EFFECT OF AN ACUTE BOUT OF AEROBIC EXERCISE ON DEHYDROEPIANDROSTERONE SULPHATE (DHEAS) IN CLINICALLY DIAGNOSED BIPOLAR SUBJECTS

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Dehydroepiandrosterone Sulfate (DHEAS) is thought to offset hypercortisolemia, which is found in individuals with bipolar disorder. While the cause of bipolar disorder remains unknown, previous studies have linked elevated cortisol levels with various mental health illnesses, including bipolar disorder. Previous studies suggest that exercise increases DHEAS levels in healthy subjects, however no studies have tested clinically diagnosed bipolar patients. It is hypothesized that the interaction between DHEAS and cortisol may be a contributing factor to the improvements in mood seen with exercise (McEwen 2002).

PURPOSE: To determine the effect of an acute bout of aerobic exercise on DHEAS levels and perceptions of well-being in clinically diagnosed bipolar disorder patients.

METHODS: Clinically diagnosed male (n=13) and female (n=13) bipolar patients (mean age 42.4 ± 11.4 years) participated in this study. Ten ml of blood were drawn prior to the exercise session. Subjects walked on a treadmill for 20 min. at individualized intensities corresponding to 70% of age predicted maximum heart rate (APMHR). The exercise session finished with a 5 min. cool down. Within five min. post- completion of the cool down, a second blood draw, identical to the first, occured. Blood samples were spun and serum frozen until all samples could be collected and analyzed. A 7-point Likert questionnaire was administered pre and post exercise to assess perceptions of well-being.

RESULTS: A two way ANOVA revealed a significant increase in DHEAS (p=0.01) after the acute bout of aerobic exercise. A dependant T-test also revealed a significant improvement in perception of global well-being following exercise (p<0.05). A non-significant (p=0.38) correlation of r=0.18 was found between DHEAS and perceptions of well-being.

CONCLUSION: Treadmill exercise performed at of 70% of APMHR for 20 min. significantly increased DHEAS in clinically diagnosed bipolar subjects. Significant post exercise perceptions of well being improved. No relationship between well-being and DHEAS was revealed. Exercise appears to be responsible for an increase in DHEAS in bipolar patients; however, it appears that this increase may not be solely responsible for improvements in well-being.

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PREFACE

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1.0   INTRODUCTION

Bipolar disorder, also known as manic-depressive illness, is a mood disorder that causes unusual changes in one's energy, mood, and ability to function. Many healthy individuals go through normal mood swings; however the symptoms of bipolar disorder are different. Symptoms are more severe and can result in poor school or job performance, damaged relationships and even suicide.

More than 2 million American adults (Narrow, 1998), or about 1 percent of the population over the age of 18 have bipolar disorder. Bipolar disorder typically develops in late adolescence or early adulthood. Similar to diabetes or heart disease, bipolar disorder is a long-term illness that must be carefully managed throughout a person's life.

In 1990 the cost associated with this disease was estimated to be 44 billion dollars (Wyatt et al., 1995). Seventeen percent of those costs were from direct care including inpatient treatment, medication, and shelter. The remaining 83% was attributed to worker absenteeism, diminished productivity, institutional costs and assisted living expenses. It is estimated that the financial impact of a single occurrence of this disease is over $11,000 per patient, while unstable and reoccurring bipolar disorder can cost upward of $625,000 across the lifetime of a single patient (Begley, 2001).

Dramatic mood swings ranging from overly "high" to irritable to sad and hopeless describe this disorder. Severe changes in energy and behavior typically accompany these changes in mood. A typical manic episode could include any of the following symptoms: increased energy, activity and restlessness, excessively high euphoric mood, irritability, racing thoughts and quick speech, distractibility, insomnia, unrealistic beliefs in one's ability or power, poor judgment, spending sprees, increased sex drive, abuse of drugs, provocative or aggressive behavior, and denial that anything is wrong. This mania is then followed by an episode of depression, which has the same symptomology as unipolar depression. These symptoms include, but are not limited to: feelings of sadness, anxiousness, empty mood, hopelessness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest in activities once enjoyed, decreased energy, difficulty concentrating, remembering, making a decision, restlessness, sleeping too much, change in appetite or unintended weight loss or gain, chronic pain or other persistent bodily symptom that is not caused by physical illness, and thoughts of suicide or death.

Studies are currently being done to clarify the possible causes of bipolar disorder. Most scientists now agree that there is no single cause of the disorder; rather many factors acting together cause the disease. Bipolar disorder tends to run in families. Therefore recent research has focused on uncovering genes that may be associated with its etiology.

Bipolar disorder is a recurrent illness, so long-term preventative treatment is strongly recommended and almost always indicated. Bipolar disorder patients are at risk of switching into mania or hypomania or of developing rapid, or ultra rapid cycling during treatment with antidepressant medication (Thase 2000). Rapid cycling can be defined as having four or more distinct periods of depression, hypomania, mixed states, or mania in one calendar year. In ultra

rapid cycling, these episodes may last no more than 24 hours and may give the individual little break from abnormal moods between mood swings. "Mood-stabilizing" medications are generally required, alone or in combination with antidepressants in an attempt to prevent patients from this cycling. Researchers continue to evaluate potential alternative therapies, as medications have known adverse side effects including: weight gain, nausea, tremor, reduced sexual drive, anxiety, hair loss, movement problems, and dry mouth, just to name a few. Lithium, which is a commonly used mood stabilizer, may cause low thyroid levels in some people resulting in the need for further medication.

One possible alternative form of therapy is physical activity or exercise. Exercise has many proven physical and mental health benefits. Physically fit individuals typically are more successful in everyday activities than sedentary individuals. In addition, they are better able to withstand disease, infection and declines in functionality. These health-fitness adaptations typically accrue when exercise is completed with appropriate intensity for 30 minutes or more on most days of the week. However, due to the complexity of various disease states associated with a sedentary lifestyle, there may be no single minimal dose of physical activity that is protective for all clinical conditions.

There is a growing body of literature dealing with the effects of exercise on mental health. There are many design flaws in this research, such as lack of control groups, potential confounding factors, inclusion of non-clinical patients and a small number of subjects. However, on balance, the research is encouraging and suggests exercise is an effective treatment for depression. (Greist et al. 1979; North et al. 1990; Lawlor et al., 2001; Craft et al., 1998; Martinesen 1990; Mutrie, 2000)

1.1   RATIONALE

Dehydroepiandrosterone (DHEA) is an adrenal steroid that is released during periods of stress. It is secreted episodically and in synchronization with cortisol in response to stress. It has been shown to have antiglucocorticoid and antiglutamatergic effects in several tissues, including the brain. Peripherally produced DHEA is thought to be a major source of brain DHEA (Browne et al. 1992). DHEA can also be found in a conjugated form as a sulphate ester, DHEAS. DHEAS is present in higher concentrations and can be thought of as a reservoir and precursor of DHEA.

The physiological role for DHEA remains unclear and a deficiency state has never been described (Ebeling 1994). Within the brain, regionally specific metabolism of DHEA may ultimately control the nature of DHEA's effects on cognition and behavior (Rose et al. 1997). There is evidence that DHEA promotes psychological resilience. A negative association between plasma DHEA levels and depressive symptoms has been reported. In addition, DHEA has been shown to have an antidepressant effect and has been used to treat major depression (Goodyer 1998, 2001; Young 2002, Wolkowitz et al. 1999). Evidence exists that exercise increases the plasma levels of DHEA (Baker 1982; Keizer 1987). Therefore, it follows that if exercise results in an acute increase in DHEA this may be an effective treatment modality for relieving depressive symptoms. This potential neuroendocrine mechanism has not been studied in patients with bipolar disorder.

In summary, it is known that 1) DHEA and DHEAS levels appear to be lower in depressed people when compared to otherwise psychologically healthy individuals; 2) DHEA and DHEAS increases in response to exercise in healthy individuals; and 3) exercise reduces symptoms of depression. The acute effect of aerobic exercise on the hormonal (DHEA / DHEAS) response of

patients with bipolar disorder has not been documented. If DHEAS levels are positively affected by acute exercise, this finding may have a significant impact on the treatment of patients with bipolar disorder. Therefore, this investigation will examine serum DHEAS levels immediately before and after an acute bout of aerobic exercise in patients with bipolar disorder.

1.2   STATEMENT OF THE PROBLEM

The primary goal of this project is to document the DHEAS response to aerobic exercise in patients with bipolar disorder. In addition, the impact of aerobic exercise on perceptions of global well-being will be evaluated in this population.

1.3   HYPOTHESIS

An acute bout of aerobic exercise will significantly increase DHEAS in patients with clinically diagnosed bipolar disorder.

Sub-hypothesis

An acute bout of aerobic exercise will significantly improve perceptions of well-being in patients suffering from bipolar disorder.

2.0   DEPRESSION/BIPOLAR DISORDER AS A PROBLEM

Bipolar disorder, also known as manic-depressive illness, is a psychological disorder that causes unusual changes in one's energy, mood, and ability to function. Many healthy individuals go through normal emotional highs and lows, however the symptoms of bipolar disorder are different. Symptoms are more severe and can result in poor school or job performance, damaged relationships and even suicide. The economic lifetime cost of the disorder is estimated to range from $11,700 per person for mild cases to over $624,000 per person for non-responsive and/or chronic cases (Begley et al, 2001).

More than 2 million American adults (Narrow, 1998), or about 1 percent of the population over the age of 18, have bipolar disorder. Looking at a wider definition of bipolar disorder, the occurrence increases to nearly 5% of the population. Bipolar disorder typically develops in late adolescence or early adulthood. Similar to diabetes or heart disease, bipolar disorder is a long-term illness that must be carefully managed throughout a person's life.

Dramatic mood swings range from overly happy to irritable to sad and hopeless. Severe changes in energy and behavior go along with changes in mood. A typical manic episode could include any of the following symptoms: increased energy, activity and restlessness, excessively high euphoric mood, irritability, racing thoughts and quick speech, distractibility, little sleep, unrealistic beliefs in one's ability or power, poor judgment, spending sprees, increased sex drive, abuse of drugs, provocative or aggressive behavior, and denial that anything is wrong. The

manic phase is often followed by an episode of depression, which has the same symptomology as unipolar depression. These symptoms include, but are not limited to: feelings of sadness, anxiousness, empty mood, hopelessness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest in activities once enjoyed, decreased energy, difficulty concentrating, remembering, making a decision, restlessness, sleeping too much, change in appetite or unintended weight loss or gain, chronic pain or other persistent bodily symptom that is not caused by physical illness and thoughts of suicide or death (DSM IV APA, 2000).

To date, diagnosis of bipolar disorder cannot be made based on physiological variables. Therefore, a diagnosis must be made on the basis of symptoms. Bipolar is typically diagnosed when a manic episode of elevated mood occurs with three or more of the other symptoms most of the day, nearly every day for one week or longer. The manic episode is then followed by a depressive episode. This means the patient has five or more symptoms of depression most of the day, nearly every day for a period of 2 weeks or longer (Spearing, et al., 2002).

Episodes of mania and depression usually recur across the life span. Between episodes, many people with this disorder are relatively free of symptoms. However, as many as one-third of the bipolar population suffers from some residual symptoms and a small percentage of people experience chronic unremitting symptoms despite treatment (Hyman et al., 2000).

Bipolar I is the classic form of the illness and is characterized by recurrent episodes of mania and depression. Some people never develop severe mania but experience milder episodes, termed hypomania, that alternate with depression. This form of the illness is called bipolar II disorder. If more than 3 episodes of illness happen in a 12-month period, a person is said to have a rapid-cycling pattern. Some people have multiple episodes within a single week, or even

within a day. Rapid cycling tends to develop later in the course of the illness and is more common among women than men (Spearing 2002).

Studies are currently being done to clarify possible causes of bipolar disorder. Most scientists now agree that there is no single cause of the disorder; rather many factors that act together to cause the disease. Bipolar disorder tends to run in families. Therefore, recent research has focused on uncovering genes that may be contributing factors. However, genes are not the entire story; research has shown that if one identical twin suffers from bipolar disorder, the other twin is not necessarily affected (NIMH Genetic Workgroup 1998). This suggests that while genes play a role, other factors may be involved in the etiology of bipolar disorder.

2.1   CURRENT TREATMENT FOR BIPOLAR DISORDER

Bipolar disorder is a recurrent illness, so long-term preventative treatment is strongly recommended and almost always indicated. A strategy that combines medication and psychosocial treatment is optimal for managing the disorder over time. Research has shown that people with bipolar disorder are at risk of switching into mania or hypomania or of switching between depression and mania multiple times per day, during treatment with antidepressant medication (Thase 2000). Therefore, "mood-stabilizing" drugs generally are required, alone or in combination with antidepressants. In general, people with this disorder continue treatment with mood stabilizers for extended periods of time, many needing the medication for a lifetime.

Lithium and Valproate are the most commonly prescribed mood-stabilizing drugs. Research continues to evaluate potential alternative therapies, as medications have known side effects, including: weight gain, nausea, tremor, reduced sexual drive, anxiety, hair loss,

movement problems and dry mouth. Lithium treatment works primarily to ease the manic phase of bipolar disorder, but is less effective in relieving the symptoms of depression. It may cause low thyroid levels in some people resulting in the need for further medication supplementation. Other medications are added when necessary, typically for shorter periods to treat episodes of mania or depression that break through despite the mood stabilizer.

2.2 CO-MORBIDITIES TYPICAL IN BIPOLAR DISORDER

Patients suffering from bipolar disorder are at higher risk for developing additional diseases. Antipsychotic drugs increase the risk of weight gain, hyperlipidemia and glucose dysregulation. Changing or combining medications may be sufficient in some cases, but many times additional drugs are needed.

The risk of developing diabetes is significantly increased in subjects with bipolar disorder (Cassidy et al 1999), however, this is only partially accounted for by medications (Henderson 2002, Baptista 2002). Atypical and traditional antipsychotics have been shown to impair glucose and lipid metabolism (Baptista 2001, Henderson 2002). Therefore, while the mood disorder symptoms may be relieved by pharmacological interventions, other negative health outcomes may occur. After an extended period of time, the bipolar patient may become diabetic, glucose intolerant, obese or display high tryglycerides and/or cholesterol. The question then becomes; what is the preferred method of treatment? Leaving the client in an unmedicated, bipolar state may be dangerous due to the high risk of suicide and/or other high-risk behaviors. Conversely, medicating the client with antipsychotic medication may increase the risk for developing other chronic diseases.

2.3   EXERCISE AS AN ALTERNATIVE TREATMENT FOR MENTAL ILLNESS

Exercise has many proven physical and mental health benefits. Physically fit individuals typically experience less stress when engaged in activities of daily living. A regular program of aerobic exercise may lead to an improved immune system, decreases in body weight and body fat, reduced cholesterol, increased levels of HDL cholesterol, etc. However, due to the complexity and variability of diseases associated with a sedentary lifestyle, there may be no single minimal dose of exercise that is protective for all potential clinical conditions (Balady, et al.2000).

In 1987 the US National Institute of Mental Health (NIMH) assembled a panel of experts to produce a consensus statement on the mental health effects of exercise and thus reconcile research and clinical practice. The results concluded that exercise (i) is positively linked with mental health and well being, (ii) reduces stress and state anxiety, and (iii) has emotional benefits for all age groups and in both genders (Morgan et al., 1988).

Running has been advocated as a more effective antidote to depression than psychoanalysis (Greist et al. 1979). Research shows that exercise may have an antidepressant effect in healthy individuals (North et al. 1990), and among those with multiple mental disabilities (Green et al. 1999). Schizophrenia is one of the most disabling of all mental illnesses. Exercise is shown to reduce auditory hallucinations, raise self-esteem, and improve sleep patterns and general behavior in schizophrenics (Faulkner et al 1999).

North et al (1990) reviewed the results of narrative and meta-analytic literature reviews investigating the effects of exercise on depression. The authors suggest that the positive impact of exercise on depression could be linked to changing people's daily routine, increasing interactions with other people, helping with weight loss and weight management, participating in

outdoor recreation and mastering difficult physical and psychological challenges. Biological factors may also explain, in part, the benefits of exercise on depression. Research shows that exercise promotes the secretion of neurotransmitters like serotonin (Ransford 1982, Morgan 1985). Also, evidence from animal studies suggests exercise stimulates the secretion of endogenous morphines and produces a state of euphoria (Pert et al. 1979). This review (Pert et al. 1979) also reported that the effects of an acute bout of exercise might be different than habitual exercise; however both have effective antidepressant effects. In general, subjects who were the most physically and psychologically unhealthy at the onset of the studies showed the greatest improvement following participation in an exercise program.

Exercise has been shown to produce a significant decrease in depression symptoms when compared with no treatment (Lawlor et al., 2001). Craft and Landers (1998) conducted a more recent meta-analytical review of studies that investigated the effects of exercise on depression and mental illness. All participants in these studies had a clinical diagnosis of depression, either as the primary or secondary disorder as the result of mental illness. Results from 30 studies showed an overall effect of -.72, indicating that individuals who exercised were less depressed than their sedentary counterparts. This analysis supports North's earlier findings that individuals who suffered more severely from depression benefited the most from exercise. Several other reviews have shown an inverse relationship between exercise and clinical depression scores (Martinsen 1994; Mutrie, 2000).

Past studies have shown that significant improvements in mood state can be achieved in clinically depressed patients following as little as five weeks of exercise training. Also, follow up assessments have indicated that treatment gains can be maintained for up to one year, especially when activity was maintained (Doyne et al., 1987; Greist et al., 1979). Most

impressively, exercise has been shown to be four to five times more cost-effective than traditional treatments for depression (Freemont et al., 1987; Greist et al., 1979).

Understanding the symptomology associated with this psychological disorder, questions arise regarding exercise compliance. The efficacy of this treatment intervention is questionable given that adherence to exercise may be problematic in this clinical cohort. Therefore, it is important to compare patient perceptions about the usefulness of traditional treatments (i.e. medication and psychotherapy) to perceptions of exercise therapy. Pelham and Campagna (1991) reported that psychiatric outpatients, who participated in a 12-week exercise program, expressed positive views of exercise. Moreover, antidepressant, mood-elevation, moderate anxiety-reduction, increased self-esteem and improved concentration were some of the described benefits. Martisen and Medhus (1989) found that patients in an exercise group ranked physical fitness training as the therapeutic element that had helped them the most. Patients in the control group ranked individual psychotherapy as most important. Collectively, these studies indicate that patients perceive exercise as a useful strategy in their rehabilitation. In Greist's study (1979) it was noted that the subject dropout rate for depressed runners was 11%. In contrast, healthy runners had a dropout rate of 30-70%. This gives strength to the theory that mentally ill individuals who reap medical benefits from exercise may be more likely to continue the activity.

