 1383-1392.

Chaouloff, F. (1997). Effects of acute physical exercise on central serotonergic systems. *Medicine & Science in Sports & Exercise, 29*(1), 58-62.

Chaouloff, F., Laude, D., & Elghozi, J. L. (1989). Physical exercise: evidence for differential consequences of tryptophan on 5-HT synthesis and metabolism in central serotonergic cell bodies and terminals. *Journal of Neural Transmission*, *78*(2), 121-130.

Chambless, D. L., Baker, M. J., Baucom, D. H., Beutler, L. E., Calhoun, K. S., Crits-Christoph, P., et al. (1998). Update on empirically validated therapies, II. *Clinical Psychologist*, *51*(1), 3-16.

Charles, P. D., Esper, G. J., Davis, T. L., Maciunas, R. J., & Robertson, D. (1999). Classification of tremor and update on treatment. *American Family Physician*, *59*, 1565-1576.

Charney, D. S., & Bremner, J. D. (1999). The neurobiology of anxiety disorders. In D.S. Charney, E.J. Nestler & B.S. Bunney (Eds.) *Neurobiology of Mental Illness* (pp. 494-517). New York: Oxford University Press.

Charney, D. S., Deutch, A. Y., Southwick, S. M., & Krystal, J. H. (1995). Neural circuits and mechanisms of post-traumatic stress disorder. In M.J. Friedman and D.S. Charney (Eds.), *Neurobiological and clinical consequences of stress: From normal adaptation to PTSD* (pp. 271-287). Philadelphia: Lippincott Williams & Wilkins.

Charney, D. S., Heninger, G. R., & Redmond Jr, D. E. (1983). Yohimbine induced anxiety and increased noradrenergic function in humans: Effects of diazepam and clonidine. *Life Sciences*, *33*(1), 19-29.

Charney, D. S., Woods, S. W., Goodman, W. K., & Heninger, G. R. (1987). Serotonin function in anxiety. *Psychopharmacology*, *92*(1), 14-24.

Charney, D. S., Woods, S. W., Krystal, J. H., Nagy, L. M., & Heninger, G. R. (1992). Noradrenergic neuronal dysregulation in panic disorder: the effects of intravenous yohimbine and clonidine in panic disorder patients. *Acta Psychiatrica Scandinavica*, *86*(4), 273-282.

Chen, H-I., Lin, L-C., Yu, L., Liu, Y-F., Kuo, Y-M., Huang, A-M. et al. (2008). Treadmill exercise enhances passive avoidance learning in rats: The role of down-regulated serotonin system in the limbic system. *Neurobiology of Learning and Memory, 89*, 489-496.

Cherubini, E., & Conti, F. (2001). Generating diversity at GAB Aergic synapses. *Trends in Neurosciences*, *24*(3), 155-162.

Childs, E., Hohoff, C., Deckert, J., Xu, K., Badner, J., & de Wit, H. (2008). Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology*, *33*(12), 2791-2800.

Chorpita, B. F., Albano, A. M., & Barlow, D. H. (1998). The structure of negative emotions in a clinical sample of children and adolescents. *Journal of Abnormal Psychology*, *107*(1), 74-85.

Clark, D. M., Salkovskis, P. M., Ost, L. G., Breitholtz, E., Koehler, K. A., Westling, B. E. et al. (1997). Misinterpretation of body sensations in panic disorder. *Journal of Consulting and Clinical Psychology*, *65*(2), 203-213.

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*, *100*(3), 316-36.

Cole, B. J., Hillmann, M., Seidelmann, D., Klewer, M., & Jones, G. H. (1995). Effects of benzodiazepine receptor partial inverse agonists in the elevated plus maze test of anxiety in the rat. *Psychopharmacology*, *121*(1), 118-126.

Condren, R. M., Dinan, T. G., & Thakore, J. H. (2002). A preliminary study of buspirone stimulated prolactin release in generalised social phobia: evidence for enhanced serotonergic responsivity? *European Neuropsychopharmacology*, *12*(4), 349-354.

Cooke, M., Chaboyer, W., Schluter, P., & Hiratos, M. (2005). The effect of music on preoperative anxiety in day surgery. *Journal of Advanced Nursing*, *52*(1), 47-55.

Copeland, J. R., Dewey, M. E., Wood, N., Searle, R., Davidson, I. A., & McWilliam, C. (1987). Range of mental illness among the elderly in the community. Prevalence in Liverpool using the GMS-AGECAT package. *The British Journal of Psychiatry*, *150*(6), 815-823.

Coplan, J. D., Liebowitz, M. R., Gorman, J. M., Fyer, A. J., Dillon, D. J., Campeas, R. B. et al. (1992). Noradrenergic function in panic disorder. Effects of intravenous clonidine pretreatment on lactate induced panic. *Biological Psychiatry*, *31*(2), 135-146.

Coplan, J. D., Mathew, S. J., Mao, X., Smith, E. L. P., Hof, P. R., Coplan, P. M. et al. (2006). Decreased choline and creatine concentrations in centrum semiovale in patients with generalized anxiety disorder: Relationship to IQ and early trauma. *Psychiatry Research: Neuroimaging*, *147*(1), 27-39.

Coplan, J. D., Papp, L. A., Martinez, J., Pine, D., Rosenblum, L. A., Cooper, T., et al. (1995). Persistence of blunted human growth hormone response to clonidine in fluoxetine-treated patients with panic disorder. *American Journal of Psychiatry, 152*, 619-622.

Corbett, R., & Dunn, R. W. (1991). Effects of HA-966 on conflict, social interaction, and plus maze behaviors. *Drug Development Research*, *24*(3), 201-205.

Coric, V., Taskiran, S., Pittenger, C., Wasylink, S., Mathalon, D. H., Valentine, G. et al. (2005). Riluzole augmentation in treatment-resistant obsessive–compulsive disorder: An open-label trial. *Biological Psychiatry*, *58*(5), 424-428.

Coryell, W., Pine, D., Fyer, A., & Klein, D. (2006). Anxiety responses to CO2 inhalation in subjects at high-risk for panic disorder. *Journal of Affective Disorders*, *92*(1), 63-70.

Coull, J. T., Buchel, C., Friston, K. J., & Frith, C. D. (1999). Noradrenergically mediated plasticity in a human attentional neuronal network. *Neuroimage*, *10*(6), 705-715.

Courneya, K. S., Friedenreich, C. M., Quinney, H. A., Fields, A. L. A., Jones, L. W., & Fairey, A. S. (2003). A randomized trial of exercise and quality of life in colorectal cancer survivors. *European Journal of Cancer Care*, *12*(4), 347-357.

Covin, R., Ouimet, A. J., Seeds, P. M., & Dozois, D. J. A. (2008). A meta-analysis of CBT for pathological worry among clients with GAD. *Journal of Anxiety Disorders*, *22*(1), 108-116.

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*(8), 655-666.

Dalvi, A., & Rodgers, R. J. (1996). GABAergic influences on plus-maze behaviour in mice. *Psychopharmacology*, *128*(4), 380-397.

Damsa, C., Kosel, M., & Moussally, J. (2009). Current status of brain imaging in anxiety disorders. *Current Opinion in Psychiatry*, *22*(1), 96-110.

Darcis, T., Ferreri, M., Natens, J., Burtin, B., & Deram, P. (1995). A multicentre double-blind placebo-controlled study investigating the anxiolytic efficacy of hydroxyzine in patients with generalized anxiety. *Human Psychopharmacology: Clinical and Experimental*, *10*(3) 181-187.

Davidson, J. R., DuPont, R. L., Hedges, D., & Haskins, J. T. (1999). Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *The Journal of Clinical Psychiatry*, *60*(8), 528-535.

Davidson, J. R., Zhang, W., Connor, K. M., Ji, J., Jobson, K., Lecrubier, Y. et al. (2010). A psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). *Journal of Psychopharmacology*, *24*(1), 3-26.

Davidson, J. R. T., Bose, A., Korotzer, A., & Zheng, H. (2004). Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depression and Anxiety*, *19*(4), 234-240.

Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, *15*(1), 353-375.

Davis, J. M., Bailey, S. P., Woods, J. A., Galiano, F. J., Hamilton, M. T., & Bartoli, W. P. (1992). Effects of carbohydrate feedings on plasma free tryptophan and branched-chain amino acids during prolonged cycling. *European Journal of Applied Physiology*, *65*(6), 513-519.

De Bellis, M. D., Casey, B. J., Dahl, R. E., Birmaher, B., Williamson, D. E., Thomas, K. M., et al. (2000). A pilot study of amygdala volumes in pediatric generalized anxiety disorder. *Biological Psychiatry*, *48*(1), 51-57.

De Moor, M. H. M., Boomsma, D. I., Stubbe, J. H., Willemsen, G., & de Geus, E. J. C. (2008). Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Archives of General Psychiatry*, *65*(8), 897-905.

Deacon, R. M. J., Bannerman, D. M., & Rawlins, J. N. P. (2002). Anxiolytic effects of cytotoxic hippocampal lesions in rats. *Behavioral Neuroscience*, *116*(3), 494-497.

Demyttenaere, K., De Fruyt, J., & Stahl, S. M. (2004). The many faces of fatigue in major depressive disorder. *The International Journal of Neuropsychopharmacology*, *8*(01), 93-105.

Derogatis, L. R. (1992). *SCL-90-R: Administration, Scoring & Procedures Manual-II for the Revised Version*. Townson: Clinical Psychometric Research Inc..

Dersh, J., Polatin, P. B., & Gatchel, R. J. (2002). Chronic pain and psychopathology: Research findings and theoretical considerations. *Psychosomatic Medicine*, *64*(5), 773-786.

Deuschl, G., Raethjen, J., Lindemann, M., & Krack, P. (2001). The pathophysiology of tremor. *Muscle & Nerve*, *24*(6), 716-735.

Di Nardo, P., Moras, K., Barlow, D. H., Rapee, R. M., & Brown, T. A. (1993). Reliability of DSM-III-R anxiety disorder categories. Using the anxiety disorders interview schedule-revised (ADIS-R). *Archives of General Psychiatry*, *50*(4), 251-256.

Di Nardo, P. A., Brown, T. A., & Barlow, D. H. (1994). *Anxiety disorders interview schedule for DSM-IV*. Albany, NY: Graywind Publications.

Di Nardo, P. A., O'Brien, G., Barlow, D. H., Waddell, M. T., & Blanchard, E. B. (1983). Reliability of DSM-III anxiety disorder categories using a new structured interview. *Archives of General Psychiatry*, *40*(10), 1070-1074.

Diaz, A. B., & Motta, R. (2008). The effects of an aerobic exercise program on posttraumatic stress disorder symptom severity in adolescents. *International Journal of Emergency Mental Health*, *10*(1), 49-59.

DiLorenzo, T. M., Bargman, E. P., Stucky-Ropp, R., Brassington, G. S., Frensch, P. A., & LaFontaine, T. (1999). Long-term effects of aerobic exercise on psychological outcomes. *Preventive Medicine*, *28*(1), 75-85.

Dishman, R. K. (1997). Brain monoamines, exercise, and behavioral stress: animal models. *Medicine and Science in Sports and Exercise*, *29*(1), 63-74.

Dishman, R. K., Dunn, A. L., Youngstedt, S. D., Davis, J. M., Burgess, M. L., Wilson, S. P. et al. (1996). Increased open field locomotion and decreased striatal GABAa binding after activity wheel running. *Physiology and Behavior, 60*, 699-705.

Dishman, R. K., Hong, S., Soares, J., Edwards, G. L., Bunnell, B. N., Jaso-Friedmann, L., et al. (2000). Activity-wheel running blunts suppression of splenic natural killer cell cytotoxicity after sympathectomy and footshock. *Physiology & Behavior*, *71*(3-4), 297-304.

Dorow, R., Duka, T., Höller, L., & Sauerbrey, N. (1987). Clinical perspectives of beta-carbolines from first studies in humans. *Brain Research Bulletin*, *19*(3), 319-326.

Dorow, R., Horowski, R., Paschelke, G., Amin, M., & Braestrup, C. (1983). Severe anxiety induced by FG 7142, a/3-carboline ligand for benzodiazepine receptors. *Lancet*, *2*, 98-99.

Duman, C. H., Schlesinger, L., Russel, D., Duman, R. S. (2008). Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. *Brain Research, 1199*, 148-158.

Dunn, A. J., & File, S. E. (1987). Corticotropin-releasing factor has an anxiogenic action in the social interaction test. *Hormones and behavior*, *21*(2), 193-202.

Dunn, A. J., Reigle, T. G., Youngstedt, S. D., Armstrong, R. B., & Dishman, R. K. (1996). Brain norepinephrine and metabolites after treadmill training and wheel running. *Medicine & Science in Sports and Exercise, 28*, 204-209.

Dunn, A. J., & Swiergiel, A. H. (1999). Behavioral responses to stress are intact in CRF-deficient mice. *Brain research*, *845*(1), 14-20.

Dunn, A. L., Trivedi, M. H., & O'Neal, H. (2001). Physical activity dose-response effects on outcomes of depression and anxiety. *Medicine & Science in Sports & Exercise*, *33*(6), S587-S597.

DuPont, R. L., Rice, D. P., Miller, L. S., Shiraki, S. S., Rowland, C. R., & Harwood, H. J. (1996). Economic costs of anxiety disorders. *Anxiety*, *2*(4), 167-172.

Durham, R. C., Murphy, T., Allan, T., Richard, K., Treliving, L. R., & Fenton, G. W. (1994). Cognitive therapy, analytic psychotherapy and anxiety management training for generalised anxiety disorder. *The British Journal of Psychiatry*, *165*(3), 315-323.

Ekkekakis, P., Hall, E. E., & Petruzzello, S. J. (1999). Measuring state anxiety in the context of acute exercise using the State Anxiety Inventory: An attempt to resolve the brouhaha. *Journal of Sport and Exercise Psychology*, *21*, 205-229.

Elble, R. J. (1996). Central mechanisms of tremor. *Journal of Clinical Neurophysiology*, *13*(2), 133-144.

Eley, T. C., & Gregory, A. M. (2004). Behavioral genetics. In T.L. Morris & J. S. March (Eds.), *Anxiety Disorders in Children and Adolescents*, (pp. 71-97). New York: Guildford Press.

Ellingsen, D. G., Bast-Pettersen, R., Efskind, J., Gjølstad, M., Olsen, R., Thomassen, Y. et al. (2006). Hand tremor related to smoking habits and the consumption of caffeine in male industrial workers. *Neurotoxicology*, *27*(4), 525-533.

Endler, N. S. (1997). Stress, anxiety and coping: The multidimensional interaction model. *Canadian Psychology*, *38*, 136-153.

Endler, N. S., Edwards, J. M., & Vitelli, R. (1991). *Endler Multidimensional Anxiety Scales (EMAS)*. Los Angeles, CA: Western Psychological Services.

Endler, N. S., Edwards, J. M., Vitelli, R., & Parker, J. D. A. (1989). Assessment of state and trait anxiety: Endler Multidimensional Anxiety Scales. *Anxiety, Stress & Coping*, *2*(1), 1-14.

Endler, N. S., & Kocovski, N. L. (2001). State and trait anxiety revisited. *Journal of Anxiety Disorders*, *15*(3), 231-245.

Endler, N. S., Parker, J. D. A., Bagby, R. M., & Cox, B. J. (1991). Multidimensionality of state and trait anxiety: Factor structure of the Endler Multidimensional Anxiety Scales. *Journal of Personality and Social Psychology*, *60*(6), 919-926.

Eng, W., & Heimberg, R. G. (2006). Interpersonal correlates of generalized anxiety disorder: Self versus other perception. *Journal of Anxiety Disorders*, *20*(3), 380-387.

Eysenck, H. J. (1967). *The Dynamics of Anxiety and Hysteria*. London: Routledge & Kegan Paul.

Eysenck, H. J. (1981). *A Model for Personality*. New York: Springer-Verlag.

Eysenck, M. W. (1992). *Anxiety: The cognitive perspective*. Hove, England: Erlbaum.

Eysenck, M. W., Mogg, K., May, J., Richards, A., & Mathews, A. (1991). Bias in interpretation of ambiguous sentences related to threat in anxiety. *Journal of Abnormal Psychology*, *100*(2), 144-150.

Fan, A. Z., Strine, T. W., Jiles, R., & Mokdad, A. H. (2008). Depression and anxiety associated with cardiovascular disease among persons aged 45 years and older in 38 states of the United States, 2006. *Preventive Medicine*, *46*(5), 445-450.

Feltner, D. E., Crockatt, J. G., Dubovsky, S. J., Cohn, C. K., Shrivastava, R. K., Targum, S. D. et al. (2003). A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *Journal of Clinical Psychopharmacology*, *23*(3), 240-249.

Fergusson, D. M., Horwood, L. J., & Boden, J. M. (2006). Structure of internalising symptoms in early adulthood†. *The British Journal of Psychiatry*, *189*(6), 540-546.

File, S. E., & Seth, P. (2003). A review of 25 years of the social interaction test. *European Journal of Pharmacology*, *463*(1-3), 35-53.

Finn, D. A., Rutledge-Gorman, M. T., & Crabbe, J. C. (2003). Genetic animal models of anxiety. *Neurogenetics*, *4*(3), 109-135.

Flint, A. J. (1994). Epidemiology and comorbidity of anxiety disorders in the elderly. *American Journal of Psychiatry, 151*, 640-649.

Foa, E. B., Feske, U., Murdock, T. B., Kozak, M. J., & McCarthy, P. R. (1991). Processing of threat-related information in rape victims. *Journal of Abnormal Psychology*, *100*(2), 156-162.

Focht, B. C. (2002). Pre-exercise anxiety and the anxiolytic responses to acute bouts of self-selected and prescribed intensity resistance exercise. *Journal of Sports Medicine and Physical Fitness*, *42*(2), 217-223.

Fone, K. C., Beckett, S. R., Topham, I. A., Swettenham, J., Ball, M., & Maddocks, L. (2002). Long-term changes in social interaction and reward following repeated MDMA administration to adolescent rats without accompanying serotonergic neurotoxicity. *Psychopharmacology*, *159*(4), 437-444.

Fossey, M. D., Lydiard, R. B., Ballenger, J. C., Laraia, M. T., Bissette, G., & Nemeroff, C. B. (1996). Cerebrospinal fluid corticotropin-releasing factor concentrations in patients with anxiety disorders and normal comparison subjects. *Biological Psychiatry*, *39*(8), 703-707.

Fox, K. R. (2007). The influence of physical activity on mental well-being. *Public Health Nutrition*, *2*(3a), 411-418.

Frankowska, M., Filip, M., & Przegaliñski, E. (2007). Effects of GABA~ B receptor ligands in animal tests of depression and anxiety. *Pharmacological Reports*, *59*(6), 645-655.

Fresco, D. M., Mennin, D. S., Heimberg, R. G., & Turk, C. L. (2003). Using the Penn State Worry Questionnaire to identify individuals with generalized anxiety disorder: A receiver operating characteristic analysis. *Journal of Behavior Therapy and Experimental Psychiatry*, *34*(3-4), 283-291.

Freud, S. (1924). The justification for detaching from neurasthenia a particular syndrome: the anxiety neurosis. *Collected Papers*, *1*, 76-106.

Gandevia, S. C. (2001). Spinal and supraspinal factors in human muscle fatigue. *Physiological Reviews*, *81*(4), 1725-1789.

Gauvin, L., Rejeski, W. J., Norris, J. L., & Lutes, L. (1997). The curse of inactivity: Failure of acute exercise to enhance feeling states in a community sample of sedentary adults. *Journal of Health Psychology*, *2*(4), 509-523.

Gelenberg, A. J., Lydiard, R. B., Rudolph, R. L., Aguiar, L., Haskins, J. T., & Salinas, E. (2000). Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with Generalized Anxiety Disorder: A 6-Month Randomized Controlled Trial. *JAMA, 283*, 3082-3088.

Glannon, W. (2008). Psychopharmacological Enhancement. *Neuroethics*, *1*(1), 45-54.

Goddard, A. W., & Charney, D. S. (1997). Toward an integrated neurobiology of panic disorder. *The Journal of Clinical Psychiatry*, *58(Supplement 2)*, 4-11.

Goldberg, D. (2008). Towards DSM-V: The relationship between generalized anxiety disorder and major depressive episode. *Psychological Medicine*, *38*(11), 1671-1675.

Gomez-Merino, D., Béquet, F., Berthelot, M., Chennaoui, M., & Guezennec, C. Y. (2001). Site-dependent effects of an acute intensive exercise on extracellular 5-HT and 5-HIAA levels in rat brain. *Neuroscience Letters*, *301*(2), 143-146.

Gomez-Pinnilla, F., Ying, Z., Roy, R. R., Motleni, R., & Edgerton, V. R. (2002). Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *Journal of Neurophysiology, 88*, 2187-2195.

Goodman, W. K., Bose, A., & Wang, Q. (2005). Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. *Journal of Affective Disorders*, *87*(2-3), 161-167.

Goodwin, R. D. (2003). Association between physical activity and mental disorders among adults in the United States. *Preventive Medicine*, *36*(6), 698-703.

Gould, R. A., Otto, M. W., Pollack, M. H., & Yap, L. (1997). Cognitive behavioral and pharmacological treatment of generalized anxiety disorder: A preliminary meta-analysis. *Behavior Therapy*, *28*(2), 285-305.

Gould, R. A., Safren, S. A., Washington, D. O., & Otto, M. W. (2004). A meta-analytic review of cognitive-behavioral treatments. In R.G. Heimburg, C.L. Turk & D.S. Mennin (Eds.), *Generalized Anxiety Disorder: Advances in Research and Practice* (pp. 248-264). New York: Guilford Press.

Graeff, F. G., Silveira, M. C. L., Nogueira, R. L., Audi, E. A., & Oliveira, R. M. W. (1993). Role of the amygdala and periaqueductal gray in anxiety and panic. *Behavioural Brain Research*, *58*(1-2), 123-131.

Graham, J. D. P. (1945). Static tremor in anxiety states. *Journal of Neurology, Neurosurgery, and Psychiatry*, *8*(3-4), 57-60.

Grant, B. F., Hasin, D. S., Stinson, F. S., Dawson, D. A., June Ruan, W., Goldstein, R. et al. (2005). Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychological Medicine*, *35*(12), 1747-1759.

Gray, J. A. (1982). Precis of the neuropsychology of anxiety: an enquiry into the functions of the septo-hippocampal system. *Behavioral and Brain Sciences*, *5*(3), 469-534.

Gray, J. A. (1985). The neuropsychology of anxiety. *Issues in Mental Health Nursing*, *7*(1), 201-228.

Gray, J. A., & McNaughton, N. (1996). The neuropsychiatry of anxiety: Reprise. In *Nebraska Symposium on Motivation: Vol. 43. Perspectives on anxiety, panic, and fear.* Lincoln: University of Nebraska Press.

Green, A. R., & McGregor, I. S. (2002). On the anxiogenic and anxiolytic nature of long-term cerebral 5-HT depletion following MDMA. *Psychopharmacology*, *162*(4), 448-450.

Greenberg, P. E., Sisitsky, T., Kessler, R. C., Finkelstein, S. N., Berndt, E. R., & Davidson, J. R. T. (1999). The economic burden of anxiety disorders in the 1900s. *Journal of Clinical Psychiatry*, *60*, 427-435.

Greenwood, B. N., Foley, T. E., Day H., Burhans, D., Brooks, L, Campaeu, S, et al. (2004). Wheel running alters serotonin (5-HT) transporters, 5-HT(1a), 5-HT(1b), and alpha(1b)-adrenergic receptor mRNA in the rat raphe nuclei. *Biological Psychiatry, 57*, 559-568.

Greenwood, B. N., Foley, T. E., Day, H. E., Campisi, J., Hammack, S. H., Campeau, S. et al. (2003). Freewheel running prevents learned helplessness/behavioral depression: Role of dorsal raphe serotonergic neurons. *Journal of Neuroscience, 23*, 2889-2898.

Greenwood, B. N., Strong, P. V., Brooks, L., Fleshner, M. (2008). Anxiety-like behaviors produced by acute fluoxetine administration in male Fischer 344 rats are prevented by prior exercise. *Psychopharmacology, 1999*, 209-222.

Greist, J. H., Jefferson, J. W., Kobak, K. A., Katzelnick, D. J., & Serlin, R. C. (1995). Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. *Archives of General Psychiatry*, *52*(1), 53-60.

Grosz, H., & Farmer, B. (1972). Pitts'and McClure's lactate-anxiety study revisited. *The British Journal of Psychiatry*, *120*(557), 415-418.

Grove, G., Coplan, J. D., & Hollander, E. (1997). The neuroanatomy of 5-HT dysregulation and panic disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences, 9*, 198-207.

Hackett, D., Haudiquet, V., & Salinas, E. (2003). A method for controlling for a high placebo response rate in a comparison of venlafaxine XR and diazepam in the short-term treatment of patients with generalised anxiety disorder. *European Psychiatry*, *18*(4), 182-187.

