Intervention: Effects of Steroids on Mood/Depression
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Abstract

Mood disorders are twice as prevalent in women compared to men. Although it was once thought that this gender predominance was due to psychosocial factors, these differences are now understood as a neurohormonal etiology. While clinical research has been unable to demonstrate direct correlations between hormones and mood, more recent work has focused on the hypothalamic pituitary axes and the interaction with the central nervous system. Affective disorders are more prevalent in women during rapid shifts in reproductive hormones associated with the premenstruum, puerperium and perimenopause. Some women are particularly vulnerable to psychiatric disorders during these times of the female life cycle. Although menopause was once thought to be a time for increased risk of depression, there is no evidence for mood vulnerability at this time. In fact, perimenopause is a more vulnerable time for affective change. Alterations in central nervous system monoamines are implicated in the etiologies of affective and psychotic disorders. The gonadal hormones provide feedback control over the HPG axis and influence the synthesis, degradation and uptake of these brain chemicals. The clinical implications of these biological substrate changes include altered mood states associated with endogenous and exogenous steroids. Although high circulating estrogen levels improve mood in women with normal affective states, progesterone reduces this effect of ERT. Mood states associated with premenstrual disorders, puerperal psychiatric disorders and HRT in postmenopausal women are discussed. Altered affective states associated with oral contraceptives and GnRH agonists are also considered. Methodological difficulties in neuroendocrine research are reviewed and implications for treatment are discussed.
I. Introduction

Gender differences in mood disorders are well recognized, and replicated in large clinical epidemiological studies [1]. Several hypotheses have been proposed for the etiology of this gender predominance. Once thought to be due to psychosocial, and/or genetic factors, these differences are now proposed to have neurohormonal etiologies [2].

Both Western and cross cultural studies agree that menopause is a normal physiological state characterized by elevated serum levels of LH and FSH and reduced levels of circulating estrogen and progesterone. It was believed that menopausal mood changes were a result of increasing chronological age, or manifestations of vasomotor symptoms which contribute to depression. We now understand a biological hypothesis centered around the relationship between decreasing levels of gonadal hormones and depressed mood. Some women experience an abnormal vulnerability to this hormonal flux [3].

Depression is a state change characterized by a persistently depressed or irritable mood. [4] Mood symptoms are associated with neurovegetative signs of increased or decreased appetite, weight or sleep. Perceptual changes such as poor self esteem and feelings of impoverishment may be prominent. The cognitive changes of major depression such as loss of memory and concentration may mimic early dementia and confront the physician with a difficult differential.

Depression is twice as prevalent in women compared to men. The Epidemiological Catchment Area study [1] found that the lifetime prevalence of depression for men is 2.3-4.4% and 4.9-8.7% for women. The preponderance of depression for women is during the childbearing years with a prevalence of 7.5-10.4% from age 23-44 years.

Clinical studies have also been unable to demonstrate direct associations between hormones and mood [2]. Recent research has
focused on the activity of the hypothalamic pituitary axis (HPA) and its interaction with the central nervous system. The neurohormonal basis of mood disorders in women is understood as steroid hormone changes which trigger alterations in brain neurochemicals. In turn, reciprocal feedback from the brain monoaminergic system modulates the hypothalamic pituitary axes.

The link between gender and mood is initially recognized at adolescence. An equal prevalence of affective disorders exist in boys and girls until the age of puberty [5]. At puberty, the onslaught of hormones is associated with an increased incidence of depression in girls compared to boys. These affective states have a temporal relationship to hormonal status, a trend which continues as shifts in reproductive hormones persist throughout the female life cycle. Reproductive hormone production and altered mood states are demonstrated in the puerperium, the premenstruum and perimenopause [6,7,8].

The view of menopause as a time of depression and melancholia for women has been challenged [9]. The term "involutional melancholia" was introduced by Kraepelin in 1896. Although the United Kingdom was skeptical of this diagnostic category as far back as the 1930s, this concept took longer to discard in America. Weissman [10] discovered that mood disorders were not more prevalent in menopausal women than women at any other time of their life cycle. She concluded that there is no evidence for a category of "involutional melancholia," a term no longer included in the World Health Organization's International Classification of Diseases [3,9,11].