2.4   TIMELINE OF RESEARCH

Research involving the impact of exercise on psychological variables is extensive, with over 1,000 reports published by 1984. Results of these studies show a mixture of outcomes. Many of

these studies were done on non- clinically diagnosed depressed patients, which may have had an affect on data outcomes (Tkachuk et al., 1999).

In 1981 Folkins and Sime concluded that many past articles regarding exercise and depression had significant methodological shortcomings. Only 15% were experimental, and 60% were pre-experimental in design. They recommended that future research should include experimental controls, accurate documentation of duration and intensity of exercise, and measurement of cardiovascular function.

Tkachuk and Martin (1999) reviewed more recent research dealing with exercise in the treatment of psychological disorders. A consistent finding was that exercise was an effective primary or adjunctive treatment for mild to moderate depression. Aerobic exercise has been found to be more effective than placebo control conditions and no-treatment conditions (Doyne et al. 1983; McCann et al., 1984; Sime 1987). Compared to psychotherapy, exercise has been shown to be equally effective in reducing depressive symptomology (Greist et al., 1979; Harris, 1987; Martinsen et al., 1985; Freemont et al., 1987, Craft et al., 1998). Conventional treatments, such as psychotherapy and medication, are costly and time consuming with many potential side effects. In comparison, exercise is relatively inexpensive and may have secondary, global health benefits.

2.5 THEORIES OF POTENTIAL MECHANISMS

There are many hypothesized mechanisms by which exercise is thought to influence mental health. Various biological, psychosocial and psychological models and theories have been developed that may help explain this proposed relationship. It is unlikely that any single

mechanism accounts for the exercise and mental health relation. Further research should address each of the following potential explanations.

2.5.1 Psychosocial/Psychological Mechanism Theories

Many proposed explanations by which exercise may influence mental health focus on mechanisms involving psychosocial or psychological rationales. Individual theories are described below.

2.5.1.1 Self Esteem Theory

There is an established link between depression and negative self-evaluation, including low self-esteem (Leary 1995; Roberts 1997) and self-efficacy (Bandura et al, 1999). It is hypothesized that effective depression interventions are successful in part, by improving self-evaluations. Research suggests that exercise increases overall self-esteem (Bosscher 1999; Ossip-Klein et al, 1989), exercise self-efficacy (McAuley et al 2000), body image (Bosscher 1999; McAuley et al., 2000) and physical self-worth (McAuley et al. 1997). This suggests that the antidepressant effects of exercise may be mediated by improved self-evaluations.

2.5.1.2 Mastery Theory

Sondstroem's (1978) model for physical activity assumes that involvement in activity increases physical ability. As individuals take pride in their bodies, they continue to exercise, thereby maintaining or increasing fitness. More physical activity leads to higher perceptions of physical ability and self-esteem, which results in even more attraction to physical activity; thus continuing a positive cycle.

2.5.1.3 Distraction Theory

The distraction theory was originally conceptualized by Bahrke & Morgan (1978) in a study that compared anxiety level between walking on a treadmill, meditating or resting in a chair. They found all three groups decreased levels of anxiety after treatment. They concluded that exercise could serve as a distraction from stressful stimuli. Later research showed that exercise distracts subjects from less favorable analytical thoughts (Just, 1997; Nolen-Hoeksema et al., 1993).

2.5.1.4 Behavioral Activation

Exercise may serve as a behavioral activation, which is a key component of Cognitive Behavioral Psychotherapy (Hollon 2001). Behavioral activation can be described as a therapeutic process that emphasizes structured attempts to encourage involvement with rewarding experiences. This produces corresponding improvements of mood and thought patterns. Improvement of mood leads to further interaction with experiences creating a decline in depressive symptoms.

2.5.1.5 Social Reinforcement

Others have theorized that beneficial effects of exercise are the result of social reinforcement that new participants may receive from the activity (Hughes 1984). Depression often leads to self-isolation. Isolation leads patients to miss out on positive social exchanges that could potentially relieve symptoms of their disease. Studies that incorporate group or supervised activity introduce a social component that would, for many clients, otherwise not exist.

2.5.2 Biological Mechanism Theories

Many proposed explanations by which exercise may influence mental health focus on biological mechanisms. Individual theories are described below.

2.5.2.1 Hyperthermic Model

The hyperthermic model suggests that the elevation in body temperature during exercise is the stimulus for relieving depressive symptoms. The alteration in psychological state is theoretically manifested in many responses that are managed by the hypothalamus. The belief that elevating body temperature can be therapeutic is longstanding. Research has shown that total body warming reduces muscle tension (DeVries et al, 1968). Later in a counterbalanced design, high intensity exercise and passive heating produced similar increases in slow wave sleep (relaxation effect) and that exercise may be a vehicle for those effects (Horne et al. 1983). Support for this theory has been mixed. There are many studies that have failed to show a positive relationship between temperature increase, exercise and psychological states. It is now thought that there are more comprehensive models that better explain the relationship between exercise and depression (Daley, 2002). Temperature and mood regulation are also postulated to be linked through the circadian rhythm system.

2.5.2.2 Endorphin Hypothesis

It is hypothesized that the euphoria that often accompanies an acute bout of exercise is caused by the production or release and subsequent binding of endogenous opiods to receptor sites in the brain (Steinberg et al., 1985). Research on rat brain tissue suggests that significant increases in opiate receptor occupancy occur after exercise (Pert et al., 1979; Wardlaw et al., 1980). In 1982, Christie and Chesher demonstrated that mice became addicted to swimming, if they exercised

regularly. Because of the inherent problems of examining endorphin receptor site occupancy in human brains, research has attempted to quantify endorphin levels after exercise in peripheral locations outside of the blood-brain barrier. Farrel (1989) suggested that exercise does not alter the blood-brain barrier in a way that allows peripheral endorphins to act directly upon the brain. The blood-brain barrier impedes the movement of opiate substances from the blood to the brain. Therefore, the exercise induced increase in beta-endorphins may not be responsible for the "euphoria" secondary to exercise. However, given the difficulty in measuring the concentration of endorphins in the cerebral spinal fluid, this theory is difficult to test.

2.5.2.3 Central Monoamines

Serotonin, noradrenaline and dopamine, have long been implicated in the etiology of depression (Delgado, 2000; Hirschfeld 2000). Current theories emphasize the complexity of the role of monoamines on the functioning of specific brain regions (Klimek et al., 1997) and in treatment of subsets of depressed patients (Charney 1998; Schatzberg 1998). If abnormal levels of monoamines are responsible for depression, it follows that depression could be treated by normalizing monoamines. There is experimental evidence that supports this hypothesis.

Animal studies have suggested that exercise affects the central nervous system noradrenaline levels and metabolism (Dunn et al. 1996) in general. They also show specific brain regions are associated with stress reactivity (Dishman 1997) and learned helplessness (Dishman et al. 2000). In humans, plasma data provide poor estimates of central nervous system (CNS) amine levels, however some studies did find that exercise is associated with increases in plasma monoamine levels (Chaouloff, 1997; Weicker 2001). Also, research indicates that exercise increases the concentration of free fatty acids and free tryptophan levels. This may lead

to an increased rate of serotonin synthesis by increasing CNS availability of amino acid precursors (Blomstrand et al. 1988).

2.5.2.4 Imbalance in Hypothalamic-Pituitary-Adrenal Axis (HPA) Functioning

Prior to describing the imbalance in the HPA axis, it is important to first explain the normal HPA functioning. Research is beginning to show that the HPA axis may be thought of as the body's energy regulator. It is ultimately responsible for controlling virtually all of the hormones, nervous system activity and energy expenditure in the human body, as well as modulating the immune system.

When the body is exposed to a stressor, the adrenal cortex releases cortisol. Multiple processes control the execution of cortisol release. First, the paraventricular nucleus (PVS) of the hypothalamus ultimately has control of the cortisol release. The hypothalamus will release corticotropin-releasing hormone (CRH) when a stress occurs. CRH then acts on the pituitary gland, which in turn, stimulates the release of adrenocorticotrophic hormone (ACTH). ACTH causes the adrenal cortex to release cortisol. CRH and ACTH are released in short pulses, each of which causes roughly a 15 minute sustained release of cortisol from the adrenal cortex with a half-life of approximately 100 minutes in the blood. Prolonged release of ACTH causes the adrenal cortex to increase in size, presumably to cope with the larger need for cortisol production. In contrast, long-term ACTH deficiency causes the adrenal cortex to shrink. Negative and positive feedback mechanisms ensure that cortisol production stays within certain physiological limits, depending on a person's current requirements and stress level (Tipperman 1980).

Similar to the central monoamine theory, imbalances in HPA axis functioning have been linked to depression. It is well established that depressed patients tend to have higher baseline

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basal cortisol levels (Akil et al, 1993; Lesch et al. 1988). Depression is generally marked by hyperactivity of the HPA axis and exercise training can lead to an attenuation of the axis response to stress. Dienstbier (1991) summarized the results of several studies by stating that exercise training resulted in physiological "toughness" marked by a delay in the HPA axis response to stress. Research in humans has been largely consistent with this model. Exercise-trained humans exhibit a hyposensitive HPA axis response to an exercise challenge (Wittert GA et al, 1996) and mental stress (Blumenthal et al. 1991).

2.5.2.5 Allostatic Load Theory
Allostasis was originally referred to by Sterling and Eyer (1988) who defined it as a physiological process involved in the adaptation to acute stress. It was described as the process of the internal environment adapting to meet the perceived and anticipated demand. McEwen (2002) expanded this theory to include the concept of a set point that changes because of the need to maintain homeostasis. The hormonal response to a threat may promote survival in the short term. However, if recovery from the acute event is incomplete, elevated resting levels of stress hormones may have a profound impact on psychological and physiological function resulting in an "allostatic load". This concept links the protective and survival values of acute responses to stress to the adverse consequences of chronic stress. Identification of techniques to lower the psychobiological allostatic load could provide insight into improved methods to prevent and treat mental disorders.

Many neurotransmitters, neuropeptides, and hormones have been linked to the acute psychobiological response to stress and the long-term psychiatric outcome. The roles of these neurotransmitters, neuropeptides, and hormones have been shown to be altered by stress and

have important functional interactions. They mediate neural circuits relevant to regulation of reward, fear conditioning, and social behavior.

Cortisol, Dehydroepiandrosterone, CRH, the locus coeruleus-norepinephrine system, neuropeptide Y, galanin, dopamine, serotonin, benzodiazepine receptors, gonadal steroids and estrogen are all implicated as being contributors, alone or through interaction, to resilience to stress. The hypothesis of allostatic load also states that the cumulative effect of modest dysregulation in multiple systems could be substantial, even if independently they have minimal impact on health.

2.6 DEFINING DHEA

Dehydroepiandrosterone, (DHEA) is a 19-carbon steroid hormone that is classified as a weak androgen (Herbert 1995). DHEA also is known as a prohormone, as it is a precursor of more potent sex hormones. DHEA, is found in the circulation in two forms, one unconjugated (DHEA) and the other conjugated as its sulphate ester DHEAS. DHEAS is present in a higher concentration than DHEA. DHEAS can be thought of as a reservoir and precursor of DHEA, since the interconversion rate between them is high (Longcope 1996). DHEAS concentrations are particularly high in the brain, (Baulieu et al, 1998; Dubrovsky 1997). DHEA and DHEAS can penetrate the blood brain barrier (Baulieu et al, 1998) and act as an inhibitor of gamma-amino butyric acid (GABA) receptors. More current research suggests that the only source of brain DHEAS may be from the periphery, specifically the adrenals and gonads (Compagnone, 2000).

DHEAS is the most abundant circulating steroid hormone in the body (Herrington 1998) and has a very high turnover rate, which suggests that it is a biologically active hormone. A physiological role for DHEAS remains unclear and a deficiency state has never been described (Ebeling 1994).

Metabolism of DHEA and DHEAS differ. DHEA circulates in the blood bound mainly to albumin with only minimal binding to globulin. A small amount of DHEA circulates freely. DHEAS, is more strongly bound to albumin, none is bound to globulin, and a small amount is free (Longcope 1996). DHEA, but not DHEAS, has a circadian rhythm related to the secretion of adrenocorticotrophic hormone (ACTH) (Liu, et al. 1990). DHEA falls considerably during three hours post awakening but remains stable after that. DHEAS has a long half-life in the circulation and exhibits little circadian rhythmicity (Goodyer at al., 1996).

It appears that DHEA and DHEAS levels provide a constant and stable index of underlying adrenal steroidogenic capacity (Wuest et al., 2000). Individual differences in levels of DHEA and DHEAS seem robust and consistent (Hucklebridge, 2005).

The effects of DHEA are complicated, as it is hard to assess whether actions can be attributed to DHEA, its metabolites, or a combination of both. DHEA effects appear to be gender specific. In addition, DHEA may differentially affect women based upon their menopausal status. The age of person also has an impact on the action of DHEA (Regelson, 1994).

In humans, DHEA and DHEAS levels in the fetus are high, but the secretion decreases soon after birth and remains low until the adrenarche (Hopper, 1975) when it peaks around ages 20-25 years. The concentrations of DHEA and DHEAS then decline at a rate of about 10% per decade to values of 20% to 30 % of peak at approximately 70 to 80 years of age. This age

related decrease has lead clinicians to promote DHEA as therapy for the cognitive impairment associated with aging. Results of clinical trials, which lasted from 3 to 12 months, suggested such a role was possible. (Morales, et al 1994; Morales, et al 1998)

Browne, et al (1992) suggested that DHEA and/or DHEAS may act as antagonists of glucocorticoids. The finding that healthy persons with high ACTH-releasing hormone and cortisol responses to exercise exhibit higher baseline levels of DHEA and DHEAS suggests that DHEA might enhance the hypothalamic-pituitary-adrenal response to exercise. (Deuster 2005)

2.6.1   DHEA/DHEAS AND MENTAL ILLNESS

DHEA has been thought to play a role in multiple medical and psychological disorders. Levels of DHEA have been shown to be lower in individuals with type II diabetes, coronary artery disease and rheumatoid arthritis (Masi, 1995). Similarly, low levels have also been noted in individuals with chronic fatigue syndrome (Scott 1999). DHEA has been shown to be low in subjects who suffer from depression (Michael, 2000; Wolkowitz, 1997; Goodyer 1996), anorexia (Zumoff et al, 1983) and schizophrenia (Oades 1994). As a generalization, reduced levels of DHEA have been found in most of those disorders thus far been reported (Figure 1), although that finding does not prove that it is causal (Corrigan, 2002).
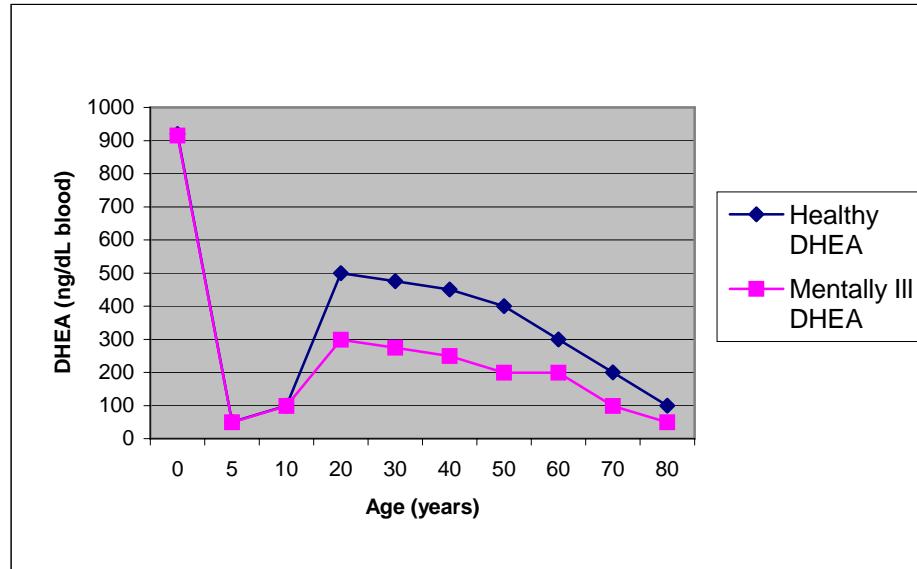
Figure 1 DHEA in Healthy vs. Mentally Ill Subjects

Yen, et al, reported an increase in physical and psychological well being associated with DHEA supplementation (Yen, et al. 1995). However, most of the evidence for supplementation is extrapolated from animal studies and there is little consensus as to the benefits of DHEA replacement therapy in humans (Hinson 1999). Physical and psychological improvement in 67% of men and 84% of women has been found secondary to DHEA supplementation. Improvement in memory and cognitive functions has been suggested, but results in general have been somewhat disappointing (Barrett-Connor, 1994; Rudman 1990). It still remains to be proven if the changes secondary to DHEA supplementation are beneficial to the aged population (Huppert 2000). DHEA and DHEAS levels decline in Alzheimer's disease unrelated to age (Sunderland, et al. 1989) but this decline is not necessarily linked to the cause of the disease (Schneider 1992).

DHEA may modulate insulin output in men and women (Mortola, 1990; Nestler, 1992) and therefore may have an antidiabetic effect (Nestler, 1992). Men with low levels of testosterone may also have low levels of DHEAS and insulin resistance (Haffner, 1994).

23

Postmenopausal women given 50 mg of DHEA a day showed enhanced insulin sensitivity and lower blood triglycerides (Casson, 1993).

Coyle and Manji (2002) have hypothesized that cellular resilience may be limited, which leads to neuronal vulnerability to ischemia and hypoglycemia. This hypothesis is a result of the neuronal decline associated with stress and glucocorticoids. This may help unravel the mystery of mood episodes and recurring stress, as seen in bipolar subjects. DHEA, as a known antiglucocorticoid, naturally may reverse the affects of glucocorticoids on the human system.

