E V E X I A S M E D I C A L

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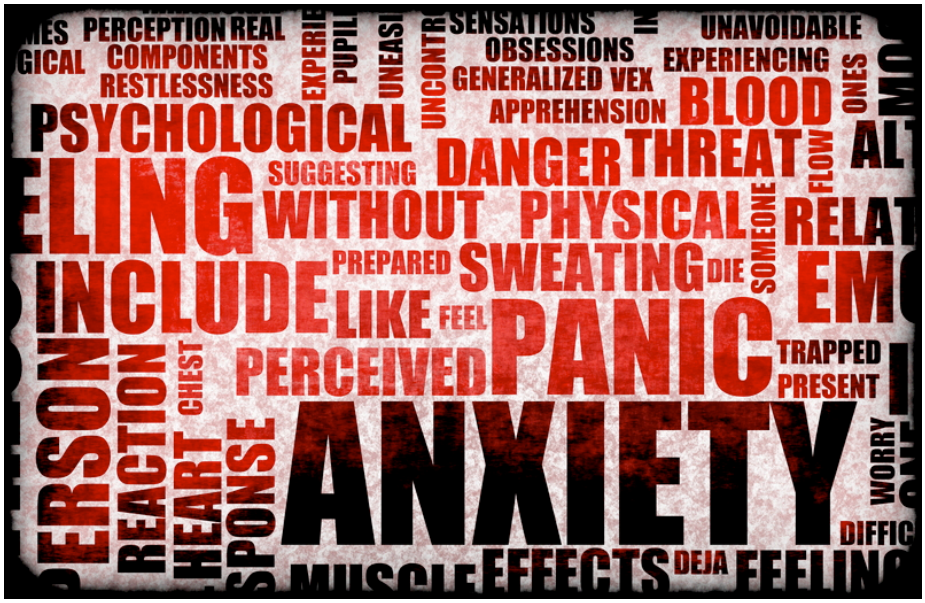
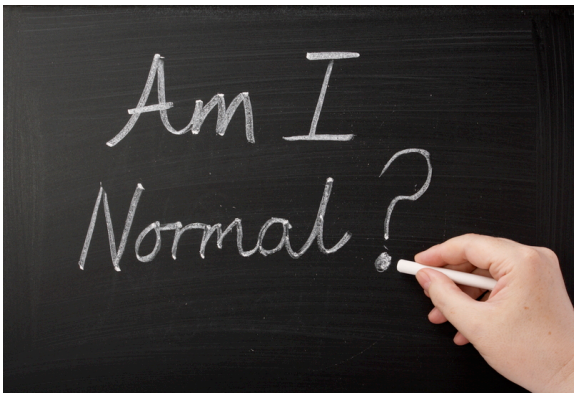
TREATMENT OPTIONS FOR DEPRESSION & ALTERED MOOD STATES IN WOMEN

UNDERSTANDING THE ROLE OF ANDROGENS



A Global Issue: *Depression and Altered Mood States in Women*

As a Nurse Practitioner focusing on advanced endocrinology in women's health over the past 8 years, I have recognized an overarching theme: *all women feel some level of lost sense of self at some point in their lives, most notably during periods of profound hormone changes.* Almost daily we have a new patient in one of our clinics who exhibits one of two predominant responses to our clinical assessment of her anxious, depressive or otherwise altered mood state: she may sigh or cry with relief that there is hope for what she has been going through, that she is not going crazy, that she is "normal"; or she may rage in disbelief and wonder why no one has ever told her this before.



"This" being the profound affect hormone fluctuations and subsequent decline can have on an otherwise happy, healthy productive life. She may go on to feel the same relief, or rage, that there is hope beyond more prescription drugs for her depression, anxiety and insomnia; that there is possibly a "root cause" and real solution for restoring her prior level of functioning.

The presence of depression and other mood disturbances in women is a widespread, worldwide phenomenon, crossing cultural and ethnic lines with a lifetime prevalence of up to 23% [1]. Depression and anxiety are twice as likely to occur in women as in men; are a leading cause of dysfunction, decreased productivity and disability in women, and noted in several studies to be a key component of decreased quality of life and sense of well being[2] .