Hallett, M. (1998). Overview of human tremor physiology. *Movement Disorders*, *13(Supplement 3)*, 43-48.

Hamilton, M. (1959). The assessment of anxiety states by rating. *The British Journal of Medical Psychology*, *32*(1), 50-55.

Hamilton, M. (1969). Diagnosis and rating of anxiety. *British Journal of Psychiatry, Special Publication*, *3*, 76-79.

Härter, M. C., Conway, K. P., & Merikangas, K. R. (2003). Associations between anxiety disorders and physical illness. *European Archives of Psychiatry and Clinical Neuroscience*, *253*(6), 313-320.

Hartford, J., Kornstein, S., Liebowitz, M., Pigott, T., Russell, J., Detke, M. et al. (2007). Duloxetine as an SNRI treatment for generalized anxiety disorder: Results from a placebo and active-controlled trial. *International Clinical Psychopharmacology*, *22*(3), 167-174.

Hartford, J. T., Endicott, J., Kornstein, S. G., Allgulander, C., Wohlreich, M. M., Russell, J. M., et al. (2008). Implications of pain in Generalized Anxiety Disorder: Efficacy of duloxetine. *Primary Care Companion to The Journal of Clinical Psychiatry*, *10*(3), 197-204.

Hazlett-Stevens, H., Craske, M. G., Mayer, E. A., Chang, L., & Naliboff, B. D. (2003). Prevalence of irritable bowel syndrome among university students: The roles of worry, neuroticism, anxiety sensitivity and visceral anxiety. *Journal of Psychosomatic Research*, *55*(6), 501-505.

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis*. New York: Academic Press.

Heinrichs, S. C., Min, H., Tamraz, S., Carmouché, M., Boehme, S. A., & Vale, W. W. (1997). Anti-sexual and anxiogenic behavioral consequences of corticotropin-releasing factor overexpression are centrally mediated. *Psychoneuroendocrinology*, *22*(4), 215-224.

Heinrichs, S. C., Stenzel-Poore, M. P., Gold, L. H., Battenberg, E., Bloom, F. E., Koob, G. F. et al. (1996). Learning impairment in transgenic mice with central overexpression of corticotropin-releasing factor. *Neuroscience*, *74*(2), 303-311.

Helton, D. R., Tizzano, J. P., Monn, J. A., Schoepp, D. D., & Kallman, M. J. (1997). LY354740: A metabotropic glutamate receptor agonist which ameliorates symptoms of nicotine withdrawal in rats. *Neuropharmacology*, *36*(11-12), 1511-1516.

Hettema, J. M. (2008). The nosologic relationship between generalized anxiety disorder and major depression. *Depression and Anxiety*, *25*(4), 300-316.

Hettema, J. M., Kuhn, J. W., Prescott, C. A., & Kendler, K. S. (2006). The impact of generalized anxiety disorder and stressful life events on risk for major depressive episodes. *Psychological Medicine*, *36*(6), 789-795.

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry, 158*, 1568-1578.

Hettema, J. M., Neale, M. C., Myers, J. M., Prescott, C. A., & Kendler, K. S. (2006). A population-based twin study of the relationship between neuroticism and internalizing disorders. *American Journal of Psychiatry*, *163*(5), 857.

Hettema, J. M., Prescott, C. A., & Kendler, K. S. (2004). Genetic and environmental sources of covariation between generalized anxiety disorder and neuroticism. *American Journal of Psychiatry*, *161*(9), 1581-1587.

Hidalgo, R. B., Tupler, L. A., & Davidson, J. R. T. (2007). An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. *Journal of Psychopharmacology*, *21*(8), 864-872.

Himle, J. A., Baser, R. E., Taylor, R. J., Campbell, R. D., & Jackson, J. S. (2009). Anxiety disorders among African Americans, blacks of Caribbean descent, and non-Hispanic whites in the United States. *Journal of Anxiety Disorders, 23*(5), 578-590.

Hirshfeld, D. R., Rosenbaum, J. F., Biederman, J., Bolduc, E. A., Faraone, S. V., Snidman, N., et al. (1992). Stable behavioral inhibition and its association with anxiety disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *31*(1), 103-111.

Hoehn-Saric, R. (2007). Physiologic Responses in Anxiety. *Current Psychiatry Reviews*, *3*(3), 196-204.

Hoehn-Saric, R., McLeod, D. R., Lee, Y. B., & Zimmerli, W. D. (1991). Cortisol levels in generalized anxiety disorder. *Psychiatry Research*, *38*(3), 313-315.

Hoehn-Saric, R., McLeod, D. R., & Zimmerli, W. D. (1989). Somatic manifestations in women with generalized anxiety disorder: psychophysiological responses to psychological stress. *Archives of General Psychiatry*, *46*(12), 1113-1119.

Hoehn-Saric, R., Schlund, M. W., & Wong, S. H. Y. (2004). Effects of citalopram on worry and brain activation in patients with generalized anxiety disorder. *Psychiatry Research*, *131*(1), 11-21.

Hoffman, D. L., Dukes, E. M., & Wittchen, H. U. (2008). Human and economic burden of generalized anxiety disorder. *Depression and Anxiety*, *25*(1), 72-90.

Hoffman, E. J., & Mathew, S. J. (2008). Anxiety disorders: a comprehensive review of pharmacotherapies. *Mount Sinai Journal of Medicine, 75*(3), 248-262.

Hofmann, S. G., & Smits, J. A. J. (2008). Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. *The Journal of Clinical Psychiatry*, *69*(4), 621-632.

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, *23*(5), 477-501.

Hope, D. A., Rapee, R. M., Heimberg, R. G., & Dombeck, M. J. (1990). Representations of the self in social phobia: Vulnerability to social threat. *Cognitive Therapy and Research*, *14*(2), 177-189.

Hornblow, A. R., & Kidson, M. A. (1976). The Visual Analogue Scale for Anxiety. *Australian and New Zealand Journal of Psychiatry*, *10*(4), 339-341.

Hoyer, D., & Schoeffter, P. (1991). 5-HT receptors: Subtypes and second messengers. *Journal of Receptors and Signal Transduction*, *11*(1-4), 197-214.

Hoyer, J., Beesdo, K., Gloster, A. T., Runge, J., Höfler, M., & Becker, E. S. (2009). Worry Exposure versus Applied Relaxation in the Treatment of Generalized Anxiety Disorder. *Psychotherpeutics and Psychosomatics*, *78*, 106-115.

Humayun, M. U., Rader, R. S., Pieramici, D. J., Awh, C. C., & De Juan, E. (1997). Quantitative measurement of the effects of caffeine and propranolol on surgeon hand tremor. *Archives of Ophthalmology*, *115*(3), 371-374.

Imanishi, J., Kuriyama, H., Shigemori, I., Watanabe, S., Aihara, Y., Kita, M., et al. (2007). Anxiolytic Effect of Aromatherapy Massage in Patients with Breast Cancer. *Evidence-based Complementary and Alternative Medicine, 6*(1), 123-128.

Jessa, M., Nazar, M., Bidzinski, A., & Plaznik, A. (1996). The effects of repeated administration of diazepam, MK-801 and CGP 37849 on rat behavior in two models of anxiety. *European Neuropsychopharmacology*, *6*(1), 55-61.

Joiner Jr, T. E., Steer, R. A., Beck, A. T., Schmidt, N. B., Rudd, M. D., & Catanzaro, S. J. (1999). Physiological hyperarousal: construct validity of a central aspect of the tripartite model of depression and anxiety. *Journal of Abnormal Psychology*, *108*(2), 290-298.

Joiner, T. E. (1996). A confirmatory factor-analytic investigation of the tripartite model of depression and anxiety in college students. *Cognitive Therapy and Research*, *20*(5), 521-539.

Joiner, T. E., Catanzaro, S. J., & Laurent, J. (1996). Tripartite structure of positive and negative affect, depression, and anxiety in child and adolescent psychiatric inpatients. *Journal of Abnormal Psychology*, *105*, 401-409.

Jorm, A. F. (1989). Modifiability of trait anxiety and neuroticism: A meta-analysis of the literature. *Australian and New Zealand Journal of Psychiatry*, *23*(1), 21-29.

Judd, L. L., Kessler, R. C., PauIus, M. P., Zeller, P. V., Wittchen, H. U., & Kunovac, J. L. (1998). Comorbidity as a fundamental feature of generalized anxiety disorders: results from the National Comorbidity Study (NCS). *Acta Psychiatrica Scandinavica*, *98*, 6-11.

Kabacoff, R. I., Segal, D. L., Hersen, M., & Van Hasselt, V. B. (1997). Psychometric properties and diagnostic utility of the Beck Anxiety Inventory and the State-Trait Anxiety Inventory with older adult psychiatric outpatients. *Journal of Anxiety Disorders*, *11*(1), 33-47.

Kagan, J. (1989). Temperamental Contributions to Social Behavior. *American Psychologist*, *44*(4), 668-74.

Kagan, J. (1994). *Galen's prophecy*. New York: Basic Books

Kagan, J., & Snidman, N. (1999). Early childhood predictors of adult anxiety disorders. *Biological Psychiatry*, *46*(11), 1536-1541.

Karcz-Kubicha, M., Jessa, M., Nazar, M., Plaznik, A., Hartmann, S., Parsons, C. G. et al. (1997). Anxiolytic activity of glycine-B antagonists and partial agonists—no relation to intrinsic activity in the patch clamp. *Neuropharmacology*, *36*(10), 1355-1367.

Karcz-Kubicha, M., & Liljequist, S. (1995). Evidence for an anxiogenic action of AMPA receptor antagonists in the plus-maze test. *European Journal of Pharmacology*, *279*(2-3), 171-177.

Kaschka, W., Feistel, H., & Ebert, D. (1995). Reduced benzodiazepine receptor binding in panic disorders measured by iomazenil SPECT. *Journal of Psychiatric Research*, *29*(5), 427-434.

Kash, S. F., Tecott, L. H., Hodge, C., & Baekkeskov, S. (1999). Increased anxiety and altered responses to anxiolytics in mice deficient in the 65-kDa isoform of glutamic acid decarboxylase. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 1698-1703.

Katon, W., Lin, E. H. B., & Kroenke, K. (2007). The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *General Hospital Psychiatry*, *29*(2), 147-155.

Katon, W., Sullivan, M., & Walker, E. (2001). Medical symptoms without identified pathology: relationship to psychiatric disorders, childhood and adult trauma, and personality traits. *Annals of Internal Medicine, 134*, 917-925.

Katon, W. J., & Walker, E. A. (1998). Medically unexplained symptoms in primary care. *The Journal of Clinical Psychiatry. Supplement*, *59*(20), 15-21.

Kawahara, H., Kawahara, Y., & Westerink, B. H. C. (2000). The role of afferents to the locus coeruleus in the handling stress-induced increase in the release of noradrenaline in the medial prefrontal cortex: A dual-probe microdialysis study in the rat brain. *European Journal of Pharmacology*, *387*(3), 279-286.

Keck, M., Holsboer, F., & Muller, M. (2004). Mouse mutants for the study of corticotropin-releasing hormone receptor function: development of novel treatment strategies for mood disorders. *Annals of the New York Academy of Sciences*, *1018*, 445-457.

Kehne, J. H., Baron, B. M., Harrison, B. L., McCloskey, T. C., Palfreyman, M. G., Poirot, M. et al. (1995). MDL 100,458 and MDL 102,288: two potent and selective glycine receptor antagonists with different functional profiles. *European Journal of Pharmacology*, *284*(1-2), 109-118.

Kendall, P. C., & Chambless, D. L. (1998). Empirically supported psychological therapies. *Journal of Consulting and Clinical Psychology*, *66*(1), 3-6.

Kendler, K. S., Davis, C. G., & Kessler, R. C. (1997). The familial aggregation of common psychiatric and substance use disorders in the national comorbidity survey: A family history study. *The British Journal of Psychiatry*, *170*(6), 541-548.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). Generalized anxiety disorder in women. A population-based twin study. *Archives of General Psychiatry*, *49*(4), 267-272.

Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry, 60*, 929-937.

Kendler, K. S., Silberg, J. L., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1991). The family history method: whose psychiatric history is measured? *American Journal of Psychiatry, 148*, 1501-1504.

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: A review of recent literature. *Current Opinion in Psychiatry*, *20*(4), 359–364.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*, 593-602.

Kessler, R. C., Demler, O., Frank, R. G., Olfson, M., Pincus, H. A., Walters, E. E. et al. (2005). Prevalence and treatment of mental disorders, 1990 to 2003. *The New England Journal of Medicine, 352*, 2515-2523.

Kessler, R. C., DuPont, R. L., Berglund, P., & Wittchen, H. U. (1999). Impairment in pure and comorbid generalized anxiety disorder and major depression at 12 months in two national surveys. *American Journal of Psychiatry, 156*, 1915-1923

Kessler, R. C., Greenberg, P. E., Mickelson, K. D., Meneades, L. M., & Wang, P. S. (2001). The effects of chronic medical conditions on work loss and work cutback. *Journal of Occupational and Environmental Medicine*, *43*(3), 218-225.

Kessler, R. C., Gruber, M., Hettema, J. M., Hwang, I., Sampson, N., & Yonkers, K. A. (2007). Co-morbid major depression and generalized anxiety disorders in the National Comorbidity Survey follow-up. *Psychological Medicine*, *38*(03), 365-374.

Kessler, R. C., Keller, M. B., & Wittchen, H. U. (2001). The epidemiology of generalized anxiety disorder. *Psychiatric Clinics of North America*, *24*(1), 19-39.

Kessler, R. C., & Wittchen, H. U. (2002). Patterns and correlates of generalized anxiety disorder in community samples. *Journal of Clinical Psychiatry*, *63*, 4-10.

Kim, T. S., Pae, C. U., Yoon, S. J., Bahk, W. M., Jun, T. Y., Rhee, W. I., et al. (2006). Comparison of venlafaxine extended release versus paroxetine for treatment of patients with generalized anxiety disorder. *Psychiatry & Clinical Neurosciences*, *60*(3), 347-351.

King, A. C., Baumann, K., O'Sullivan, P., Wilcox, S., & Castro, C. (2002). Effects of moderate-intensity exercise on physiological, behavioral, and emotional responses to family caregiving: A randomized controlled trial. *Journals of Gerontology Series A: Biological and Medical Sciences*, *57*(1), 26-36.

King, A. C., Oman, R. F., Brassington, G. S., Bliwise, D. L., & Haskell, W. L. (1997). Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. *JAMA*, *277*(1), 32-37.

Kjelstrup, K. G., Tuvnes, F. A., Steffenach, H. A., Murison, R., Moser, E. I., & Moser, M. B. (2002). Reduced fear expression after lesions of the ventral hippocampus. *Proceedings of the National Academy of Sciences*, *99*(16), 10825-10830.

Klodzinska, A., Chojnacka-Wójcik, E., Palucha, A., Branski, P., Popik, P., & Pilc, A. (1999). Potential anti-anxiety, anti-addictive effects of LY 354740, a selective group II glutamate metabotropic receptors agonist in animal models. *Neuropharmacology*, *38*(12), 1831-1839.

Koek, W., & Colpaert, F. C. (1991). Use of a conflict procedure in pigeons to characterize anxiolytic drug activity: evaluation of N-methyl-D-aspartate antagonists. *Life sciences*, *49*(9), PL37-PL42.

Koponen, H., Allgulander, C., Erickson, J., Dunayevich, E., Pritchett, Y., Detke, M. J. et al. (2007). Efficacy of duloxetine for the treatment of generalized anxiety disorder: Implications for primary care physicians. *Primary Care Companion to the Journal of Clinical Psychiatry*, *9*(2), 100-107.

Korostil, M., & Feinstein, A. (2007). Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Multiple Sclerosis*, *13*(1), 67-72.

Köster, B., Lauk, M., Timmer, J., Winter, T., Guschlbauer, B., Glocker, F. X. et al. (1998). Central mechanisms in human enhanced physiological tremor. *Neuroscience Letters*, *241*(2-3), 135-138.

Kotlinska, J., & Liljequist, S. (1998). The putative AMPA receptor antagonist, LY 326325, produces anxiolytic-like effects without altering locomotor activity in rats. *Pharmacology, Biochemistry and Behavior*, *60*(1), 119-124.

Kraus, C. A., Kunik, M., Rhoades, H., Novy, D. M., Wilson, N., & Stanley, M. A. (2005). Cross cultural differences in older adults with GAD. In *39th Annual Convention of the Association for Advancement of Behavior Therapy, Washington, DC, November*.

Kroboth, P. D., Folan, M. M., Bauer, K. S., Tullock, W., Wright, C. E., & Sweeney, J. A. (1998). Do alprazolam-induced changes in saccadic eye movement and psychomotor function follow the same time course? *The Journal of Clinical Pharmacology*, *38*(4), 337-346.

Kroenke, K., & Price, R. K. (1993). Symptoms in the community. Prevalence, classification, and psychiatric comorbidity. *Archives of Internal Medicine*, *153*(21), 2474-2480.

Kroenke, K., Spitzer, R. L., Williams, J. B., Linzer, M., Hahn, S. R., deGruy 3rd, F. V. et al. (1994). Physical symptoms in primary care. Predictors of psychiatric disorders and functional impairment. *Archives of Family Medicine*, *3*(9), 774-779.

Kroenke, K., Spitzer, R. L., Williams, J. B. W., Monahan, P. O., & Lowe, B. (2007). Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Annals of Internal Medicine*, *146*(5), 317-325.

Krueger, R. F. (1999). The structure of common mental disorders. *Archives of General Psychiatry, 56*, 921-926.

Krystal, J. H., McDougle, C. J., Woods, S. W., Price, L. H., Heninger, G. R., & Charney, D. S. (1992). Dose-response relationship for oral idazoxan effects in healthy human subjects: comparison with oral yohimbine. *Psychopharmacology*, *108*(3), 313-319.

Kubzansky, L. D., Davidson, K. W., & Rozanski, A. (2005). The clinical impact of negative psychological states: expanding the spectrum of risk for coronary artery disease. *Psychosomatic Medicine*, *67*(Supplement 1), 10-14.

Kuehn, B. M. (2008). Asthma linked to psychiatric disorders. *JAMA*, *299*(2), 158.

Kugler, J., Seelbach, H., & Krüskemper, G. M. (1994). Effects of rehabilitation exercise programmes on anxiety and depression in coronary patients: A meta-analysis. *The British Journal of Clinical Psychology, 33*, 401-410.

Kulcu, D. G., Kurtais, Y., Tur, B. S., Gülec, S., & Seckin, B. (2007). The effect of cardiac rehabilitation on quality of life, anxiety and depression in patients with congestive heart failure. A randomized controlled trial, short-term results. *Europa medicophysica*, *43*, 489-497.

Kunik, M. E., Roundy, K., Veazey, C., Souchek, J., Richardson, P., Wray, N. P., et al. (2005). Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest, 127*, 1205-1211.

Lader, M., & Scotto, J. C. (1998). A multicentre double-blind comparison of hydroxyzine, buspirone and placebo in patients with generalized anxiety disorder. *Psychopharmacology*, *139*(4), 402-406.

Lähdesmäki, J., Sallinen, J., MacDonald, E., Kobilka, B. K., Fagerholm, V., & Scheinin, M. (2002). Behavioral and neurochemical characterization of a2A-adrenergic receptor knockout mice. *Neuroscience*, *113*(2), 289-299.

Lang, A. J. (2004). Treating generalized anxiety disorder with cognitive-behavioral therapy. *The Journal of Clinical Psychiatry*, *65*, 14-19.

Lapiz, M. S., Mateo, Y., Durkin, S., Parker, T., & Marsden, C. A. (2001). Effects of central noradrenaline depletion by the selective neurotoxin DSP-4 on the behaviour of the isolated rat in the elevated plus maze and water maze. *Psychopharmacology*, *155*(3), 251-259.

LeDoux, J. (1998). Fear and the brain: where have we been, and where are we going? *Biological Psychiatry*, *44*(12), 1229-1238.

LeDoux, J. E. (1994). The amygdala: contributions to fear and stress. *Seminars in the Neurosciences, 6*, 231-237.

LeDoux, J. E., Iwata, J., Cicchetti, P., & Reis, D. J. (1988). Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *Journal of Neuroscience*, *8*(7), 2517-2529.

Lemonde, S., Du, L., Bakish, D., Hrdina, P., & Albert, P. R. (2004). Association of the C (–1019) G 5-HT1A functional promoter polymorphism with antidepressant response. *The International Journal of Neuropsychopharmacology*, *7*(04), 501-506.

Leonardo, E. D., & Hen, R. (2006). Genetics of affective and anxiety disorders. *Annual Review of Psychology, 57*, 117-137.

Lépine, J. P. (2002). The epidemiology of anxiety disorders: Prevalence and societal costs. *Journal of Clinical Psychiatry*, *63*, 4-8.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S. et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science*, *274*(5292), 1527-1531.

Levy, E., & Mineka, S. (1998). Anxiety and mood-congruent autobiographical memory: A conceptual failure to replicate. *Cognition & Emotion, 12*(5), 625-634.

Liechti, M. E., & Vollenweider, F. X. (2001). Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. *Human Psychopharmacology*, *16*, 589-598.

Lin, E. H. B., Von Korff, M., Katon, W., Bush, T., Simon, G. E., Walker, E., et al. (1995). The role of the primary care physician in patients' adherence to antidepressant therapy. *Medical Care*, *33*(1), 67-74.

Lin, E. H. B., Von Korff, M., Ludman, E. J., Rutter, C., Bush, T. M., Simon, G. E. et al. (2003). Enhancing adherence to prevent depression relapse in primary care. *General Hospital Psychiatry*, *25*(5), 303-310.

Llinas, R. (1984). Rebound excitation as the physiological basis for tremor: A biophysical study of the oscillatory properties of mammalian central neurones in vitro. In L.J. Findley & R. Capildeo (Eds.), *Movement Disorders: Tremor*. (pp. 165-182).

Llinas, R., & Yarom, Y. (1981). Electrophysiology of mammalian inferior olivary neurones in vitro. Different types of voltage-dependent ionic conductances. *The Journal of Physiology*, *315*(1), 549-567.

Llorca, P. M., Spadone, C., Sol, O., Danniau, A., Bougerol, T., Corruble, E., et al. (2002). Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. *The Journal of Clinical Psychiatry*, *63*(11), 1020-1027.

Long, B. C., & van Stavel, R. (1995). Effects of exercise training on anxiety: A meta-analysis. *Journal of Applied Sport Psychology*, *7*(2), 167-189.

Löthgren, M. (2004). Economic evidence in anxiety disorders: A review. *The European Journal of Health Economics*, *5*, 20-25.

Ludman, E., Katon, W., Russo, J., Simon, G., Von Korff, M., Lin, E., et al. (2006). Panic episodes among patients with diabetes. *General Hospital Psychiatry*, *28*(6), 475-481.

Lundh, L. G., & Öst, L. G. (2001). Attentional bias, self-consciousness and perfectionism in social phobia before and after cognitive-behaviour therapy. *Cognitive Behaviour Therapy*, *30*(1), 4-16.

MacLeod, A., & Byrne, A. (1996). Anxiety, depression, and the anticipation of future positive and negative experiences. *Journal of Abnormal Psychology*, *105*(2), 286-289.

Maier, W., Buller, R., Philipp, M., & Heuser, I. (1988). The Hamilton Anxiety Scale: Reliability, validity and sensitivity to change in anxiety and depressive disorders. *Journal of Affective Disorders*, *14*(1), 61-68.

Malizia, A. L., Cunningham, V. J., Bell, C. J., Liddle, P. F., Jones, T., & Nutt, D. J. (1998). Decreased brain $GABA_A$-benzodiazepine receptor binding in panic disorder. Preliminary results from a quantitative PET study. *Archives of General Psychiatry, 55*, 715-720.

Manger, T. A., & Motta, R. W. (2005). The impact of an exercise program on posttraumatic stress disorder, anxiety, and depression. *International Journal of Emergency Mental Health*, *7*(1), 49-57.

Manzoni, G. M., Pagnini, F., Castelnuovo, G., & Molinari, E. (2008). Relaxation training for anxiety: A ten-years systematic review with meta-analysis. *BMC Psychiatry*, *8*(1), 41.

Marciniak, M. D., Lage, M. J., Dunayevich, E., Russell, J. M., Bowman, L., Landbloom, R. P. et al. (2005). The cost of treating anxiety: The medical and demographic correlates that impact total medical costs. *Depression and Anxiety*, *21*(4), 178-184.

Maren, S., & Fanselow, M. S. (1996). The amygdala and fear conditioning: has the nut been cracked? *Neuron*, *16*(2), 237-40.

Martijena, I. D., Rodriguez Manzanares, P. A., Lacerra, C., & Molina, V. A. (2002). Gabaergic modulation of the stress response in frontal cortex and amygdala. *Synapse*, *45*(2), 86-94.

Martin, J. L. R., Sainz-Pardo, M., Furukawa, T. A., Martin-Sanchez, E., Seoane, T., & Galan, C. (2007). Benzodiazepines in generalized anxiety disorder: Heterogeneity of outcomes based on a systematic review and meta-analysis of clinical trials. *Journal of Psychopharmacology*, *21*(7), 774-782.