Perimenopause appears to be a time of particular vulnerability for women. It has been suggested that the hormonal fluctuations during the immediate premenopausal years are responsible for this affective instability [12]. Similarly, surgical menopause induces mood changes because of the rapid hormonal loss at this time.
A. Depression and Neuroendocrine Regulation

The neuroendocrine system is complex and well integrated. It involves the release of anterior pituitary hormones by hypothalamic factors and feedback control by circulating target organ hormones. The entire system is controlled by internal biological rhythms or external events affecting the hypothalamus [13].

Patients with depression tend to have neuroendocrine dysregulation, which includes a hyperactive hypothalamic pituitary adrenal (HPA) axis and non-suppression of dexamethosone by cortisol [14]. This dysregulation also extends to pregnant and postpartum depressed women [3].

This HPA axis dysregulation may be a result of disturbed physiology of the hypothalamic and limbic system centers that control secretion of corticotrophin releasing factor (CRF) and adrenocorticotropic hormones (ACTH). Alternatively, abnormal neurophysiology and central nervous system function may cause the depressed state and HPA axis over activity. With successful antidepressant treatment [14], the HPA system normalizes. As the mood normalizes, the HPA axis is more susceptible to normal cortical feedback inhibition by cortisol [Figure 1].

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Cortisol is a major glucocorticoid secreted from the adrenal cortex (15) Under stress both serotonin (5HT) and norepinephrine (NE) regulate release of Cortisol Releasing Factor (CRF) which in turn, activates the secretion of ACTH from the anterior pituitary. Sporadic bursts of ACTH increase plasma cortisol.

The effects of corticosteroids on the electrical properties of brain cells have been described [16]. Temporary fluctuations in corticosteroid levels after acute stress modulate neurotransmitter responses in the hippo campus, a brain structure
involved in mood and cognition. This data may explain mood
disturbances observed in association with stress related
disorders.

Cortisol changes correlate with sleep electroencephalogram (EEG) activity. EEG patterns in depressed patients show short REM latency, decreased slow wave sleep and sleep continuity disturbance. When Jarrett et al. [16] measured cortisol with sleep EEG function, the short cortisol latency in the sleep measure correlated with the short REM latency in depressed subjects.

Gender differences in brain physiology are reflected in the electrical activity of the brain and related to the hormonal status of the reproductive cycle. Altered EEG alpha wave activity reflects changes in gross electrical activity which parallel altered hormone levels [17]. The brain monoaminergic pathways involved in steroid feedback appear to be the underlying mechanism.

B. Female Gonadal Steroids

Estrogen is the most likely component of the hypothalamic pituitary ovarian axis related to mood. Estrogen has demonstrated antidepressant properties in vivo and in vitro, while progesterone has opposite effects [2]. Lipophilic ovarian hormones easily cross the blood brain barrier. Estrogen receptors are widely disseminated in the brain [18] at sites such as the pituitary, hypothalamus, limbic forebrain and monoaminergic neurons in the brainstem. Estrogen modulates the synthesis of central nervous system (CNS) enzymes, peptides, neurotransmitters and receptors all of which contribute to altered affective states. It also affects monoamine synthesis and turnover, and spontaneous electrical activity in the brain [2].

Both estrogen and progesterone effect neurotransmitter function [19] of dopamine (DA), norepinephrine, serotonin (5HT) and gamma amino butyric acid (GABA). Progesterone decreases NE concentration in the rat brain suggesting its etiological role in depression. Progesterone mediates DA release from the corpus
striatum, while estrogen modulates dopamine (DA) transmission and release in the nucleus accumbans [20].

Gonadotropin Releasing Factor (GnRH) is released from the hypothalamus to cause secretion of luteinizing and follicular stimulating hormones (LH/FSH) with subsequent ovarian steroid production [21]. GnRH has demonstrated some antidepressant effects in animal models and humans. Because GnRH neurons are close to fibers containing NE and 5HT, it has complex actions on mental status. Paradoxically, GnRH treatment may facilitate depression [22], yet it also abolishes negative mood symptoms in the premenstruum by impairing ovarian cyclicity [21]. This complicated situation extends to neurotransmitter interactions and is further complicated by the likelihood that the hypothalamic pituitary gonadal (HPG) axis is also interactive with the hypothalamic pituitary adrenal (HPA) axis and the hypothalamic pituitary thyroid (HPT) axes, all implicated in affective disorders.