2.6.2   DHEA AND EXERCISE

Previous studies generally have shown that DHEA and DHEAS levels increase in response to exercise. Significant elevations in DHEA have been found in women who have completed a 10-mile run (Baker 1982) and following treadmill running (Keizer 1987). In 1997, Johnson et. al saw an elevation in DHEA with a 30 minute treadmill exercise bout at 80% of VO2 max in postmenopausal women .

Dressendorfer et. al (1991) found that DHEA levels increased, although not significantly, over a 15 day endurance bike race. The subjects were all trained, healthy individuals and DHEA was measured after 20 hours of recovery. During marathon running, healthy individuals showed a non-significant rise in DHEA levels as well (Ponjee, 1994). Baker's study (1982) suggested that DHEA concentrations are higher among trained individuals when compared to untrained controls. Cumming and Rebar (1983) documented increases in DHEA concentrations in untrained and trained women in response to a graded exercise test.

In 2004, Tremblay studied the effects of acute bouts of aerobic and resistance exercises on DHEA in trained and sedentary individuals. This study found that DHEA increased with

resistance and aerobic exercise, although the response was greater after resistance exercise than a run. The exercise that elicited the longest levels of DHEA elevation proved to be resistance exercise in resistance-trained subjects. This contradicts Hakkinen's findings (2000) that saw no change in DHEA after resistance exercise in elderly men.

2.6.3 RESPONSES OF DHEA AND CORTISOL DUE TO MEDICATION

Bipolar subjects are rarely clinically diagnosed and non-medicated. This issue forces investigation of medication on DHEA. In a study done by Assies et al (2004), DHEA and DHEAS seemed to be a more sensitive indicator of depression and symptom severity than cortisol in medicated but still clinically depressed patients. This indicates that medication may have little or no effect on DHEA and DHEAS production. However, significant and strong inverse associations between DHEAS and the number but not with any specific type of medications have been observed. (Ravaglia et al., 2002) Therefore, medications could be a confounding factor in the present research. Since the number of medications may influence baseline DHEAS levels, it follows that medications could have an impact on the amount of DHEAS change in response to exercise.

2.7 SUMMARY

Exercise has long been used as a means of preventing disease and promoting health and well-being. A great deal of scientific evidence supports exercise as being beneficial to mental health. These benefits include a reduction in anxiety, depression and negative mood. There are significant reports' showing that exercise improves self-esteem and cognitive functioning, yet, exercise is

seldom recognized by mainstream mental health services as an effective intervention in the care and treatment of mental health problems, specifically bipolar disorder. Exercise may well be an important but neglected intervention in mental health care.

Many studies have shown positive changes in mood state in response to exercise. However the causes of these improvements in mood remain unclear. While many of these studies suggest that there could be a physiological reason for the change, psychological factors such as increased socialization or goal accomplishment cannot be excluded as viable explanations. To our knowledge, no study has examined the change in DHEA or DHEAS in response to exercise in mentally ill subjects. If DHEAS levels in bipolar subjects are shown to increase following sub-maximal exercise, a profound impact in the treatment of mood disorders could be expected. Ultimately, it is hoped that this inquiry may lead to the incorporation of an exercise routine as part of the treatment for bipolar patients. Exercise, unlike many medications, has no negative side effects and a wide range of positive outcomes when prescribed and applied correctly.

3.0   METHODS

A review of related literature has demonstrated the following: 1) bipolar disorder is an economic and medical concern in the United States today, 2) current pharmacological treatment and behavioral therapy for bipolar disorder is not refined to a perfect solution, 3) exercise has been shown to reduce symptoms of various types of mental illness 4) several theories have linked Dehydroepiandosterone (DHEA) and its sulphate ester (DHEAS) to depression and other mental disorders 5) an acute bout of exercise may change DHEAS levels which may cause a reduction in the depression symptoms seen in bipolar disorder.

Despite the findings that exercise may play a significant role in reducing the symptoms of bipolar disease, clinicians rarely include exercise as part of their treatment plan. The goal of this investigation is to better understand the impact of an acute bout of exercise on DHEAS levels in bipolar patients. This information may be the basis for the use of aerobic exercise instead of or in conjunction with the current standard treatment, which typically involves prescription medications. Information generated in this investigation may lead to improved treatment outcomes, decreased costs associated with the disorder, and improved health of patients.

3.1   SUBJECT POPULATION

Male and female outpatients, aged 18-65 years who were participants in the Bipolar Disorder Center for Pennsylvanians (BDCP) and who had been diagnosed with Bipolar Disorder served as subjects for this investigation.   The racial, gender, and ethnic characteristics of the subject population reflected the demographics of Pittsburgh and the surrounding areas and/or the patient population of the University of Pittsburgh Medical Center.   No exclusion criteria were biased on race, gender, or HIV issues.

Patients were asked by their primary BDCP psychiatrist to participate in this study if the psychiatrist believed an exercise session would be appropriate for that individual.   Some participants of the BDCP suffered from other mental co-morbidities, such as panic disorder or severe anxiety.   The treating psychiatrist concluded this study to be over stimulating and inappropriate for such patients.

Appropriate physician referrals were forwarded to the primary investigator, who contacted potential subjects to discuss participation in the study.

When a power analysis was run, it was determined that 27 subjects were needed to achieve statistical significance at $p < .05$ with a medium effect size.

3.1.1   Inclusion Criteria

1. Provided written informed consent before enrollment and any study-specific procedures were conducted.
2. Male and female patients between 18-65 years of age.
3. Met DSM-IV criteria for Bipolar I or Bipolar II disorder.
4. Outpatient status.

3.1.2 Exclusion Criteria

1. Women who were pregnant.

2. Previous occurrence of myocardial infarction.

3. At time of study receiving Beta Blocker treatment.

4. Type I or Type II diabetic.

5. Unable to perceive performing aerobic exercise of 70% $\pm$ 5 beats/min of age predicted heart rate maximum for a minimum of 30 minutes.

3.1.3 Recruitment Procedures

Subjects were referred to the study by their BDCP psychiatrist (Drs. Denko, Spiker, Friedman, or Fagiolini) if it was believed that their patient would tolerate exercise. No cold calling occurred. The primary investigator (PI) discussed the research project with the potential subject. If he/she expressed interest in the study, the PI read the prescreening script (Appendix A) to determine participant eligibility. Next, the investigator asked the potential subject the seven questions listed on the Physical Activity Readiness Questionnaire (PAR-Q) (Appendix B). In addition to the PAR-Q, all potential subjects completed a medical history questionnaire (Appendix C). Both forms were helpful in determining participant safety and eligibility. Lastly, a medical clearance (Appendix D) was signed by all subject's primary care physicians which indicated all subjects were deemed safe to participate in the exercise protocol.

The Principal Investigator obtained an informed consent (Appendix E) after the objectives, procedures, and a clear explanation of the risks and benefits of the study were presented. The voluntary nature of research participation was clearly explained, as well the alternatives for non-

research treatment. A copy of the signed informed consent form was given to the patient and the original placed in the subject's research file. All files were kept in a secured cabinet to maintain confidentiality. All procedures were approved by the Biomedical Institutional Review Board at the University of Pittsburgh prior to the start of this study.

3.2   EXPERIMENTAL DESIGN

This was an experimental trial with 27 participants. Baseline measurements included body weight, height, body composition, waist to hip ratio, serum DHEAS, resting blood pressure and resting heart rate. All medications taken by the subject were recorded. This trial consisted of subjects walking or jogging on a motor driven treadmill for 20 minutes at an intensity that resulted in a heart rate response of 70% ±5 bpm of his/her age-predicted maximal heart rate. Body composition and body fat distribution analysis was used to help inform the subject of his/her current health status and assisted in describing this cohort. Figure 2 describes the flow of testing procedures.

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┌─────────────────────────────────────────────────────────────┐
│   Patient referral from Dr. Friedman, Denko, Spiker, or Fagiolini │
└─────────────────────────────────────────────────────────────┘
                              │
                              ▼
┌─────────────────────────────────────────────────────────────┐
│   PI read pre-screening script (Appendix A) to determine subject │
│                          eligibility                          │
└─────────────────────────────────────────────────────────────┘
                              │
                              ▼
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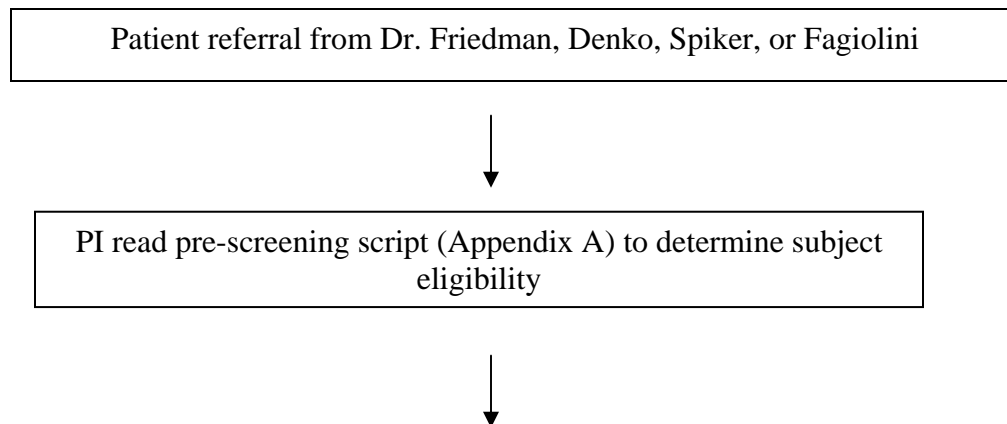
Subjects completed PAR-Q (Appendix B) and Medical History Questionnaire (Appendix C)

Medical Clearance (Appendix D) was obtained from subject's primary care physician

Fitness Test was scheduled

Client arrived on scheduled day to Human Energy Research Lab, Trees Hall, University of Pittsburgh

Subject read and signed the IRB approved informed consent (Appendix E)

Experimental procedures were explained (Explanation of Testing Procedures, Appendix F) and any subject questions answered

Likert 7 point scale for well-being was administered (Appendix G)

Anthropometric, skinfold, and circumference measurements taken

↓

2 tubes of blood drawn with one standard venipuncture of an anticubital vein

↓

Subject were fitted with a Polar Heart Rate

↓

Resting heart rate recorded (Data Collection Form, Appendix H)

↓

Minutes 0-2: walk at 2.2 mph/ 0% grade

↓

Minutes 2-5: acquisition of heart rate range by increasing speed and/or grade

↓

Minutes 5-25: exercised at 70% $\pm$ 5 bpm of age predicted heart rate max, BP measured every 5 minutes, heart rate measured every minute

↓

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┌─────────────────────────────────────────────────────────────────┐
│      Minutes 25-30: returned treadmill to 2.2 mph, 0% grade.      │
└─────────────────────────────────────────────────────────────────┘
                                │
                                ▼
┌─────────────────────────────────────────────────────────────────┐
│  Subject moved to a seated position until heart rate and blood    │
│  pressure normalized.                                             │
└─────────────────────────────────────────────────────────────────┘
                                │
                                ▼
┌─────────────────────────────────────────────────────────────────┐
│     Second Likert 7 point scale, identical to the first,          │
│     administered                                                  │
└─────────────────────────────────────────────────────────────────┘
                                │
                                ▼
┌─────────────────────────────────────────────────────────────────┐
│     Second blood draw, identical to the first, conducted 5        │
│     minutes after the treadmill test was terminated.              │
└─────────────────────────────────────────────────────────────────┘
                                │
                                ▼
┌─────────────────────────────────────────────────────────────────┐
│     Subject were offered juice and/or water and PI reviewed       │
│     Health Summary (Appendix I)                                   │
└─────────────────────────────────────────────────────────────────┘
                                │
                                ▼
┌─────────────────────────────────────────────────────────────────┐
│     Subject paid $25 stipend and escorted out of the building     │
└─────────────────────────────────────────────────────────────────┘
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Figure 2. Flow of Testing Procedures

3.3   PRE-TEST INSTRUCTIONS

Prior to scheduling the exercise test, the investigator read the prescreening evaluation script to the potential subject (Appendix A). This script introduced the investigator, screened the subject for inclusion and exclusion criteria and also informed the subject of the exercise testing protocol. The subject answered the Physical Activity Readiness Questionnaire (PAR-Q) questions (Appendix B) and completed the medical history questionnaire (Appendix C). If the subject met the inclusion criteria without meeting any exclusion criteria, an exercise test date was scheduled for a time in which the subject would have been awake for a minimum of 3 hours. Next, the PI asked the subject to maintain their regular schedule of eating and medication, asked them not to exercise the day prior to or the day of the exam, and asked them not to consume alcoholic beverages the day prior to or the day of the exam. The PI reminded them to wear comfortable exercise clothing to the test and to drink plenty of water the day of the exam.   Prior to the scheduled exercise test date, the PI obtained a medical clearance from the subject's primary care physician (Appendix D).

3.4   ASSESSMENT COMPONENTS (DATA COLLECTION FORM APPENDIX H)

3.4.1   Hours of awake time

The subject was asked what time he/she awoke on the scheduled test date. The starting time of test was recorded. This was done to ensure the subject has been awake for three or more hours, as requested during the prescreening evaluation. All subjects indicated they had been awake for three or more hours prior to the appointment.

3.4.2   Weight

Subjects wore shorts and a t-shirt. Subjects were instructed to remove their shoes, jewelry, and all objects from their pockets prior to the measurement of body weight. Body weight was measured using a Tanita Bioelectrical Impedance Analysis (BIA) Scale (TANITA TBF-300A Body Composition Analyzer, Arlington Heights, IL).

3.4.3   Height

Height was measured using a calibrated, scale mounted stadiometer (Detecto, Webb City, MO model number 3P7044). Subjects were instructed to remove their shoes and to stand upright with their back and heels of their feet against the scale.

3.4.4   Body Composition

An estimate of body composition was determined using a Tanita Bioelectrical Impedance Analysis (BIA) Scale (TANITA TBF-300A Body Composition Analyzer, Arlington Heights, IL). The benefits of measuring body composition via BIA include ease of use and speed of measurement.

3.4.5   Regional Adiposity

Girth measures of the waist and hip were assessed as described by the American College of Sports Medicine (Lippincott Williams and Wilkins, 2005).   The waist circumference measurement was obtained at the smallest portion of the waist above the umbilicus. The largest

circumference of the hips and buttocks was used as the denominator in the ratio. A Gulick fiberglass measuring tape with a calibrated tension device was used for all circumference measurements. The waste to hip ratio has been shown to correlate with health related risk factors in men and women (Depres, et al 1995).

3.4.6 Resting Heart Rate

A Polar Heart Rate monitor (model A3, Woodbury, NJ) was used to determine resting heart rate. The back of the heart rate sensor was moistened and applied directly to the skin at the xiphoid process of the sternum. The monitor was affixed to the subject with an elastic band to ensure a proper skin to sensor interface. The Polar Heart Watch (part of the monitor unit, model A3) displayed the subjects' heart rate and was worn by the subject at his/her wrist. Resting heart rate was recorded after the subject has been seated for 3 minutes.

3.4.7 Blood Chemistry

The blood draws were taken from an antecubital vein by a certified phlebotomist while the subjects are in a seated position. Two tubes of blood were drawn with a Vacutainer butterfly 23-gauge needle (3/4"), one, a 7.5 ml serum separator tube and the other a sterile 2 ml vacutainer that was used to assess Hematocrit.

Plasma volume changes were determined from the hematocrit values to control for hemoconcentration that could alter hormone levels. A 2 ml sterile vacutainer was used to collect blood for the assessment of Hematocrit. A capillary tube was inserted into the blood sample and blood was drawn into the tube until the graduation mark had been reached. The capillary tube was inserted into critoseal to seal one end of the tube. Two capillary tubes were obtained for each

sample and spun in a centrifuge for 5 minutes. Hematocrit was calculated using the average of the two measures. (Knowlton et al, 1990)

The serum separator tubes were spun for 30 minutes. Once the serum was successfully separated, the serum was poured into a storage vial and the blood cell, or solid portion of the sample, was disposed of in a biohazard container. DHEAS was analyzed at The University of Kentucky's General Clinic Research Center (GCRC).

The GCRC asked for all samples to be delivered at the same time. Therefore, all serum samples were collected and frozen at –80 degrees C at the University of Pittsburgh's GCRC located in Montifiour Hospital until data collection was complete. Upon completion of data collection, the samples were sent to the University of Kentucky for analysis in a single batch.

The basic principle of DHEAS (dehydroepiandrosterone sulfate) analysis involved a solid-phase, competitive chemiluminescent enzyme immunoassay. Serum was used and the usual precautions for venipuncture were observed. Specimens were stored at –80 degrees C until analyzed.

3.4.8   Exercise session

All exercise tests were conducted in the Human Energy Research Laboratory at the University of Pittsburgh by a qualified exercise physiologist. Room temperature was maintained between 65 and 72 degrees Fahrenheit. A target heart rate range corresponding to 70% of the subject's age predicted heart rate max was calculated. The subject was given a brief orientation to treadmill walking. All subjects initially walked on The Trackmaster (model number TMX426C; Newton KS) treadmill at 2.2 mph with zero percent grade for 2 minutes. Next, the exercise physiologist titrated the treadmill to the desired speed and grade of the subject that elicited the appropriate

heart rate response (70% of age predicted heart rate maximum $\pm$ 5 bpm). The subject was asked to choose a faster pace or increased incline to increase intensity. Heart rate was displayed by the Polar Heart Watch and monitored every 15 seconds to determine when the subject had reached the target heart rate zone. The correct training speed and grade was identified by the beginning of the 5th minute of exercise. If the correct load had not been selected by the 5th minute, the 20 minutes of exercise did not begin. Instead, the next few minutes were used to find the correct training load to elicit the required heart rate. Once the target heart rate has been attained, the 20-minute exercise bout began. The client continued to exercise at this pace for 20 minutes. Heart rate was monitored and recorded every minute. If a subject's exercising heart rate became out of the prescribed range, the investigator changed the speed and/or incline of the treadmill as desired by the client until the heart rate was appropriate. Every five minutes a blood pressure measure was taken to enhance subject safety. ACSM criterion for termination of an exercise test was used to establish test end points if necessary (Appendix J). After the subject has exercised in their target heart rate range for 20 minutes, the exercise physiologist slowed the treadmill to 2.2 mph and decrease the grade to 0%. The subject walked at this stage for 5 minutes. The subject was then moved to a seated position and monitored every minute until blood pressure and heart rate normalized.