Martins, A. P., Marras, R. A., & Guimaraes, F. S. (1997). Anxiogenic effect of corticotropin-releasing hormone in the dorsal periaqueductal grey. *Neuroreport*, *8*(16), 3601-3604.

Martinsen, E. W., Hoffart, A., & Solberg, O. Y. (1989). Aerobic and non-aerobic forms of exercise in the treatment of anxiety disorders. *Stress Medicine*, *5*(2), 115-120.

Martinsen, E. W., Sandvik, L., & Kolbjørnsrud, O. B. (1989). Aerobic exercise in the treatment of nonpsychotic mental disorders: An exploratory study. *Nordic Journal of Psychiatry*, *43*(6), 521-529.

Mathew, S. J., Amiel, J. M., Coplan, J. D., Fitterling, H. A., Sackeim, H. A., & Gorman, J. M. (2005). Open-label trial of riluzole in generalized anxiety disorder. *American Journal of Psychiatry, 162*, 2379-2381.

Mathew, S. J., Mao, X., Coplan, J. D., Smith, E. L. P., Sackeim, H. A., Gorman, J. M., et al. (2004). Dorsolateral prefrontal cortical pathology in generalized anxiety disorder: a proton magnetic resonance spectroscopic imaging study. *American Journal of Psychiatry, 161*, 1119-1121.

Mathew, S. J., Price, R. B., Mao, X., Smith, E. L. P., Coplan, J. D., Charney, D. S. et al. (2008). Hippocampal N-acetylaspartate concentration and response to riluzole in generalized anxiety disorder. *Biological Psychiatry*, *63*(9), 891-898.

Mathews, A. (1997). Information-processing biases in emotional disorders. In D.M. Clark & C.G. Fairburn (Eds.), *Science and Practice of Cognitive Behaviour Therapy* (pp. 47-66). Oxford, UK: University Press.

Mathews, A., & MacLeod, C. (1994). Cognitive approaches to emotion and emotional disorders. *Annual Review of Psychology*, *45*(1), 25-50.

Mathews, A., Mogg, K., Kentish, J., & Eysenck, M. (1995). Effect of psychological treatment on cognitive bias in generalized anxiety disorder. *Behaviour Research and Therapy*, *33*(3), 293-303.

Mathews, A., Richards, A., & Eysenck, M. (1989). Interpretation ofHomophonesRelated to Threat in Anxiety States. *Journal of Abnormal Psychology*, *98*(1), 31-34.

Matthews, P. B. (1997). Spindle and motoneuronal contributions to the phase advance of the human stretch reflex and the reduction of tremor. *The Journal of Physiology*, *498*(1), 249-275.

Mattia, J. I., Heimberg, R. G., & Hope, D. A. (1993). The revised Stroop color-naming task in social phobics. *Behaviour Research and Therapy*, *31*(3), 305-313.

McAuley, E., Mihalko, S. L., & Bane, S. M. (1996). Acute Exercise and Anxiety Reduction: Does the Environment Matter? *Journal of Sport and Exercise Psychology*, *18*, 408-419.

McDonald, D. G., & Hodgdon, J. A. (1991). *The Psychological Effects of Aerobic Fitness Training: Research and Theory*. New York: Springer-Verlag.

McLaughlin, T. P., Khandker, R. K., Kruzikas, D. T., & Tummala, R. (2006). Overlap of anxiety and depression in a managed care population: Prevalence and association with resource utilization. *The Journal of Clinical Psychiatry*, *67*(8), 1187-1193.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1992). *POMS Manual: Profile of Mood States.* San Diego, CA: Educational and Industrial Testing Service.

McNally, R. J., Hornig, C. D., Otto, M. W., & Pollack, M. H. (1997). Selective encoding of threat in panic disorder: Application of a dual priming paradigm. *Behaviour Research and Therapy*, *35*(6), 543-549.

McNeil, D. W., Ries, B. J., Taylor, L. J., Boone, M. L., Carter, L. E., Turk, C. L. et al. (1995). Comparison of social phobia subtypes using Stroop tests. *Journal of Anxiety Disorders*, *9*(1), 47-57.

McWilliams, L. A., Cox, B. J., & Enns, M. W. (2003). Use of the Coping Inventory for Stressful Situations in a clinically depressed sample: Factor structure, personality correlates, and prediction of distress. *Journal of Clinical Psychology*, *59*(4), 423-427.

McWilliams, L. A., Goodwin, R. D., & Cox, B. J. (2004). Depression and anxiety associated with three pain conditions: results from a nationally representative sample. *Pain*, *111*(1-2), 77-83.

Means-Christensen, A. J., Roy-Byrne, P. P., Sherbourne, C. D., Craske, M. G., & Stein, M. B. (2008). Relationships among pain, anxiety, and depression in primary care. *Depression and Anxiety*, *25*(7), 593-600.

van Megen, H., Westenberg, H. G. M., den Boer, J. A., & Kahn, R. S. (1996). Cholecystokinin in anxiety. *European Neuropsychopharmacology*, *6*(4), 263-280.

Mendlewicz, J., Papadimitriou, G., & Wilmotte, J. (1993). Family study of panic disorder: comparison with generalized anxiety disorder, major depression and normal subjects. *Psychiatric Genetics*, *3*(2), 73-78.

Merikangas, K. R., Angst, J., & Isler, H. (1990). Migraine and psychopathology. Results of the Zurich cohort study of young adults. *Archives of General Psychiatry*, *47*(9), 849-853.

Merom, D., Phongsavan, P., Wagner, R., Chey, T., Marnane, C., Steel, Z., et al. (2008). Promoting walking as an adjunct intervention to group cognitive behavioral therapy for anxiety disorders—A pilot group randomized trial. *Journal of Anxiety Disorders*, *22*(6), 959-968.

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the penn state worry questionnaire. *Behaviour Research and Therapy*, *28*(6), 487-495.

Milanov, I. (2007). Clinical and electromyographic characteristics of tremor in patients with generalized anxiety disorder. *Electromyography and Clinical Neurophysiology*, *47*(1), 3-9.

Millan, M. J. (2003). The neurobiology and control of anxious states. *Progress in Neurobiology*, *70*(2), 83-244.

Millan, M. J., Maiofiss, L., Cussac, D., Audinot, V., Boutin, J. A., & Newman-Tancredi, A. (2002). Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. *Journal of Pharmacology and Experimental Therapeutics*, *303*(2), 791-804.

Miller, L. S., Lombardo, T. W., & Fowler, S. C. (1998). Caffeine, but not time of day, increases whole-arm physiological tremor in non-smoking moderate users. *Clinical & Experimental Pharmacology & Physiology*, *25*(2), 131-133.

Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of anxiety and unipolar mood disorders. *Annual Review of Psychology*, *49*(1), 377-412.

Mitte, K. (2005). Meta-analysis of cognitive-behavioral treatments for generalized anxiety disorder: A comparison with pharmacotherapy. *Psychological Bulletin*, *131*(5), 785-795.

Mitte, K., Noack, P., Steil, R., & Hautzinger, M. (2005). A meta-analytic review of the efficacy of drug treatment in generalized anxiety disorder. *Journal of Clinical Psychopharmacology*, *25*(2), 141-150.

Mody, I. (2001). Distinguishing between $GABA_A$ receptors responsible for tonic and phasic conductances. *Neurochemical Research*, *26*(8), 907-913.

Moffitt, T. E., Caspi, A., Harrington, H., Milne, B. J., Melchior, M., Goldberg, D. et al. (2007). Generalized anxiety disorder and depression: Childhood risk factors in a birth cohort followed to age 32. *Psychological Medicine*, *37*(3), 441-452.

Moffitt, T. E., Harrington, H. L., Caspi, A., Kim-Cohen, J., Goldberg, D., Gregory, A. M. et al. (2007). Depression and generalized anxiety disorder: cumulative and sequential comorbidity in a birth cohort followed prospectively to age 32 years. *Archives of general psychiatry*, *64*(6), 651-660.

Mogenson, G. J. (1987). Limbic-motor integration. *Progress in Psychobiology and Physiological Psychology*, *12*, 117-170.

Mogg, K., Bradbury, K. E., & Bradley, B. P. (2006). Interpretation of ambiguous information in clinical depression. *Behaviour Research and Therapy*, *44*(10), 1411-1419.

Mogg, K., & Bradley, B. P. (1998). A cognitive-motivational analysis of anxiety. *Behaviour Research and Therapy*, *36*(9), 809-848.

Mogg, K., & Bradley, B. P. (2005). Attentional bias in generalized anxiety disorder versus depressive disorder. *Cognitive Therapy and Research*, *29*(1), 29-45.

Mogg, K., Bradley, B. P., Williams, R., & Mathews, A. (1993). Subliminal processing of emotional information in anxiety and depression. *Journal of Abnormal Psychology*, *102*, 304-311.

Molina, S., & Borkovec, T. D. (1994). The Penn State Worry Questionnaire: Psychometric properties and associated characteristics. In G.C.L. Davies & F. Tallis (Eds.), *Worrying: Perspectives on Theory, Assessment and Treatment*, (pp. 265–283). New York: Wiley.

Möller, H. J., Volz, H. P., Reimann, I. W., & Stoll, K. D. (2001). Opipramol for the treatment of generalized anxiety disorder: A placebo-controlled trial including an alprazolam-treated group. *Journal of Clinical Psychopharmacology*, *21*(1), 59-65.

Mombereau, C., Kaupmann, K., Froestl, W., Sansig, G., Van Der Putten, H., & Cryan, J. F. (2004). Genetic and pharmacological evidence of a role for GABA (B) receptors in the modulation of anxiety-and antidepressant-like behavior. *Neuropsychopharmacology, 29*(6), 1050-1062.

Monteleone, P., & Maj, M. (2008). The circadian basis of mood disorders: Recent developments and treatment implications. *European Neuropsychopharmacology*, *18*(10), 701-711.

Monti, J. M., & Monti, D. (2000). Sleep disturbance in generalized anxiety disorder and its treatment. *Sleep Medicine Reviews*, *4*(3), 263-276.

Moor, M. D., Beem, A., Stubbe, J., Boomsma, D., & Geus, E. D. (2006). Regular exercise, anxiety, depression and personality: A population-based study. *Preventive Medicine*, *42*(4), 273-279.

Morgan, J. C., & Sethi, K. D. (2005). Drug-induced tremors. *Lancet Neurology*, *4*(12), 866-876.

Morris, P. L. P., Dahl, A. A., Kutcher, S. P., Sogaard, J. A., Allgulander, C., & Burt, T. (2003). Efficacy of sertraline for the acute treatment of generalized anxiety disorder (GAD). *European Neuropsychopharmacology*, *13*(Supplement 4), S375.

Motl, R. W., Berger, B. G., & Leuschen, P. S. (2000). The role of enjoyment in the exercise-mood relationship. *International Journal of Sport Psychology*, *31*(3), 347-363.

Moyer, C. A., Rounds, J., & Hannum, J. W. (2004). A meta-analysis of massage therapy research. *Psychological Bulletin*, *130*(1), 3-18.

Muhsen, K., Lipsitz, J., Garty-Sandalon, N., Gross, R., & Green, M. S. (2008). Correlates of generalized anxiety disorder: independent of co-morbidity with depression: Findings from the first Israeli National Health Interview Survey (2003-2004). *Social Psychiatry and Psychiatric Epidemiology*, *43*(11), 898-904.

Müller, M. B., Zimmermann, S., Sillaber, I., Hagemeyer, T. P., Deussing, J. M., Timpl, P. et al. (2003). Limbic corticotropin-releasing hormone receptor 1 mediates anxiety-related behavior and hormonal adaptation to stress. *Nature Neuroscience*, *6*(10), 1100-1107.

Munafo, M. R., Clark, T., & Flint, J. (2005). Promise and pitfalls in the meta-analysis of genetic association studies: A response to Sen and Schinka. *Molecular Psychiatry*, *10*(10), 895-897.

Nascimento, I., Nardi, A. E., Valença, A. M., Lopes, F. L., Mezzasalma, M. A., Nascentes, R. et al. (2002). Psychiatric disorders in asthmatic outpatients. *Psychiatry Research*, *110*(1), 73-80.

Nathan, P. E., & Gorman, J. M. (1998). Treatments that work-and what convinces us they do. *A Guide to Treatments that Work*, 3–25.

Navarro, J. F., & Maldonado, E. (2002). Acute and subchronic effects of MDMA ("ecstasy") on anxiety in male mice tested in the elevated plus-maze. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *26*(6), 1151-1154.

Neeper, S. A., Gomez-Pinilla F., Choi, J., & Cotman, C. (1995). Exercise and brain neurotrophins. *Nature, 373*, 109.

Neeper, S. A., Gomez-Pinilla, F., Choi, J., & Cotman. (1996). Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Research, 726*, 49-56.

Newman, C. L., & Motta, R. W. (2007). The effects of aerobic exercise on childhood PTSD, anxiety, and depression. *International Journal of Emergency Mental Health*, *9*(2), 133-158.

Newman, M. G., Castonguay, L. G., Borkovec, T. D., Fisher, A. J., & Nordberg, S. S. (2008). An open trial of integrative therapy for generalized anxiety disorder. *Psychotherapy: Theory, Research, Practice, Training*, *45*(2), 135-147.

Newman, S. C., & Bland, R. C. (2006). A population-based family study of DSM-III generalized anxiety disorder. *Psychological Medicine*, *36*(09), 1275-1281.

Niehoff, D. L., & Kuhar, M. J. (1983). Benzodiazepine receptors: localization in rat amygdala. *Journal of Neuroscience*, *3*(10), 2091-2097.

Nitschke, J. B., Sarinopoulos, I., Mackiewicz, K. L., Schaefer, H. S., & Davidson, R. J. (2006). Functional neuroanatomy of aversion and its anticipation. *Neuroimage*, *29*(1), 106-116.

Nitschke, J. B., Sarinopoulos, I., Oathes, D. J., Johnstone, T., Whalen, P. J., Davidson, R. J. et al. (2009). Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *American Journal of Psychiatry*, *166*(3), 302-310.

Noyes, R., Clarkson, C., Crowe, R. R., Yates, W. R., & McChesney, C. M. (1987). A family study of generalized anxiety disorder. *American Journal of Psychiatry, 144*, 1019-1024.

Noyes, R. (2001). Comorbidity in generalized anxiety disorder. *Psychiatric Clinics of North America*, *24*(1), 41-55.

Nugent, K., & Mineka, S. (1994). The effect of high and low trait anxiety on implicit and explicit memory tasks. *Cognition & Emotion*, *8*(2), 147-163.

Nutt, D., Mandel, F., & Baldinetti, F. (2008). Early onset anxiolytic efficacy after a single dose of pregabalin: double-blind, placebo-and active-comparator controlled evaluation using a dental anxiety model. *Journal of Psychopharmacology* [Epub of print] July.

Nutt, D. J. (2001). Neurobiological mechanisms in generalized anxiety disorder. *Journal of Clinical Psychiatry*, *62*, 22-28.

O Connor, P. J., Raglin, J. S., & Martinsen, E. W. (2000). Physical activity, anxiety and anxiety disorders. *International Journal of Sport Psychology*, *31*(2), 136-155.

O'Brien, C. P. (2005). Anticraving medications for relapse prevention: a possible new class of psychoactive medications. *American Journal of Psychiatry, 162*, 1423-1431.

Ochsner, K. N., Ray, R. D., Cooper, J. C., Robertson, E. R., Chopra, S., Gabrieli, J. D. E. et al. (2004). For better or for worse: neural systems supporting the cognitive down-and up-regulation of negative emotion. *Neuroimage*, *23*(2), 483-499.

O'Connor, P. J., Smith, J. C., & Morgan, W. P. (2000). Physical activity does not provoke panic attacks in patients with panic disorder: A review of the evidence. *Anxiety, Stress & Coping*, *13*(4), 333-353.

O'Connor, P., & Cook, D. (1999). Exercise and pain: The neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. *Exercise and Sport Sciences Reviews*, *27*(1), 119.

Ohayon, M. M., Shapiro, C. M., & Kennedy, S. H. (2000). Differentiating DSM-IV anxiety and depressive disorders in the general population: comorbidity and treatment consequences. *Canadian Journal of Psychiatry*, *45*(2), 166-172.

Oken, B. S., Kishiyama, S., Zajdel, D., Bourdette, D., Carlsen, J., Haas, M. et al. (2004). Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology*, *62*(11), 2058-2064.

Olfson, M., & Gameroff, M. J. (2007). Generalized anxiety disorder, somatic pain and health care costs. *General Hospital Psychiatry*, *29*(4), 310-316.

Ongur, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*, *10*(3), 206-219.

Otto, M. W., Tuby, K. S., Gould, R. A., McLean, R. Y. S., & Pollack, M. H. (2001). An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *American Journal of Psychiatry*, *158*(12), 1989-1992.

Pagliari, R., & Peyrin, L. (1995). Norepinephrine release in the rat frontal cortex under treadmill exercise: A study with microdialysis. *Journal of Applied Physiology*, *78*(6), 2121-2130.

Pande, A. C., Crockatt, J. G., Feltner, D. E., Janney, C. A., Smith, W. T., Weisler, R. et al. (2003). Pregabalin in generalized anxiety disorder: a placebo-controlled trial. *American Journal of Psychiatry*, *160*(3), 533-540.

Parrott, A. C. (2000). Human research on MDMA (3, 4-methylene-dioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. *Neuropsychobiology*, *42*, 17-24.

Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry*, *60*(4), 383-387.

Paz-Diaz, H., de Oca, M. M., López, J. M., & Celli, B. R. (2007). Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. *American Journal of Physical Medicine & Rehabilitation*, *86*(1), 30-36.

Perks, A., Chakravarti, S., & Manninen, P. (2009). Preoperative anxiety in neurosurgical patients. *Journal of Neurosurgical Anesthesiology*, *21*(2), 127-130.

Peterson, R. A., & Reiss, S. (1987). *Test manual for the Anxiety Sensitivity Index*. Orland Park, IL: International Diagnostic Systems.

Petruzzello, S. J., Landers, D. M., Hatfield, B. D., Kubitz, K. A., & Salazar, W. (1991). A meta-analysis on the anxiety-reducing effects of acute and chronic exercise: Outcomes and mechanisms. *Sports Medicine*, *11*(3), 143-182.

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction Learning in Humans Role of the Amygdala and vmPFC. *Neuron*, *43*(6), 897-905.

Pine, D. S., Cohen, P., Johnson, J. G., & Brook, J. S. (2002). Adolescent life events as predictors of adult depression. *Journal of Affective Disorders*, *68*(1), 49-57.

Pitman, R. K., Sanders, K. M., Zusman, R. M., Healy, A. R., Cheema, F., Lasko, N. B. et al. (2002). Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biological Psychiatry*, *51*(2), 189-192.

Pittenger, C., Coric, V., Banasr, M., Bloch, M., Krystal, J. H., & Sanacora, G. (2008). Riluzole in the treatment of mood and anxiety disorders. *CNS drugs*, *22*(9), 761-786.

Pitts Jr, F. N., & McClure Jr, J. N. (1967). Lactate metabolism in anxiety neurosis. *The New England Journal of Medicine*, *277*(25), 1329-1336.

Pluess, M., Conrad, A., & Wilhelm, F. H. (2009). Muscle tension in generalized anxiety disorder: A critical review of the literature. *Journal of Anxiety Disorders*, *23*(1), 1-11.

Pollack, M. H., Meoni, P., Otto, M. W., & Hackett, D. (2003). Predictors of outcome following venlafaxine extended-release treatment of DSM-IV generalized anxiety disorder: A pooled analysis of short-and long-term studies. *Journal of Clinical Psychopharmacology*, *23*(3), 250-259.

Pollack, M. H., Zaninelli, R., Goddard, A., McCafferty, J. P., Bellew, K. M., Burnham, D. B. et al. (2001). Paroxetine in the treatment of generalized anxiety disorder: Results of a placebo-controlled, flexible-dosage trial. *The Journal of Clinical Psychiatry*, *62*(5), 350-357.

Pomara, N., Willoughby, L. M., Sidtis, J. J., Cooper, T. B., & Greenblatt, D. J. (2005). Cortisol response to diazepam: its relationship to age, dose, duration of treatment, and presence of generalized anxiety disorder. *Psychopharmacology*, *178*(1), 1-8.

Price, J. L., & Amaral, D. G. (1981). An autoradiographic study of the projections of the central nucleus of the monkey amygdala. *Journal of Neuroscience*, *1*(11), 1242-1259.

Puetz, T. W., Beasman, K. M., & O'Connor, P. J. (2006). The effect of cardiac rehabilitation exercise programs on feelings of energy and fatigue: A meta-analysis of research from 1945 to 2005. *European Journal of Cardiovascular Prevention & Rehabilitation*, *13*(6), 886-893.

Puetz, T. W., O Connor, P. J., & Dishman, R. K. (2006). Effects of chronic exercise on feelings of energy and fatigue: A quantitative synthesis. *Psychological Bulletin*, *132*(6), 866-876.

Quirk, G. J., Likhtik, E., Pelletier, J. G., & Pare, D. (2003). Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *Journal of Neuroscience*, *23*(25), 8800-8807.

Raethjen, J., Lindemann, M., Morsnowski, A., Dumpelmann, M., Wenzelburger, R., Stolze, H. et al. (2004). Is the rhythm of physiological tremor involved in cortico-cortical interactions? *Movement Disorders*, *19*(4), 458-465.

Raglin, J. S. (1997). Anxiolytic effects of physical activity. In W.P. Morgan (Ed.), *Physical Activity and Mental Health* (pp. 107-126). Washington, D.C.: Taylor & Francis.

Ramboz, S., Oosting, R., Amara, D. A., Kung, H. F., Blier, P., Mendelsohn, M. et al. (1998). Serotonin receptor 1A knockout: An animal model of anxiety-related disorder *Proceedings of the National Academy of Sciences of the United States of America, 95*(24), 14476-14481.

Ramsawh, H. J., Stein, M. B., Belik, S. L., Jacobi, F., & Sareen, J. (2009). Relationship of anxiety disorders, sleep quality, and functional impairment in a community sample. *Journal of Psychiatric Research, 43*(10), 926-933.

Rauch, S. L., Savage, C. R., Alpert, N. M., Fischman, A. J., & Jenike, M. A. (1997). The functional neuroanatomy of anxiety: A study of three disorders using positron emission tomography and symptom provocation. *Biological Psychiatry*, *447*(42), 446-452.

Rauch, S., Shin, L., & Wright, C. (2003). Neuroimaging studies of amygdala function in anxiety disorders. *Annals of the New York Academy of Sciences*, *985*(1), 389-410.

Rausch, S. M., Gramling, S. E., & Auerbach, S. M. (2006). Effects of a single session of large-group meditation and progressive muscle relaxation training on stress reduction, reactivity, and recovery. *International Journal of Stress Management*, *13*(3), 273-290.

Reiman, E. M. (1997). The application of positron emission tomography to the study of normal and pathologic emotions. *The Journal of Clinical Psychiatry. Supplement*, *58*(16), 4-12.

Rejeski, W. J., Hardy, C. J., & Shaw, J. (1991). Psychometric confounds of assessing state anxiety in conjunction with acute bouts of vigorous exercise. *Journal of Sport & Exercise Psychology*, *13*(1), 65-74.

Reynolds, S. M., & Zahm, D. S. (2005). Specificity in the projections of prefrontal and insular cortex to ventral striatopallidum and the extended amygdala. *Journal of Neuroscience*, *25*(50), 11757-11767.

Rice, M. E., & Harris, G. T. (1995). Violent recidivism: Assessing predictive validity. *Journal of Consulting and Clinical Psychology*, *63*(5), 737-748.

Richards, A., & Whittaker, T. M. (1990). Effects of anxiety and mood manipulation in autobiographical memory. *The British Journal of Clinical Psychology*, *29*, 145-153.

Rickels, K., Downing, R., Schweizer, E., & Hassman, H. (1993). Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Archives of General Psychiatry*, *50*(11), 884-895.

Rickels, K., Pollack, M. H., Sheehan, D. V., & Haskins, J. T. (2000). Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. *American Journal of Psychiatry*, *157*(6), 968-974.

Rickels, K., & Rynn, M. (2002). Pharmacotherapy of generalized anxiety disorder. *The Journal of Clinical Psychiatry*, *63*(Supplement 14), 9-16.

Rickels, K., Zaninelli, R., McCafferty, J., Bellew, K., Iyengar, M., & Sheehan, D. (2003). Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. *American Journal of Psychiatry*, *160*(4), 749-756.

Rippe, J. M., Price, J. M., Hess, S. A., Kline, G., DeMers, K. A., Damitz, S. et al. (1998). Improved psychological well-being, quality of life, and health practices in moderately overweight women participating in a 12-week structured weight loss program. *Obesity Research*, *6*(3), 208-218.

Riskind, J. H., Beck, A., Brown, G., & Steer, R. A. (1987). Taking the measure of anxiety and depression. Validity of the reconstructed Hamilton Scales. *Journal of Nervous & Mental Disease*, *175*(8), 474-479.