II. Mood Disorders Across the Female Life Cycle

Affective disorders in women are associated with specific times of the reproductive life cycle [23]. Because there appear to be alterations in the steroid hormones with negative mood states, recent thinking is focused on the existence of a particular vulnerability in some women to the normal hormonal changes. In addition, women with affective disorder at one particular phase of the female life cycle often experience recurrence at other times of hormonal flux.

Stewart and Boydell [23] screened 44 women in a menopause clinic who scored high on a psychological distress scale and compared them to 42 women in a low distress group. Women with high distress were more likely than the low distress women to report a past psychiatric diagnosis, depressive symptoms associated with oral contraceptive use, premenstrual depression, postpartum blues or postpartum depression.

Association between female affective disorders, steroid
hormones and brain neurotransmitter function supports a neurohormonal etiology which is demonstrated along the life cycle continuum. In order to understand this relationship of steroid related mood states to menopause, the biological underpinnings of other female life cycle phases will be reviewed. In particular, a review of each phase and the association with substrate changes along the HPG axis are considered.

Recent findings on the relationship of mood and the neuroendocrine system have challenged the field of neuroendocrinology. Studies reveal underlying mechanisms for the interaction of gender and mood. Gender differences in the central nervous system (CNS) begin in the perinatal period upon exposure to sex steroids. This process is responsible for the development of dimorphic brain morphology and function [24]. Differences in neuromorphology, neurochemistry and physiology may contribute to the prevalence of neuropsychiatric disorders in women, and may account for the contrast in processing emotions between the sexes. The limbic, hippo campus, and the hypothalamus (HT) are sexually dimorphic systems. The HT demonstrates gender differences in distribution of neurotransmitters and shape of synapses. PET scans reveal 15% greater cerebral cortical blood flow and glucose metabolism in women compared to men.

Because both male and female reproductive hormones are derived from cholesterol, there is considerable overlap in circulating blood levels of estradiol in normal men and women. Therefore estrogen is not found exclusively in women, nor androgen in men.

Hamilton et al.[25] reviewed the variability of gonadal hormones between sexes. Estrogen receptors are found in male and female rodents. An example of a hormone found predominately in one sex but having similar effects in both is androgen which increases libido in women and in hypogonadal men. Progesterone elevates basal body temperature in both.

Steroids may have gender specific effects in some brain regions. For example, the inter conversion among hormones can occur in the brain so that estrogen may mediate testosterone's
effects on some monoamine systems such as DA.

The diurnal variation, of cortisol and testosterone is greater in men than women. Although both hormones vary by season in men, women demonstrate more seasonal behavior changes. Therefore it does not appear that the amplitude of hormonal changes correlate with changes in behavioral symptoms.

A. Premenstruum

A reported 75% of women complain of premenstrual somatic and behavioral symptoms during the 10-14 day luteal phase of the menstrual cycle. However, only 3-8% fulfill diagnostic criteria described in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM4) [4]. This criteria for Premenstrual Dysphoric Disorder (PMDD) includes depression, irritability, sleep and appetite change which are serious enough to interfere with social, occupational or family functioning [27]. PMDD is described under the general category of mood disorders.

The International Classification of Diseases [11] considers this disorder under the category of medical genitourinary disorders. DSM4 criteria for this diagnosis includes severe incapacitating behavioral changes which are 30% worse in the luteal phase than in the follicular phase of the cycle. Physical symptoms of PMS are not necessary to fulfill criteria for this disorder.

The fact that women with diagnosed PMDD are more likely to suffer major depressive episodes in later life supports a common vulnerability [28] which is likely represented in the activity of the hypothalamic pituitary gonadal (HPG) axis. In addition, the likelihood of suicide and psychiatric admissions in women increases at this time, while women with existing psychiatric illness experience worsening symptoms [28]. Because symptoms intensify with the rise of progesterone after ovulation and with the rapid fall in both estrogen and progesterone, the relationship of mood with altered gonadal steroids has been a primary area of study. Data on the relationship of steroid hormones, mood and the
menstrual cycle are discussed in the section below.