3.4.9 Post-Exercise Blood Analysis

Within five minutes post completion of the cool down phase, a second blood draw, identical to the first, occured. Blood was analyzed for DHEAS and Hct as previously described.

3.4.10 Health Summary

Upon completion of the exam, the primary investigator reviewed the exercise test results with the subject.   The PI explained and answered any questions the subject had regarding their information. (Appendix G)

3.4.11   Likert 7 point scale for perception of global well-being (Appendix F)

Before the exercise session began and concurrent with the signing of the informed consent form and testing instructions, the subject was asked to rate his/her perception of well-being on a 7 point Likert scale. This scale consisted of seven options. The subject rated how they felt at that moment in time. The scale ranged from "severely depressed" to "excessively happy". After the exercise session was over and health summary form was given, the subject was asked to rate his well-being again. The purpose of this is to assess any change in perception of well-being that may have been correlated with the exercise bout.

3.5   STATISTICAL ANALYSIS

All analyses were performed using Statistical Packages for the Social Sciences (SPSS version 7.5). The type I error rate was controlled at 5% for all analyses ($p < 0.05$). A Repeated Measures ANOVA was used to test for main effects for exercise and gender. A two tailed, dependant T-Test was used to analyze changes in perceptions of global well-being. Lastly, a Pearson Correlation was used to assess any potential relationship between DHEAS changes and changes in perceptions of global well-being.

4.0 RESULTS

The primary aim of this study was to examine the effect of an acute bout of aerobic exercise on DHEAS in clinically diagnosed bipolar subjects. A secondary aim was to explore changes in perceptions of global well-being following exercise and examine the relationship between improvement in perceptions of well-being and DHEAS. Male (n=13) and female (n=13) outpatients diagnosed with bipolar disorder served as subjects for this pilot investigation. All subjects were participants in the Bipolar Disorder Center for Pennsylvanians (BDCP) and were between the ages of 18 and 65 years. The racial, gender, and ethnic characteristics of the subject population reflected the demographics of the University of Pittsburgh Medical Center.

No participant reported suffering a myocardial infarction or the presence of diabetes mellitus. No subject was receiving Beta Blocker treatment. All prospective subjects indicated a perceived ability to perform the intended exercise protocol. A total of 27 subjects were tested, however one female subject had an immeasurable DHEAS score. Data from this subject were not included in the statistical analysis. Characteristics of the 26 subjects are presented in Table 1.

Table 1 Subject Characteristics (Mean $\pm$ standard deviation)

Gender	Age (years)	Height (cm)	Weight (kg)	Body fat (%)
Male (n=13)	45.2 ± 13.0	176.5 ± 5.6	88.9 ± 14.9	25.1 ± 2.9
Female (n=13)	39.5 ± 9.2	167.4 ± 6.4	84.7 ± 28.6	35.3 ± 11.4

4.1 DHEAS RESULTS

A Repeated Measures ANOVA revealed significant main effects for exercise (p=0.013) and gender (p=0.047). The exercise by gender interaction was not significant. The summary ANOVA table can be found in Appendix K.

4.1.1 DHEAS and Exercise

Levels of DHEAS rose from a baseline value of 187.6 ± 152.2 ug/dl to 196.2 ± 158.7 ug/dl following exercise. These results are presented in Figure 3. Individual DHEAS responses can be found in Appendix L.
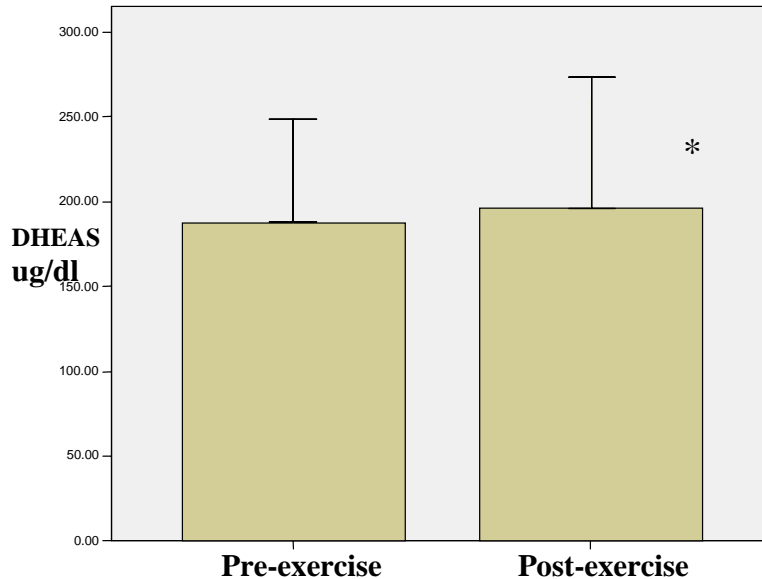
Figure 3. DHEAS before and after a 20-minute bout of treadmill exercise at a intensity of 70% of age predicted maximal heart rate.

* Significantly different (p=0.013) from pre-exercise

A Bland-Altman plot of DHEAS levels pre and post exercise compared to individual change in DHEAS levels is presented in Figure 4. The solid line indicates mean DHEAS change from pre to post exercise. The dotted lines represent $\pm$ two standard deviations.
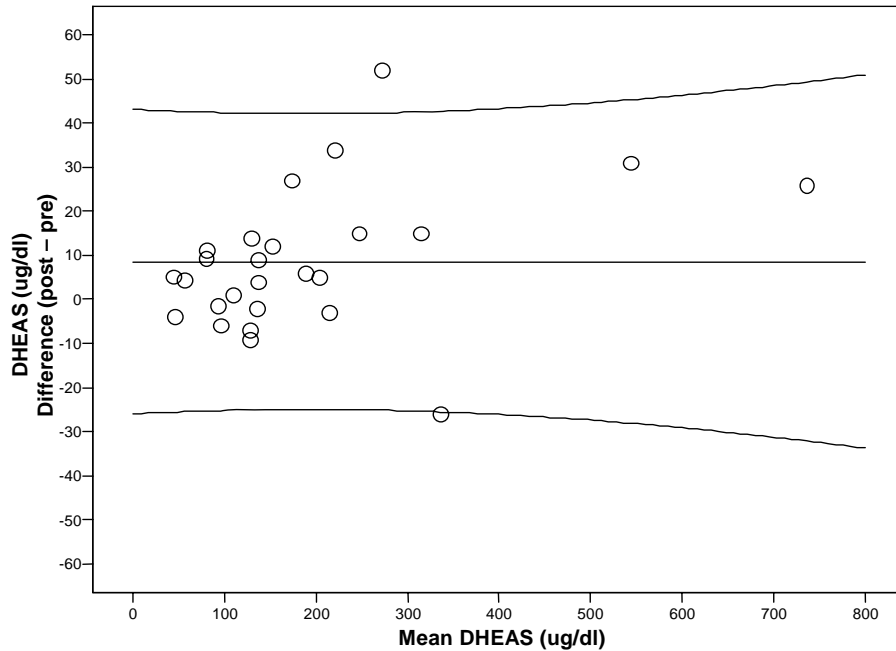
Figure 4 DHEAS changes compared with overall mean DHEAS levels

4.1.2   DHEAS and gender

Men displayed a significantly (p=0.047) higher level of DHEAS at baseline and after exercise when compared to females (Figure 5). There was no statistically significant difference in the amount of change in DHEAS between the men (10.0$\pm$19.5 ug/dl) and women (7.1$\pm$12.1 ug/dl).

Figure 5. DHEAS for male and female subjects before and after a 20-minute bout of treadmill exercise at an intensity of 70% of age predicted maximal heart rate.

*Significantly different (p=0.047) from female

4.1.3   DHEAS change and age

Results from the correlation analysis revealed a non-significant (p=0.097) negative correlation (r=-0.33) between change in DHEAS in response to 20 minutes of treadmill exercise at 70% of age predicted heart rate maximum and age.

4.2   PERCEPTIONS OF GLOBAL WELL-BEING AS MEASURED BY A 7 POINT LIKERT SCALE

A seven point Likert scale (Appendix G) was used to assess perceptions of global well-being before and after exercise. Reports of well-being significantly ($p<0.05$) increased from a pre-exercise score of 4.4 ± 1.3 to 5.2 ± 0.9 post-exercise. Figure 6 depicts perception scores before and after the exercise session.
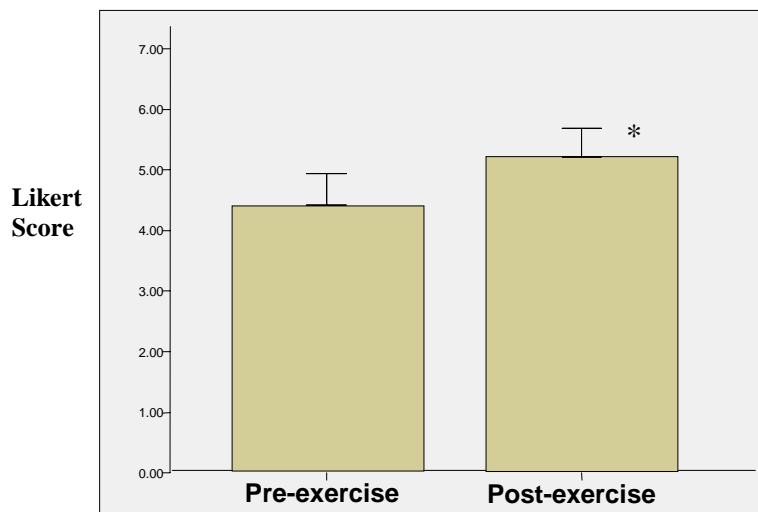
Figure 6. Perceptions of global well-being scores before and after 20 minutes of treadmill exercise at an intensity of 70% of age predicated maximal heart rate.
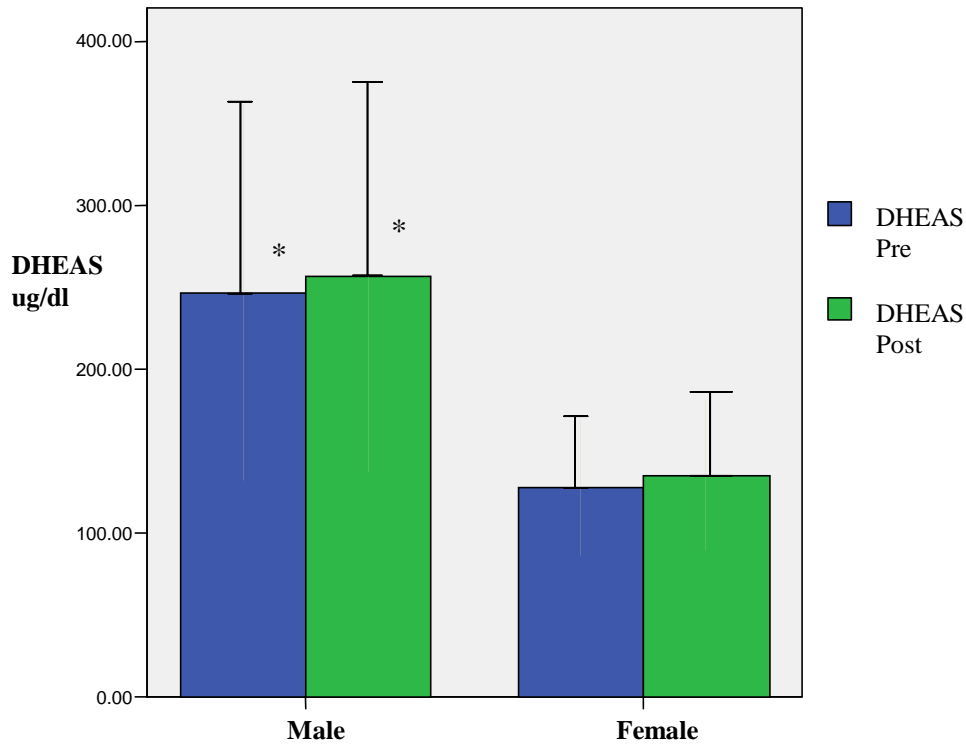*Significantly different ($p<0.05$) from pre-exercise

Figure 7 depicts individual changes in perceptions of global well-being as a result of exercise compared to pre-exercise perceptions. Fifteen subjects reported an improvement in well-being and ten subjects reported no change. The subject with the highest pre-test well-being score (subject #13) reported normalization in well-being status. This figure reveals a trend of greater improvement in perceptions of well-being in subjects who reported low (<4) pre-exercise perceptions of well-being.
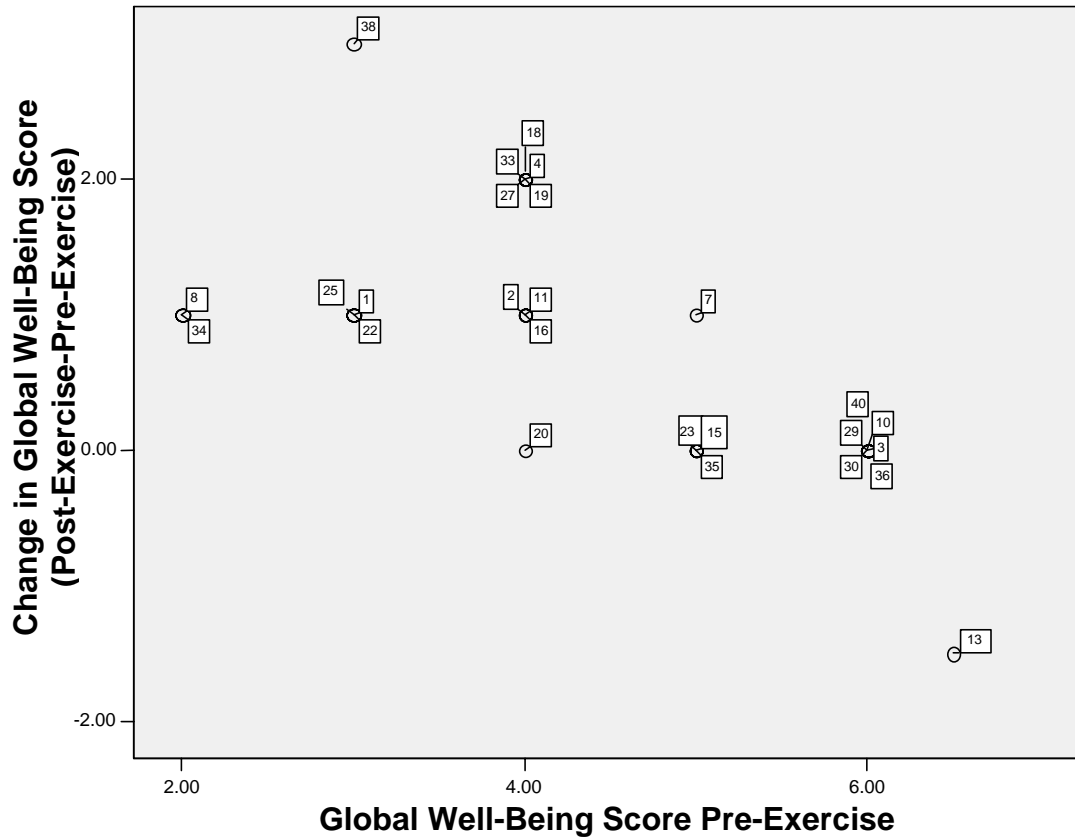
Figure 7 Individual change in perceptions of global well-being post-exercise compared to pre-exercise scores.

Note: Numbers correspond to individual subjects

4.2.1 Perceptions of global well-being and age

Results from the correlation analysis revealed a non-significant (p=0.43) negative correlation (r=-0.14) between change in perceptions of global well-being following exercise and age.

4.2.2 Perceptions of global well-being and gender

No significant difference was found between genders in the change of perceptions of global well-being following exercise (p=0.50). Prior to exercise, males had a Likert Score of 4.7±1.1 on the 7-point scale. This increased to 5.3±0.8 after the exercise bout. Females reported a baseline

Likert score of 4.2±1.5. This increased to 5.1±1.2 after undergoing the exercise protocol. The

results are presented in Figure 8.
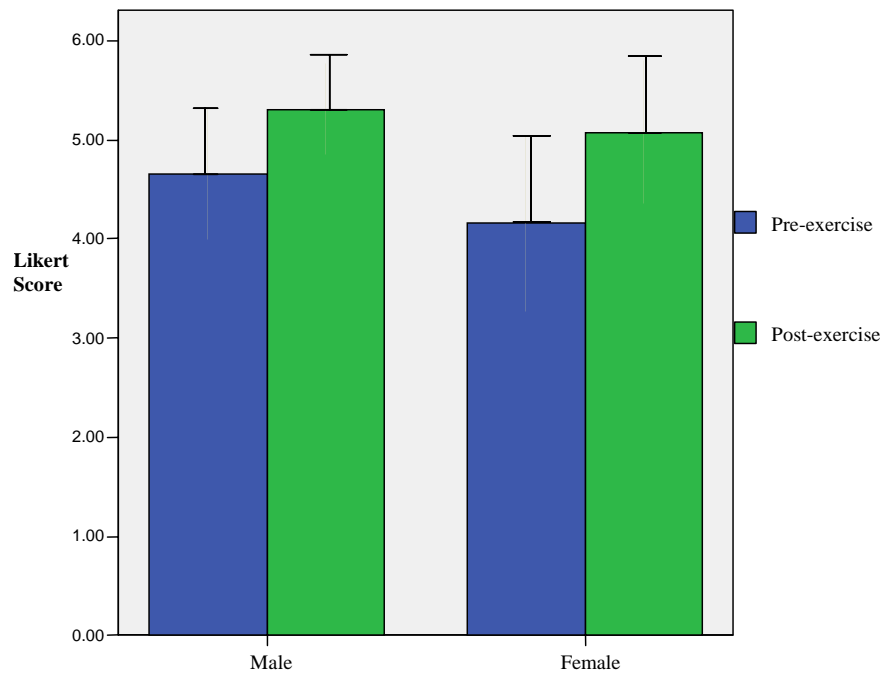
Figure 8. Scores in male and female global well-being before and after a 20-minute bout of treadmill exercise at a intensity of 70% of age predicted maximal heart rate.