Rosenbaum, J. F., Biederman, J., Hirshfeld, D. R., Bolduc, E. A., & Chaloff, J. (1991). Behavioral inhibition in children: A possible precursor to panic disorder or social phobia. *The Journal of Clinical Psychiatry*, *52*, 5-9.

Rosenbaum, J. F., Woods, S. W., Groves, J. E., & Klerman, G. L. (1984). Emergence of hostility during alprazolam treatment. *American Journal of Psychiatry, 141*, 792-793.

Rosenthal, R. (1991). *Meta-analytic procedures for social research*. Sage.

Rossy, L. A., Buckelew, S. P., Dorr, N., Hagglund, K. J., Thayer, J. F., McIntosh, M. J. et al. (1999). A meta-analysis of fibromyalgia treatment interventions. *Annals of Behavioral Medicine*, *21*(2), 180-191.

Roth, A., & Fonagy, P. (1996). *What Works for Whom? A Critical Review of Psychotherapy Research.* New York: Guilford.

Roth, A., Nelson, C. J., Rosenfeld, B., Warshowski, A., O'Shea, N., Scher, H. et al. (2006). Assessing anxiety in men with prostate cancer: further data on the reliability and validity of the Memorial Anxiety Scale for Prostate Cancer (MAX-PC). *Psychosomatics*, *47*(4), 340-347.

Roy, M. A., Neale, M. C., Pedersen, N. L., Mathe, A. A., & Kendler, K. S. (1995). A twin study of generalized anxiety disorder and major depression. *Psychological Medicine*, *25*(5), 1037-1049.

Roy-Byrne, P. P., Davidson, K. W., Kessler, R. C., Asmundson, G. J. G., Goodwin, R. D., Kubzansky, L. et al. (2008). Anxiety disorders and comorbid medical illness. *General Hospital Psychiatry, 30*(3), 208-225.

Rynn, M., Russell, J., Erickson, J., Detke, M. J., Ball, S., Dinkel, J. et al. (2008). Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: A flexible-dose, progressive-titration, placebo-controlled trial. *Depression and Anxiety*, *25*(3), 182-189.

Rynn, M. A., Riddle, M. A., Yeung, P. P., & Kunz, N. R. (2007). Efficacy and safety of extended-release venlafaxine in the treatment of generalized anxiety disorder in children and adolescents: Two placebo-controlled trials. *American Journal of Psychiatry*, *164*(2), 290-300.

Sajdyk, T. J., & Shekhar, A. (1997). Excitatory amino acid receptors in the basolateral amygdala regulate anxiety responses in the social interaction test. *Brain Research*, *764*(1-2), 262-264.

Sanacora, G., Kendell, S. F., Levin, Y., Simen, A. A., Fenton, L. R., Coric, V. et al. (2007). Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biological Psychiatry*, *61*(6), 822-825.

Sanchez, X., Boschker, M. S. J., & Llewellyn, D. J. (2009). Pre-performance psychological states and performance in an elite climbing competition. *Scandinavian Journal of Medicine & Science in Sports* [Epub ahead of print] March 25.

Sanders, S. K., & Shekhar, A. (1995). Regulation of anxiety by $GABA_A$ receptors in the rat amygdala. *Pharmacology, Biochemistry, and Behavior*, *52*(4), 701-706.

Sandford, J. J., Argyropoulos, S. V., & Nutt, D. J. (2000). The psychobiology of anxiolytic drugs Part 1: basic neurobiology. *Pharmacology and Therapeutics*, *88*(3), 197-212.

Sanger, D. J. (1985). GABA and the behavioral effects of anxiolytic drugs. *Life sciences*, *36*(16), 1503-1513.

Sareen, J., Cox, B. J., Clara, I., & Asmundson, G. J. G. (2005). The relationship between anxiety disorders and physical disorders in the US National Comorbidity Survey. *Depression and anxiety*, *21*(4), 193-202.

Sareen, J., Jacobi, F., Cox, B. J., Belik, S. L., Clara, I., & Stein, M. B. (2006). Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. *Archives of Internal Medicine*, *166*(19), 2109-2116.

Sarter, M., & Bruno, J. P. (1999). Cortical cholinergic inputs mediating arousal, attentional processing and dreaming: Differential afferent regulation of the basal forebrain by telencephalic and brainstem afferents. *Neuroscience*, *95*(4), 933-952.

Sarter, M., Bruno, J. P., & Berntson, G. G. (2001). Psychotogenic properties of benzodiazepine receptor inverse agonists. *Psychopharmacology*, *156*(1), 1-13.

Schaller, K., Mechau, D., Scharmann, H. G., Weiss, M., Baum, M., & Liesen, H. (1999). Increased training load and the beta -adrenergic-receptor system on human lymphocytes. *Journal of Applied Physiology*, *87*(1), 317-324.

Scherrer, J. F., True, W. R., Xian, H., Lyons, M. J., Eisen, S. A., Goldberg, J. et al. (2000). Evidence for genetic influences common and specific to symptoms of generalized anxiety and panic. *Journal of Affective Disorders*, *57*(1-3), 25-35.

Schinka, J. A., Busch, R. M., & Robichaux-Keene, N. (2004). A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. *Molecular Psychiatry*, *9*(2), 197-202.

Schlegel, S., Steinert, H., Bockisch, A., Hahn, K., Schloesser, R., & Benkert, O. (1994). Decreased benzodiazepine receptor binding in panic disorder measured by IOMAZENIL-SPECT. *European Archives of Psychiatry and Clinical Neuroscience*, *244*(1), 49-51.

Schlicht, W. (1994). Does physical exercise reduce anxious emotions? A meta-analysis. *Anxiety, Stress & Coping*, *6*(4), 275-288.

Schmitz, N., Kruse, J., & Kugler, J. (2004). The association between physical exercises and health-related quality of life in subjects with mental disorders: results from a cross-sectional survey. *Preventive Medicine*, *39*(6), 1200-1207.

Schoevers, R. A., Deeg, D. J. H., Van Tilburg, W., & Beekman, A. T. F. (2005). Depression and Generalized Anxiety Disorder Co-Occurrence and Longitudinal Patterns in Elderly Patients. *The American Journal of Geriatric Psychiatry, 13*, 31-39.

Schramm, N. L., McDonald, M. P., & Limbird, L. E. (2001). The alpha2A-adrenergic receptor plays a protective role in mouse behavioral models of depression and anxiety. *Journal of Neuroscience*, *21*(13), 4875-4882.

Schuler, V., Lüscher, C., Blanchet, C., Klix, N., Sansig, G., Klebs, K. et al. (2001). Epilepsy, hyperalgesia, impaired memory, and loss of pre-and postsynaptic GABAB responses in mice lacking GABAB (1). *Neuron*, *31*(1), 47-58.

Schuurmans, J., Comijs, H., Emmelkamp, P. M. G., Gundy, C. M. M., Weijnen, I., Van Den Hout, M., et al. (2006). A randomized, controlled trial of the effectiveness of cognitive-behavioral therapy and sertraline versus a waitlist control group for anxiety disorders in older adults. *American Journal of Geriatric Psychiatry, 14*(3), 255-263.

Schwartz, C. E., Snidman, N., & Kagan, J. (1999). Adolescent social anxiety as an outcome of inhibited temperament in childhood. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*, 1008-1015.

Scott, K. M., Bruffaerts, R., Tsang, A., Ormel, J., Alonso, J., Angermeyer, M. C. et al. (2007). Depression–anxiety relationships with chronic physical conditions: results from the World Mental Health surveys. *Journal of Affective Disorders*, *103*(1-3), 113-120.

Seki, E., Watanabe, Y., Sunayama, S., Iwama, Y., Shimada, K., Kawakami, K. et al. (2003). Effects of phase III cardiac rehabilitation programs on health-related quality of life in elderly patients with coronary artery disease: Juntendo Cardiac Rehabilitation Program (J-CARP). *Circulation Journal*, *67*(1), 73-77.

Sen, S., Burmeister, M. L., & Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American Journal of Medical Genetics, 127B(1)*, 85-89.

Sevy, S., Papadimitriou, G. N., Surmont, D. W., Goldman, S., & Mendlewicz, J. (1989). Noradrenergic function in generalized anxiety disorder, major depressive disorder, and healthy subjects. *Biological Psychiatry*, *25*(2), 141-152.

Sexton, H., Maere, A., & Dahl, N. H. (1989). Exercise intensity and reduction in neurotic symptoms. *Acta Psychiatrica Scandinavia*, *80*, 231-235.

Shear, M. K., Vander Bilt, J., Rucci, P., Endicott, J., Lydiard, B., Otto, M. W. et al. (2001). Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depression and Anxiety*, *13*(4), 166-178.

Shekhar, A., & Keim, S. R. (2000). LY354740, a potent group II metabotropic glutamate receptor agonist prevents lactate-induced panic-like response in panic-prone rats. *Neuropharmacology*, *39*(7), 1139-1146.

Silove, D., Parker, G., Hadzi-Pavlovic, D., Manicavasagar, V., & Blaszczynski, A. (1991). Parental representations of patients with panic disorder and generalised anxiety disorder. *The British Journal of Psychiatry*, *159*(6), 835-841.

Simon, G., Gater, R., Kisely, S., & Piccinelli, M. (1996). Somatic symptoms of distress: An international primary care study. *Psychosomatic Medicine, 58*, 481-488.

Simon, G., & Von Korff, M. (1991). Somatization and Psychiatric Disorders in the epidemiological study area of the National Institute of Mental Health. *American Journal of Psychiatry*, *40*(4), 1494-1500.

Simpson, J. R., Drevets, W. C., Snyder, A. Z., Gusnard, D. A., & Raichle, M. E. (2001). Emotion-induced changes in human medial prefrontal cortex: II. During anticipatory anxiety. *Proceedings of the National Academy of Sciences*, *98*(2), 688-693.

Singewald, N., & Sharp, T. (2000). Neuroanatomical targets of anxiogenic drugs in the hindbrain as revealed by Fos immunocytochemistry. *Neuroscience*, *98*(4), 759-770.

Singh, N. A., Clements, K. M., & Fiatarone, M. A. (1997). A randomized controlled trial of the effect of exercise on sleep. *Sleep*, *20*(2), 95-101.

Singh, N. A., Stavrinos, T. M., Scarbek, Y., Galambos, G., Liber, C., & Fiatarone Singh, M. A. (2005). A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *Journals of Gerontology Series A: Biological and Medical Sciences*, *60*(6), 768-776.

Slade, T., & Watson, D. (2006). The structure of common DSM-IV and ICD-10 mental disorders in the Australian general population. *Psychological Medicine*, *36*(11), 1593-1600.

Smith, G. W., Aubry, J. M., Dellu, F., Contarino, A., Bilezikjian, L. M., Gold, L. H. et al. (1998). Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. *Neuron*, *20*(6), 1093-1102.

Smith, J. C., & Crabbe, J. B. (2000). Emotion and exercise. *International Journal of Sport Psychology*, *31*(2), 156-174.

Smits, J. A. J., Berry, A. C., Powers, M. B., Greer, T. L., & Otto, M. W. (2007). The Promise of Exercise Interventions for the Anxiety Disorders. *Anxiety in Health Behaviors and Physical Illness*, 81-104.

Soares, J., Holmes, P. V., Renner, K. J., Edwards, G. L., Bunnell, B. N., & Dishman, R. K. (1999). Brain noradrenergic responses to footshock after chronic activity-wheel running. *Behavioral Neuroscience*, *113*(3), 558-566.

Southwick, S. M., Bremner, J. D., Rasmusson, A., Morgan, C. A., Arnsten, A., & Charney, D. S. (1999). Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. *Biological Psychiatry*, *46*(9), 1192-1204.

Spence, S. H. (1997). Structure of anxiety symptoms among children: A confirmatory factor-analytic study. *Journal of Abnormal Psychology*, *106*, 280-297.

Spielberger, C. D. (1966). *Anxiety and Behavior*. New York: Academic Press.

Spielberger, C. D. (1985). Anxiety, cognition and affect: A state-trait perspective. In A.H. Tuma and J.D. Maser (Eds.), *Anxiety and the anxiety disorders* (pp. 171-182). New Jersey: Erlbaum.

Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). *Manual for the State-Trait Anxiety Inventory (Form Y): Self-evaluation Questionnaire*. Palo Alto, CA: Consulting Psychologists Press.

Stanley, M. A., Beck, J. G., & Zebb, B. J. (1996). Psychometric properties of four anxiety measures in older adults. *Behaviour Research and Therapy*, *34*(10), 827-838.

Stanley, M. A., Wilson, N. L., Novy, D. M., Rhoades, H. M., Wagener, P. D., Greisinger, A. J., et al. (2009). Cognitive behavior therapy for generalized anxiety disorder among older adults in primary care: A randomized clinical trial. *JAMA*, *301*(14), 1460-1467.

Stefanski, R., Palejko, W., Bidzinski, A., Kostowski, W., & Plaznik, A. (1993). Serotonergic innervation of the hippocampus and nucleus accumbens septi and the anxiolytic-like action of midazolam and 5-HT1A receptor agonists. *Neuropharmacology*, *32*(10), 977.

Stein, M. B., Roy-Byrne, P. P., Craske, M. G., Bystritsky, A., Sullivan, G., Pyne, J. M. et al. (2005). Functional Impact and Health Utility of Anxiety Disorders in Primary Care Outpatients. *Medical Care*, *43*(12), 1164-1170.

Stein, M. B., Simmons, A. N., Feinstein, J. S., & Paulus, M. P. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *American Journal of Psychiatry*, *164*(2), 318-327.

Stenzel-Poore, M. P., Duncan, J. E., Rittenberg, M. B., Bakke, A. C., & Heinrichs, S. C. (1996). Behavioral and Immune System Modulation. *Annals of the New York Academy of Sciences*, *780*(1), 36-48.

Stenzel-Poore, M. P., Heinrichs, S. C., Rivest, S., Koob, G. F., & Vale, W. W. (1994). Overproduction of corticotropin-releasing factor in transgenic mice: a genetic model of anxiogenic behavior. *Journal of Neuroscience*, *14*(5), 2579-2584.

Stephens, T. (1988). Physical activity and mental health in the United States and Canada: evidence from four population surveys. *Preventive Medicine*, *17*(1), 35-47.

Stork, O., Ji, F. Y., & Obata, K. (2002). Reduction of extracellular GABA in the mouse amygdala during and following confrontation with a conditioned fear stimulus. *Neuroscience Letters*, *327*(2), 138-142.

Stathopoulou, G., Powers, M. B., Berry, A. C., Smits, J. A. J., & Otto, M. W. (2006). Exercise interventions for mental health: A quantitative and qualitative review. *Clinical Psychology: Science and Practice*, *13*(2), 179-193.

Straube, T., Weiss, T., Mentzel, H. J., & Miltner, W. H. R. (2007). Time course of amygdala activation during aversive conditioning depends on attention. *Neuroimage*, *34*(1), 462-469.

Strine, T. W., Chapman, D. P., Kobau, R., & Balluz, L. (2005). Associations of self-reported anxiety symptoms with health-related quality of life and health behaviors. *Social Psychiatry and Psychiatric Epidemiology*, *40*(6), 432-438.

Strobel, A., Gutknecht, L., Rothe, C., Reif, A., Mössner, R., Zeng, Y. et al. (2003). Allelic variation in 5-HT 1A receptor expression is associated with anxiety-and depression-related personality traits. *Journal of Neural Transmission*, *110*(12), 1445-1453.

Strohle, A., Hofler, M., Pfister, H., Muller, A., Hoyer, J., Wittchen, H. U. et al. (2007). Physical activity and prevalence and incidence of mental disorders in adolescents and young adults. *Psychological Medicine*, *37*(11), 1657-1666.

Sullivan, G. M., Coplan, J. D., Kent, J. M., & Gorman, J. M. (1999). The noradrenergic system in pathological anxiety: A focus on panic with relevance to generalized anxiety and phobias. *Biological Psychiatry*, *46*(9), 1205-1218.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry, 157*, 1552-1562.

Swain, R. A., Harris, A. B., Wiener, E. C., Dutka, M. V., Morris, H. D., Theien, B. E. et al. (2003). Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience, 117*, 1037-1046.

Swerdlow, N. R., Geyer, M. A., Vale, W. W., & Koob, G. F. (1986). Corticotropin-releasing factor potentiates acoustic startle in rats: blockade by chlordiazepoxide. *Psychopharmacology*, *88*(2), 147-152.

Tanaka, M., Yoshida, M., Emoto, H., & Ishii, H. (2000). Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: basic studies. *European Journal of Pharmacology*, *405*(1-3), 397-406.

Tata, P. R., Leibowitz, J. A., Prunty, M. J., Cameron, M., & Pickering, A. D. (1996). Attentional bias in obsessional compulsive disorder. *Behaviour Research and Therapy*, *34*(1), 53-60.

Tate, A. K., & Petruzzello, S. J. (1995). Varying the intensity of acute exercise: implications for changes in affect. *The Journal of Sports Medicine and Physical Fitness*, *35*(4), 295-302.

Tauscher, J., Bagby, R. M., Javanmard, M., Christensen, B. K., Kasper, S., & Kapur, S. (2001). Inverse relationship between serotonin 5-HT1A receptor binding and anxiety: a [11C] WAY-100635 PET investigation in healthy volunteers. *American Journal of Psychiatry, 158*, 1326-1328.

Taylor, A. H., Cable, N. T., Faulkner, G., Hillsdon, M., Narici, M., & Van Der Bij, A. K. (2004). Physical activity and older adults: a review of health benefits and the effectiveness of interventions. *Journal of Sports Sciences*, *22*(8), 703-725.

Taylor, J. A. (1953). A personality scale of manifest anxiety. *Journal of Abnormal and Social Psychology*, *48*(2), 285-290.

Teh, C. F., Morone, N. E., Karp, J. F., Belnap, B. H., Zhu, F., Weiner, D. K., et al. (2009). Pain interference impacts response to treatment for anxiety disorders. *Depression and Anxiety*, *26*(3), 222-228.

Tellegen, A. (1985). Structures of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In H. Tuma & J.D. Maser (Eds.), *Anxiety and the Anxiety Disorders* (pp. 681-706). New Jersey: Erlbaum.

Telzer, E. H., Mogg, K., Bradley, B. P., Mai, X., Ernst, M., Pine, D. S. et al. (2008). Relationship between trait anxiety, prefrontal cortex, and attention bias to angry faces in children and adolescents. *Biological Psychology*, *79*(2), 216-222.

Thomson, I. R., Peterson, M. D., & Hudson, R. J. (1998). A comparison of clonidine with conventional preanesthetic medication in patients undergoing coronary artery bypass grafting. *Anesthesia & Analgesia*, *87*(2), 292-299.

Thorsen, L., Nystad, W., Stigum, H., Dahl, O., Klepp, O., Bremnes, R. M. et al. (2005). The association between self-reported physical activity and prevalence of depression and anxiety disorder in long-term survivors of testicular cancer and men in a general population sample. *Supportive Care in Cancer*, *13*(8), 637-646.

Tiihonen, J., Kuikka, J., Rasanen, P., Lepola, U., Koponen, H., Liuska, A. et al. (1997). Cerebral benzodiazepine receptor binding and distribution in generalized anxiety disorder: A fractal analysis. *Molecular Psychiatry*, *2*(6), 463-471.

Tillfors, M., Furmark, T., Marteinsdottir, I., Fischer, H., Pissiota, A., Langstrom, B. et al. (2001). Cerebral blood flow in subjects with social phobia during stressful speaking tasks: A PET study. *American Journal of Psychiatry*, *158*(8), 1220-1226.

Timpl, P., Spanagel, R., Sillaber, I., Kresse, A., Reul, J., Stalla, G. K. et al. (1998). Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. *Nature Genetics*, *19*(2), 162-166.

Troelsen, K. B., Nielsen, E., & Mirza, N. R. (2005). Chronic treatment with duloxetine is necessary for an anxiolytic-like response in the mouse zero maze: The role of the serotonin transporter. *Psychopharmacology*, *181*(4), 741-750.

Truitt, W. A., Johnson, P. L., Dietrich, A. D., Fitz, S. D., & Shekhar, A. (2009). Anxiety-like behavior is modulated by a discrete subpopulation of interneurons in the basolateral amygdala. *Neuroscience, 160*(2), 284-294.

Truitt, W. A., Sajdyk, T. J., Dietrich, A. D., Oberlin, B., McDougle, C. J., & Shekhar, A. (2007). From anxiety to autism: Spectrum of abnormal social behaviors modeled by progressive disruption of inhibitory neuronal function in the basolateral amygdala in Wistar rats. *Psychopharmacology*, *191*(1), 107-118.

Tsai, J. C., Wang, W. H., Chan, P., Lin, L. J., Wang, C. H., Tomlinson, B. et al. (2003). The beneficial effects of Tai Chi Chuan on blood pressure and lipid profile and anxiety status in a randomized controlled trial. *The Journal of Alternative & Complementary Medicine*, *9*(5), 747-754.

Tsutsumi, T., Don, B. M., Zaichkowsky, L. D., Takenaka, K., & Oka, K. (1998). Comparison of high and moderate intensity of strength training on mood and anxiety in older adults. *Perceptual and Motor Skills*, *87*(3), 1003-1011.

Turner, S. M., Beidel, D. C., & Wolff, P. L. (1996). Is behavioral inhibition related to the anxiety disorders? *Clinical Psychology Review*, *16*(2), 157-172.

Tyrer, P., & Baldwin, D. (2006). Generalised anxiety disorder. *The Lancet*, *368*(9553), 2156-2166.

Vacha-Haase, T. (1998). Reliability generalization: Exploring variance in measurement error affecting score reliability across studies. *Educational and Psychological Measurement*, *58*(1), 6-20.

Vaiva, G., Ducrocq, F., Jezequel, K., Averland, B., Lestavel, P., Brunet, A. et al. (2003). Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biological Psychiatry*, *54*(9), 947-949.

Valença, A. M., Falcão, R., Freire, R. C., Nascimento, I., Nascentes, R., Zin, W. A. et al. (2006). The relationship between the severity of asthma and comorbidites with anxiety and depressive disorders. *Revista Brasileira de Psiquiatria*, *28*, 206-208.

Valentino, R. J., & Aston-Jones, G. S. (1995). Physiological and anatomical determinants of locus coeruleus discharge. In F.E. Bloom and D.J. Kupfer (Eds.), *Psychopharmacology: The Fourth Generation of Progress* (pp. 373-385). New York: Raven Press.

Van Ameringen, M., Mancini, C., & Oakman, J. M. (1998). The relationship of behavioral inhibition and shyness to anxiety disorder. *The Journal of Nervous and Mental Disease*, *186*(7), 425-431.

Vanderveen, J. E., Armstrong, L. E., Butterfield, G. E., Chenoweth, W. L., Dwyer, J. T., Fernstrom, J. D. et al. (2001). Caffeine for the sustainment of mental task performance: Formulations for military operations. *National Academy, Washington, DC.*

van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 13427-13431.

van Praag, H., Chunm, T. S., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *The Journal of Neuroscience, 25*, 8680-8686.

van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience, 2*, 266-270.

van Praag, H., Kempermann, G., & Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nature Reviews Neuroscience, 1*, 191-198.

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Exercise induces BDNF and synapsin 1 to specific hippocampal subfields. *Journal of Neuroscience Research, 76*, 356-362.

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience, 20*, 2580-2590.

Vesga-López, O., Schneier, F. R., Wang, S., Heimberg, R. G., Liu, S. M., Hasin, D. S. et al. (2008). Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *The Journal of Clinical Psychiatry*, *69*(10), 1606-1616.

Vila, G., Nollet-Clemencon, C., de Blic, J., Falissard, B., Mouren-Simeoni, M. C., & Scheinmann, P. (1999). Assessment of anxiety disorders in asthmatic children. *Psychosomatics, 40*, 404-413.

Viveros, M. P., Marco, E. M., & File, S. E. (2005). Endocannabinoid system and stress and anxiety responses. *Pharmacology Biochemistry and Behavior*, *81*(2), 331-342.

Walker, D. L., Toufexis, D. J., & Davis, M. (2003). Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. *European Journal of Pharmacology*, *463*(1-3), 199-216.

Walker, E. A., Katon, W., Russo, J., Ciechanowski, P., Newman, E., & Wagner, A. W. (2003). Health care costs associated with posttraumatic stress disorder symptoms in women. *Archives of General Psychiatry, 60*, 369-374.

Walkup, J. T., Labellarte, M. J., Riddle, M. A., Pine, D. S., Greenhill, L., Klein, R. et al. (2001). Fluvoxamine for the treatment of anxiety disorders in children and adolescents. *The New England Journal of Medicine, 344*, 1279-1285.

Wand, B. M., BAppSc, G., Bird, C., McAuley, J. H., PgDip, P. D., Doré, C. J. et al. (2004). Early intervention for the management of acute low back pain: A single-blind randomized controlled trial of biopsychosocial education, manual therapy, and exercise. *Spine*, *29*(21), 2350-2356.