A review by Roca [7] suggests that an identifiable pattern of estrogen and progesterone secretion with premenstrual symptoms has not been established. The dynamic nature of the HPG system and the complicated interaction with CNS substrates create a difficult area for neuroendocrine research. While basal hormone studies reveal no conclusive evidence of correlation to premenstrual symptoms [7], dynamic endocrine studies of the hypothalamic pituitary axis have revealed only inconsistent results.

Halbreich et al. [29] found temporal relationships between hormones and premenstrual symptoms associated with the higher levels of progesterone, its decline over time and the ratio of progesterone to estrogen. A time lag of 4-7 days between progesterone changes and the onset of clinical symptoms was demonstrated.

Walker and Bancroft [30] examined possible hormonal relationship and mood during the normal menstrual cycle compared to a cycle on oral contraceptives (OCs). OCs block but provide a constant exogenous source of steroid hormones, while the dynamics of a normal menstrual cycle continues.

The study evaluated effects of ovulation blockade with and without cyclical changes in progesterone. Patterns of menstrual cycle changes were compared in 3 groups of women. There were 35 in the "monophasic group" on low dose "combined pills" which provide stable levels of estrogen and progestagen while 30 in the "triphase group" on low dose pills received increasing doses of progestagen mimicking the luteal rise in progesterone. Another 57 in a "non-pill" control group used nonsteroidal contraceptives.

A visual analog scale rated mood, energy, tension, irritability and physiological changes. The "monophasic group" had less breast tenderness and a tendency toward menstrual rather than premenstrual changes.

The only group effect was slightly lower mood scores throughout the cycle for the combined group which received stable exogenous estrogen and progesterone levels. Although none of the groups demonstrated cyclical variability in symptoms, the authors
stress the study limitation as the absence of a group with severe premenstrual symptomatology.

While hormone intervention studies with estrogen or progesterone have not demonstrated therapeutic efficacy in premenstrual dysphoric disorder, several studies have shown that GnRH agonists which suppress ovulation are effective [21]. Contrary to some beliefs, oral contraceptives show no benefit in treatment of premenstrual disorders.

B. Puerperium

Postpartum blues, depression and psychosis were once thought to be 3 separate entities. Recent research suggests a spectrum of severity in each of these states, notable for the rapid shift in female hormones.

Postpartum Blues: The postpartum period begins with maternity "blues" in 39-85% of new mothers [31]. This syndrome of mood lability is self limiting and subsides without treatment within 2 weeks.

In an effort to investigate prospectively the etiology of postpartum blues, O'Hara et al. [31] followed 182 women from the second trimester of pregnancy through 9 weeks postpartum. Women who reported a history of depression, premenstrual dysphoria or increased antepartum depressive symptoms were more likely to experience postpartum blues. In this series, O'Hara found no differences in demographic measures, socioeconomic status or obstetrical complications.

The relationship between hormonal variations and mood symptoms was also studied. The authors found that women experiencing the blues had significantly higher free estriol levels at week 38 of gestation with a greater decrease in estriol from mean prepartum levels to day 1 postpartum levels. Postpartum blues did not correlate with other hormone measures.

Postpartum depression: One in ten women begin motherhood with a depressive episode [6], and 1 in 500 or 1000 who suffer postpartum psychosis [32,33,34]. It is a well-supported fact that
psychiatric hospital admissions increase 7 times in the first three postpartum months compared to pre pregnancy [34]. Eighty percent of these mothers receive a diagnosis of affective disorder, most commonly major depression. Symptoms of depression tend to fit the diagnostic pattern of DSMIV major depression [4]. Clinical markers of postpartum depression include profound anxiety, sleeplessness and egodystonic obsessional thoughts of harming the infant.