4.3   RELATION BETWEEN CHANGES IN LIKERT SCORES AND DHEAS

As previously discussed, there was a significant improvement in perceptions of global well-being

after 20 minutes of aerobic exercise. In addition, DHEAS scores significantly increased after

subjects completed the exercise protocol.   However, correlation analysis revealed a non-

significant (p=0.38) relation (r=0.18) between these variables.

5.0   CHAPTER 5

The primary purpose of this study was to examine the effect of a 20 minute aerobic exercise bout performed at an intensity equal to 70% of age predicted maximal heart rate on DHEAS in patients diagnosed with bipolar disorder. In addition, the effect of the exercise session on perceptions of global well-being was examined. These findings are discussed below.

5.1   DHEAS CHANGE WITH EXERCISE

Previous studies have shown an increase in DHEA, and its sulfate ester DHEAS, in healthy subjects after performance of an aerobic exercise bout (Baker 1982; Cumming and Rebar 1983; Keizer 1987; Johnson et. al 1997). To date, this is the first study to document a similar outcome in clinically diagnosed bipolar subjects, as results indicate a significant increase in DHEAS after a 20-minute, moderately intense exercise session in this population.

Although a significant increase in DHEAS was found following exercise, it is important to note that not all subjects responded with an increase in DHEAS post-exercise. In this study, DHEAS decreased in response to exercise in equal amounts of men (n=4) and women (n=4). Three of the four women that produced a decline in DHEAS were between the ages of 42-44 years and one was 20 years old. The male subjects in whom a decrease in DHEAS was observed, ranged in age from 45-61 years.

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It is noteworthy that 3 of the 8 subjects who had a decrease in DHEAS indicated the existence of thyroid disease on their medical clearance form. In contrast, only one subject with self-reported thyroid disorder had an increase in DHEAS. Ravaglia et al. (2002) found a significant association between low DHEAS levels and decreased thyroid function, so there is potential for thyroid disorders to adversely effect DHEAS production. It is also important to note that the lone subject who began his exercise bout as "excessively happy or manic" had both a decrease in DHEAS and a normalization in perceptions of well-being.

Past research has shown that DHEAS decreases in healthy individuals with age (Chiu 1999), increases in response to exercise (Baker 1982, Keizer 1987, Johnson 1997) and is significantly higher in age-matched men compared to women (Perrini et. al 2005, Mazat et al, 2001). The present study revealed similar results when comparing DHEAS responses in men and women. Men had significantly higher levels of DHEAS pre and post exercise when compared to women. However, the increase in DHEAS as a result of the exercise session was similar between women and men.

The Bland-Altman plot (Figure 4) of baseline DHEAS levels compared with individual DHEAS changes suggests that individual's with high mean levels of DHEAS (i.e. $\geq$200 ug/dl) tend to have a greater magnitude of DHEAS response with exercise.

5.2   CHANGES IN PERCEPTIONS OF GLOBAL WELL-BEING WITH EXERCISE

The positive effect of exercise on the mood of depressed individuals has been well documented (Greist et al. 1979, Pert et al. 1979, Morgan et al. 1988, North et al. 1990,). The present study showed similar improvements in perceptions of global well-being following exercise.

Of the 26 subjects, 10 reported no change in perceptions of well-being after exercise. Fourteen of the subjects reported that exercise improved global well-being by one to two points on the 7-point scale and one subject reported improvement of 3 points. In contrast, one subject reported a decrease in global well-being after exercise. This single subject reported that his well-being changed from between moderately happy (6) and excessively happy or manic (7) to mildly happy (5). This subject was one of the eight participants whose DHEAS decreased after the exercise bout. While a decline in DHEAS cannot be proven as a cause for mediation of mania, it may become a useful focal point of future investigations.

5.3   RELATION BETWEEN LIKERT SCORE AND DHEAS CHANGE

The present study produced results similar to previous research, which suggests that acute exercise increases serum DHEAS levels as well as improves depressive symptoms. It is interesting to note that the subjects in the present study who demonstrated the greatest improvement in perceptions of global well-being were not the subjects that produced the greatest increase in DHEAS. Correlation analysis revealed a non-significant (p=0.38) relation (r=0.18) between changes in DHEAS and perceptions of global well-being. Therefore, although DHEAS did increase significantly with exercise, it did not appear to be solely responsible for improvements in perceptions of well-being.

Imbalances in HPA axis functioning have been linked to depression. It is well established that depressed patients tend to have higher baseline basal cortisol levels (Akil et al., 1993; Lesch et al., 1988). Observations of abnormal cortisol levels in patients with depression were first noted as early as the late 1950's (Michael et al., 1963). These observations have been

consistently replicated (Webster et al., 2000; Wolkowitz 1994, Lauc et al., 2004). Subsequent studies have shown that HPA hyperactivity occurs in sufferers of several mood disorders. Hypersecretion of Corticotropin-releasing hormone (CRH) causing hypercortisolemia may be a result of impaired feedback mechanisms. While prolonged increases in cortisol levels could lead to changes in mood, a causal relationship has not firmly been established. Elevation of cortisol through a prolonged stress response is only one factor that may be related to the mood changes associated with depression.

Depression is generally marked by hyperactivity of the HPA axis and exercise training may lead to an attenuation of the axis response to stress. Many neurotransmitters, neuropeptides, and hormones have been linked to the acute psychobiological response to stress and the long-term psychiatric outcome. The roles of these neurotransmitters, neuropeptides, and hormones have been shown to be altered by stress and have important functional interactions. They mediate neural circuits relevant to regulation of reward, fear conditioning, and social behavior. (Holsboer 1995, 2000)

Cortisol, Dehydroepiandrosterone, CRH, the locus coeruleus-norepinephrine system, neuropeptide Y, galanin, dopamine, serotonin, benzodiazepine receptors, gonadal steroids and estrogen are all implicated as being contributors, alone or through interaction, to resilience to stress. The hypothesis of the allostatic load theory states that the cumulative effect of modest dysregulation in multiple systems could be substantial, even if independently they have minimal impact on health. (Charney, 2004)

Browne, et al (1992) suggested that DHEA and/or DHEAS may act as antagonists of glucocorticoids. Healthy persons with high ACTH-releasing hormone and cortisol responses to exercise exhibit higher baseline levels of DHEA and DHEAS, which may enhance the

hypothalamic-pituitary-adrenal response to exercise (Deuster 2005). Furthermore, the allostatic load theory hypothesizes that when cortisol and DHEA/DHEAS work together in harmony, the organism optimally adapts to stress. When the body is unable to maintain a normal cortisol to DHEAS ratio, a state of maladaptation to stress may ensue. Therefore, it is possible that the ratio of cortisol to DHEAS is of utmost importance; not solely the level of DHEAS. Further research in this area is necessary to further understand this mechanism.

5.4   IMPLICATIONS

This results of the present study suggest the following: 1) moderately intense aerobic exercise is beneficial in improving the perceptions of well-being in bipolar individuals, 2) DHEAS increases as a result of participating in 20 minutes of moderately intense exercise, and 3) other unmeasured factors in addition to an increase in DHEAS may be responsible for improvements in perceptions of global well-being that result from exercise.

Prescribing aerobic exercise for bipolar subjects may help these individuals better cope with Bipolar Disorder. Exercise is inexpensive, easily prescribed and a safe adjunct to other treatment modalities. Exercise is helpful in prevention of chronic physical diseases and has a positive impact on cardiovascular disease risk factors. In addition, thyroid disorders have been shown to adversely affect DHEAS levels. Alterations of DHEAS levels have been reported in hypothyroidism (Ravaglia et al., 2002). While the majority of thyroid-disordered subjects in the present study did not show an increase in DHEAS in response to exercise, they did report improvement in perceptions of global well-being. Therefore, bipolar patients, regardless of

thyroid condition, derive a benefit from exercise in combination with their regular pharmaceutical and therapeutic treatment.

As indicated in Figure 7, there appears to be a trend in perceptions of global well-being such that subjects who reported lower scores prior to exercise had the greatest improvements in perceptions of well-being. In addition the sole subject who presented as hypo-manic (Likert score of 6.5) reported a "neutralization" of well-being post-exercise. The majority of subjects who began the exercise bout in a "normal" well-being state reported little change in well-being scores post-exercise. These results indicate that exercise could possibly help bipolar suffers moderate well-being and further research in this area should be conducted.

5.5 LIMITATIONS

There are several limitations in this study. First, all of the subjects in this study were medicated with various combinations of prescription medications. Secondly, we used a novel 7-point Likert Scale to measure perceptions of global well-being. Third, it is possible there was a training response of DHEAS in some subjects. Finally, the possibility of an anticipatory effect could have resulted from testing subjects who had knowledge of a desired result (improved perceptions of well-being from exercise).

5.5.1 Medication as a Confounder

Bipolar subjects typically are prescribed multiple combinations of medications to control their disorder. Limited research exists on the impact of specific medications and DHEAS levels. However, significant and strong inverse associations between DHEAS and the number but not

with any specific type of medications have been observed. (Ravaglia et al., 2002) Therefore, medications could be a confounding factor in the present research. Since the number of medications may influence baseline DHEAS levels, it follows that medications could have an impact on the amount of DHEAS change in response to exercise. While the present study found that DHEAS increases with exercise, the impact of medication on the response is unknown.

5.5.2   7-point Likert Scale

A 7-point Likert Scale, developed specifically for this study was used to analyze perceptions of global well-being. Previous studies have utilized the Profile of Mood State Questionnaire (POMS) or Becks Depression Inventory (BDI) to assess levels of depression or mood status. Both of these questionnaires ask subjects to report feelings inclusive of the past week. The POMS is 65 questions in length and the BDI contains 21 questions. As such, these tools were not ideal instruments to assess current perceptions of well-being in the present investigation. The 7-point Likert scale proved easy to use and simple in design and has face validity. Therefore, it may be a reasonable measure of perceptions of well-being. Validation of this scale could be a focal point of future research.

5.5.3   Training history and fitness level

This study did not control for training history or fitness level. It is possible that the DHEAS response to acute aerobic exercise may be influenced by these factors. Tissandier et al., (2001) suggested that DHEAS concentrations are higher among trained individuals when compared to untrained controls. Although the experimental paradigm employed by Tissandier et al. did not

involve acute exercise, many other studies have demonstrated an increase in DHEAS with acute exercise (Cumming et al., 1986; Diamond et al., 1989; Velardo et al., 1991). Two studies conducted in small samples of middle-aged and older subjects (n=42, n=42) reported no changes in resting DHEAS with 6 months of training. (Hakkinen et al., 2000; Hersey et al., 1994) In addition, Riechman et al., (2004) reported increased plasma DHEAS levels following acute resistance training in healthy, young subjects. However the magnitude of the acute changes in DHEAS decreased following 10 weeks of resistance exercise training. In the current study, individual training history and fitness status were not documented. Future investigations should examine the impact of these variables on the DHEAS response to aerobic exercise.

5.5.4   Potential for Hawthorne Effect

Another possible limitation to this study includes the Hawthorne effect of testing human subjects. The research team did not inform subjects of any desired outcome, however many of the subjects expressed knowledge of the potential for exercise to improve mood. It is possible that subjects wanted to report a "normal" response to exercise and they may have reported an improvement in well-being on the 7-point Likert scale. Knowledge of the expected response may have lead to faulty perceptions of well-being reports as subjects may have indicated an improvement without properly assessing their true mood state.

5.6   FUTURE DIRECTIONS

The results of this study demonstrated that treadmill walking at an intensity of 70% of age predicted heart rate max for 20 minutes produced a significant increase in DHEAS and

improvement in perceptions of global well-being. Possible future directions of research are described below.

5.6.1 Causes of changes in perceptions of global well-being

The rise in DHEAS does not appear to be the sole cause of improvement in perceptions of global well-being following an acute bout of exercise. Therefore, future studies should explore alternative mechanisms for the improvement in perceptions of well-being. Many neurotransmitters, neuropeptides, and hormones have been linked to the acute psychobiological response to stress and long-term psychiatric outcome. The roles of these neurotransmitters, neuropeptides, and hormones have been shown to be altered by stress and have important functional interactions. They mediate neural circuits relevant to regulation of reward, fear conditioning, and social behavior. Cortisol, Dehydroepiandrosterone, CRH, the locus coeruleus-norepinephrine system, neuropeptide Y, galanin, dopamine, serotonin, benzodiazepine receptors, gonadal steroids and estrogen have been implicated as being contributors, alone or through interaction, to resilience to stress. (Charney, 2004) The hypothesis of allostatic load also states that the cumulative effect of modest dysregulation in multiple systems could be substantial, even if independently they have minimal impact on health (McEwen 2002). Due to the potential for DHEAS to mediate the effect of elevated cortisol levels, the cortisol/DHEAS ratio in exercising bipolar subjects needs to be explored as well as other possible combinations of hormones.

5.6.2 Effect of exercise DHEAS levels in mania

The single participant that indicated a hypomanic state of well-being prior to exercise reported normalization in well-being and a reduction in DHEAS level after the exercise session. Whether

mania can be affected by exercise via a reduction in DHEAS and/or other hormonal regulation should be investigated.

5.6.3   Effect of various exercise modes, durations, intensities and fitness levels

In 2004, Tremblay studied the effects of acute bouts of aerobic and resistance exercise on DHEA in trained and sedentary individuals. This study found that DHEA increased following both resistance and aerobic exercise. However, increases in DHEA were greater after resistance exercise than aerobic exercise. The exercise that elicited the greatest levels of DHEA elevation proved to be resistance exercise in resistance-trained subjects. Tremblay et al., also demonstrated a significant increase in cortisol only after resistance exercise. Therefore, DHEAS in response to various modes of exercise and in conjunction with other hormones should be further explored.

Tramblay et al. (2005) found the duration of exercise to have an impact on DHEAS levels. DHEAS increased in a dose-response manner with the greatest increases observed in response to a 120 minute run compared to 40 and 80 minute runs at an intensity of 55% of VO_2 max. In addition the relation between DHEAS and VO_2 max suggests that higher intensity exercise may elicit a greater increase in DHEAS (Bonnefoy et al., 1998). Therefore, exercise duration and intensity may have independent effects on the hormonal responses to aerobic exercise.

Changes in perceptions of well-being in response to various modes and intensities of exercise in bipolar subjects could also be important information to explore in future studies. The present study was limited to 20 minutes of aerobic exercise. It is possible that longer or shorter bouts of exercise could produce different DHEAS and perception responses. Identification of a

"threshold" or optimal volume and intensity of exercise to improve perceptions of well-being and hormonal response needs to be defined.

This study did not control for training status or fitness level in subjects. Current literature provides mixed results regarding the effects of training on DHEAS and change in DHEAS in response to an acute bout of activity. Future studies should examine the impact of fitness level and training response on DHEAS and perceptions of well-being.

While not a hypothesis or outcome of this study, issues related to exercise intensity and duration are frequently a concern especially when developing experimental paradigms involving unique clinical populations. In this study, the protocol involved treadmill walking at an intensity of 70% of age predicted maximal heart rate for 20 minutes. All subjects were able to complete this protocol safely; therefore, future investigations could utilize this, or perhaps an even more vigorous exercise protocol.

5.6.4   Control for medications

While limited research exists on DHEAS levels and use of specific medications, significant and strong inverse associations of DHEAS with the number but not with any specific type of medications have been observed. (Ravaglia et al., 2002) Therefore, medications could be a confounding factor in this research and effects of medications on DHEAS need to be further explored.

5.7   CONCLUSIONS

The present study has shown that an acute bout of treadmill exercise at an intensity of 70% of age predicated maximal heart rate significantly increased serum DHEAS levels in clinically diagnosed bipolar subjects. Bipolar subjects reported an improvement in perceptions of global well-being after participating in this 20-minute aerobic exercise protocol. The increase in DHEAS may contribute to improvements in perceptions of well-being; however, this hormonal response may be only one part of the complex etiology associated with bipolar disorder. Regardless of the etiology, the improvement in perceptions of well-being seen with exercise in this population is an important finding. Ultimately, it is hoped that the incorporation of an exercise program as part of the treatment for bipolar patients becomes more widely utilized. Exercise, unlike many medications, has no negative side effects and a wide range of positive outcomes when prescribed and applied correctly.

APPENDIX A

PRESCREENING SCRIPT

"Hello, my name is Anne Hays from the University of Pittsburgh. Dr. Friedman of the Bipolar Disorder Clinic of Pennsylvania and I are working on a study involving exercise and brain chemistry. Is now an OK time to discuss this project with you?"

"The test is a simple one that would take about an hour to complete and for your time you would receive $25. This is a one-time visit and you would not be obligated for any other time on this study. All information will remain confidential."

(Conformation of the following)

1. You are currently clinically diagnosed with bipolar disorder, correct?
2. You are currently in outpatient status at the Bipolar Disorder Clinic of Pennsylvania, correct?
3. Females: Are you pregnant? If not, do you currently use birth control so that you are confident that you will not be able to become pregnant with in the next two months?
4. Have you ever had a heart attack?
5. Are you currently on beta-blocker medication?
6. Are you diabetic?
7. Are you able to perform moderate exercise for at least 30 minutes?

If question 1 or 2 are no or 3-7 yes:

"Unfortunately there is a problem. With our protocol, we require that _____.(you are not diabetic, for example). I thank you for your time. Have a great day."

If question 1 and 2 are yes, and 3-7 no, agree to continue:

"Great, your information qualifies you for the study. Is this something you would be interested in participating in? If you decide you'd like to take part in this study, I will collect your primary care doctor's contact information. I will obtain a medical clearance from him/her that states he/she is aware you will be participating in an exercise study. This will be done to ensure your safety in the study. After your doctor signs that it is safe for you to exercise, you can appear for the actual testing session. I will take care of all the paper work involved with that."

"Would you like to participate in this study?"
(If yes, continue.)

"Please answer the following questions." (Read PAR-Q or have subject fill out PAR-Q)

"Please fill out this medical history questionnaire which helps me know that you are safe to exercise." (Give Medical History Questionnaire)

"Everything looks good. Let's schedule a time for your exercise test that is at least 3 days from now. That will give me time to send the medical clearance form to your primary care physician. In addition, we must schedule your test for a time when you think you will have been awake for at least 3 hours before the test."

(Schedule test date and time)

"Please remember to maintain your regular schedule of eating and medication the day of the exercise test. Please do not exercise the day prior to or the day of your scheduled exercise test.

Do not consume alcoholic beverages the day prior to or the day of your exam. Remember to wear comfortable exercise clothing to the test and to drink plenty of water the day of the exam."