Watson, D. (2000). *Mood and temperament*. New York: Guilford Press.

Watson, D. (2005). Rethinking the mood and anxiety disorders: a quantitative hierarchical model for DSM-V. *Journal of Abnormal Psychology*, *114*(4), 522-536.

Watson, D. (2009). Differentiating the mood and anxiety disorders: A quadripartite model. *Annual Review of Clinical Psychology, 5*, 221-247.

Watson, D., Weber, K., Smith Assenheimer, J., Clark, L. A., Strauss, M. E., & McCormick, R. A. (1995). Testing a tripartite model: I. Evaluating the convergent and discriminant validity of anxiety and depression symptom scales. *Journal of Abnormal Psychology*, *104*, 3-14.

Wells, A., & King, P. (2006). Metacognitive therapy for generalized anxiety disorder: An open trial. *Journal of Behavior Therapy and Experimental Psychiatry*, *37*(3), 206-212.

Westen, D., & Morrison, K. (2001). A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: An empirical examination of the status of empirically supported therapies. *Journal of Consulting and Clinical Psychology*, *69*(6), 875-899.

Wetherell, J. L., Gatz, M., & Craske, M. G. (2003). Treatment of generalized anxiety disorder in older adults. *Journal of Consulting and Clinical Psychology*, *71*(1), 31-39.

Whalen, P. J., Johnstone, T., Somerville, L. H., Nitschke, J. B., Polis, S., Alexander, A. L. et al. (2008). A functional magnetic resonance imaging predictor of treatment response to venlafaxine in generalized anxiety disorder. *Biological Psychiatry*, *63*(9), 858-863.

Willetts, J., Clissold, D. B., Hartman, T. L., Brandsgaard, R. R., Hamilton, G. S., & Ferkany, J. W. (1993). Behavioral pharmacology of NPC 17742, a competitive N-methyl-D-aspartate (NMDA) antagonist. *Journal of Pharmacology and Experimental Therapeutics*, *265*(3), 1055-1062.

Williams, J. M. G., Mathews, A., & MacLeod, C. (1996). The emotional Stroop task and psychopathology. *Psychological Bulletin*, *120*(1), 3-24.

Williams, J. M. G., Watts, F. N., MacLeod, C., & Mathews, A. (1997). *Cognitive Psychology and Emotional Disorders*. Chichester, NY: Wiley.

Wingerson, D., Sullivan, M., Dager, S., Flick, S., Dunner, D., & Roy-Byrne, P. (1993). Personality traits and early discontinuation from clinical trials in anxious patients. *Journal of Clinical Psychopharmacology*, *13*(3), 194-197.

Wipfli, B. M., Rethorst, C. D., & Landers, D. M. (2008). The anxiolytic effects of exercise: A meta-analysis of randomized trials and dose-response analysis. *Journal of Sport & Exercise Psychology*, *30*(4), 392-410.

Wittchen, H. U. (2002). Generalized anxiety disorder: prevalence, burden, and cost to society. *Depression and Anxiety*, *16*(4), 162-171.

Wittchen, H. U., Kessler, R. C., Beesdo, K., Krause, P., Hofler, M., & Hoyer, J. (2002). Generalized anxiety and depression in primary care: Prevalence, recognition, and management. *Journal of Clinical Psychiatry*, *63*, 24-34.

Wittchen, H. U., Kessler, R. C., Pfister, H., & Lieb, M. (2000). Why do people with anxiety disorders become depressed? A prospective-longitudinal community study. *Acta Psychiatrica Scandinavica Supplement*, (406), 14-23.

Wittchen, H. U., Zhao, S., Kessler, R., & Eaton, W. W. (1994). DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Archives of General Psychiatry*, *51*, 355-364.

Wright, C. I., Martis, B., McMullin, K., Shin, L. M., & Rauch, S. L. (2003). Amygdala and insular responses to emotionally valenced human faces in small animal specific phobia. *Biological Psychiatry*, *54*(10), 1067-1076.

Wu, J. C., Buchsbaum, M. S., Hershey, T. G., Hazlett, E., Sicotte, N., & Johnson, J. C. (1991). PET in generalized anxiety disorder. *Biological Psychiatry*, *29*(12), 1181-1199.

Wyshak, G. (2001). Women's college physical activity and self-reports of physician-diagnosed depression and of current symptoms of psychiatric distress. *Journal of Women's Health & Gender-Based Medicine*, *10*(4), 363-370.

Xie, Z., & Commissaris, R. L. (1992). Anxiolytic-like effects of the noncompetitive NMDA antagonist MK 801. *Pharmacology, Biochemistry, and Behavior*, *43*(2), 471-477.

Youngstedt, S. D., & Kripke, D. F. (2007). Does bright light have an anxiolytic effect?- an open trial. *BMC Psychiatry*, *7*(1), 62.

Youngstedt, S., O'Connor, P., Crabbe, J., & Dishman, R. (1998). Acute exercise reduces caffeine-induced anxiogenesis. *Medicine & Science in Sports & Exercise*, *30*(5), 740-745.

Zarate, C. A., Payne, J. L., Quiroz, J., Sporn, J., Denicoff, K. K., Luckenbaugh, D. et al. (2004). An open-label trial of riluzole in patients with treatment-resistant major depression. *American Journal of Psychiatry, 161*, 171-174.

Zhu, B., Zhao, Z., Ye, W., Marciniak, M. D., & Swindle, R. (2009). The cost of comorbid depression and pain for individuals diagnosed with generalized anxiety disorder. *The Journal of Nervous and Mental Disease*, *197*(2), 136-139.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361-370.

Zinbarg, R. E., & Barlow, D. H. (1996). Structure of anxiety and the anxiety disorders: A hierarchical model. *Journal of Abnormal Psychology*, *105*(2), 181-193.

Zuckerman, M., & Lubin, B. (1985). *The Multiple Affect Adjective Check List Revised*. San Diego, CA: Educational and Industrial Testing Service.

CHAPTER 3

THE EFFECT OF EXERCISE TRAINING ON ANXIETY SYMPTOMS AMONG PATIENTS: A SYSTEMATIC REVIEW[1]

[1] Herring, M.P., O'Connor, P.J. and R.K. Dishman. 2010. *Archives of Internal Medicine.* 170(4):321-331. Reprinted here with permission of publisher.

REVIEW ARTICLE

The Effect of Exercise Training on Anxiety Symptoms Among Patients

A Systematic Review

Matthew P. Herring, MS, MEd; Patrick J. O'Connor, PhD; Rodney K. Dishman, PhD

Background: Anxiety often remains unrecognized or untreated among patients with a chronic illness. Exercise training may help improve anxiety symptoms among patients. We estimated the population effect size for exercise training effects on anxiety and determined whether selected variables of theoretical or practical importance moderate the effect.

Methods: Articles published from January 1995 to August 2007 were located using the Physical Activity Guidelines for Americans Scientific Database, supplemented by additional searches through December 2008 of the following databases: Google Scholar, MEDLINE, PsycINFO, PubMed, and Web of Science. Forty English-language articles in scholarly journals involving sedentary adults with a chronic illness were selected. They included both an anxiety outcome measured at baseline and after exercise training and random assignment to either an exercise intervention of 3 or more weeks or a comparison condition that lacked exercise. Two co-authors independently calculated the Hedges *d* effect sizes from studies of 2914 patients and extracted information regarding potential moderator variables. Random effects models were used to estimate sampling error and population variance for all analyses.

Results: Compared with no treatment conditions, exercise training significantly reduced anxiety symptoms by a mean effect Δ of 0.29 (95% confidence interval, 0.23-0.36). Exercise training programs lasting no more than 12 weeks, using session durations of at least 30 minutes, and an anxiety report time frame greater than the past week resulted in the largest anxiety improvements.

Conclusion: Exercise training reduces anxiety symptoms among sedentary patients who have a chronic illness.

Arch Intern Med. 2010;170(4):321-331

Anxiety, an unpleasant mood characterized by thoughts of worry, is an adaptive response to perceived threats that can develop into a maladaptive anxiety disorder if it becomes severe and chronic.[1] Anxiety symptoms and disorders are common among individuals with a chronic illness,[2-8] yet health care providers often fail to recognize or treat anxiety and may consider it to be an unimportant response to a chronic illness.[9]

Anxiety symptoms can have a negative impact on treatment outcomes in part because anxious patients can be less likely to adhere to prescribed medical treatments.[10,11] Personal costs of anxiety among patients include reduced health-related quality of life[12] and increased disability, role impairment,[13] and health care visits.[14]

Adequate evidence is available to justify screening for anxiety problems in primary care settings and prescribing effective treatments for those likely to benefit.[9,14] While pharmacological and cognitive behavioral therapies are both efficacious in reducing anxiety,[15,16] there continues to be interest in alternative therapies such as relaxation and exercise.[17-19]

Exercise training is a healthful behavior with a minimal risk of adverse events that could be an effective and practical tool for reducing anxiety among patients.[20-22] Meta-analytic reviews have summarized the association between exercise and anxiety symptoms both in samples of primarily healthy adults[23-26] and exercise training studies of patients with fibromyalgia and cardiovascular disease, but these analyses did not focus on the best available evidence.[27-29]

We used the results from randomized controlled trials to evaluate the effects of exercise training on anxiety. One goal was to estimate the population effect size for anxiety outcomes. A second goal was to learn whether variables of theoretical or practical importance, such as features of the exercise stimulus and the method for

Author Affiliations:
Department of Kinesiology, The University of Georgia, Athens.

CHAPTER 4

A RANDOMIZED CONTROLLED TRIAL OF THE FEASIBILITY OF EXERCISE TRAINING FOR THE TREATMENT OF GENERALIZED ANXIETY DISORDER[2]

[2] Herring, M.P., M. L. Jacob, C. Suveg, R.K. Dishman, & P. J. O'Connor. To be submitted to *Journal of Clinical Psychiatry*.

Abstract

Objectives: To quantify effects of six weeks of resistance (RET) or aerobic exercise training (AET) on remission and worry symptoms among sedentary patients with generalized anxiety disorder (GAD), and to compare the magnitude of the effects of RET and AET on other symptoms and signs that characteristic GAD patients.

Methods: This randomized controlled trial was conducted between August 2009 and May 2010. Thirty sedentary women, aged 18-37 years, with a primary *DSM-IV* diagnosis of GAD were randomly allocated to RET, AET, or wait list (WL). RET involved two weekly sessions of lower-body weightlifting. AET involved two weekly sessions of leg cycling matched with RET on positive work and exercise time. Primary outcomes were remission, measured by the number needed to treat (NNT), and worry symptoms measured by the Penn State Worry Questionnaire.

Results: There were no adverse events. Remission rates were 60%, 40%, and 30% for RET, AET, and WL, respectively. NNT (95%CI) was 3.33 (1.72, 55.56) for RET and 10 (-6.79, 2.88) for AET. A significant condition by time interaction was found for worry symptom scores ($F_{(3.962, 49.529)}$= 2.815; p= .035). A follow-up contrast showed statistically significant reductions in worry symptoms scores for combined AET and RET versus WL ($t_{(25.943)}$= 2.168; p= .039). RET and AET resulted in moderate-to-large improvements in secondary outcomes (Hedge's d ≥ .36).

Conclusions: Exercise training reduces worry symptoms among GAD patients, RET is an effective treatment for GAD, and a larger trial of exercise training effects on GAD patients is warranted.

Clinical Trial Registration: (Clinical Trials.gov) Identifier: NCT00953654

Introduction

At least 25 randomized controlled trials have documented exercise training effects on patients with depressive disorders[1], but only two investigations of this type have focused on anxiety disorder patients. In one trial, ten weeks of outdoor exercise performed 3 to 4 times per week was compared to daily clomipramine and pill placebo among 46 adults with panic disorder. Compared to placebo, both aerobic exercise training (AET) and drug therapy resulted in large symptom improvements[2]. Two thirds of the anxiety symptom reduction was observed after six weeks of exercise training. In the other trial, the addition of moderate intensity walking exercise to eight-to-ten weeks of group cognitive-behavioral therapy resulted in larger symptom reductions compared with group cognitive behavioral therapy alone among 74 patients with social phobia, panic or generalized anxiety disorder[3]. In these trials, the influence of exercise training *per se* on anxiety symptoms is uncertain because of research design issues. These issues include anxiety symptom improvements potentially caused by nuisance factors coincident with the exercise training such as sunlight exposure resulting from outdoor exercise[4] or social interactions during group exercise[5].

Several types of indirect evidence suggest that exercise training may be especially helpful for generalized anxiety disorder (GAD) patients. The evidence includes: (1) GAD patients tend to be physically inactive[6]; (2) exercise training reduces anxiety symptoms among healthy adults[7, 8] and patients with a chronic illness[9]; (3) exercise training benefits patients with major depressive disorder, and depression and GAD are influenced by similar genetic factors[10, 11] ; and, (4) exercise has salutary effects on other signs and symptoms that characterize GAD patients, including fatigue[12], poor concentration[13], and muscle tension[14].

Beyond the need for a well designed exercise training trial with GAD patients, there is a need to better understand the mental health consequences of resistance exercise training (RET, e.g., weight lifting). RET can produce large beneficial effects on psychological symptoms[15], yet RET has been infrequently investigated compared to AET[16]. In a systematic review of exercise training effects on anxiety outcomes among medical patients only one of 75 effects was derived from a randomized controlled trial involving RET alone[9]. It is difficult to interpret the few investigations that have compared the psychological consequences of RET to AET in part because the exercise stimulus was not well matched in the two conditions[17, 18].

The primary purpose of the present investigation was to use a randomized controlled trial design to quantify the effects of six weeks of RET and AET on remission and worry symptoms among sedentary GAD patients. It was hypothesized that, compared to a wait list control condition, both RET and AET would result in higher remission rates and significantly larger improvements in worry symptoms. A secondary purpose was to compare the magnitude of the effects of RET and AET, matched on the body area exercised (legs), total positive work, the total time actively engaged in exercise, and weekly progression, on other signs and symptoms that characterize patients with GAD. It was expected that there would be no differences in any of the secondary outcomes between RET and AET.

Methods

Design and Patients

This investigation used a randomized controlled trial design. The study protocol was approved by an Institutional Review Board, and all patients provided written informed consent.

Thirty women were recruited from: (1) psychology classes at a large University in the Southeastern United States; (2) local medical and psychological service centers; and, (3) the

local community using newspaper advertisements. Inclusion criteria were: (1) a primary *DSM-IV* diagnosis of GAD[19]; (2) no concurrent psychiatric or psychological therapy other than medication; (3) age of 18-39 years; and, (4) no contraindications for performing moderate intensity exercise as defined by the American College of Sports Medicine[20].

Screening Process

An online survey site was used to post a series of screening questionnaires which included medical and physical activity histories, the Penn State Worry Questionnaire (PSWQ[21]), the Psychiatric Diagnostic Screening Questionnaire (PDSQ[22]), and a seven-day physical activity recall questionnaire (7PAR[23]). Exclusion criteria included: (1) too few worry symptoms, defined by both a PDSQ-GAD subscale score < six and a PSWQ score < 45; (2) too high a level of physical activity, defined by a 7PAR value > 260 kilocalories per kilogram body weight per week[24] (3) pregnancy; and, (4) any medical contraindications to safe participation in moderate intensity exercise. Eligible participants were contacted via email to establish interest in the investigation. Interested participants were then scheduled for a diagnostic interview.

Diagnostic Interview

The Anxiety Disorders Interview Schedule Adult Version (*ADIS-IV*[25]) was administered by a clinical psychology doctoral student (MLJ) trained to high reliability of .85. All diagnostic interviews were supervised by a licensed clinical psychologist (CS). MLJ performed 90% of the interviews and another individual, also trained in diagnostic interviewing, conducted interviews when there were unavoidable scheduling conflicts (10%). Potential participants who were assigned a clinician severity rating (CSR) of at least four using a 0-8 scale of severity were given a diagnosis of GAD[25]. Eligible patients were enrolled in the intervention from one to 15 days following the initial administration of the *ADIS-IV*.

Random Allocation to Conditions

Patients were enrolled and assigned in equal numbers to three intervention conditions using blocked randomization with the Research Randomizer tool (http://www.randomizer.org). Patients were blocked on both the intervention condition [RET, AET, and wait list control (WL)] and psychoactive medication use (no medication or medication use). Random allocation was conducted by one researcher (MPH). Patients were informed of the randomization following a baseline testing session. No patient refused randomization.

Procedures

Baseline Strength Assessments

Once enrolled patients came to the testing facility for a baseline testing session during which study details were provided, written informed consent was obtained, and baseline assessments of leg muscle strength and outcome variables were completed. Following the completion of baseline assessments of outcome variables, each patient's four-repetition maximum (4-RM) was obtained on three lower-body resistance exercises: (1) leg press; (2) leg curl; and, (3) leg extension using Cybex Eagle equipment. A safe yet accurate estimate of one-repetition maximum (1-RM) can be calculated from a 4-RM value (1-RM = 4-RM weight x 1.13)[26]. Following two warm-up sets of ten and eight repetitions with self-selected light and moderate loads each patient performed sets that began with a load the patient expected could be easily lifted for four repetitions. The weight used in each set was increased until reaching her 4-RM. Each contraction was guided by a metronome, and two-minute rest periods separated each set.

During the baseline session the distance through which each patient moved the weight on each machine was measured (in centimeters) from the top of the weight stack at rest to the top of

the weight stack at full extension or contraction. These distance measurements were used to calculate the total positive work to be performed during subsequent exercise sessions in order to equate the AET protocol to the RET protocol on total positive work performed during each exercise session.

Intervention Conditions

Both exercise training protocols involved two sessions per week for six weeks and were based on established guidelines for safely exercising sedentary individuals[20]. Exercise training sessions were conducted on Monday-Wednesday, Tuesday-Thursday, or Wednesday-Friday at approximately the same time of day with at least a 48-hour interval between each weekly session. Because social interaction can influence mental health outcomes, each exercise session was supervised by a single exercise specialist who purposefully avoided unnecessary conversation. Each patient was informed at the outset that this was being done to standardize the exercise sessions.

Resistance Exercise Training

Each RET session lasted approximately 46 minutes and 40 seconds and required 16 minutes of resistance exercise. Each patient performed seven sets of 10 repetitions each of leg press, leg curl and leg extension exercises beginning at an intensity of 50% of predicted 1-RM during week one and progressing by five percent of predicted 1-RM each week. Each exercise was preceded by a single warm-up set of 10 repetitions beginning at an intensity of 35% of predicted 1-RM during week one and progressing by five percent of predicted 1-RM each week. The pace of each repetition was guided by a metronome such that each eccentric and concentric action were performed for two seconds each so that each set was performed in 40 seconds. A rest interval of 80 seconds separated each set and each exercise. Heart rate, which was assessed

using a Polar Vantage XL heart rate monitor (Polar Electro Oy, Kempele, Finland), and ratings of perceived exertion (RPE) and leg muscle pain intensity were obtained within the first 15 seconds following the completion of the final set of each exercise using well-validated exertion (6 – 20) and pain intensity (0 – 10) scales and instructions[27-29]. Following the completion of the workout session, patients also provided RPE for the entire session.

Aerobic Exercise Training

The AET protocol was matched to the RET protocol on (1) the total amount of time spent actively engaged in exercise, (2) the total amount of positive work completed, (3) a five percent progression in load (intensity) each week, and (4) a focus on leg muscles.

Matching process and calculations

Using predicted 1-RM values and the distance that weight was moved on each machine during the baseline testing session, a calculation was made of the total positive work that would have been completed in the first RET session by each AET participant had she been allocated to the RET condition. The warm-up period in the first AET session corresponded to the cumulative positive work that would have been completed during the warm-up set of 10 repetitions at 35% of predicted 1-RM on each resistance exercise during the first RET session. The weight, in pounds, that would have been used for each warm-up set of each exercise was converted to kilograms (kg) by dividing by 2.2046. The corresponding value (kg) was multiplied by 10 (repetitions) to calculate the total weight that would have been lifted for the set and then multiplied by the distance through which the weight would have been moved (meters; m) to calculate total positive work (kilogram-meters; kg-m). The value for the three warm-up sets was then summed and divided by the exercise time. Because each set required 40 seconds, the cumulative work (kg-m) completed in the three warm-up sets was divided by 120 seconds. The

resulting value in kg-m·s^{-1} was converted to Newton-meters per second (Nm· s^{-1}) by multiplying by 9.807. The corresponding value was then converted to Watts (1 Nm· s^{-1} = 1 W) to obtain the appropriate power output at which the 120 seconds of cycling warm-up would be performed.

The same procedure was used to calculate the workload for the 14 minutes of cycling exercise performed following warm-up. The matching calculations described above were employed to calculate the total positive work completed across 70 repetitions for each of the three resistance exercises using the weight that would have been lifted and the distance through which the weight would have been moved. The sum of the resulting values was divided by the exercise time (840 seconds) and multiplied by 9.807 to obtain the equivalent power output (W) for 14 minutes of cycling that would yield total positive work equivalent to that which would have been performed if RET had been completed. Each week of the AET protocol the exercise duration was unchanged but the workload was increased by five percent, corresponding to an increase of five percent in load on the three resistance exercises.

AET Sessions

Each patient performed two sessions per week of 16 minutes of continuous, dynamic leg cycling exercise. Pedal rate was maintained at 60 revolutions per minute. Heart rate, RPE and leg muscle pain intensity were obtained during the last 10 seconds of the 2^{nd}, 7^{th} and 15^{th} minutes of every exercise session. An overall session RPE was obtained immediately following exercise.

Wait List Control

Patients assigned to the WL condition delayed entry into an exercise program for six weeks, but were tested on the dependent measures along the same time progression as the intervention conditions. Following the completion of the WL condition, a six-week supervised RET or AET program was offered to WL patients but no data were obtained.

Primary Outcomes

Clinicians blinded to intervention allocation used the *ADIS-IV* to determine GAD diagnosis one to 16 days post-intervention.

Worry, the hallmark symptom of GAD, was assessed at baseline and at the beginning of the second weekly session during weeks two, four, and six with the Penn State Worry Questionnaire (PSWQ[21]). The PSWQ has been supported by favorable psychometric data[30]. In the present investigation PSWQ scores (using all trials) demonstrated appropriate internal consistency (Chronbach's $\alpha = 0.92$) and stability (ICC (2, 4) = 0.73, 95%CI: 0.59, 0.85).

Secondary Outcomes

Other symptoms and signs associated with GAD were measured as secondary outcomes including difficulty concentrating, trait anxiety, symptoms of depression, tension, low vigor, fatigue and confusion, irritability, muscle tension (physiological tremor), pain, non-intervention physical activity and non-psychoactive medication and supplement use. Secondary outcomes were assessed at the beginning of the baseline session and at the beginning of the second weekly session during weeks two, four and six. The exception was physiological tremor which was measured at baseline and post-intervention. The total time to complete these measurements ranged from 15 to 30 minutes.

Trait anxiety symptoms were assessed using the trait scale of the State-Trait Anxiety Inventory (STAI-Trait[31]). Feelings of tension, vigor, fatigue and confusion were assessed using subscales of the Profile of Mood States – Brief Form[32]. Patients were instructed to respond as to "*how you have been feeling during the past week including today*." The frequency and intensity of irritability symptoms were assessed using the 21-item scales of the Irritability Questionnaire (IRQ[33]). Symptoms of depression were assessed using the Beck Depression Inventory–II (BDI-

II[34]). Using the ninth item of the BDI-II (Suicidal Thoughts or Wishes), suicidal ideation was examined as a potential adverse event. In addition to the POMS-B confusion subscale, difficulty concentrating was assessed using the mean reaction time and the ratio of errors to valid responses on a psychomotor vigilance task (PVT 2.0.0[35]). For the PVT, blackened bullseye style targets repeatedly appeared on the liquid crystal display of a palm pilot hand-held personal data assistant. Patients were instructed to respond as quickly as possible by pressing a button on the device.

Physiological tremor was used as a marker of muscle tension because it has been shown to be directly related to muscle tension in animal and human experiments[36-40]. Physiological tremor of the non-dominant hand was measured using a Grass Model SPA1 single plane accelerometer attached to a Grass P511 amplifier. Output of the amplified signal was stored on a Dell computer running Spike2 (version 5.16) software (Cambridge Electronic Design micro1401 mk II) used to acquire and analyze data.

Using silhouettes with numbered body areas, patients were asked to draw the locations of any pain currently being experienced[41]. The number of painful locations was the criterion measure. Pain intensity ratings also were made using well validated 0 to 100, 10 centimeter visual analogue scales anchored from *no pain* to the *worst pain imaginable*[42].

Medication and supplement use and non-intervention physical activity were assessed by self-report. Each patient was asked to recall all prescription and non-prescription medications and supplements ingested within the past 24 hours. Non-intervention physical activity was assessed using a seven-day physical activity recall questionnaire (7PAR[23]). Raw data from the questionnaire were used to calculate energy expenditure. The 7PAR provides a reliable and valid measure of weekly energy expenditure among college students[24].