"Depression and anxiety are a leading cause of dysfunction, decreased productivity and disability in women"

The differences between men and women in depression rates have also been observed worldwide, and these documented sex differences have led to the observation that hormone fluctuations are a major contributor to female rates of depression, anxiety and other altered mood states[3] .

[1] Gyllstrom, et.al, 2007

[2] Davis & Tran, 2001; Gyllstrom, et.al., 2007; McHenry, et.al., 2014; Rohr, 2002; Woods & Mitchell, 2005

[3] Gyllstrom, et.al, 2007

The definition of non-major clinical depression holds a great deal of ambiguity. Depressive symptoms can be present that do not meet the diagnostic criteria of major depressive disorder (MDD), yet still have profound life altering consequences when they persist; further, mild to moderate depression has been shown to be more prevalent in the general population than MDD and is often overlooked or ignored[4] .

"Only about 10% of women will report these symptoms to their primary care provider"

Of utmost concern is only about 10% of women will report these symptoms to their primary care provider, and many practitioners misunderstand and underestimate the encumbering effects of these symptoms[5].

Menopausal Transition: ***Consequences of Hormone decline***

Menopause comes from the root words "pause in menses" and is defined as the 12-month period after the last menstrual cycle (one year without a menstrual cycle); post menopause is defined as the time after menopause[6]. The peri-menopausal period is the time of irregular menstrual patterns combined with elevated or fluctuating follicle stimulating hormone (FSH) levels preceding menopause, starting as young as the mid 30's and lasting anywhere from 2-8 years[7]. The terms pre-menopause, peri-menopause, menopause, and post-menopause are often erroneously interchanged or misused and create further confusion when dialoging about this stage of a woman's life.

Hormone decline during the third through fifth decades of life, referred to clinically as the menopausal transition, is central to decreased health and quality of life (QOL). An often misdiagnosed and mismanaged sequela during this time is depression, anxiety and altered mood states resulting from hormone decline and exacerbated by symptomatology of hormone decline; specifically androgen decline and deficiency.

The far reaching impact of restoring androgen homeostasis on quality of life is also an often misunderstood phenomenon in both the healthcare and lay communities.

[4] Gyllstrom, et.al, 2007

[5] Woods & Mitchell, 2005

[6] Gyllstrom, et.al., 2007; Utain, 1994

[7] Gyllstrom, et.al., 2007

The peri-menopausal and post-menopausal stages of a woman's life is most devastating regarding symptoms and the impact of symptoms on overall functioning and quality of life. Further, as many healthcare providers are unaware of the connection, hormone fluctuations are often overlooked as a cause of their female patients nonspecific symptoms of mood alterations, fatigue and sleeplessness; she is often diagnosed as "too stressed" and either clinically ignored and told to rest and exercise, or given a prescription for an antidepressant, sleeping pill or anxiety pill to band-aide her symptoms. An astute provider may suggest a trial of estrogen hormone, but often this only accomplishes partial relief of symptoms, and only if she is clinically deficient in estrogen.

"Hormone fluctuations are often overlooked as a cause of the nonspecific symptoms of mood alterations, fatigue and sleeplessness"

It's Not Just Estrogen: ***The Role of Testosterone in the Menopause Transition***

Historically it has been postulated estrogen is a woman's key hormone, and estrogen decline has been the primary area of focus for researching women experiencing the menopausal transition; however emerging data supports the greater role androgens, primarily testosterone, play in neuropsychology, and demands further exploration and study[8] .

Androgen receptors are found on virtually every cell in the female human body, indicating the role they play in normal tissue homeostasis. When testosterone is deficient, the risk of pathologies including breast cancer, osteoporosis and cognitive decline may increase[9].

Androgen deficiency results in several variables that have an impact on health related quality of life (HRQOL), and a woman's response to symptoms can have deleterious effects ranging from physiological, psychological, biosocial and behavioral outcomes[10].

Some of these symptoms may include, but are not limited to, sleep deprivation, mood swings, depression, anxiety, brain fog, difficulty focusing, and memory loss; night sweats, weight gain, low libido, and extreme fatigue.

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[8] Glaser, et.al., 2013; McHenry, et.al., 2014

[9] Dimitrikakis, 2011

[10] Dodd, et.al., 2001

Of these, sleep deprivation has the most significant compounding effect and exacerbates the depression, anxiety, moodiness and impaired cognitive function a woman may be experiencing.