PHYSICAL ACTIVITY READINESS QUESTIONNAIRE

<u>PAR – Q</u>

Date: _____

Subject number: _____

<u>Yes / No</u>

_____   1. Has your doctor ever said you have a heart condition and that you should only do physical activity recommended by a doctor?

_____   2. Do you feel pain in your chest when you do physical activity?

_____   3. In the past month, have you had chest pain when you were not doing physical activity?

_____   4. Do you lose your balance because of dizziness or do you ever lose consciousness?

_____   5. Do you have a bone or joint problem (for example back, knee or hip) that could be made worse by a change in your physical activity?

_____ 6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?

_____ 7. Do you know of any other reasons why you should not participate in physical activity?

MEDICAL HISTORY QUESTIONNAIRE

<u>Demographic Information</u>

Last Name	First Name	Middle Initial

Age	Gender	Home Phone

Address	City, State	Zip Code

Work Phone		E-Mail Address

Emergency Contact		Phone Number

Primary Therapist	Phone Number	E-Mail Address

Primary Care Physician	**Phone Number**	**Fax Number**

List all medications you are currently taking (include dosage):

_____

_____

Risk Factors:

1. **Have any of your parents, brothers, sisters had a heart attack, bypass surgery angioplasty, or sudden death prior to the age of 55 (male relatives) or 65 (female relatives)?**   **YES   NO**

2. **Have you smoked cigarettes in the past 6 months?**   **YES   NO**

3. **What is your usual blood pressure ($\geq$140/90)?** _____
   Do you take blood pressure medication?   **YES   NO**

4. **What is your LDL cholesterol? If you don't know your LDL, what is your total cholesterol? What is your HDL cholesterol?**
   (Either LDL >130 (use total cholesterol >200 if LDL is not known) OR HDL <40)

      LDL_____   **TC_____   HDL_____**

5. **What is your fasting glucose ($\geq$110)?**   _____

6. **What is your height and weight (BMI >30)?**

      Height_____   Weight_____   **BMI_____**

7. **Do you get at least 30 minutes of moderate physical activity most days of the week?**

        YES   NO

Signs and Symptoms:

1. **Do you have pain or discomfort in your chest or surrounding areas?**

        YES   NO

2. **Do you ever feel faint or dizzy (other than sitting up rapidly)?**

        YES   NO

3. **Do you find it difficult to breathe when you are lying down or sleeping?**

        YES   NO

4. **Do your ankles ever become swollen (other than after long periods of standing or sitting)?**

        YES   NO

5. **Do you ever have heart palpitations, or an unusual period of rapid heart rate?**

        YES   NO

6. **Has a physician ever said you had a heart murmur? (Has he/she said it is OK, and safe for you to exercise?)**

        YES   NO

7. **Do you feel unusually fatigued or find it difficult to breathe with usual activities?**

        YES   NO

8. **Do you ever experience cramp-like pain in your calves?**

YES   NO

Other:

1.   When   was   the   last   time   you   had   a   physical   examination?
_____

2. Do you have any of the following diseases: heart disease, peripheral vascular disease,   cerebrovascular   disease,   chronic   obstructive   pulmonary   disease (emphysema or chronic bronchitis), asthma, interstitial lung disease, cystic fibrosis, diabetes mellitus, thyroid disorders, disease, or liver disease?

YES   NO

If   you   answered   "yes"   to   the   above   question   list   the condition(s)_____

_____

3. Do you have any bone or joint problems, such as arthritis or a past injury that might get worse with exercise?

YES   NO

If   you   answered   "yes"   to   the   above   question   list   the condition(s)_____

_____

4. Have you ever been hospitalized or undergone surgery?

YES   NO

If   you   answered   "yes"   to   the   above   question   describe conditions_____

_____

5. **Are you pregnant or lactating?**

                    YES   NO

6. **Do you have any other problem that might make it difficult for you to exercise?**

                    YES   NO

If you answered "yes" to the above question list the condition(s)_____

_____

****

To be completed by the interviewer:

<u>Interpretation:</u>

_____ Low Risk: young and no more than one risk factor

_____ Moderate Risk: older, or 2 or more risk factors

_____ High Risk: known disease or at least one major sign or symptom

MEDICAL CLEARANCE FORM

TO: _____

Fax #: _____

FROM: Anne Hays, MS
Fax #: (412) 648-7092
Phone: (412) 478-1190

Dear Dr. _____,

Your patient _____ has agreed to be in a research study investigating the effects of an acute bout of aerobic exercise on Dehydroepiandostrone-sulfate (DHEAS) in bipolar subjects. With your approval, your patient will undergo a 5-minute light walk on a motor driven treadmill. Next, a 20-minute walk/run sequence that elicits a 70% of age predicted heart rate maximal response would occur. After 20 minutes of walking/running at this pace, your patient will cool down for 5 minutes to allow for heart rate and blood pressure to normalize.

Approximately 9 ml of blood will be drawn from an anticubital vein by a certified phlebotomist both before and after the exercise session to analyze DHEA.

Please sign the statement below and fax back to: (412) 648-7092 at your earliest convenience. Should you have any questions or concerns regarding this study or should you want more information, feel free to contact me at (412) 478-1190 at any time.

Thanks, in advance, for your cooperation.

In Health,

Anne E. Hays
Primary Investigator
U of Pittsburgh School of Education / WPIC

_____

My patient _____, is safe to exercise at a submaximal (70% of age predicted heart rate maximum) aerobic exercise rate for 20 minutes, and has my encouragement to do so.

Primary Care Physician Signature:_____

INFORMED CONSENT

CONSENT TO PARTICIPATE AS A SUBJECT IN A CLINICAL RESEARCH STUDY

TITLE: Effects of an Acute Bout of Aerobic Exercise on Dehydroepiandosterone Levels in Clinically Diagnosed Bipolar Subjects.

PRINCIPAL INVESTIGATOR:

Anne Hays, Ph.D. Candidate, Exercise Physiology

140 Trees Hall

University of Pittsburgh

Pittsburgh, PA 15213

412) 478-1190

CO-INVESTIGATORS:

Edward S. Friedman, M.D.	Fred Goss, Ph.D.
Associate Professor of Psychiatry	Professor of Exercise Physiology
Western Psychiatric Institute and Clinic	113 Trees Hall
3811 O'Hara Street, Room 848 BT	University of Pittsburgh
Pittsburgh, PA 15213	Pittsburgh, PA 15213
(412) 246-6111	(412) 648-8259

SOURCE OF SUPPORT: School of Education Grant, University of Pittsburgh

INTRODUCTION:

You are being asked to participate in a research study that is attempting to find out if aerobic exercise is helpful for people with bipolar disorder. Before agreeing to participate in this research study, it is important that you read and understand this form. It describes the purpose, procedures, benefits, risks, discomforts, and precautions of the study.

Why is this research being done?

We are also particularly interested in examining if Dehydroepiandrosterone (DHEA), a hormone in the human body that may be associated with the way the human brain works, may help relieve symptoms of depression. We will determine the effect of an aerobic exercise session on this hormone in the blood stream of people with bipolar disorder. DHEA is present in every human body, however, it may be lower in people with bipolar disorder and exercise may increase it, helping relieve symptoms of the disease.

There are no medications used in this trial. Exercise, unlike many medications, has no negative side effects and a wide range of positive outcomes when prescribed and applied correctly. There is a great deal of evidence linking physical activity to a decrease in depressive symptoms. There is a need for reliable evidence about how aerobic exercise can help reduce the need for medical and psychiatric intervention for bipolar disorder. To date much of the research into bipolar disorder has focused on the immediate management of symptoms of mania and depression rather than on the management of illness thru an exercise program.

Who is being asked to take part in this research study?

You have been asked to take part in this study because you have been diagnosed with bipolar disorder and because your study psychiatrist feels you will benefit from participation in this research exercise program. Your study psychiatrist will continue providing your care and will work closely with the investigators of this study.

We expect to enroll 28 male and female subjects (age range) in this study at Western Psychiatric Institute and Clinic and those participants in the Bipolar Disorders Center for Pennsylvanians. Individuals of all ethnic backgrounds and ages will be included so that we may learn more about how an exercise program along with bipolar treatment may help bipolar patients regardless of ethnicity or age.

What procedures will be performed for research purposes?

Screening Procedure

After you have signed the informed consent, you will be screened for eligibility by a review of the inclusion and exclusion criteria via phone. You will also be asked several questions regarding your current health to insure your safety in this study. Your primary care doctor will be required to sign a clearance form, which states he/she is aware of your participation in an exercise study and he/she believes you are safe to do so. There is no cost to

you for this procedure. The primary investigator in the study will ask you for your primary care physician's contact information and proceed with gathering the necessary signatures.

You must be free of diagnosed heart, lung or blood pressure disease, able to perform moderate aerobic exercise for a minimum of 20 minutes. Your Primary Care Physician (PCP) will need to sign a medical clearance to participate in this aerobic exercise research portion. Additionally, you will be required to have had a recent (within three months of entering this study) electrocardiogram(ECG) to assess your heart health. This ECG is simply a test that measures the electricity of your heart. You will be asked via phone to complete a questionnaire called the Physical Activity Readiness Questionnaire (PAR-Q). It asks you questions about your current activity level. You will also be asked questions regarding your medical history (Medical History Questionnaire) to ensure your safety in this study. They are simple questions about your current health status.

If you agree to participate in this study, you will continue to see the same psychiatrist you are already seeing in the BDCP study. You will maintain your regular schedule of eating and taking medication. You will not exercise or consume any alcoholic beverages the day prior to or the day of the exercise exam. The day of the exam you will wear comfortable exercise clothing and drink plenty of water. The appointment will be scheduled three hours after you normally awaken. The exam will take approximately one hour and you are only required to appear one time.

Experimental Procedures:
Before the testing begins you will complete the Likert 7 point scale for perceptions of global well-being. This scale simply asks you to rate your mood at the time of testing.

1.   You will have your blood drawn by a trained technician at the Human Energy Laboratory. They will draw a small sample of your blood from a vein in your arm (about 3 tablespoons (tbsp) and prepare it to be sent to Montifour Hospital for analysis.   The primary investigator of this research project will be in control of all blood samples. Each sample will be de-identified and replaced with a specific study code number. The informational sheet that will be the only correlate between subject name and subject study number, will be kept in a locked room separate from other study materials.   All blood samples must be acquired prior to submission to an analysis laboratory at Montifour Hospital. Therefore, all samples will be kept indefinitely.   Once all samples have been analyzed, they will be discarded in appropriate biohazard containers. No samples will be used in future studies or given to other investigators.

2.   You will have your height, weight, muscle mass and body measurements measured by a qualified exercise physiologist in the Human Energy Laboratory.

3.   You will wear a Polar Heart Rate Monitor (Model number A3) on your chest that is affixed with an elastic band to keep it secured.

4.   You will be asked to perform a two-minute warm-up on a Trackmaster treadmill. You will be monitored by heart rate every 15 seconds and recorded every minute. Your blood pressure will be monitored every 5 minutes.

5.   The warm-up will immediately be followed by increased difficulty based on your heart rate response to the activity. Once your heart rate has increased to a moderate intensity, your activity will be maintained at that level for a minimum of twenty minutes. Your heart rate will be monitored every minute and your blood pressure recorded every five minutes.

6.   After twenty minutes of exercise, you will be returned to resting heart rate and blood pressure using standard cool down procedures. You will be given water and/or juice. This testing will occur in the Human Energy Research Laboratory at the University of Pittsburgh and will take approximately 1 – 1½ hours.

7.   After a five-minute cool down a second blood draw, identical to the first, (3 tbsp) will be performed and will again be analyzed.

8.   After completion of the exam, the investigator will review the exercise test results with you and answer any questions you may have. You will then complete the Likert 7 point scale for mood again.

What are the possible risks, side effects, and discomforts of this research study?

As with any research study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life threatening. Once you have enrolled in this study, your clinician's decisions are based solely on his or her best clinical judgment, and are not influenced by or guided by the research protocol in any way.

**Risk of Venipuncture****:** There does exist the possibility of certain undesirable outcomes with a standard blood draw. It is common for bruising and/or inflammation to occur at the site of the draw (25-30% of subjects will experience this). The site may also become tender, and sore. Rarely the site may become infected or you may feel dizzy or faint (5% risk). All precautions will be taken to ensure the site will not become infected, but realize infection of the site is a risk (5%).

**Risk of Exercise Testing:** You will perform an exercise test on a motor driven treadmill. The exercise intensity will begin at a low level and will be stopped any anytime because of signs of fatigue or inappropriate changes in your heart rate or blood pressure (10% risk). You may stop when you wish because of feelings of fatigue or any other discomfort. If you experience those feelings or any other discomfort, you must agree to inform the testing personnel involved.

There exists the possibility of certain side effects occurring during this test. This includes abnormal blood pressure, panting, irregular, fast or slow heart rhythm, and in rare instances, heart attack, stroke or death. To minimize risks associated with aerobic exercise, you will be asked to complete a Physical Activity Readiness Questionnaire that asks question about your current health status. In addition, you will be asked to complete a medical history form, which helps the investigators understand your risk of adverse effect from exercise. Incidence of heart attack or stroke in individuals cleared in this manner is rare (less than 1%). Every effort will be made to minimize your risk and should abnormal responses be observed, the test will be terminated.

In the event of an abnormal response to exercise, and test termination, emergency equipment and trained personnel are available in the Human Energy Research Laboratory to deal with any unusual situation. Additionally, security and emergency equipment are within the building.

If you have any current health status or previous experiences of unusual feelings with any physical effort that may affect the safety and value of this exercise test, you must notify the investigator. It is important that you report any feelings that your experience with effort during

the exercise test itself. You need to acknowledge, agree and understand the importance of fully disclosing such information when requested during the test by testing staff.

As with any experimental procedure, there may be adverse events or side effects that are currently unknown, and certain of these unknown risks could be permanent, severe, or life threatening.

Previous studies on the effect of aerobic exercise at 70% of maximal effort, have not been done on pregnant women, therefore the risks on a fetus is unknown. To avoid risk to a fetus, it is important that any female subject in this study remain impregnate until the exercise test date has been completed. Avoiding sexual activity is the only certain way to avoid pregnancy, however if you choose to become sexually active, you should use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. Such birth control methods should be used until your exercise test date has been completed. If you choose to be sexually active during this study, you understand that even with the use of these birth control measures pregnancy could still result. The risks of undergoing aerobic exercise while pregnant include potential loss of pregnancy or possible birth defects.

What are the possible benefits from taking part in this research study?

There may be no benefit to you for participating in this trial. The goal of this project is to demonstrate a physiological response that could begin to explain how if when you exercise, your mood becomes more stable. This will help clinicians develop exercise as a prescription for bipolar disorder. Data collected from this study may later help clinicians determine the best methods for maintenance treatment for patients with bipolar disorder. In the future, other patients may benefit from your participation.

What treatments or procedures are available if I decide not to take part in this research study?

You may continue to receive care through your psychiatrist, and your quality of care will not be affected.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You will be notified if any new information develops during the conduct of this research study, which may cause you to change your mind about continuing to participate.

Who will be responsible for the compensation of illness or injury?

The University of Pittsburgh investigators and their associates who provide services at the University of Pittsburgh Medical Center (UPMC) recognize the importance of your voluntary participation to their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

If you believe that you are injured as the result of the research procedure being performed, please immediately contact the Principal Investigator or one of the co-investigators listed on the coversheet of this form at (412) 246-6111. Emergency medical procedures for injuries solely and directly relating to your participation in this research will be provided to you by hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency care, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency procedure, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary payment for, or associated with, any injury that you suffer in relation to this research.

You do not, however, waive any legal rights by signing this form.

Will I or my insurance provider be charged for the costs of any procedures performed as part of this research study?

No charge will be made to you or your health care provider for your participation in this exercise test.

Will I be paid if I take part in this research study?

You will be paid $25 after the completion of your individual test.

Who will know about my participation in this research study?

Any information about you obtained from or for this research study will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a study number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. The confidentiality of your research records will be maintained in the same way that your medical records are kept confidential, according to Federal, State, and UPMC regulations. You will not be identified by name in any publication of the research results unless you sign a separate form giving your permission (release).

Will this research study involve the use or disclosure of my identifiable medical record information?

This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other health care provider (e.g., physician office) records. The information that will be recorded will be limited to information concerning your current and past psychiatric and medical history. This information will be used for the purpose of determining your eligibility for this study.

Who will have access to identifiable information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study: Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical record information) for the purpose of monitoring the appropriate conduct of this research study.   In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical record information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information related to your participation in this research study for the purpose of (1) fulfilling orders, made by investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance.)

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical record information) related to your participation in this research study.   Your research records will be destroyed as per University policy. It is a University policy that all research records must be maintained for at least 5 years following study completion.

May I have access to my medical record information that results from my participation in this research study?

In accordance with UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider unless otherwise specifically stated below.

Is my participation in this research study voluntary?

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable medical record information for the purposes described above, you will not be allowed, in general, to participate or continue to participate in the research study.)   You are free to deny any consent you so desire both now and at any time during the exercise test or the participation in this protocol.

Whether or not you provide your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Whether or not

you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your doctor is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw, at a future date, my authorization (consent) for the use of my identifiable medical record information for the purpose of this research study?

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable medical record information for the purposes described above. (Note, however, if you withdraw your consent for the use and disclosure of your identifiable medical record information, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable medical record information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your authorization may continue to be used and disclosed by the investigators for the purposes described above. You may withdraw consent due to any reason, such as an inability to comply with study procedures. It is important to remember that any additional treatment you may require is an outcome for this study, and therefore is always an option for you.

To formally withdraw your consent you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for the research use and disclosure of your medical record information will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw this consent will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If I agree to participate in this research study, can I be removed from the study without my consent?

You may be withdrawn from study participation if, by process of review, your completed Health History Questionnaire and Physical Activity Readiness Questionnaire deem participation unsafe for you. If your primary care physician declines to sign a medical clearance for your participation, you will be removed from this study. You will continue to receive care from your BDCP physician regardless of your participation in this study. In the event medical information is recorded for you that may help your physician better treat you, that medical information may be given to your doctor.

****

VOLUNTARY CONSENT: All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of the study, and that such future questions will be answered by the researchers listed on the first page of this form. Any questions I have concerning my rights as a research participant will be answered by the Human Subjects Protection Advocate of the IRB office, University of Pittsburgh (866-212-2668).