Preliminary Analyses

All data analyses were performed using SPSS 16.0. Missing data were addressed using the "last value carried forward" imputation method[43]. Descriptive statistics are presented in text and tables as mean (SD) and in figures as mean (SE). Distributional and outlier analyses were conducted to ensure that assumptions needed for the primary analysis had been met and revealed no violations. There was less than one percent missing data for the following variables only: heart rate, session RPE, session ratings of leg muscle pain intensity, and physiological tremor. Chi-square tests corrected for multiple comparisons were conducted to assess baseline differences in the number of comorbid psychiatric diagnoses and psychoactive medication use between conditions. Other baseline comparisons of participant characteristics were performed using univariate ANOVA. The intervention intensity variables (i.e., RPE, heart rate, leg pain intensity ratings) were averaged across all 12 exercise sessions and compared using independent samples t-tests. In the t-test and ANOVA analyses, Levene's test was used to assess homogeneity of variance. If violated, the degrees of freedom were adjusted.

Outcome Analyses

Clinician diagnosis of GAD was analyzed using the number needed to treat (NNT), an accepted metric of treatment effect that conveys both statistical and clinical significance[44-46]. The NNT and associated 95% confidence interval were calculated as the inverse of the absolute risk reduction for the RET or AET condition compared with the WL condition.

Worry symptom scores were analyzed using a mixed model 3 (condition: RET, AET, WL) X 3 (time: Week two, Week four, Week six) ANCOVA with baseline scores as a covariate and repeated measures on the time factor. An *a priori* statistical power analysis showed that a sample of 30 patients would provide a statistical power of .80 to detect a condition-by-time

interaction for PSWQ scores assuming a two-tailed α value of 0.05, a correlation across repeated measures of 0.75 and a desire to detect a standardized effect size of 0.65[47]. Bonferroni-corrected pairwise comparisons were conducted to assess group differences. Because only 30% (n = 9) of patients were tested during the first four months of the trial (Aug-Dec), a one-way intraclass correlation coefficient [ICC(1)] was calculated[48] to examine the percentage of overall variance accounted for by testing period (Aug-Dec, Jan-Apr). Five percent of overall variance was accounted for by testing period, so a follow-up mixed model 3 X 3 ANCOVA with baseline scores and testing period as covariates was conducted. Because no differences between RET and AET were hypothesized, a follow-up contrast (adjusted for testing period) comparing WL with the combined exercise conditions on week six scores was computed. The Huynh-Feldt epsilon (ε) was reported and degrees of freedom were adjusted when the sphericity assumption was violated based on Mauchly's test.

For all outcomes, Hedge's d effect sizes and associated 95%CIs were calculated to assess the magnitude of treatment effects for RET and AET conditions compared with the WL condition at each time point (weeks two, four and six). At each time point, the mean change from baseline for the WL condition was subtracted from the mean change from baseline for the RET or AET condition and the difference was divided by the baseline pooled standard deviation[49]. Effect sizes were adjusted for small sample bias and calculated such that an improvement in symptoms resulted in a positive effect size[49].

Results

Patient Flow

The recruitment phase of the trial spanned 233 days beginning August 19th, 2009, and continuing through March 17th, 2010. The first exercise training session was completed on September 1st, 2009. The final exercise session was conducted on May 5th, 2010. Figure 4.1 illustrates the flow of patients through the trial. There were no musculoskeletal injuries or adverse events reported by the patients. No patient discontinued the intervention, and all patient data were used in analyses.

Baseline Patient Characteristics

Table 4.1 presents baseline demographic, medical and psychiatric characteristics of the sample. There were no significant baseline differences for age ($F_{(2, 27)} = 1.928$, $p = .17$), weight ($F_{(2, 27)} = 1.547$, $p = .23$), height ($F_{(2, 27)} = .899$, $p = .42$), body mass index ($F_{(2, 27)} = 1.264$, $p = .30$) or weekly energy expenditure ($F_{(2, 27)} = .940$, $p = .40$).

Patients reported using an average of one (range: 0 to 4) non-psychoactive medication and/or supplement during the intervention. The most commonly taken medication was an oral contraceptive while the most commonly taken supplement was a multivitamin. There were no significant baseline differences between conditions for number of non-psychoactive medications used ($F_{(2, 27)} = .124$, $p = .884$). Chi-square tests revealed no significant differences among conditions for the total number of psychoactive medications used ($p = 1.00$).

For comorbid psychiatric diagnoses, corrected chi-square tests ($p < .017$) showed no significant differences between AET and WL ($X^2_{(1)} = 4.56$, $p = .03$) or RET and AET ($X^2_{(1)} = .20$, $p = .65$), but did show a significantly larger number of comorbid psychiatric diagnoses among WL patients compared with RET patients ($X^2_{(1)} = 6.107$, $p = .01$).

Intervention Fidelity

Patients in the WL condition completed 100% of outcome assessments. Patients in the RET condition attended 100% (120/120) of testing sessions and complied with 99.1% of the RET protocol, completing 2855 of 2880 sets (28550 of 28800 repetitions). One RET session was not completed due to illness. Patients in the AET condition attended 100% (120/120) of testing sessions and complied with 100% of the AET protocol, each completing 12 bouts of 16 minutes of cycling exercise at the required power output. Thus, the average total minutes of exercise for the AET and RET patients was 192 and 190, respectively out of a total of 192 possible minutes. Five total exercise bouts, four RET bouts and one AET bout, were completed away from the testing facility but were documented via phone calls in which exercise session duration and RPE were provided.

During the exercise sessions, the RET condition was characterized by overall mean (SD) RPE, heart rate (beats per minute), and rating of leg muscle pain intensity of 14 (1), 125 (12), and 2.4 (1.9), respectively. The overall means for the AET condition were 8 (1), 122 (8), and 0.5 (0.4), respectively. There was not a significant difference between RET and AET in heart rate ($t_{(18)} = .81$, $p = .429$). Mean RPE during exercise was significantly higher for RET compared with AET ($t_{(18)} = 9.52$, $p < .0001$). Mean rating of leg muscle pain intensity also was higher for RET compared with AET ($t_{(9.7)} = 3.122$, $p = .011$). The session RPE and leg muscle pain intensity were 14 (1) and 2.2 (1.9) for RET and 9 (1) and 0.4 (0.4) for AET, respectively. Independent samples t-tests revealed significantly higher session RPE ($t_{(18)} = 8.74$, $p < .001$) and session leg muscle pain intensity ($t_{(9.7)} = 2.92$, $p = .016$) for RET compared with AET.

Table 4.2 presents baseline and post-intervention strength assessment data. Baseline strength was significantly greater for AET compared to RET patients for leg extension ($t_{(18)} =$

2.97, $p = .018$) and non-significantly greater for leg press and leg curl. Consequently, the work performed during the exercise sessions (averaged across all sessions) was non-significantly greater for AET compared to RET patients (451618 vs. 366308 Joules, respectively). As planned, RET resulted in increases in strength across six weeks that were larger than those observed for AET and WL (all Hedge's $d \geq .64$). Evaluation of Hedge's d and associated 95%CIs showed significantly larger strength increases ($p < .05$) for RET compared with WL for leg press ($d = 1.02$, 95%CI: .08, 1.95) and leg extension ($d = 1.59$, 95%CI: .58, 2.60), and for RET compared with AET for leg extension ($d = 1.33$, 95%CI: .42, 2.30).

All patients were asked to refrain from participating in other therapy programs during the intervention. However, four patients reported after the trial that they had some engagement in an additional form of therapy during the intervention. One RET patient reported participating in two sessions with a clinical psychologist, one session during the final week of the intervention and one session during the week of the post-intervention diagnostic interview. Two AET patients reported engaging in two sessions with a psychiatrist during the last two weeks of the intervention. One WL patient reported engaging in two sessions with a psychologist during the last two weeks of the intervention. A sensitivity analysis in which these four patients were removed did not change the statistical significance of the findings for the primary outcomes.

Primary Outcomes

Figure 4.2 illustrates the number of patients diagnosed with GAD at baseline and post-intervention. Remission rates were 60%, 40% and 30% for the RET, AET and WL conditions, respectively. The absolute risk reduction for RET was 0.30 (95%CI: .02, .58) and the number needed to treat (NNT) was 3.33 (95%CI: 1.72, 55.56). The absolute risk reduction for AET was 0.10 (95%CI: -.15, .35) and the NNT was 10 (95%CI: -6.79, 2.88). There was no significant

moderating effect of psychoactive medication use. The remission rate for patients in the exercise conditions taking psychoactive medication (50%; 2/4 RET and 2/4 AET) was the same as exercisers who were not taking psychoactive medication (50%; 4/6 RET and 2/6 AET).

Table 4.3 and Figure 4.3 present the descriptive data for PSWQ scores. There was a significant condition by time interaction ($F_{(3.72, 48.4)} = 2.74$, $p = .042$, $\varepsilon = .931$). Bonferroni-corrected pairwise comparisons of week six scores for RET ($t_{(18)} = 1.106$, $p = .28$) and AET ($t_{(18)} = 1.845$, $p = .081$) compared with WL were not significant, however, moderately-large reductions in worry symptoms were found for both exercise conditions (Hedge's d = .45). A follow-up model adjusted for baseline scores and testing period showed a significant condition-by-time interaction ($F_{(3.962, 49.529)} = 2.815$, $p = .035$; $\varepsilon = .991$). A follow-up contrast of week six scores showed larger reductions for the combined exercise conditions compared to WL ($t_{(25.943)} = 2.168$, $p = .039$). There was no significant moderating effect of psychoactive medication use on worry symptoms.

Secondary Outcomes

Internal consistency reliabilities for all secondary outcomes were adequate and the Chronbach's alphas ranged between .73 and .95. Table 4.4 and Figure 4.4 present descriptive data for the secondary outcome variables along with extra-intervention physical activity data. Estimated weekly extra-intervention energy expenditure at weeks two, four and six did not change significantly from baseline for RET, AET or WL groups ($F_{(2, 52)} = .056$; $p = .946$). These data suggest that the WL patients did not adopt any exercise program during the six week WL period. These data also suggest that the AET and RET patients did not significantly increase their level of exercise in any mode to which they were not assigned. Thus, the intervention does not appear to be confounded by changes in extra-intervention physical activity.

Mean baseline BDI-II suicidal ideation item scores were .10, 0, and .50 for RET, AET, and WL, respectively. Mean scores did not increase for any condition across the six-week investigation.

Discussion

Compelling evidence regarding the feasibility of exercise training for treatment of anxiety disorders is limited, and research design and methodological limitations preclude the meaningful interpretation of findings from several previous investigations[1, 2, 50-54]. The present investigation addressed these methodological issues and extended previous related research by (1) examining the effects of exercise training on symptoms among GAD patients within the framework of a randomized controlled trial, (2) focusing on sedentary women with a primary *DSM-IV* diagnosis of GAD, (3) evaluating exercise training effects on both diagnostic status (i.e., presence or absence of pathology) and symptoms associated with GAD, and, (4) equating RET and AET conditions on lower body exercise, the total positive work completed and total time actively engaged in exercise. The major findings of the present experiment were: (1) remission rates were higher among exercise conditions and significantly better in the RET condition compared with WL, (2) six weeks of exercise training for the RET and AET groups combined significantly reduced worry symptoms, and, (3) both RET and AET interventions resulted in moderate-to-large improvements in most symptoms associated with GAD, and especially for symptoms of irritability, anxiety, and low energy.

GAD Diagnosis

The present findings suggest that RET was effective in treating GAD. The remission rate for RET (60%) was significantly higher than that for WL (30%). The WL remission rate was consistent with prior research documenting that only about one-third of GAD patients show

partial or full remission over a six-month period[55]. The NNT of 3.33 suggests that on average for every 10 GAD patients who would perform six weeks of RET three additional remissions would occur compared to the expected number of spontaneous remissions among untreated patients. The NNT for RET compares favorably to other empirically supported GAD treatments including antidepressants (NNT = 5.15[56, 57]; NNT = 3.23[58]) and multifaceted treatment programs[59] employing pharmacotherapy, cognitive-behavioral therapy or both in a sample of approximately 1,000 primary care patients of which 75% were diagnosed with GAD (NNT = 5.50). It is noteworthy that these trials had substantially longer treatment durations of six to 12 months compared to six weeks for the present investigation.

The fact that the AET stimulus was inadequate to elicit GAD remission suggests that the therapeutic effect of exercise training for this outcome was likely linked to the relative exercise intensity as revealed here by perceived exertion ratings. The AET exercise sessions were perceived as significantly less intense (RPE = 9; "very light") than the RET sessions (RPE = 14; between "somewhat hard" and "hard"). These findings are consistent with previous evidence of larger effects of higher intensity exercise training on depression symptoms[15, 60].

Symptoms of Worry

Worry symptoms were significantly reduced following six weeks of exercise training. Both RET and AET produced moderate reductions in worry symptoms (Hedge's d = .45). These findings are generally comparable to moderate-sized effects reported from meta-analytic reviews of empirically supported GAD treatments including relaxation, cognitive, and cognitive-behavioral therapy[61-63]. The present findings also are generally consistent with both the mean effect of short duration pharmacological and cognitive-behavioral therapies among anxiety disorder patients[64] and the mean effect of short duration exercise training programs on anxiety

symptoms among medical patients[9], depression symptoms among depressed patients[65], and quality of life among patients with multiple sclerosis[66]. Given continued interest in knowing the minimum exercise stimulus necessary to elicit mental health benefits[60], it is noteworthy that moderate-sized effects resulted from six-week training protocols in which patients were exposed to the active ingredient of the exercise stimulus for a total of only 3 hours and 12 minutes.

It is plausible that findings were affected by the large number of baseline comorbid diagnoses. Prior research has indicated that higher clinical complexity, including the presence of Axis I comorbidity, is associated with diminished treatment outcomes particularly in short duration interventions[67, 68]. Non-remitters in the present investigation had a significantly larger number of baseline comorbid psychiatric diagnoses ($t_{(22.891)} = 3.029$, $p = .006$).

Associated Symptoms

Both exercise conditions resulted in moderate-to-large improvements in symptoms that characterize GAD. RET significantly improved feelings of tension and the frequency and intensity of irritability. These large reductions in feelings of tension are consistent with exercise training effects on feelings of tension and general anxiety symptoms among panic disorder patients[2]. The large effects of exercise training on the frequency and intensity of irritability found in the present investigation may be of particular importance because of the growing evidence of the association between negative moods related to irritability (e.g., anger and hostility) and heart disease[69, 70].

Although not statistically significant, the RET condition resulted in six-week Hedge's d effect sizes of $\geq .36$ in trait anxiety, depression, concentration, fatigue, vigor and pain intensity, while the AET condition resulted in improvements of this magnitude in trait anxiety, concentration, fatigue, vigor, irritability and muscle tension. Exercise effects for these outcomes

compare favorably with relaxation, cognitive-behavioral and worry exposure therapies completed by GAD patients[71, 72].

For nine of the 12 secondary outcome variables, the magnitude of effects were larger for RET than AET. Because the exercise protocols were matched on total positive work and exercise time, we did not hypothesize differences between AET and RET. However, significantly higher ratings of perceived exertion and leg muscle pain intensity for RET suggest differences in the relative intensity of the exercise stimulus between conditions. Thus, future investigations may benefit from equating patient perceived exertion during the time actively engaged in exercise.

AET and RET produced no adverse events including no musculoskeletal injuries or increases in BDI-II suicidal ideation item scores. Exercise training was associated with improvements in all the symptoms measured except for the number of pain locations. Although the number of pain locations was increased by one after six weeks of RET, the intensity of pain was reported as 9.3 raw VAS units less after RET training. Low intensity exercise training performed by patients in chronic pain typically reduces their pain intensity while high intensity RET performed by anyone usually increases the number of pain locations and produces muscle and tendon pain[16].

Limitations

One limitation of the present investigation was the small sample size. Although the research design was sufficiently powered to detect a statistically significant effect for the primary outcome, a larger trial is warranted to thoroughly investigate the effects of exercise training on the associated symptoms that characterize patients with GAD. Another potential limitation is that, because of initial strength differences, the exercise training conditions were not perfectly

equated total positive work; consequently, differences between AET and RET cannot be completely ruled out. Nonetheless, exercise had favorable effects on remission rates and worry symptoms regardless of exercise condition.

Implications for Future Research

The present findings suggest several research needs. A better understanding of the potential efficacy of exercise training as a treatment for GAD could be realized through well-designed investigations that: (1) use large samples sizes both to compare the effects of exercise training alone to empirically-supported treatments for GAD (e.g., cognitive-behavioral therapy, pharmacotherapy) and to compare the effects of the combination of exercise training with empirically-supported treatments to the same empirically-supported treatment alone; (2) compare the effects of different types of exercise training that use different training intensities and durations matched on perceptual responses during the time actively engaged in exercise to better understand the minimal and optimal dose necessary to improve symptoms; and (3) block randomize patients to conditions based upon potential confounding variables including comorbid psychiatric diagnoses.

Conclusions

The present findings support the feasibility and potential efficacy of exercise training as a safe treatment for GAD. Significant improvements in worry symptoms and other associated symptoms that characterize GAD patients, including irritability, anxiety, and low vigor, warrant further investigation with larger trials.

References

1. Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. *Cochrane Database Syst Rev*. 2008;October 8, (4).
2. Broocks A, Bandelow B, Pekrun G, et al. Comparison of aerobic exercise, clomipramine, and placebo in the treatment of panic disorder. *Am J Psychiatry.* 1998;155:603-609.
3. Merom D, Phongsavan P, Wagner R, et al. Promoting walking as an adjunct intervention to group cognitive behavioral therapy for anxiety disorders—A pilot group randomized trial. *J Anxiety Disord*. 2008;22(6):959-968.
4. Youngstedt SD, Kripke DF. Does bright light have an anxiolytic effect? An open trial. *BMC Psychiatry*. 2007;7:62. Medline:17971237
5. McNeil JK, LeBlanc EM, Joyner M. The effect of exercise on depressive symptoms in the moderately depressed elderly. *Psychol Aging*. 1991;6(3):487-488.
6. Goodwin RD. Association between physical activity and mental disorders among adults in the United States. *Prev Med*. 2003;36(6):698-703.
7. Long BC, van Stavel R. Effects of exercise training on anxiety: A meta-analysis. *J Appl Sport Psychol*. 1995;7(2):167-189.
8. Wipfli BM, Rethorst CD, Landers DM. The anxiolytic effects of exercise: A meta-analysis of randomized trials and dose-response analysis. *J Sport Exerc Psychol*. 2008;30(4):392-410.
9. Herring MP, O'Connor PJ, Dishman RK. Exercise training reduces anxiety symptoms among patients: A systematic review. *Arch Intern Med.* 2010;170(4):321-331.
10. Goldberg D. Towards DSM-V: The relationship between generalized anxiety disorder and major depressive episode. *Psychol Med*. 2008;38(11):1671-1675.

11. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Generalized anxiety disorder in women. A population-based twin study. *Arch Gen Psychiatry*, 1992;49(4):267-72.
12. Puetz TW, O'Connor PJ, Dishman RK. Effects of chronic exercise on feelings of energy and fatigue: A quantitative synthesis. *Psychol Bull*. 2006;132(6):866-876.
13. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14(2):125-130.
14. Smith JC, O'Connor P, Crabbe J, Dishman R. Emotional responsiveness after low- and moderate-intensity exercise and seated rest. *Med Sci Sports Exerc*. 2002;34(7):1158-1167.
15. Singh NA, Stavrinos TM, Scarbek Y, Galambos G, Liber C, Fiatarone Singh MA. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *J Gerontol A Biol Sci Med Sci*. 2005;60(6):768-776.
16. O'Connor PJ, Herring MP, Caravalho A. Mental health benefits of strength training in adults. *Am J Lifestyle Med*. [Epub ahead of print] May 7, 2010.
17. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. *J Clin Oncol*. 2007;25(28):4396-4404.
18. Krogh J, Saltin B, Gluud C, Nordentoft M. The DEMO trial: A randomized, parallel-group, observer-blinded clinical trial of strength versus aerobic versus relaxation training for patients with mild to moderate depression. *J Clin Psychiatry.* 2009;70(6):790-800.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington, DC: American Psychiatric Association; 2000.

20. Franklin BA, Whaley MH, Howley ET. *ACSM's Guidelines for Exercise Testing and Prescription* (6th ed.). Philadelphia, PA: Lippincott Williams & Wilkins; 2000.

21. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the penn state worry questionnaire. *Behav Res Ther*. 1990;28(6):487-495.

22. Zimmerman M, Mattia, JI. A self-report scale to help make psychiatric diagnoses: The Psychiatric Diagnostic Screening Questionnaire. *Arch Gen Psychiatry.* 2001;58:787-794.

23. Blair S, Haskell W, Ho P, et al. Assessment of habitual physical activity by a sevenday recall in a community survey and controlled experiments. *Am J Epidemiol*. 1985;122(5):794-804.

24. Dishman RK, Steinhardt M. Reliability and concurrent validity for a 7-d re-call of physical activity in college students. *Med Sci Sports Exerc.* 1988;20(1):14-25.

25. Brown T, Di Nardo P, Barlow DH. Anxiety disorders interview schedule adult version (ADIS-IV): Client interview schedule. Albany, New York: Graywind Publications; 1994.

26. Lombardi VP**.** *Beginning Weight Training: The Safe and Effective Way.* Dubuque, IA: Brown, 1989.

27. Borg, G. *Borg's perceived exertion and pain scales*. Champaign, IL: Human Kinetics; 1983.

28. Cook D, O'Connor P, Eubanks S, Smith J, Lee M. Naturally occurring muscle pain during exercise: assessment and experimental evidence. *Med Sci Sports Exerc*. 1997;29(8):999-1012.

29. Gearhart R, Goss F, Lagally K, Jakicic J, Gallagher J, Robertson R. Standardized scaling procedures for rating perceived exertion during resistance exercise. *J Strength Cond Res*. 2001;15(3):320-325.

30. Brown TA, Antony MM, Barlow DH. Psychometric properties of the Penn state worry questionnaire in a clinical anxiety disorders sample. *Behav Res Ther*. 1992;30(1):33-37.

31. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory (Form Y): Self-evaluation Questionnaire*. Palo Alto, CA: Consulting Psychologists Press; 1983.

32. McNair DM, Lorr M, Droppleman LF. *POMS Manual: Profile of Mood States.* San Diego, CA: Educational and Industrial Testing Service; 1992.

33. Craig KJ, Hietanen H, Markova IS, Berrios GE. The Irritability Questionnaire: A new scale for the measurement of irritability. *Psychiatry Res*. 2008;159(3):367-375.

34. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory*-II. Psychological Corporation: San Antonio, TX; 1992.

35. Thorne DR, Johnson DE, Redmond DP, Sing HC, Belenky G, Shapiro JM. The Walter Reed palm-held psychomotor vigilance test. *Behav Res Methods*. 2005;37(1):111-118.

36. Harwell RC, Ferguson RL. Physiologic tremor and microsurgery. *Microsurgery.* 1983;4:187-192.

37. MacKay WA, Johnson F, Kwan HC, Murphy JT. Response of frog muscle spindle symptoms to whole-muscle input parameters. *Am J Physiol.* 1973;224(5):1037-1043.

38. Murbe D, Huttenbrink KB, Zahnert T, et al. Tremor in otosurgery: Influence of physical strain on hand steadiness. *Otol Neurotol,* 2001;22(5):672-677.

39. Noteboom JT, Barnholt KR, Enoka RM. Activation of the arousal response and impairment of performance increase with anxiety and stressor intensity. *J Appl Physiol*. 2001;91(5):2093-2101.

40. Noteboom JT, Fleshner M, Enoka RM. Activation of the arousal response can impair performance on a simple motor task. *J Appl Physiol*. 2001;91(2):821-831.

41. Margolis RB, Tait RC, Krause SJ. A rating system for use with patient pain drawings. *Pain*, 1986;24(1):57-65.

42. Jensen MP, Karoly P, Turk DC, Melzack R. *Handbook of Pain Assessment*. New York: Guilford Press; 1992.

43. Twisk J, de Vente W. Attrition in longitudinal studies How to deal with missing data. *J Clin Epidemiol*. 2002;55(4):329-337.

44. Cook RJ, Sackett DL. The number needed to treat: A clinically useful measure of treatment effect. *BMJ. 1995;*310:452-454.

45. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Eng J Med.* 1988;318:1728-1733.

46. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ.* 1999;319:1492-1495.

47. D'Amico E, Neilands ST, Zambarano R. Power analysis for multivariate and repeated measures designs: A flexible approach using the SPSS MANOVA procedure. *Behav Res Methods Instrum Comput*. 2001;33(4):479-484.

48. Bliese PD, Halverson RR. Group size and measures of group-level properties: An examination of eta-squared and ICC values. *J Management.* 1998;24(2):157-172.

49. Hedges LV, Olkin I. *Statistical methods for meta-analysis*. New York: Academic Press; 1985.

50. Brown RA, Abrantes AM, Strong DR, et al. A pilot study of moderate-intensity aerobic exercise for Obsessive Compulsive Disorder. *J Nerv Ment Dis*. 2007;195(6):514-520.