"Emerging data supports the greater role androgens, primarily testosterone, play in neuropsychology"

Androgen replacement has been shown in women improve mood, lift anxiety and depression, and improve sleep patterns[11]. Along with improving overall sense of well-being and quality of life, the sex hormones have been shown to prevent osteoporosis, increase muscle mass, increase muscle strength, increase bone density, reduce visceral fat, reduce total cholesterol levels, induce glucose homeostasis, increase metabolism, manage PMS, reduce severity and frequency of migraine headaches, improve cognition and memory, and prevent Alzheimer's disease[12].

Despite the plethora of data to support androgen replacement in women globally, and the fact that it has been used safely in women for almost a century, as of 2013, and currently, there are no testosterone only products licensed by the FDA for use in women in the U.S.[13].

A synthetic estrogen, progesterone and testosterone combination is on market in the U.S. (Estratest® and Syntest®) however peri-menopausal women who do not need estrogen therapy, or women that cannot take synthetic progestins or estrogen are left with no treatment alternatives that are FDA approved.

All other treatment modalities using testosterone in women in the U.S. are considered off-label.

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[11] Bachmann, 1999; Conner, et. al., 2008; Carnahan & Perry, 2004; Davis, et. al., 2001; Davis, 1999; Ebinger, et. al., 2009; Glaser, et.al., 2011; Nappi & Lachowsky, 2009; Panay & Fenton, 2009; Sands & Studd, 1995; Studd & Panay, 2004

[12] Bachmann, 1999; Beauchet, 2006; Bialek, et. al., 2004; Boyanov, et. al., 2003; Cherrier, et. al., 2001; Davis, 1999; Davis & Tran, 2001; Davison, et. al., 2011; Glaser, et. al., 2012; Hammond, et. al., 2001; , 2005; Okun, 2006; Pike, et. al., 2009; van Geel, 2009; Vanderschueren, et. al., 2004

[13] Glaser & Dimitrakakis, 2013; Maclaran & Panay, 2012

Part of the reason for these findings is related to the great deal of confusion and myth surrounding androgen replacement in women, leaving practitioners either unaware or ill informed about the safety and efficacy of this treatment alternative[14].

Dazed and Confused: ***Healthcare Providers Lack Understanding***

Many family practice, internal medicine, and women's health physicians, nurse practitioners, PAs and other healthcare providers have stated they are severely lacking instruction on safely and effectively guiding women through the menopausal transition. There is little consensus across National Guidelines regarding hormone replacement therapies, and confusion around the results of the WHI have left many providers with more questions than answers when it comes to managing their female patients during this time.

"Healthcare providers are severely lacking instruction on how to guide women through the menopausal transition and post menopause"

As there are no FDA approved testosterone products for women on the market, many practitioners are not educated about the role of this vital hormone in women; further, many practitioners have reported they were unaware women even made testosterone, much less needed it for optimal functioning.

Healthcare providers report there is data lacking in our most popular peer reviewed medical journals regarding hormone decline and as it relates to HRQOL, as well as the short and long-term safety and efficacy of androgen replacement methodologies.

In actuality, there are hundreds of research articles that speak to the positive role androgens play in the areas of psychological, neurological, cardiac, gynecological and urological functioning, as well as the musculoskeletal and metabolic systems.

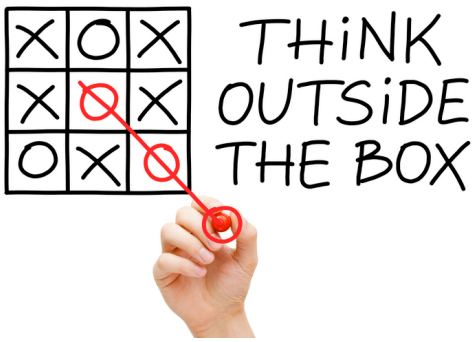
Studies abound regarding the roles androgen hormones play in all body systems and disease processes, as well as the safety and efficacy of androgen replacement modalities; they are simply not easily accessible in the common peer reviewed journals to which most practitioners prescribe.

[14] Glaser & Dimitrakakis, 2013

These types of articles can be found in journals such as: *Journal of the National Cancer Institute, Circulation, Frontiers in Neuroendocrinology, Clinical Endocrinology and Metabolism, World Journal of Urology, European Journal of Endocrinology, JAMA, and Maturitas: The European Menopause Journal,* to name a few; not the common journals noted in many healthcare practitioners mailboxes, email inboxes or desks.