By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

_____   _____
Date   Patient's Signature

                                                              _____
                                                              Patient's Printed Name

CERTIFICATION OF INFORMED CONSENT: I certify that I have explained the nature and purpose of this research study to the above-named individual and I have discussed the potential benefits and risks of study participation. Any questions the individual has about this study have been answered, and we will always be available to address future questions as they arise.

_____   _____
Printed name of Person Obtaining Consent   Role in Research Study

_____   _____
Signature of Person Obtaining Consent   Date

APPENDIX F

EXPLANATION OF TESTING PROCEDURES

_____

"You are about to take part in an exercise study investigating the effects of aerobic exercise on a blood chemical in clinically diagnosed bipolar subjects. We will assess your height, weight, body circumference measurements and body composition. We will then ask you to rate your current mood on a Likert 7 point scale. Next, a certified phlebotomist will draw a small sample of blood. You will then be asked to exercise on a treadmill for 30 minutes. If at any time you feel light headed, dizzy, nauseous, or overly fatigued it is important to inform the investigator. If you are having any of these symptoms, you may terminate the test. Remember, you have the ultimate say in stopping the test if you are feeling at all ill during the exam."

"After the 30-minute exercise bout, a second sample of blood will be drawn. You will be asked to again, rate your mood. You will be offered water and/or juice and paid your stipend."

"As with any bout of exercise there is always a risk of abnormal blood pressure, fainting, irregular heart rhythm and in rare instances heart attack, as outlined in this informed consent. You have read and signed the informed consent and noted that you understand and are aware of the outlined risks and will not hold the university or any of its staff responsible for any liability."

"Do you have any questions before we begin the exam?"

APPENDIX G

LIKERT 7 POINT SCALE FOR GLOBAL WELL-BEING

ID #: _____ Date: _____ Pre-test ☐ Post-test ☐

Please place a check mark next to the phrase that best describes how you are feeling at this moment:

O Severely Depressed

O Moderately Depressed

O Mildly Depressed

O Neutral (not depressed or manic)

O Mildly Happy

O Moderately Happy

O Excessively Happy (manic)

DATA COLLECTION FORM

Data Collection Form
The effects of an acute bout of aerobic exercise on DHEA levels in bipolar subjects.

Anne E. Hays

Date_____Time_____ID # _____Room Temp _____Age_____

Gender: Male ___Female ___Time of awakening today ____Awake Time (3+hours)_____

Height in Inches _____   Weight in pounds _____   Resting BP _____/_____

Waist _____   Hip _____   Ratio _____

Time of Blood Draw 1: _____   Hct: _____

APHRM: _____   70% APHRM _____

Heart Rate Range for Test: (70% APRHM$\pm$ 5) _____

Exercise Test

Minute	Speed	Grade	HR	Minute	Speed	Grade	HR
0	2.2	0		15- BP:			
1	2.2	0		16			
2				17			
3				18			
4				19			
5 – BP:				20- BP:			
6				21			
7				22			
8				23			
9				24			
10- BP:				25 cool down			
11				26- BP:			
12				27			
13				28			
14				29- BP:			

Time of Blood Draw 2: _____   Hct: _____

APPENDIX I

HEALTH SUMMARY

Date: _____

Thank you for participating in this research study. We'd like to help you understand some of the health information we learned about you today.

Today your height was measured at: _____ in or _____ ft, _____ in

_____

BODY COMPOSITION

Your current weight is:_____lbs

We estimated your body composition to be _____%.

For men, a healthy body fat range is between 10%-22%. Females are considered healthy in the 20-32% range.

_____

WAIST TO HIP RATIO

Another indicator of health is abdominal adiposity or "apple" and "pear" shaped. Your health is affected not only by how much fat you have, but also where that fat is stored. People who gain weight in their hips and buttocks have a lower risk for heart diseases when compared to people that store fat primarily in their abdominal region.

If you are an "apple" rather than a "pear" you have a higher risk for health problems such as diabetes, coronary heart disease and high blood pressure. There is nothing you can do to change your body type. That is something that is inherited, however you can take special care to keep your weight at a healthy level, eat nutritiously, exercise and maintain other healthy lifestyle habits.

As long as you avoid excess weight, being an "apple" vs. a "pear" doesn't put you at special risk. Pears need to keep their weight at a healthy level too.

For men, the optimal value for a waist to hip ratio is below .95. For women, the ratio should be lower than .86.

Your waist to hip ratio is:_____.

BLOOD PRESSURE

The American Heart Association has blood pressure guidelines to help you understand what your blood pressure reading means. Under these guidelines, a resting blood pressure reading below 120/80 millimeters of mercury (mm Hg) is considered "normal." If your resting blood pressure is consistently 140/90 mm Hg or higher, you have high blood pressure. A reading in between these levels places you in the prehypertensive category. Under the new guidelines, a reading of 115/75 is the level above which your risk of cardiovascular complications starts to increase.

The prehypertensive category sets systolic pressure from 120 to 139 and diastolic pressure from 80 to 89 as a warning zone — time to take action against increasing your risk for heart disease, stroke and kidney disease. Consult your healthcare professional if you are in the prehypertensive range or hypertensive range and start managing your blood pressure now.

Today's Resting Blood Pressure Reading: _____/_____

HEART RATE RANGE

Your age predicted maximal heart rate is: _____ beats per minute. It is recommended that a healthy individual exercise at 55-85% of their maximal heart rate when participating in cardiovascular activity. That means that when you exercise your heart rate should be between _____ and _____ beats in a 60 second count, or between _____ and _____ in a 10 second count.

APPENDIX J

ACSM CRITERIA FOR TERMINATION OF AN EXERCISE TEST

General Indications for Stopping Exercise Testing in Low-Risk Adults
ACSM Guidelines for Exercise Testing and Prescription

1. Onset of angina or angina-like symptoms
2. Drop in systolic blood pressure of >10mm Hg from baseline blood pressure despite an increase in work load
3. Excessive rise in blood pressure: systolic pressure > 250 mm Hg or diastolic pressure >115 mm Hg
4. Shortness of breath, wheezing, leg cramps or claudication
5. Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
6. Failure of heart rate to increase with increased exercise intensity
7. Noticeable change in heart rhythm
8. Subject requests to stop
9. Physical or verbal manifestations of severe fatigue
10. Failure of the testing equipment

REPEATED MEASURES ANOVA WITH MAIN EFFECTS FOR EXERCISE AND GENDER

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
DHEAS	Sphericity Assumed	956.327	1	956.327	7.244	.013
	Greenhouse-Geisser	956.327	1.000	956.327	7.244	.013
	Huynh-Feldt	956.327	1.000	956.327	7.244	.013
	Lower-bound	956.327	1.000	956.327	7.244	.013
DHEAS * Gender	Sphericity Assumed	27.188	1	27.188	.206	.654
	Greenhouse-Geisser	27.188	1.000	27.188	.206	.654
	Huynh-Feldt	27.188	1.000	27.188	.206	.654
	Lower-bound	27.188	1.000	27.188	.206	.654
Error(DHEAS)	Sphericity Assumed	3168.505	24	132.021		
	Greenhouse-Geisser	3168.505	24.000	132.021		
	Huynh-Feldt	3168.505	24.000	132.021		
	Lower-bound	3168.505	24.000	132.021		

Tests of Between-Subjects Effects

Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	1915545.849	1	1915545.849	45.086	.000
Gender	186169.422	1	186169.422	4.382	.047
Error	1019676.388	24	42486.516		

APPENDIX L

INDIVIDUAL DHEAS RESPONSES TO EXERCISE

Subject Number	DHEAS Pre-exercise (ug/dl)	DHEAS Post-exercise (ug/dl)
1.00	185.00	191.00
3.00	216.00	213.00
7.00	146.00	158.00
11.00	122.00	136.00
13.00	132.00	123.00
15.00	528.00	559.00
19.00	47.60	43.70
23.00	723.00	749.00
25.00	201.00	206.00
27.00	74.20	85.40
29.00	239.00	254.00
33.00	246.00	298.00
35.00	348.00	322.00
2.00	131.00	124.00
4.00	159.00	186.00
8.00	134.00	138.00
10.00	41.20	46.40
16.00	307.00	322.00
18.00	74.70	84.00

20.00	132.00	141.00
22.00	98.50	92.60
30.00	108.00	109.00
34.00	53.60	58.00
36.00	92.90	91.60
38.00	136.00	134.00
40.00	203.00	237.00

BIBLIOGRAPHY

Akil, H., Haskett, R.F., Young, E.A. (1993). Multiple HPA profiles in endogenous depression: effect of age and sex on cortisol and beta-endorphin. Biol Psychiatry, 33 (2): 73-85.

American College of Sports Medicine's Guidelines for Exercise Testing and Prescription. (2005) 7th Ed. Lippincott Williams and Wilkins.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV). Washington, DC: APA.

Assies, J., Visser, I., Nicolson, N.A., Eggelte, T.A., Wekking, E.M., Huyser, J., Lieverse, R., Schene, A.H. (2004). Elevated salivary dehydroepiandrosterone-sulfate but normal cortisol levels in medicated depressed patients: preliminary findings. Psychiatry Res., 128 (2): 117-22.

Bahrke, M.S. & Morgan, W.P. (1978). Anxiety reduction following exercise and meditation. Congitive Therapy and Research, 2: 323-333.

Baker, E., Matheur, R., Kirk, R., Landgrede, S., Moody, L., Williamson, H. (1982). Plasma gonadotropins, prolactin, and steroid hormone concentration in female runners immediately after a long distance run. Fertil Steril, 38:38-41.

Balady, G., Ades, P., Comoss, P., Limacher, M., Pina, I.L., Southard, D., Williams, M., Bazzarre, T. (2000). Core components of cardiac rehabilitation/secondary prevention programs: a statement for healthcare professionals from the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation Writing Group. Circulation, 102: 1069-1073.

Bandura, A., Pastorelli, C., Barbaranelli, C. (1999). Self-efficacy pathways to childhood depression. J Pers Soc Psychol, 76(2):258-69.

Baptista, T., Lacruz, A., Angeles, F. (2001). Endocrine and metabolic profile in the obesity associated to typical antipsychotic drug administration. Pharmacopsychiatry, 34:223-31.

Baptista, T., Kin, N.M., Beaulieu, S. (2002). Obesity and related metabolic abnormalities during antipsychotic drug administration: mechanisms, management and research perspectives. Pharmacopsychiatry, 35(6):205-219.

Barrett-Connor, E., Edelstein, S.L. (1994). A prospective study of dehydroepiandrosterone sulfate and cognitive function in an older population: the Rancho Bernardo Study. J Am Geriatr Soc., 42(4):420-3.

Bauliew, E.E., Robel, P. (1998). Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) as neuroactive neurosteroids. Proc Nat Acad Sci, 95:4089-4091.

Begley, C.E., Annergers, J.F., Swann, A.C., Lewis, C., Coan S., Schnapp, W. B., Bryant-Comstock, L. (2001). The lifetime cost of bipolar disorder in the United States: an estimate for new cases in 1998. Pharmacoeconomics, 19:483-495.

Blomstrand, E., Celsing, F., Newsholme, E.A. (1998). Changes in plasma concentrations of aromatic and branched-chain amino acids during sustained exercise in man and their possible role in fatigue. Acta Physiol Scand, 133(1):115-121.

Blumenthal, J.A., Fredrikson, M., Matthews, K.A. (1991). Stress reactivity and exercise training in premenopausal and postmenopausal women. Health Psychol, 10(6): 384-391.

Bosscher RJ. (1999). Running and mixed physical exercises with depressed psychiatric patients. Int J Sport Psychol, 24(2):170-184.

Browne, E.S., Wright, B.E., Porter, J.R., Sved, F. (1992). Dehydroepiandtrosterone and antiglucocorticoid action in mice. Am J Med Sci, 303:366-371.

Callaghan, P. (2004) Exercise: a neglected intervention in mental health care? J Psychiatric and Mental Health Nursing, 11:476-483.

Cassidy, F., Ahearn, E., Carroll, B.J. (1999) Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry , 156:1417-1420.

Casson, P.R., Andersen, R.N., Herrod, H.G., Stentz, F.B., Straughn, A.B., Abraham, G.E., Buster, J.E. (1993). Oral dehydroepiandrosterone in physiologic doses modulates immune function in postmenopausal women. Am J Obstet Gynecol, 169(6):1536-9.

Chaouloff, F. (1997). Effects of acute physical exercise on central serotonergic systems. Med Sci Sports Exerc., 29(1):58-62.

Charney, D.S. (1998). Monoamine dysfunction and the pathophysiology and treatment of depression. J Clin psychiatry, 59 Suppl.14:11-4.

Charney, D.S. (2004). Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. Am J Psychiatry, 161: 195-216.

Chiu, K.M., Schmidt, M.J., Havighurst, T.C., Shug, A.L., Daynes, R.A., Keller, E.T., Gravenstein, S. (1999). Correlation of serum L-carnitine and dehydroepiandrosterone-sulphate levels with age and sex in healthy adults. Age Ageing, 28(2)211-216.

Christie, M.J. & Chesher, G.B. (1982). Physical dependence on physiologically released endogenous opiates. Lofe Science, 30:1173-1117.

Compagnone, N.A., Mellon, S.H. (2000). Neurosteroids: biosynthesis and function of these novel neuromodulators. Front Neuroendocrinol, 21:1-56.

Corrigan, B. (2002). DHEA and Sport. Clin J of Sport Medicine, 12(4):236-241.

Coyle, J.T., Manji, H.K. (2002). Getting balance: drugs for bipolar disorder share target. Nat Med, 8(6):557-8.

Craft, L.L.& Landers, D.M. (1998). The effects of exercise on clinical depression and depression resulting form mental illness: A meta-analysis. Journal of Sport and Exercise Psychology, 20, 339-357.

Cumming, D., Rebar, R. (1983) Exercise and reproductive function in women. Am J Ind Med, 2:113-125.

Cumming, D.C., Brunsting, L.A., Strich, G., Ries, A.L., Rebar, R.W. (1986). Reproductive hormone increases in response to acute exercise in men. Med Sci Sports Exerc, 18(4):369-73.

Daley, A. (2002). Exercise therapy and mental health in clinical populations: is exercise therapy a worthwhile intervention? Advances in Psychiatric Treatment, 8: 262-270.

Delgado, P.L., Morena, F.A. (2000). Role of norepinephrine in depression. J Clin Psychiatry, 61 Suppl. 1:5-12.

Delgado, P.L. (2000). Depression: the case for monoamine deficiency. J Coin Psychiatry, Suppl. 6:7-11.

Depres, J.P., Lemieux, S., Lamarche, B. (1995). The insulin resistance-dyslipidemic syndrome: contribution of visceral obesity and therapeutic implications. Int J Obes Relat Metab Disord, Suppl 19: S76-86.

Deuster, P.A., Faraday, M.M, Chrousos, G.P., Poth, M.A. (2005). Effects of dehydroepiandrosterone and alprazolam on hypothalamic-pituitary responses to exercise. J Clin Endocrinol Metab, 90(8):4777-83.

DeVries, H.A., Bechman, P., Hubner, H... (1968). Electromyographic evaluation of the effects of sauna on the neuromuscular system. Journal of Sports Medicine and Physical Fitness, 8, 1-11.

Dienstbier, R.A. (1991). Behavioral correlates of sympathoadrenal reactivity: the toughness model. Med Sci Sports Exerc, 23(7): 846-852.

Dishman, R.K. (1997). Brian monoamines, exercise and behavioral stress: animal models. Med Sci Sports Exerc, 29(1):63-74.

Dishman, R.K., Renner, K.J., White-Welkley, J.E. (2000). Treadmill exercise training augments brain norepinephrine response to familiar and novel stress. Brain Res Bull, 52 (5): 337-342.

Doyne, E.J., Chambless, D.L., & Beutler, L.E. (1983). Aerobic exercise as a treatment for depression in women. Behaviour Therapy, 14, 434-440.

Doyne, E.J., Ossip-Klein, F.J., Bowman, E.D., Osborn, K.M., McDougall-Wilson, I.B., & Neimeyer, R.A. (1987). Running versus weight lifting in the treatment of depression. Journal of Consulting and Clinical Psychology, 55: 748-754.

Dressendorfer, R., Wade, C. (1991). Effects of a 15-d race on plasma steroid levels and leg muscle fitness in runners. Med Sci Sports Exerc, 23(8):954-958.

Dubrovsky, B. (1997). Natural steroids counteracting some actions of putative depressogenic steroids on the central nervous system: potential therapeutic benefits. Med Hypotheses, 49:51-55.

Duester, P., Faraday, M., Chrousos, G., Poth, M. (2005). Effects of Dehydroepiandostrone and Alprazolam on Hypothalamic-Pituitary Responses to Exercise. J of Clinical End and Met, 90(8):4777-4783.

Dunn, A.L., Reigle, T.G., Youngstedt, S.D. (1996). Brain norepinephrine and metabolites after treadmill training and wheel running in rats. Med Sci Sports Exerc, 28(2):204-9.

Ebeling, P., Koivisto, V.A. (1994). Physiological importance of dehydroepiandrosterone. Lancet, 343(8911):1479-81.

Farrel, P.A. (1989) Lack of exercise on peripheral enkephalin entry into whole brain of rats. Medicine and Science in Sports and Exercise, (abstract) 21,S35.

Faulkener, G. & Sparkes, A. (1999). Exercise as therapy for Schizophrenian ethnographic study. Journal of Sport and Exercise Psychology, 21:52-69.

Folkins, C.H., & Sime, W.E. (1981). Physical fitness training and mental health. American Psychologist, 36: 373-389.

Freemont, J., & Craighead, L.W. (1987). Aerobic exercise and cognition therapy in the treatment of dysphoric moods. Cognitive Therapy and Research: 11, 241-251.

Goodyer, I.M., Herbert, J., Altham, P.M.E., Pearson, J., Secher, S.M., Shiers, H.M. (1996). Adrenal secretion during major depression in 8-16 year olds, I: altered diurnal rhythms in

salivary cortisol and dehydroepiandrosterone (DHEA) at presentation. Psychol Med., 26:245-256.