51. Cromarty P, Robinson G, Callcott P, Freeston M. Cognitive therapy and exercise for panic and agoraphobia in primary care: Pilot study and service development. *Behav Cogn Psychother.* 2004;32:371-374.

52. Diaz AB, Motta R. The effects of an aerobic exercise program on posttraumatic stress disorder symptom severity in adolescents. *Int J Emerg Ment Health*. 2008;10(1):49-59.

53. Manger TA, Motta RW. The impact of an exercise program on posttraumatic stress disorder, anxiety, and depression. *Int J Emerg Ment Health*. 2005;7(1):49-57.

54. Newman CL, Motta RW. The effects of aerobic exercise on childhood PTSD, anxiety, and depression. *Int JEmerg Ment Health*. 2007;9(2):133-158.

55. Wittchen H-U, Zhao S, Kessler R, et al. DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Arch Gen Psychiatry.* 1994;51:355–364

56. Kapczinski F, Lima MS, Souza JS, Cunha A, Schmitt R. Antidepressants for generalized anxiety disorder. *Cochrane Database Syst Rev*. 2003;2(2):CD003592.

57. Schmitt R, Gazalle FK, Lima MS, Cunha A, Souza J, Kapczinski F. The efficacy of antidepressants for generalized anxiety disorder: A systematic review and meta-analysis. *Rev Bras Psiquiatr*. 2005;27(1):18-24.

58. Donovan MR, Glue P, Kolluri S, Emir B. Comparative efficacy of antidepressants in preventing relapse in anxiety disorders – A meta-anlysis. *J Affect Disord.* 2010;123:9-16.

59. Roy-Byrne P, Craske MG, Sullivan G, et al. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: A randomized controlled trial. *JAMA.* 2010;303(19):1921-1928.

60. Dunn AL, Trivedi MH, O'Neal HA. Physical activity dose-response effects on outcomes of depression and anxiety. *Med Sci Sports Exerc*. 2001;33(6)(suppl):S587-S597, discussion 609-610. Medline:11427783

61. Fisher PL. The efficacy of psychological treatments for generalized anxiety disorder? In CL Davey and A Wells (Eds.), *Worry and Its Psychological Disorders: theory, assessment, and treatment* (pp.359-378). London: John Wiley and Sons, Ltd; 2006.

62. Gould RA, Safren SA, Washington DO, Otto MW. A meta-analytic review of cognitive-behavioral treatments. In R Heimber, CL Turk and DS Mennin (Eds.), *Generalized Anxiety Disorder: advances in research and practice* (pp. 248-264). New York: The Guilford Press; 2005.

63. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *J Consult Clin Psychol.* 2010;78(2):169-183.

64. Gould RA, Buckminster S, Pollack MH, Otto MW, Yap L. Cognitive-behavioral and pharmacological treatment for social phobia: A meta-analysis. *Clin Psychol Sci Prac.* 1997;4:291-306.

65. Lawlor DA, Hopker SW. The effectiveness of exercise as an intervention in the management of depression: Systematic review and meta-regression analysis of randomized controlled trials. *BMJ*. 2001;322(7289):763-767.

66. Motl RW, Gosney JL. Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. *Mult Scler*. 2008;14(1):129-135. Medline:17881388

67. Durham RC, Allan T, Hackett CA. On predicting improvement and relapse in generalized anxiety disorder following psychotherapy. *Br J Clin Psychol.* 1999;36:101-119.

68. Durham RC, Fisher PL, Dow MGT, Sharp D, Power KG, Swan JS, Morton RV. Cognitive behavior therapy for good and poor prognosis generalized anxiety disorder: A clinical effectiveness study. *Clin Psychol Psychother.* 2004;11:145-157.

69. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: A meta-analytic review of prospective evidence. *J Am Coll Cardio.* 2009;53(11):936-946.

70. Kubzansky LD, Kawachi I. Going to the heart of the matter: Do negative emotions cause coronary heart disease? *J Psychosom Res.* 2000;48:323-337.

71. Dugas MJ, Brillon P, Savard P, et al. A randomized clinical trial of cognitive-behavioral therapy and applied relaxation for adults with Generalized Anxiety Disorder. *Behav Ther.* 2010;41:46-58.

72. Hoyer J, Besdo K, Gloster AT, Runge J, Hofler M, Becker ES. Worry exposure versus applied relaxation in the treatment of Generalized Anxiety Disorder. *Psychother Psychosom.* 2009;78:106-115.

Tables

Table 4.1. Baseline Demographic, Physical Activity, Medical, and Psychiatric Characteristics

	Overall (n = 30)		RET (n = 10)		AET (n = 10)		WL (n = 10)	
Variable	**No. of Patients**	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**	**No. of Patients**	**%**
Demographic								
Age, years								
Mean (SD)	23.5 (5.9)		25.6 (7.1)		20.7 (3.0)		24.2 (6.3)	
Range	18-37		19-37		18-26		18-36	
College Graduate	8	26.7	3	30.0	1	10.0	4	40.0
Married	3	10.0	1	10.0	0	0	2	20.0
Race/Ethnicity								
Caucasian	19	63.3	5	50.0	8	80.0	6	60.0
African-Amer.	3	10.0	0	0	1	10.0	2	20.0
Hispanic	3	10.0	2	20.0	1	10.0	0	0
Middle Eastern	2	6.7	2	20.0	0	0	0	0
Asian	2	6.7	1	10.0	0	0	1	10.0
Indian	1	3.3	0	0	0	0	1	10.0
Medical Profile								
Weight, kg								
Mean	65.7		60.6		70.0		66.4	
SD	12.2		9.1		15.5		8.1	
Height, cm								
Mean	164.7		162.6		165.0		166.5	
SD	6.6		6.2		7.6		4.6	
BMI, $kg \cdot m^2$								
Mean	24.2		22.8		25.7		24.0	
SD	5.8		2.8		5.2		3.0	
Physical Activity								
7PAR ($kcals \cdot kg^{-1} \cdot wk^{-1}$)								
Mean	253.5		263.3		249.2		248.0	
SD	27.7		36.6		21.5		22.6	
Medication								
Contraceptive	15	50.0	5	50.0	5	50.0	5	50.0
Psychoactive								
SSRI	7	23.3	2	20.0	2	20.0	3	30.0
SNRI	2	6.7	1	10.0	1	10.0	0	0
NDRI	2	6.7	0	0	1	10.0	1	10.0
Muscle Relaxant	2	6.7	1	10.0	1	10.0	0	0
Psychostimulant	1	3.3	0	0	0	0	1	10.0
Other								
Antibiotic	1	3.3	0	0	1	10.0	0	0
Antihistamine	1	3.3	1	10.0	0	0	0	0
Psychiatric								
Comorbidity, (cases)	21 (50)	70.0	5 (9)	50.0	6 (14)	60.0	10 (27)	100.0
Social Phobia	12	24.0	2	22.2	5	35.7	5	18.5
Specific Phobia	19	38.0	2	22.2	5	35.7	12	44.4
OCD	5	10.0	1	11.1	1	7.1	3	11.1
PTSD	2	4.0	0	0	0	0	2	7.4
MDD	7	14.0	1	11.1	3	21.4	3	11.1

Dysthymia	4	8.0	2	22.2	0	0	2	7.4
Substance Abuse	1	2.0	1	11.1	0	0	0	0

Abbreviations: RET, resistance exercise training; AET, aerobic exercise training; WL, wait list; SD, standard deviation; BMI, body mass index; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; MDD, major depressive disorder; 7PAR, seven day physical activity recall; kcals, kilocalories, kg, kilograms.

Table 4.2. Baseline and Post-intervention Predicted One-repetition Maximum Means (SD)

	RET (n = 10)	**AET (n = 10)**	**WL (n = 10)**
Baseline			
Leg Press, kg	**111±18**	**139±29**	**108±28**
Leg Curl, kg	**48±11**	**57±13**	**47±8**
Leg Extension, kg	**55±11**	**69±12**	**54±8**
Post-intervention			
Leg Press, kg	**136±18**	**142±25**	**108±23**
Leg Curl, kg	**57±11**	**58±12**	**48±15**
Leg Extension, kg	**73±9**	**71±14**	**56±10**
Strength change			
Leg Press, kg	**25±5**	**4±21**	**0±20**
Leg Curl, kg	**10±3**	**1±9**	**1±11**
Leg Extension, kg	**18±8**	**2±10**	**2±5**

Abbreviations: RET = resistance exercise training; AET = aerobic exercise training, WL = wait list; kg = kilogram

Table 4.3. Worry Symptom Scores (PSWQ) and Effects of Resistance and Aerobic Exercise Training

	Baseline	Week 2		Week 4		Week 6	
Outcome	**Mean SD**	**Mean SD**	**Hedge's d 95%CI**	**Mean SD**	**Hedge's d 95%CI**	**Mean SD**	**Hedge's d 95%CI**
PSWQ							
RET	63.80	59.83	0.33	60.30	0.30	61.10	0.45
	9.78	9.93	-0.56,1.21	8.29	-0.58,1.19	10.01	-0.45,1.33
AET	62.10	63.20	0.23	58.80	0.28	59.30	0.45
	6.40	4.16	-1.10,0.65	5.20	-0.60,1.16	7.38	-0.44,1.34
WL	64.30	63.40		63.50		65.50	
	7.01	8.91		7.04		7.62	

Abbreviations: SD, standard deviation; 95%CI, 95% confidence interval; RET, resistance exercise training; AET, aerobic exercise training; WL, wait list; PSWQ, Penn State Worry Questionnaire

Table 4.4. Effects of RET and AET on Secondary Outcome Variables

	Baseline	Week 2		Week 4		Week 6	
Outcome	**Mean SD**	**Mean SD**	**Hedge's d 95%CI**	**Mean SD**	**Hedge's d 95%CI**	**Mean SD**	**Hedge's d 95%CI**
STAI-Trait							
RET	51.00	47.00	0.14	47.50	0.36	44.10	0.52
	8.35	10.66	-0.74,1.02	10.38	-0.52,1.24	11.46	-0.37,1.41
AET	51.80	47.90	0.15	47.70	0.47	45.30	0.54
	5.85	7.96	-0.73,1.02	7.94	-0.42,1.36	8.15	-0.36,1.43
WL	54.50	51.90		54.60		52.80	
	10.62	8.06		10.10		9.43	
POMS-T							
RET	7.90	4.90	0.62	5.10	0.15	2.80	1.05
	3.78	3.25	-0.28,1.51	4.56	-0.72,1.03	2.66	0.12,1.99*
AET	8.90	5.60	0.58	5.70	0.21	4.50	0.73
	5.17	3.41	-0.32,1.47	4.35	-0.67,1.09	4.43	-0.18,1.63
WL	8.00	7.40		5.80		7.00	
	3.68	5.34		4.67		4.16	
BDI-II							
RET	17.50	10.00	0.50	10.40	0.50	8.10	0.52
	8.15	7.45	-0.39,1.39	6.59	-0.39,1.39	7.59	-0.37,1.41
AET	14.00	12.70	-0.04	10.50	0.18	10.10	0.04
	8.84	10.44	-0.92,0.83	10.46	-0.69,1.06	12.11	-0.84,0.91
WL	20.40	18.60		19.00		16.90	
	13.14	13.88		13.64		10.87	
PVT – Mean Reaction Time, sec							
RET	0.31	0.31	-0.36	0.29	0.67	0.31	0.30
	0.03	0.04	-1.25,0.52	0.02	-0.23,1.57	0.04	-0.58,1.18
AET	0.30	0.29	-0.07	0.30	0.33	0.27	1.07
	0.03	0.05	-0.09,0.81	0.03	-0.55,1.21	0.01	0.14,2.01*
WL	0.31	0.30		0.32		0.33	
	0.04	0.04		0.04		0.12	
PVT – Ratio							
RET	0.03	0.01	0.17	0.01	0.23	0.03	0.40
	0.04	0.01	-0.71,1.04	0.02	-0.65,1.11	0.05	-0.49,1.28
AET	0.01	0.02	-0.12	0.03	-0.04	0.01	0.36
	0.01	0.02	-1.00,0.76	0.04	-0.92,0.84	0.01	-0.52,1.25
WL	0.01	0.01		0.03		0.06	
	0.18	0.01		0.04		0.16	
POMS-C							
RET	5.30	3.40	0.37	4.30	0.30	3.10	0.54
	2.21	1.17	-0.51,1.26	3.71	-0.58,1.19	1.79	-0.35,1.43
AET	4.80	3.90	0.03	3.00	0.53	3.10	0.34
	2.78	1.91	-0.85,0.91	2.36	-0.36,1.42	2.42	-0.54,1.23
WL	6.30	5.50		6.20		5.70	
	3.34	3.10		4.13		2.21	

POMS-F							
RET	10.50	6.50	0.16	6.70	0.21	4.90	0.39
	5.25	3.54	-0.71,1.04	5.58	-0.67,1.08	3.90	-0.49,1.28
AET	10.10	7.20	-0.07	5.70	0.35	4.70	0.37
	4.70	3.77	-0.94,0.81	3.92	-0.53,1.24	4.83	-0.51,1.26
WL	10.20	7.00		7.40		6.50	
	3.97	5.23		4.53		4.93	
POMS-V							
RET	6.30	6.80	0.23	6.00	0.07	7.30	0.65
	3.37	3.65	-0.65,1.11	3.27	-0.81,0.94	4.47	-0.25,1.55
AET	6.50	7.00	0.24	8.30	0.66	7.20	0.59
	3.03	3.40	-0.64	3.60	-0.24,1.56	3.68	-0.30,1.49
WL	5.10	4.90	1.12	5.00		4.10	
	2.42	3.03		3.13		3.70	
IRQ-F							
RET	27.90	22.10	0.64	22.30	0.75	19.80	1.18
	7.31	7.94	-0.26,1.54	9.41	-0.16,1.66	8.66	0.33,2.03*
AET	26.20	23.50	0.23	22.90	0.40	19.10	0.88
	10.56	10.07	-0.65,1.11	9.17	-0.49,1.28	9.59	-0.04,1.80
WL	30.60	30.20		31.30		32.40	
	8.71	8.52		10.19		7.38	
IRQ-I							
RET	30.00	27.10	0.29	24.00	0.80	19.90	1.23
	8.29	11.40	-0.59,1.17	10.21	-0.11,1.71	9.96	0.28,2.19*
AET	25.70	23.80	0.17	23.20	0.38	19.50	0.74
	10.10	8.97	-0.71,1.05	9.67	-0.50,1.27	7.72	-0.17,1.64
WL	32.80	32.60		34.20		34.10	
	9.39	9.16		12.19		6.95	
Pain – No. Locations							
RET	1.60	2.10	-0.43	2.00	0.30	2.60	-0.64
	1.65	2.10	-1.31,0.46	2.05	-0.58,1.18	3.06	-1.54,0.26
AET	2.70	0.80	0.53	2.00	0.68	2.30	-0.04
	2.36	1.14	-0.36,1.42	2.87	-0.22,1.58	2.95	-0.91,0.84
WL	2.00	1.50		3.10		1.50	
	2.71	3.06		3.70		3.44	
Pain – VAS							
RET	21.60	13.20	0.80	10.90	1.37	12.30	0.43
	23.31	13.07	-0.11,1.71	11.86	0.40,2.35*	12.33	-0.45,1.32
AET	19.45	10.40	0.93	14.70	1.18	20.30	-0.13
	20.42	19.21	0.01,1.86*	19.99	0.23,2.13*	24.24	-1.01,0.75
WL	9.00	15.30		23.60		7.70	
	8.92	18.73		26.08		12.76	
7PAR $(kcals \cdot kg^{-1} \cdot wk^{-1})$							
RET	263.34	250.18	-0.31	255.54	-0.50	257.05	-0.50
	36.59	23.53	-1.19, 0.57	18.56	-1.39, 0.39	28.09	-1.38, 0.40
AET	249.24	259.18	0.58	266.34	0.40	260.01	0.06
	21.51	31.85	-0.32, 1.47	33.20	-0.49, 1.28	35.11	-0.82, 0.94
WL	248.04	244.70		256.05		257.43	
	22.55	21.52		25.85		33.51	

Tremor, milli-G				
RET	4.99		3.83	0.33
	3.04		4.41	-0.74, 1.39
AET	8.06		4.48	0.50
	8.43		1.30	-0.58, 1.57
WL	5.96		6.63	
	7.29		2.58	

Abbreviations: SD, standard deviation; 95%CI, 95% confidence interval; RET, resistance exercise training; AET, aerobic exercise training; WL, wait list; STAI-Trait, trait subscale of the State-Trait Anxiety Inventory; POMS-T, tension subscale of the Profile of Mood States – Brief Form; BDI-II, Beck Depression Inventory – II; PVT-Mean Reaction Time, mean reaction time on psychomotor vigilance task; sec, seconds; PVT-ratio, ratio of errors to valid responses on psychomotor vigilance task; POMS-C, confusion subscale of the Profile of Mood States – Brief Form; POMS-F, fatigue subscale of the Profile of Mood States – Brief Form; POMS-V, vigor subscale of the Profile of Mood States – Brief Form; IRQ-F, frequency subscale of the Irritability Questionnaire; IRQ-I, intensity subscale of the Irritability Questionnaire; Pain-No. Locations, number of painful locations on Pain Figure Drawing; Pain-VAS, visual analogue scale for pain.

* $p < .05$

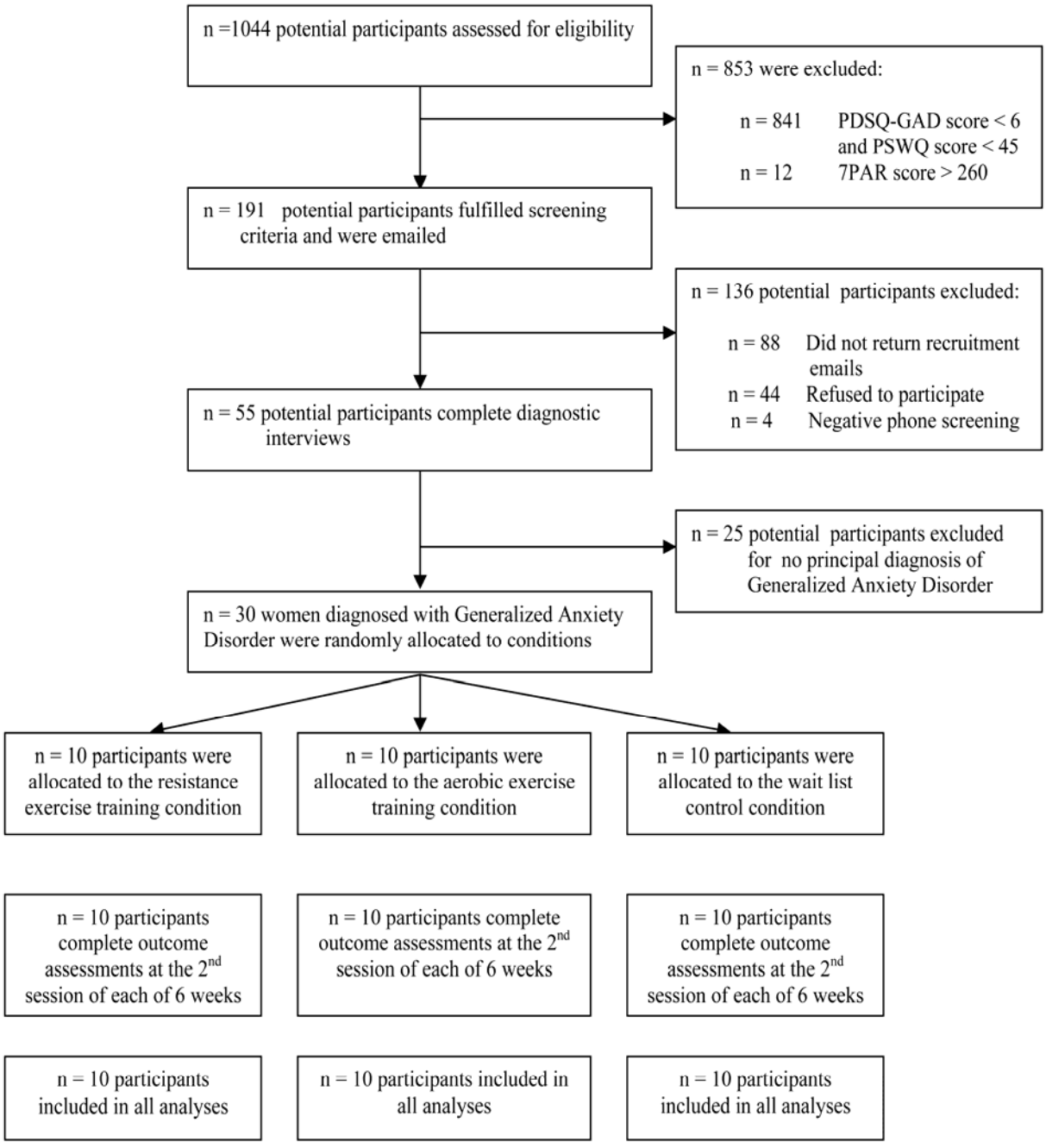

Figure 4.1. Patient Flow Through the Six-week Randomized, Controlled Trial

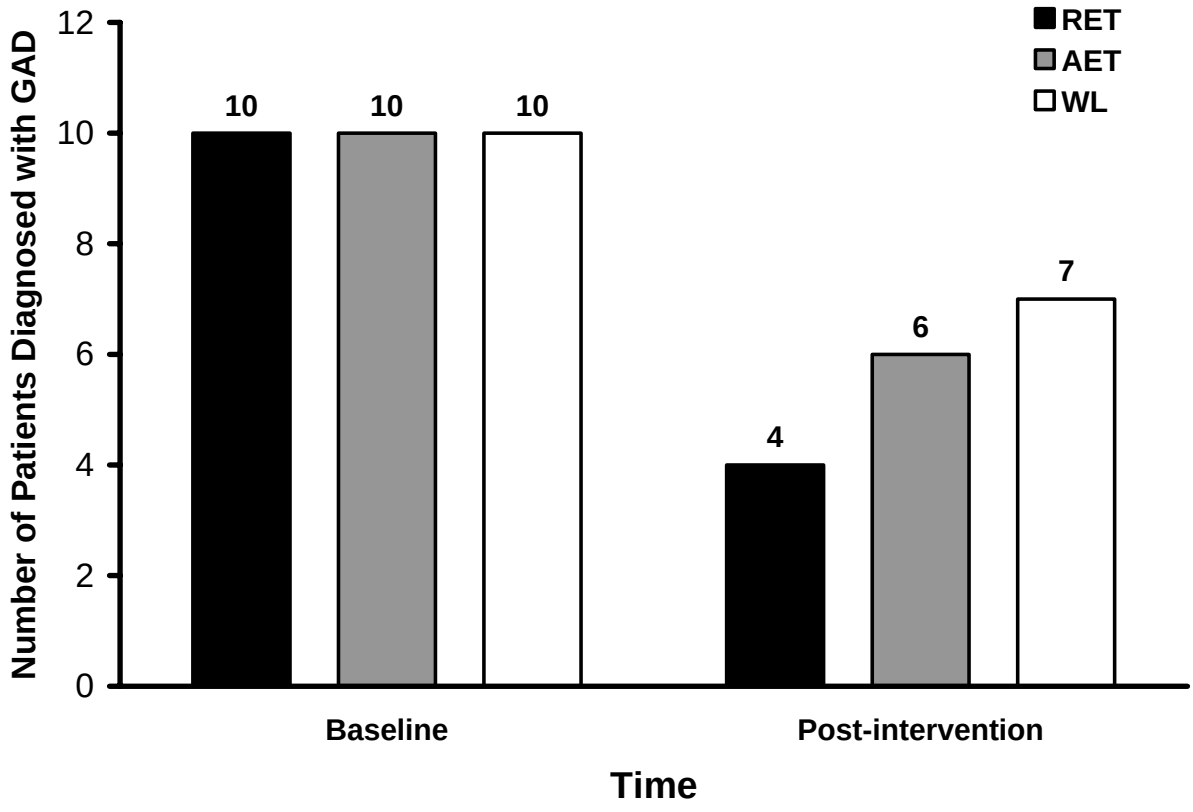

Figure 4.2. The Number of Patients Diagnosed with GAD at Baseline and Post-intervention in the Resistance Exercise Training (RET), Aerobic Exercise Training (AET), and Wait List (WL) Groups