There is a gradual rise in estrogen and progesterone during gestation. With the loss of placenta at delivery, hormone levels plummet within 24 to 48 hours. This precipitous drop from the extremely high levels of gestation is a first step in the sequence of biological events which may trigger psychiatric symptoms in the vulnerable woman [2]. Because alterations in serotonergic and noradrenergic transmission are well-correlated with affective disorders and gonadal hormones affect monoamine transmission, this chemical cascade profoundly alters brain chemistry.

When mood symptoms are associated with abnormal perceptual experiences and loss of contact with reality, a post partum psychosis has occurred [32,33]. Postnatal psychosis begins abruptly within the first week of delivery. It may also occur up to 6 weeks after childbirth. The onset begins with insomnia, restlessness, anxiety, and hyperactivity associated with depressed or elated mood. Often thought disordered, the woman may have delusional beliefs about herself or her infant.

Wisner et al [33] found that women with postpartum psychosis compared to those with nonpostpartum psychosis displayed prominent cognitive disorganization, hallucinations, bizarre behavior, impaired insight and sensorium and disorientation. These symptoms indicate organic etiology as suggested by cognitive examinations. The precipitous onset and the unusual psychotic symptoms such as tactile, olfactory and visual hallucinations are generally recognized as those representative of physiologic influences such as toxic substance or hormonal etiology [4].
C. Menopause

Recent literature has dispelled the myths associated with menopause and mood [12]. Mood variations are more common in the perimenopause, a phase associated with fluctuating gonadal hormones. While menopause is not a pathological state, many women experience somatic symptoms such as hot flashes and insomnia [3]. While the biologically sensitive woman may demonstrate neurohormonal vulnerability associated with affective states, other elements such as psychosocial stress, aging and environmental factors also play a role in the etiology of depression. Because depression does not manifest differently during menopause than another time of life [10], it is not categorized as a psychiatric diagnosis.

Evidence for benefit of hormone replacement therapy (HRT) for psychological symptoms of menopause are inconclusive. In women with surgical menopause, the evidence for beneficial response to HRT is more convincing, particularly if androgen is also administered [8,35]. Recent studies address methodological problems in menopausal research.

In a prospective study of menopausal women, Hunter [36] found significant but small increases in depressive symptoms in peri/post menopausal women compared to pre menopausal women. Although 6 of 36 subjects became depressed, the author suggests that past depression, cognitive and social factors account for 51% of the variance in the depressed women with a history of depression.

Patterns of affective change differ in those with natural menopause compared to perimenopause and surgical menopause [12]. Of 95 subjects in an Edinburgh Menopause Clinic, 78 women had natural menopause and 17 had total abdominal hysterectomy (TAH) with or without bilateral salpingo-oophorectomy (BSO). Of the 78 who experienced a natural menopause, 35 were depressed and 43 had no mood changes. However 83% of the depressed subjects had
previous depression, a well established precipitant for recurrence. Fourteen of the 43 (33%) without mood symptoms had a previous occurrence.

A clear peak of illness was found in the first time onset in the perimenopausal period (4 years on either side of last menstrual period). In fact, 35% of women experienced their first episode of depression at this time. Overall there was a high percentage of subjects with recurrent depression at menopause and a high percentage experiencing their first episode of depression in the perimenopausal period. In addition, the percentage of depressed women is within the range of those reported for other types of outpatient clinics. An issue of note is the self referred nature of this sample, 50% who came with a chief complaint of mood disorder and therefore a selective population. When the time distribution of first episode depression was clustered by chronological age, no clustering was noted. However when the episodes were distributed by age at menopause, they found a cluster of 17 (35%) in the perimenopausal period.

D. Exogenous Steroid Administration

Exogenous administration of steroid hormones may also contribute to negative affective states. This relationship has been demonstrated with oral contraceptives [30]. Some women complain of depressed mood which appears to be associated with the progesterone component of treatment. While this has improved with low dose pills, some cannot tolerate the affective response with treatment.

GnRH agonists are synthetic derivatives of the native decapeptide produced by the hypothalamus which reverse the suppression of LH and FSH by the anterior pituitary gland. Such agents as leuprolide and goserelin acetate cause ovarian suppression with vasomotor instability, flushes, and emotional lability. Although the agonists have been implicated in depression and psychosis [22], they paradoxically relieve symptoms of premenstrual disorder [21]. The manipulation of the HPG axis with
GnRH analogs induces an abrupt hormonal change which in turn, induces negative affective states.