Goodyer, I.M., Herbert, J., Altham, P.M.E. (1998). Adrenal steroid secretion and major depression in 8 to 16 year olds, Ill: influence of cortisol/DHEA ratio at presentation on subsequent rates of disappointing life events and persistent major depression. Psychol Med., 28: 265-273.

Goodyer, I.M., Park, R.J., Netherton, C.M., Herberg, J. (2001). Possible role of corisol and DHEA in human development and psychopathology. Br J Psychiaty, 179:243-249.

Greist, J., Klein, M., Eischens, R., Faris, J., Gurman, A., Morgan, W. (1979). Running as a treatment for depression. Comprehensive Psychiatry 20, 41-54.

Haffner, S.M., Valdez, R.A., Mykkanen, L., Stern, M.P., Katz, M.S. (1994). Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. Metabolism, 43(5):599-603.

Hakkinen, K., Pakarinen, A., Draemer, W.J., Newton, R.U., and Alen, M. (2000). Basal concentrations and acute responses of serum hormones and strength development during heavy resistance training in middle-aged and elderly men and women. J Gerontol A Biol Sci Med Sci, 55: B95-B105.

Harris, D.V. (1987). Comparative effectiveness of running therapy and psycholtherapy. IN: W.P. Morgan & S.E. Goldston (Eds.), Exercise and mental health (pp. 123-130). Washington, DC: Hemisphere.

Henderson, DC. (2002). Atypical antipsychotic-incuded diabetes mellitus; how strong is the evidence? CNS Drugs, 16:77-89.

Herbert, J. (1995). The age of dehydroepiandrosterone. Lancet, 345(8965):1648.

Herrington, D.M. (1998). DHEA: a biological conudrum. J Lab Clin Med, 131:292-294.

Hersey, W.C. III, Graves, J.E., Pollock, M.L., Gingerich, R., Shireman, R.B., Heath, G.W., Spierto, F., McCole, S.D., and Hagberg, J.M. Endurance exercise training improves body composition and plasma insulin responses in 70 to 79 year old men and women. Metabolism, 43:847–854, 1994.

Hinson., J.P., Raven, P.W. (1999). DHEA deficiency syndrome: a new term for old age? J Endocrinol, 163(1):1-5.

Hirshfeld, RM., (2000). History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry, 61 Suppl. 6:4-6.

Hollon, S.D. (2001). Behavioral activation treatment for depression: a commentary. Clin Psychol Sci Pract, 8(3):271-4.

Holsboer, D.F. (1995). Neuroendocrinology of mood disorders. IN: Bloom F.E., Kupfer, D.J. (eds) Psychopharmacology: the fourth generation of progress. Raven Press, New York, N.Y. pp 957-969.

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

Hopper, V.R., Yen, S.C. (1975). Circulating concentrations of DHEA and DHEAS during puberty. J Clin Endocrin Metab, 40:458-461.

Horne, J.A. & Staff, C.H. (1983). Exercise and sleep: Body heating effects. Sleep, 6:36-46.

Hucklebridge, F., Hussain, T., Evans, P., Clow, A. (2005). The diurnal patterns of the adrenal steroids cortisol and dehydroepiandrosterone (DHEA) in relation to awakening. Psychoneuroendocrinology, 30:51-57.

Hughes, J.R. (1984). Psychological effects of habitual aerobic exercise: a critical review. Prev Med, 13(1):66-7.

Huppert, F.A., Van Niekerk, J.K., Herbert, J. (2000). Dehydroepiandrosterone (DHEA) supplementation for cognition and well-being. Cochrane Database Syst Rev. 2000, (2):CD000304.

Hyman, S.E., Rudorfer, M.V. (2000). Depressive and bipolar mood disorders. IN: Dale DC, Federman DD, eds. Scientific American®; Medicine. Vol. 3. New York: Healtheon/WebMD Corp.; Sect. 13, Subsect. II, p. 1.

Johnson, L., Kraemer, R., Haltom, R., Kraemer, G., Gaines, H., Castracane, V. (1997). Effects of estrogen replacement therapy on dehydroepiandrosterone, dehydroepiandrosterone sulfate, and cortisol responses to exercise in postemnopausla women. Fertility and Sterility, 68(5):836-843.

Just, N. (1997). The response styles theory of depression: tests and an extension of the theory. J Abnorm Psychol, 106(2): 221-229.

Keizer, H.A., Kuipers, H., de Hann, J., Beckers, E., Habets, L. (1987). Multiple hormonal responses to physical exercise in eumenorrheic trained and untrained women. Int J Sports Med, 8:139-150.

Klimek, V., Stockmeier, C., Overholser, J., Meltzer, H., Kalka, S., Dilley, G., Ordway, G.A. (1997). Reduced levels of norepinephrine transporters in th elocus coeruleus in major depression. Journal of Neuroscience, 17(21): 8451-8458.

Knowlton, R., Brown, D., Hetzler, R., Sikora, R.(1990). Venous and fingertip blood to calculate plasma volume shift following exercise. Med and Sci Sport Ex, 22(6):854-857.

Lauc, G., Zvonar, K., Flogel, M. (2004). Post-awakening changes in calivary cortisol in veterans with and without PTSD. Stress and Health, 20(2)99-102.

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 randomized controlled trials. British Medical Journal, 322:763-766.

Leary, M.R. (1995.) The role of low self-esteem in emotional and behavioral problems: why is low self-esteem dysfunctional?. J Soc Clin Psychol, 14(3):297-314.

Lesch, K.P., Laux, G., Schulte, H.M. (1988). Corticotropin and cortisol response to human CRH as a probe for HPA system integrity in major depressive disorder. Psychiatry Res, 24(1): 25-34.

Liu, C.H., Lauglin, G., Fischer, U. (1990). Marked attenuation of ultradian and circadian rhythms of DHEA in postmenopausal women: evidence for a reduced 17, 20 desmolase enzymatic activity. J Clin Endocrin Metab. 71:900-906.

Longcope, C. (1996). DHEA metabolism. J Endocrin, 150:S125-S127.

Marieb, E.N., (2001). Human Anatomy & Physiology, Fifth ed. Benjamin Cummings, an imprint of Addison Weslty Longman, Inc. New York, NY pp 629-637

Martinsen, E.W., Medhus, A., & Sandvik, L. (1985). Effects of aerobic exercise on depression: A controlled study. British Medical Journal, 291:109.

Martisen, E.W, & Medhus, A. (1989). Adherence to exercise and patients' evaluation of physical exercise in a comprehensive treatment program for depression. Nordic Journal of Psychiatry, 43:411-415.

Martinsen, E.W. (1990). Benefits of exercise for the treatment of depression. Sports Medicine, 9:380-389.

Martisen, E.W. (1994). Physical activity and depression: clinical experience. Acta Psychiatr Scand Suppl, 377:23-27.

Massi, A.T. (1995). Sex hormones and rheumatoid arthritis: cause or effect relationships in a complex pathophysiology? Clin Exp Rheumatol., 13:227-240.

Mazat, L., Lafont, S., Berr, C., Debuire, B., Tessier, J.F., Dartigues, J.F., Baulieu, E.E. (2001). Prospective measurements of dehydroepiandrosterone sulfate in a cohort of elderly subjects: relationship to gender, subjective health, smoking habits, and 10-year mortality. Proc Natl Acad Sci USA, 98(14):8145-50.

McAuley, E., Mihalko, S.L., Bane, S.M. (1997). Exercise and self-esteem in middle-aged adults: multidimensional relationships and physical fitness and self-efficacy influences. J Behav Med, 20(1):67-83.

McAuley, E., Blissmer, B., Katula, J. (2000). Physical activity, self-esteem, and self-efficacy relationships in older adults: a randomized controlled trial. Ann Behav Med, 22(2):131-139.

McCann, I.L., & Holmes, D.S. (1984). Influence of aerobic exercise on depression. Journal of Personality and Social Psychology, 46:1142-1147.

McEwen, B.S. (2002). Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. Neurobiol Aging, 23:921-939.

Michael, A., Jenaway, A., Paykel, E.S., Herbert, J. (2000). Altered salivary dehydroepiiandrosterone levels in major depression in adults. Diol Psychiatry, 48:989-995.

Michael, R.P., Gibbons, J.L. (1963). Interrelationships between the endocrine system and neuropsychiatry. Int Rev Neurobiol, 11:243-302.

Morales, A.J., Nolan, J.J., Nelson, J.C. (1994). Effects of replacement dose of DHEA in men and women of advancing age. J Clin Endocrin Met, 78:1360-1367.

Morales, A.J., Haubrich, R.H., Hwang, J.Y. (1998). Effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating steroids, body composition and muscle strength in advanced men and women. Clin Endocrin, 49:421-432.

Morgan, W.P., (1985). Affective beneficence of vigorous physical activity. Medicine, Science, Sports and Exercise, 17:94-100.

Morgan, W.P., & O'Connor, P.J., (1988). Exercise and mental health. IN: Exercise Adherence: Its Impact on Public Health (ed Dishman, R.K.), Human Kineteic Books, Champaign, IL. pp.91-121.

Mortola, J.F., Yen, S.S. (1990). The effects of oral dehydroepiandrosterone on endocrine-metabolic parameters in postmenopausal women. J Clin Endocrinol Metab, 71(3):696-704.

Mutrie, N. (2000). The relationship between physical activity and clinically defined depression. In: S.J.H. Biddle, & K.R. Fox, (Eds.), Physical activity and psychological well-being. Routledge, London, pp.46-62.

Narrow, W.E., (1998). One-year prevalence of depressive disorder among adults 18 and over in the U.S.: NIMH ECA prospective data. Population estimates based on U.S. census estimated residential poulation age 18 and over on July 1, 1998. Unpublished.

Nester, J.E., Clore, J.N., Blackard, W.G. (1992). Dehydroepiandrosterone: the "missing link" between hyperinsulinemia and atherosclerosis? FASEB J, 6(12):3073-5.

NIMH Genetics Workgroup. (1998). Genetics and mental disorders. NIH Publication No. 98-4268. Rockville, MD: National Institute of Mental Health.

Nolen-Hoeksema S, Morrow J. (1993). Effects of rumination and distraction on naturally occurring depressed mood. Cogn Emot, 7(6): 561-570.

North, T.C., McCullagh, P., Tran, Z.V. Effect of exercise on depression. (1990). Exercise and Sport Sciences Reviews, 18:379-415.

Oades, R.D., Schepker, R. (1994) Serum gonadal steroid hormones in young schizophrenic patients. Psychoneuroendocrinology, 19:373-38.

Ossip-Klein, D.J., Doyne, E.J., Bowman, E.D. (1989) Effects of running or weight lifting on self-concept in clinically depressed women. J Cnsult Clin Psychol, 57(1):158-161.

Pelham, T. & Campagna, P. (1991). Benefits of exercise in psychiatric rehabilitation of persons with schizophrenia. Canadian Journal of Rehabilitation, 4:159-168.

Perrini, S., Laviola, L., Natalicchio, A., Giorgino, F. (2005). Associated hormonal declines in aging: DHEAS. J Endocrinol Invest, 28(3 Suppl):85-93

Pert, C.B. & Bowie, D.L. (1979). Behavioral manipulation of rats causes alterations in opiate receptor occupancy. Endorphins and Mental Health. Eds E. Usdin, W.E.Bunney & N.S. Kline, New York: Oxford University Press, pp. 93-104.

Ponjee, G., Hans, A., De Rooy, M., Vader, H. (1994) Androgen turnover during marathon running. Med Sci Sport Exerc, 26:1274-1277.

Ransford, C.P., (1982). A role for amines in the antidepressant effect of exercise: a review. Medicine, Science, Sports and Exercise, 14:1-10.

Ravaglia, G., Forti, P., Maioli, F., Sacchetti, L., Nativio, V., Scali, C.R., Mariani, E., Zanardi, V., Stefanini, A., Macini, P.L. (2002). Dehydroepiandrosterone-sulfate serum levels and common age-related diseases: results from a cross-sectional Italian study of a general elderly population. Exp Gerontol, 37(5):701-12.

Regelson, W., Kalimi, M. DHEA – the multifunctional steroid.11. Effects on the CNS, cell proliferation, metabolic and vascular, clinical and other effects. Mechanism of action? Annals NY Acad Sci, 719:564-575.

Roberts, J.E., Gotlit, I.H. (1997). Temporal variability in global self-esteem and specific self-evaluation as prospective predictors of emotional distress: specificity in predictors and outcomes. J Abnorm Psychol, 106(4):521-9.

Rose, K.A., Stapleton, G., Dott, K., Kieny, M.P., Best, R., Schwartz, M., Russell, D.W., Bjorkheim, I., Seckl, J., Lathe, R. (1997). Cyp7b, a novel brain cytochrome P450, catalyzes the synthesis of neurosteroids 7alpha-hydroxy dehydroepiandrosterone and 7alpha-hydroxy pregnenolone. Proc Natl Acad Sci USA, 94:4925-4930.

Rudman, D., Shetty, K.R., Mattson, D.E. (1990. Plasma dehydroepiandrosterone sulfate in nursing home men. J Am Geriatr Soc, 38(4):421-427.

Schatzberg, A.F. (1998). Noradrenergic versus serotonergic antidepressants: predictors of treatment response. J Clin Psychiatry, (59) Suppl. 14:15-8.

Schneider, L.S., Hinsey, M., Lyness, S. (1992). Plasma dehydroepiandrosterone sulfate in Alzheimer's disease. Biol Psychiatry, 31(2): 205-208.

Scott, L.V., The, J., Reznek, R., Martin, A., Sohaib, A., Dinan, T.G. (1999). Small adrenal glands in chronic fatigue syndrome: a preliminary computer tomography study. Psychoneuroendocrinology, 24:759-768.

Sime, W.E. (1987). Exercise in the prevention and treatment of depression. IN: W.P. Morgan and S.E. Goldston (Eds.), Exercise and mental health. Washington, DC: Hemisphere, pp. 145-152.

Sonstroem, R.J. (1984). Exercise and self-esteem. Exercise and Sports Sciences Review 12:123-155.

Spearing, M., Hendrix, M.L., Hyman, S., Rudorfer, M., Pearson, J., Wittenberg, M.S., Alberts, L.D. (2002) *What is Bipolar Disorder?* Retrieved Jan. 2006 from http://www.nimh.nih.gov/publicat/bipolar.cfm#intro.

Steinberg, H. & Sykes, E.A. (1985). Introduction to symposium on endorphins and behavioral processes: a review of literature on endorphins and exercise. Phyamacology. Biochemistry and Behavior, 23:857-862.

Sterling, P., Eyer, J. (1988). Allostasis: a new paradigm to explain arousal pathology. *Handbook of Life Stress, Congition, and Health.* Edited by Fisher S, Reason J. New York, John Wiley and Sons, pp 629-649.

Sunderland, T., Merril, C.R., Harrington, M.G., Lawlor, B.A., Molchan, S.E., Martinez, R., Murphy, D.L. (1989). Reduced plasma dehydroepiandrosterone concentrations in Alzheimer's disease. Lancet 2(8662): 570.

Thase, M.E., Sachs, G.S. (2000). Bipolar depression: pharmacotherapy and related therapeutic strategies. Biological Psychiatry, 48(6):558-572.

Tipperman, Jay. (1980) *Metabolic and Endocrine Physiology, 4th ed.* Year Book Medical Publisher, Inc. Chicago, IL pp.172-174.

Tissandier, O., Peres, G., Fiet, J., Piette, F. (2001). Testosterone, dehydroepiandrosterone, insulin-like growth factor 1, and insulin in sedentary and physically trained aged men. Eur J Appl Physiol, 85(1-2):177-84.

Tkachuk, G., Martin, G. (1999). Exercise Therapy for Patients with Psychiatric Disorders: Research and Clinical Implications. Professional Pscyhology: Research and Practice: 3(3):275-282.

Tremblay M, Copeland J, Van Helder W. (2004). Effects of training status and exercise mode on endogenous steroid hormones in men. J Appl Physiol, 96:531-539.

Wardlaw, S.L. & Frantz, A.G. (1980). Effects of swimming stress on brain-endorphin and ACTH. Clinical Research, 28:482.

Webster, M.J., O'Grady, J., Orthmann, J., Weickert, C.S. (2000). Decreased glucocorticoid receptor mRNA levels in individuals with depression, bipolar disorder and schizophrenia. Schizophr Res, 41(1): 111-112.

Weicker, H., Struder, H.K. (2001). Influence of exercise on serotonergic neuromodulation in the brain. Amino Acitds: 20(1):35-47.

Wittert, G.A., Livesey, J.H., Espiner, E.A. (1996). Adaptation of the hypothalamopituitary adrenal axis to chronic exercise stress in humans. Med Sci Sports Exerc, 28(8):1015-1019.

Wolkowitz, O.M. (1994). Prospective controlled studies of the behavioral and biological effects of exogenous corticosteroids. Psychoneuroendocrinology, 19:233-255.

Wolkowitz, O.M., Reus, V.I., Roberts, E., Manfredi, F., Chan, T., Raum, W.J., Ormistron, Johnson, R., Canick, J., Brizendine, L., Weingartner, H. (1997). Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry, 41:311-318.

Wolkowitz, O.M., Reus, V.I., Keebler, A., Nelson, N., Friedland, M., Brizendine, L., Roberts, E. (1999). Double-blind treatment of major depression with DHEA. Am J Psychiatry, 156:646-649.

Wuest, I., Federenko, D., Hallhammer, H., Kirschbaum, C. (2000) Genetic factors, perceived chroic stress, and the free cortisol response to awakening, Psychoneuroendocrinology, 25: 707-7220.

Wyatt, R.J., Henter, I.D. (1995). An economic evaluation of manic-depressive illness – 1991. Soc Psychiatry Psychiatr Epidemiol. 30:213-219.

Yen, S.S., Morales, A.J., Khorram, O. (1995). Replacement of DHEA in aging men and women. Potential remedial effects. Ann N Y Acad Sci., 774:128-42.

Young, A.H., Gallagher, P., Porter, R.J. (2002). Elevation of the corisol-DHEA ratio in drug-free depressed patients. Am J Psychiatry, 159:1237-1239.

Zumoff, B., Walsh, B.T., Katz, J.L., Levin, J., Rosenfeld, R.S., Kream, J., Weiner, H. (1983). Subnormal plasma dehydroepiandrosterone to cortisol ratio in anorexia nervosa: a second hormonal parameter of ontogenic regression. J Clin Endocrinol Metab, 56:668-672.