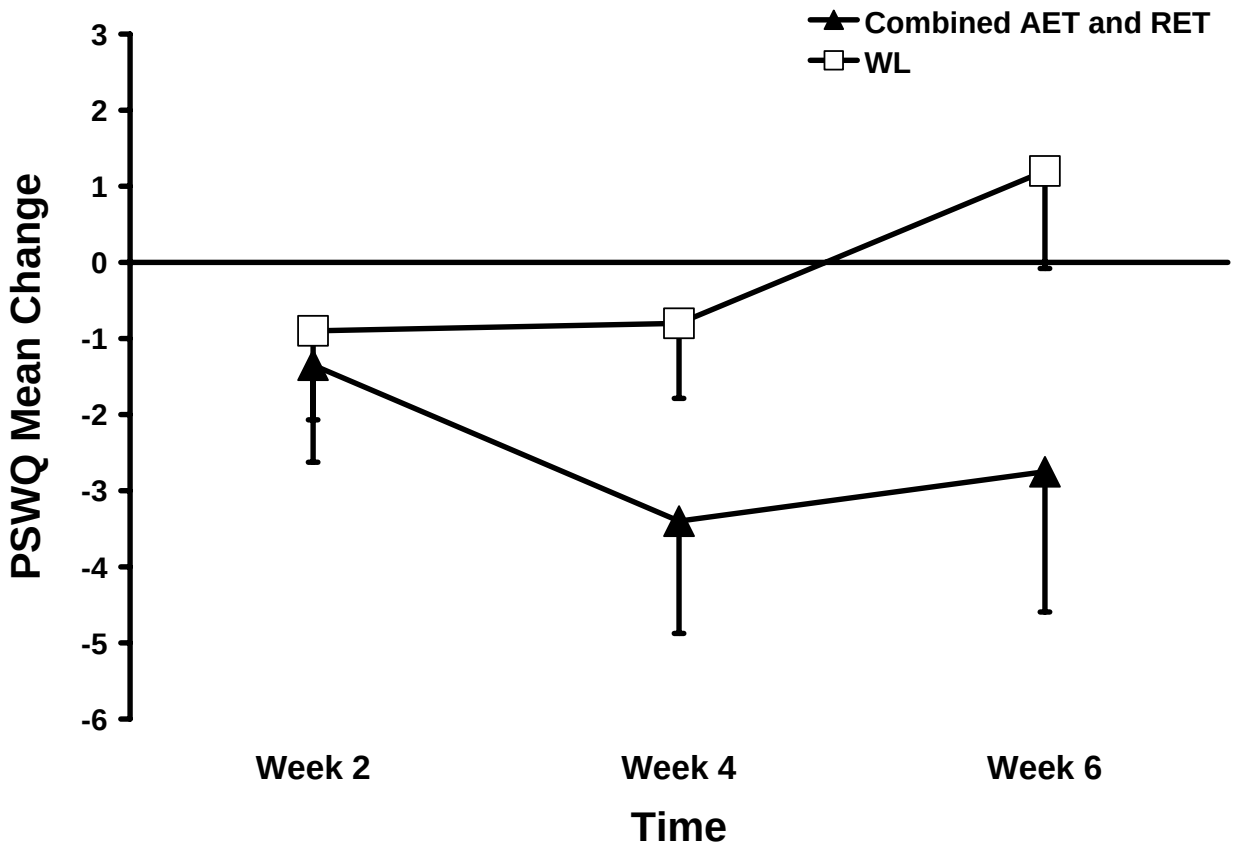

Figure 4.3. Changes in Worry Symptom Scores (PSWQ) in the Combined Aerobic Exercise Training (AET) and Resistance Exercise Training (RET) Groups Compared to the Wait List Condition Group (WL) Across Time

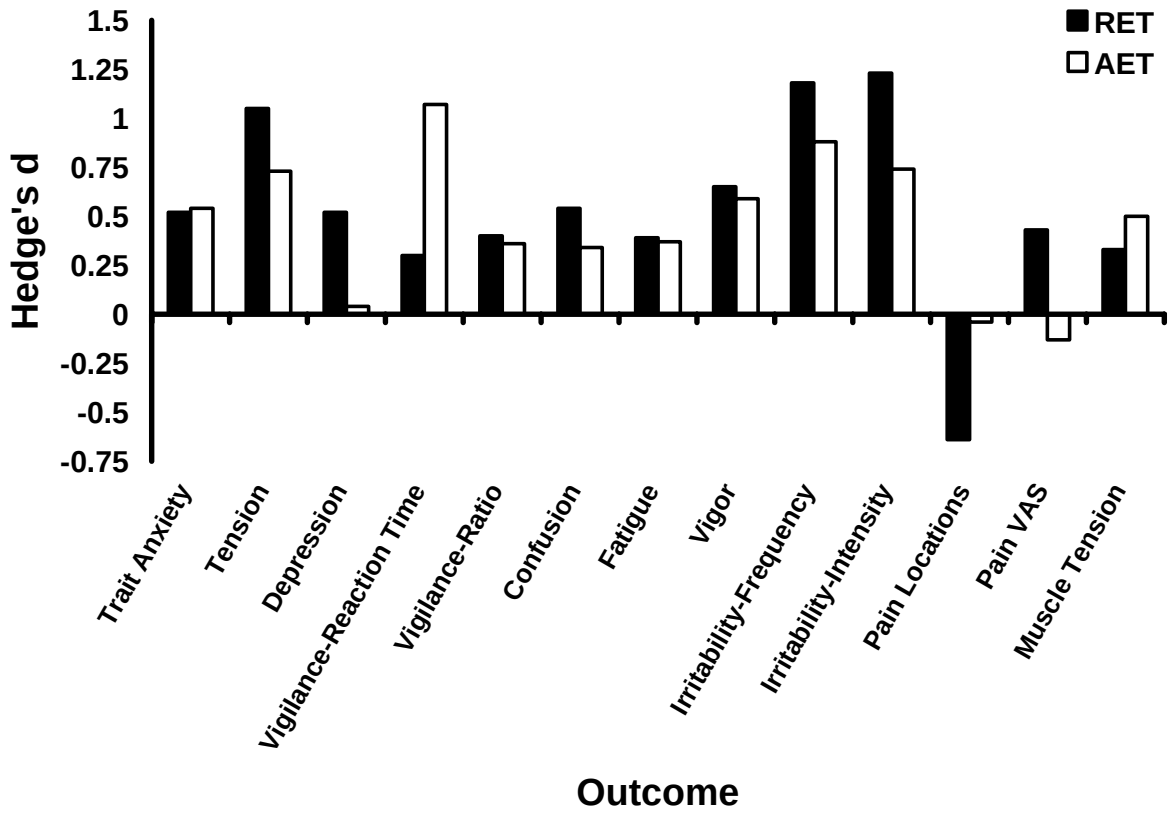

Figure 4.4. Effect (Hedge's d effect size) of Aerobic Exercise Training (AET) and Resistance Exercise (RET) on Secondary Outcomes

CHAPTER 5

CONCLUSIONS

This dissertation investigated the effects of exercise training on generalized anxiety disorder (GAD) and medical patients. The primary objectives of this research were (i) to conduct a systematic review of randomized, controlled trials (RCT) of the effects of exercise training on anxiety symptoms among medical patients to both quanitify the magnitude of the estimated population effect and determine the extent to which variables of theoretical or practical importance account for variation in the estimated population effect; and, (ii) to use the findings of the systematic review to design a RCT to experimentally investigate both the effects of exercise training on symptoms among sedentary women with GAD and any differences between the magnitude of effects for resistance exercise and aerobic exercise training.

The findings of this dissertation support the efficacy of exercise training as a potential treatment both for anxiety symptoms among patients with a chronic illness and for worry and associated symptoms that characterize patients with GAD. These findings contribute to a better understanding of the effects of exercise training on anxiety symptoms and disorders among patients. These findings also could contribute to efforts to ameliorate the increased health care costs and reduced quality of life frequently associated with anxiety symptoms and disorders.

Medical Patients

The systematic review evaluated the results of RCTs examining the effects of exercise training on anxiety symptoms among patients with a chronic illness. Compared with no treatment conditions, exercise training significantly reduced anxiety symptoms by a mean effect

Δ of 0.29 (95% confidence interval, 0.23-0.36) among patients (Herring, O'Connor & Dishman, 2010). The overall findings were generally consistent with exercise training effects on related mental health outcomes including fatigue symptoms among patients (Puetz, O'Connor & Dishman, 2006) and cognitive function among older adults (Colcombe & Kramer, 2003).

The overall effect was moderated by exercise program length, exercise session duration, and the time frame of anxiety report. Investigations that used exercise program lengths of 3 to 12 weeks resulted in significantly larger anxiety reductions than longer program lengths. This finding is consistent both with reviews of the effect of exercise training on depression (Lawlor & Hopker, 2001), cognitive function in older adults (Colcombe & Kramer, 2003), and quality of life among patients with multiple sclerosis (Motl & Gosney, 2008) and with the generally expected response time of pharmacological treatments of four to 12 weeks for individuals with anxiety (Davidson, Zhang, Connor et al., 2010). One potential explanation for this finding was better adherence among the shorter program lengths.

Investigations that used exercise session durations greater than 30 minutes resulted in significantly larger anxiety reductions than durations of 10 to 30 minutes. This finding is consistent with prior findings of better mental outcomes with longer exercise session durations found for cognitive function in older adults (Colcombe & Kramer, 2003; Heyn, Abreu & Ottenbacher, 2004) and claudication pain reduction among patients with peripheral artery disease (Gardner & Poehlman, 1995) and, as more compelling data emerge, may be due in part to interactions with adherence and anxiety report time frame.

Investigations that used anxiety outcome measures with instructional sets that asked patients to report anxiety symptoms over a time frame longer than the past week resulted in larger anxiety reductions compared with a combination of shorter anxiety report time frames of

"the past week including today" and "right now." Although larger anxiety reductions resulted from longer anxiety report time frames, approximately 80% of investigations used a shorter report time frame. The hesistancy to use a longer time frame may have stemmed from a misinterpretation that trait anxiety scores would not be sensitive to change in response to exercise training of only a few months. The findings suggest that one limitation to this area of research is the atheoretical nature of using an anxiety outcome measure with a short anxiety report time frame to quantify the chronic effects of exercise training. Theory, evidence from the systematic review, and findings from related investigations support the idea that future investigations would benefit from including anxiety outcome measures with a time frame of anxiety report greater than one week.

The findings of the systematic review highlighted the need for well-designed RCTs into the effects of exercise training on understudied patient groups, particularly patients with an anxiety disorder, which use understudied types of exercise such as resistance exercise training.

Generalized Anxiety Disorder Patients

A randomized controlled trial design was used both to quantify the effects of six weeks of resistance (RET) or aerobic exercise training (AET) on remission and worry symptoms among sedentary patients with generalized anxiety disorder (GAD) and to compare the magnitude of the effects of RET and AET on other symptoms and signs characteristic of GAD patients. The trial was conducted between August 2009 and May 2010 (Clinical Trials.gov Identifier: NCT00953654).

Thirty sedentary women, aged 18-37, with a primary *DSM-IV* diagnosis of GAD were block randomized based both on intervention condition [RET, AET, or wait list (WL)] and psychoactive medication use (medication or no medication). The RET condition involved two

weekly sessions seven sets of 10 repetitions each of three lower-body weightlifting exercises, leg press, leg curl and leg extension, that began at an intensity of 50% of predicted one-repetition maximum (1-RM) and progressed by five percent each week. The AET condition involved two weekly sessions of dynamic leg cycling exercise matched with the RET condition on the body area exercised (legs), total positive work, total time actively engaged in exercise, and a five percent progression in load each week. Patients allocated to the WL condition were asked to refrain from initiating an exercise training program for six weeks and were offered participation in a six week RET or AET program following the six weeks of the investigation.

Primary outcomes were remission, measured by the number needed to treat (NNT; Cook & Sackett, 1995; Laupacis, Sackett & Roberts, 1988), and worry symptoms, the hallmark symptom among GAD patients, measured by the Penn State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger & Borkovec, 1990). Secondary outcomes were associated symptoms that often characterize GAD patients including anxiety, depression, difficulty concentrating, feelings of tension, fatigue, low vigor and confusion, irritability, muscle tension and pain. Hedge's d was calculated to examine the magnitude of changes for outcome variables following the six week intervention (Hedges & Olkin, 1985).

Adherence and compliance were 100% and 99.13% for RET and 100% and 100% for AET, respectively. Because of nonsignificant baseline strength differences, total positive work for AET patients was nonsignificantly larger than RET patients (451618 vs. 366308 Joules, respectively). RET resulted in increases in strength across six weeks that were larger than those observed for AET and WL (all Hedge's $d \geq 0.64$).

There were no adverse events reported during the investigation. Remission rates were 60%, 40% and 30% for RET, AET, and WL, respectively. The NNT (95%CI) was 3.33 (1.72,

55.56) for RET and 10 (-6.79, 2.88) for AET. A significant condition by time interaction was found for worry symptom scores ($F_{(3.962, 49.529)} = 2.815$; $p = .035$). Bonferroni-corrected pairwise comparisons of week six scores for RET ($t_{(18)} = 1.106$, $p = 0.28$) and AET ($t_{(18)} = 1.845$, $p = 0.081$) compared with WL were not significant; however, moderately-large reductions in worry symptoms were found for both exercise conditions (Hedge's d = 0.45). A follow-up contrast of week six scores showed significantly larger reductions for the combined exercise conditions compared to WL ($t_{(25.943)} = 2.168$, $p = 0.039$). RET and AET resulted in moderate-to-large improvements in secondary outcomes (Hedge's $d \geq .36$).

The randomized controlled trial of GAD patients addressed previous methodological issues and extended previous related research by (1) examining the effects of exercise training on symptoms among GAD patients within the framework of a randomized controlled trial, (2) focusing on sedentary women with a primary *DSM-IV* diagnosis of GAD, (3) evaluating exercise training effects on both diagnostic status (i.e., presence or absence of pathology) and symptoms associated with GAD, and, (4) equating RET and AET conditions on lower body exercise, the total positive work completed and total time actively engaged in exercise. The major findings of the experiment were: (1) remission rates were higher among exercise conditions and significantly better in the RET condition compared with WL, (2) six weeks of exercise training for the RET and AET groups combined significantly reduced worry symptoms, and, (3) RET and AET resulted in moderate-to-large improvements in symptoms associated with GAD including, irritability, anxiety, and low energy.

The findings suggested that RET was effective in treating GAD. The remission rate for RET (60%) was significantly higher than that for WL (30%). The WL remission rate was consistent with prior research documenting that only about one-third of GAD patients show

partial or full remission over a six-month period (Wittchen, Zhao, Kessler, et al., 1994). The NNT of 3.33 suggests that on average for every 10 GAD patients who would perform six weeks of RET three additional remissions would occur compared to the expected number of spontaneous remissions among untreated patients. The NNT for RET compares favorably to other empirically supported GAD treatments including antidepressants (NNT = 5.15, Kapczinski, Lima, Souza, Cunha & Schmitt, 2003; Schmitt, Gazalle, Lima, Cunha, Souza & Kapczinski, 2005; NNT = 3.23, Donovan, Glue, Kolluri & Emir, 2010), and multifaceted treatment programs employing pharmacotherapy, cognitive-behavioral therapy or both (NNT = 5.50, Roy-Byrne, Craske, Sullivan et al., 2010) among GAD patients. The fact that the AET stimulus was inadequate to elicit GAD remission suggests that the therapeutic effect of exercise training for this outcome was likely linked to the relative exercise intensity as revealed here by perceived exertion ratings. The AET exercise sessions were perceived as significantly less intense (RPE = 9; "very light") than the RET sessions (RPE = 14; between "somewhat hard" and "hard"). These findings are consistent with previous evidence of larger effects of higher intensity exercise training on depression symptoms (Dunn, Trivedi & O'Neal, 2001; Singh, Stavrinos, Scarbek, Galambos, Liber & Fiatarone Singh, 2005).

Worry symptoms were significantly reduced and both RET and AET produced moderate reductions in worry symptoms. The findings were consistent with both the mean effect of short duration pharmacological and cognitive-behavioral therapies among anxiety disorder patients (Gould, Buckminster, Pollack, Otto & Yap, 1997) and the mean effect of short duration exercise training programs on anxiety symptoms among medical patients (Herring et al., 2010), depression symptoms among depressed patients (Lawlor & Hopker, 2001), and quality of life among patients with multiple sclerosis (Motl & Gosney, 2008). It is plausible that findings were

affected by the large number of baseline comorbid diagnoses. Non-remitters had a significantly larger number of baseline comorbid psychiatric diagnoses ($t_{(22.891)} = 3.029$, $p = 0.006$).

Both exercise conditions resulted in moderate-to-large improvements in symptoms that characterize GAD. RET significantly improved feelings of tension and the frequency and intensity of irritability. Although not statistically significant, the RET condition resulted in Hedge's d effect sizes of approximately ≥ 0.36 in trait anxiety, depression, concentration, fatigue, vigor and pain, while the AET condition resulted in improvements in trait anxiety, concentration, fatigue, vigor, irritability and muscle tension. Exercise effects for these outcomes compare favorably with relaxation, cognitive-behavioral therapy and worry exposure completed GAD patients (Dugas, Brillon, Savard, et al., 2010; Hoyer, Beesdo, Gloster, Runge, Hofler & Becker, 2009) and warrant further investigation in larger trials.

AET and RET produced no adverse events including no musculoskeletal injuries or increases in suicidal ideation scores. Exercise training was associated with improvements in all the symptoms measured except for the number of pain locations. Although the number of pain locations was increased by one after six weeks of RET, the intensity of pain was reported as 9.3 raw VAS units less after RET training.

One limitation of the present investigation was the small sample size. Although the research design was powered to detect a statistically significant effect for the primary outcome, a larger trial is warranted to thoroughly investigate the effects of exercise training on the associated symptoms that characterize patients with GAD. Another potential limitation is that, because of initial strength differences, the exercise training conditions were not perfectly equated on total positive work; consequently, differences between AET and RET cannot be completely

ruled out. Nonetheless, exercise had favorable effects on remission rates and worry symptoms regardless of exercise condition.

The overall findings of the trial supported the feasibility and potential efficacy of exercise training as a safe treatment for GAD. Significant improvements in worry symptoms and other associated symptoms that characterize GAD patients, including irritability, anxiety, and low vigor, warrant further investigations with larger trials.

Implications for Future Research

Several research needs are suggested by the findings of this dissertation. Findings of the systematic review highlighted the continued need for well-designed investigations into the effects of exercise training on anxiety symptoms among individuals with an understudied illness, including those with an anxiety disorder, chronic obstructive pulmonary disorder, cancer, chronic pain, epilepsy, lupus, and multiple sclerosis. Also needed is better reporting of study features, particularly regarding the exercise stimulus. A better understanding of the role of exercise stimulus variables in maximizing positive mental health outcomes could be realized through investigations that (1) examine useful types of exercise that have been understudied, including resistance exercises; (2) compare difference exercise training intensities and durations while controlling total energy expenditure to better understand the minimal and optimal dose necessary to elicit mental health benefits; and (3) select characteristics of the exercise stimulus to optimize program adherence and compliance with intensity and duration prescription (Herring et al., 2010).

A better understanding of the potential efficacy of exercise training as a treatment for GAD could be realized through well-designed investigations that: (1) use large sample sizes both to compare the effects of exercise training alone to empirically-supported treatments for GAD

(e.g., cognitive-behavioral therapy, pharmacotherapy) and to compare the effects of the combination of exercise training with empirically-supported treatments to the same empirically-supported treatment alone; (2) compare the effects of different types of exercise training that use different training intensities and durations matched on perceptual responses during the time actively engaged in exercise to better understand the minimal and optimal dose necessary to improve symptoms; and (3) block randomize patients to conditions based upon potential confounding variables including comorbid psychiatric diagnoses.

References

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science*, *14*(2), 125-130.

Cook, R. J. & Sackett, D. L. (1995). The number needed to treat: A clinically useful measure of treatment effect. *British Medical Journal, 310*, 452-454.

Davidson, J. R., Zhang, W., Connor, K. M., Ji, J., Jobson, K., Lecrubier, Y. et al. (2010). A psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). *Journal of Psychopharmacology*, *24*(1), 3-26.

Donovan, M. R., Glue, P., Kolluri, S. & Emir, B (2010). Comparative efficacy of antidepressants in preventing relapse in anxiety disorders – A meta-anlysis. *Journal of Affective Disorders, 123*, 9-16.

Dugas, M. J., Brillon, P., Savard, P., et al. (2010). A randomized clinical trial of cognitive-behavioral therapy and applied relaxation for adults with Generalized Anxiety Disorder. *Behavior Therapy, 41*, 46-58.

Dunn, A. L., Trivedi, M. H., & O'Neal, H. A. (2001). Physical activity dose-response effects on outcomes of depression and anxiety. *Medicine and Science in Sports and Exercise, 33*(6)(suppl), S587-S597.

Gardner, A. W. & Poehlman, E. T. (1995). Exercise rehabilitation programs for the treatment of claudication pain: A meta-analysis. *Journal of the American Medical Association, 274*(12), 975-980.

Gould, R. A., Buckminster, S., Pollack, M. H., Otto, M. W. & Yap, L. (1997). Cognitive-behavioral and pharmacological treatment for social phobia: A meta-analysis. *Clinical Psychology: Science and Practice,4*, 291-306.

Hedges, L. V. & Olkin, I. (1985). *Statistical Methods for Meta-analysis.* New York, NY: Academic Press.

Herring, M. P., O'Connor, P. J., & Dishman, R. K. (2010). The effect of exercise training on anxiety symptoms among patients: A systematic review. *Archives of Internal Medicine, 170*(4), 321-331.

Heyn, P., Abreu, B. C., & Ottenbachner, K. J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. *Archives of Physical Medicine and Rehabilitation, 85*(10), 1694-1704.

Hoyer, J., Beesdo, K., Gloster, A. T., Runge, J., Hofler, M. & Becker, E. S. (2009). Worry exposure versus applied relaxation in the treatment of Generalized Anxiety Disorder. *Psychotherapy and Psychosomatics, 78*, 106-115.

Kapczinski, F., Lima, M. S., Souza, J. S., Cunha, A. & Schmitt, R (2003). Antidepressants for generalized anxiety disorder. *Cochrane Database System Reviews, 2*(2), CD003592.

Laupacis, A., Sackett, D. L. & Roberts, R. S. (1988). An assessment of clinically useful measures of the consequences of treatment. *New England Journal of Medicine, 318*, 1728-1733.

Lawlor, D. A. & Hopker, S. W. (2001). The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *British Medical Journal, 322*(7289), 763-767.

Meyer, T. J., Miller, M. L., Metzger, R. L., & Borkovec, T. D. (1990). Development and validation of the penn state worry questionnaire. *Behaviour Research and Therapy*, *28*(6), 487-495.

Motl, R. W. & Gosney, J. L. (2008). Effect of exercise training on quality of life in multiple sclerosis: a meta-analysis. *Multiple Sclerosis, 14*(1), 129-135.

Puetz, T. W., Beasman, K. M., & O'Connor, P. J. (2006). The effect of cardiac rehabilitation exercise programs on feelings of energy and fatigue: A meta-analysis of research from 1945 to 2005. *European Journal of Cardiovascular Prevention & Rehabilitation*, *13*(6), 886-893.

Roy-Byrne, P., Craske, M. G., Sullivan, G., et al. (2010). Delivery of evidence-based treatment for multiple anxiety disorders in primary care: A randomized controlled trial. *Journal of the American Medical Association, 303*(19), 1921-1928.

Schmitt, R., Gazalle, F. K., Lima, M. S., Cunha, A., Souza, J. & Kapczinski, F (2005). The efficacy of antidepressants for generalized anxiety disorder: A systematic review and meta-analysis. *Revista Brasileira de Psiquiatria, 27*(1), 18-24.

Singh, N. A., Stavrinos, T. M., Scarbek, Y., Galambos, G., Liber, C., & Fiatarone Singh, M. A. (2005). A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *Journals of Gerontology Series A: Biological and Medical Sciences*, *60*(6), 768-776.

Wittchen, H-U., Zhao, S., Kessler, R., et al. (1994). DSM-III-R generalized anxiety disorder in the National Comorbidity Survey. *Archives of General Psychiatry, 51*, 355-364.

APPENDIX

COPYRIGHT RELEASE FROM AMERICAN MEDICAL ASSOCIATION

Monday, June 21, 2010

Permission Granted Notification

Client Number: 16426
Request Number: 26442

Matthew P. Herring
University of Georgia
Department of Kinesiology
330 River Road
Athens, GA 30602-6554 USA

In response to your request to use:

Journal	Citation	Year	Specific Item
Archives of Internal Medicine	170(4):321-331	2010	First Article Page; Toll-Free Weblink

PERMISSION has been GRANTED for the following use:

AMA Journal content reuse in Doctoral Dissertation titled "Effects of Exercise Training on Generalized Anxiety Disorder and Medical Patients", for presentation at the University of Georgia Graduate School; Athens, GA:
1) First article page (including article abstract) for use in printed doctoral dissertation.
2) Placement of toll-free weblink, provided by the AMA, to full text Archives of Internal Medicine Article, in electronic form of doctoral dissertation.

Rights granted herein are non-exclusive for reproduction in print, online and electronic media as specified in this request. If the permission requested is for inclusion of AMA material in a book or CD-ROM, such permission is granted for the single edition only as specified in this request.

Your credit line must include the name of the publication, issue date, volume and page number, as well as "Copyright © (Year of Publication) American Medical Association. All rights reserved."