What Can Healthcare Providers Do: *Thinking Outside the Box*

The overarching concept relating to HRQOL in this white paper is androgen homeostasis. Androgen deficiency results in several vague and often misdiagnosed symptoms that impact HRQOL. Response to symptoms can have deleterious effects ranging from physiological, psychological, biosocial and behavioral outcomes[15]. The combination of symptoms during the menopausal transition, such as hot flashes and sleep loss, can exacerbate the feelings of depression, anxiety and decreased QOL, yet it varies from patient to patient.



Historically androgen deficiency is not the focus of assessment, diagnosis and subsequent treatment for altered mood states in females, and additional education for healthcare practitioners around the role of androgen decline in depression, anxiety and mood changes and subsequent symptom relief of with replacement of androgens in women is needed.

With access to thousands of women daily in clinics across the nation, primary care and women's healthcare practitioners have a unique opportunity to open the dialogue of altered mood states in their midlife female patients, and discuss viable treatment options. Androgen decline can start as early as 30 years old, so these conversations are not limited to the obvious menopausal or post menopausal women.

"Androgen therapy is highly effective in relieving depression, anxiety, mood swings and insomnia"

It is imperative healthcare providers expand their horizons in the areas of treating hormone related depression, anxiety

[15] Dodd, et.al., 2001

and altered mood states; broaden the scope of their education and knowledge in the role of androgen, namely testosterone replacement, in optimizing women's health.

Evexias Medical Centers has treated well over 5000 androgen deficient women experiencing varying degrees of hormone related psychological symptoms with androgen replacement therapy. Using a validated tool, the MRS questionnaire, and informal interviews, thought leaders at Evexias have measured 100% relief of altered mood states in the vast majority of women treated with testosterone replacement.

When dosed and monitored appropriately, androgen therapy is highly effective in relieving depression, anxiety, mood swings and insomnia, which in turn may improve over-all sense of well-being and quality of life in women.

Based on years of experience using evidence based treatment modalities, collaborating with top medical providers and researchers in the field of menopausal hormone therapies, including androgen replacement, and spearheading the training of over 1000 practitioners across the country, Evexias Medical is passionate about sharing what we have learned with other like-minded healthcare providers whose focus is to increase the quality of life and sense of well being, and offer hope to every patient they serve.

Case Study: ***A story of hope and restoration***

When her husband proposed to her over 35 years ago, Bobbie V. was a vivacious, energetic, loving woman full of all the hope and promise her life ahead had to offer. Through the years of marriage and rearing of four children, Bobbie V. maintained that spark and enthusiasm in everything she did.

About the time she was in her early 40's however, the light began to dim in this once spirited wife and mother, and her well established OB/GYN spouse was at a loss of what to do. Bobbie began to exhibit signs of depression, anxiety and extreme moodiness that was unexplainable and confusing to her entire family.
By the time she was in peri-menopause some 6 years later, she began to take oral estrogen and progesterone for her symptoms with little to no improvement in her depression or extreme mood swings. At age 65 her then retired husband, desperate for a solution, brought her to our clinic.

"Thank you for giving me my wife back"

Mrs. V. had all the classic symptoms of androgen deficiency, and a treatment plan that included a regime of low dose androgen, estrogen and progesterone was started. Four weeks later at her follow up visit, Mrs. V. broke in to tears when I walked in the room. My first thought was I had gotten her treatment plan all wrong, but after she composed herself she went on to share " *I haven't liked my husband for 25 years, and now I realize all of this time it was me and not him....I feel like I have lost so much time with him and I cant get it back, he is 85 years old and I don't know how much more time we have".*
A few weeks later, Mr. V was on my schedule as a patient, when I walked in the room he stopped me and said: "*Before we start, I have to say two things. First, thank you for giving me my wife back. Second, had I known about this therapy when I was a practicing gynecologist, I would have used it on all of my patients based on the changes I have seen in my wife".*

This story never ceases to inspire me. You see, both Mr. V and Mrs. V were lamenting the loss of time, the years of hopelessness and helplessness that resolved as a result of a simple assessment and treatment plan that included optimizing androgen levels with testosterone replacement therapy.

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