These hormonal interventions have been used for endometriosis and assisted reproduction [22]. The difficulties which face the infertile couple often cause interpersonal difficulties and mood symptoms. In addition, biological interventions which induce affective symptoms in some women further complicate this difficult time.

Ovulation suppression with GnRH agonists induces a reversible medical menopause which results in remitted PMS symptoms [21]. Treatment with these agents is limited by the loss of bone density. In an effort to maintain the therapeutic response without loss of bone density, estrogen/progesterone add back therapy is used.

The authors tested the effectiveness and safety of long-term administration of GnRH plus hormone replacement for women with moderate to severe PMS. Over a 12 month period, this study evaluated physiological and psychological variables in ten women [20] with regular menstrual cycles who complained of a 25% increase in PMS during the luteal phase of the cycle.

Four week cycles of intramuscular injections of placebo or leuprolide acetate were tested with all patients followed by 12 cycles of GnRH 7.5 mg. Conjugated equine estrogen 0.625 mg./day was started for 6 consecutive days within the first cycle and increased as needed. Medroxyprogesterone acetate 10 mg/d was taken orally for 10 days after 4,8, and 10 days of GnRH therapy.

A significant decrease in all symptoms was demonstrated. There were no changes in lipids, no evidence of uterine hyperplasia and no statistically significant loss of bone density.

The authors concluded that GnRH hormone agonist therapy, with hormonal add back therapy is effective in treating and improving PMS symptoms over a 12 month period.

Female gonadal steroids influence platelet imipramine binding. A likely mechanism for premenstrual relief of symptoms associated with these hormones is the 5 HT system.
The GnRH agonist d-TRP6-LHRH Decapeptyl was given to women undergoing assisted reproduction to determine the effect of platelet serotonin transporter density in these women compared to those without pre treatment with Decapeptyl [37].

In this open label trial of 19 women, 10 received active drug and 9 were treated with human menopausal gonadatropin (Pergonal). Hamilton rating scales [38] were compared and platelet plasma samples were collected for estrogen, progesterone, FSH and LH.

The GnRH analog induced ovarian suppression reflected by low plasma estradiol levels while Pergonal induced ovarian stimulation. Elevated depression and anxiety scores were observed in the Decapeptyl group and associated with a significant decrease in density (Bmax) of platelet imipramine binding sites. No change in Bmax was observed in the Pergonal treated group. The authors concluded that ovarian suppression is associated with depressed and anxious mood and decreased serotonin transporter density.

Clinical correlates of mood lability with GnRH agonists were further described by Warnock et al [22]. Four pre menopausal women with no prior psychiatric history developed severe anxiety, mood disorder and menopausal symptoms following GnRH agonist therapy for endometriosis.

The first case received leuprolide injection of 3.75 mg monthly for endometriosis. Two weeks after the first injections, she experienced depression, panic attacks and suicidal ideation. All symptoms were alleviated by sertraline, and leuprolide continued without adverse mood effects. Case 2 experienced depression with psychotic features 1 month after the second injection of 3.75 mg IM for polycystic ovarian disease. Irritability and auditory hallucinations responded to sertraline 50 mg/day while she continued the next 4 months of GnRH agonist treatment. A third case received leuprolide for infertility, but rejected treatment for depression. The final case of endometriosis experienced paranoia, volatile physical outbursts and stalking behavior after two weeks of agonist treatment. Sertraline reversed symptoms.

This data prompted Warnock and Bundren to perform a
retrospective pilot study [39] of 42 subjects with laparoscopy diagnosed endometriosis treated with 24 weeks of GnRH agonist therapy. Their mood was assessed with the Hamilton Depression Rating Scale [38].

Twenty-two patients receiving sertraline had fewer depressive symptoms but did not differ significantly in physical symptoms from 20 control women who received a GnRH agonist alone. Patients requiring GnRH agonist (Lupron) may benefit from concomitant sertraline therapy, particularly if they have a personal or family history of depression.

Another hormonal intervention to cause altered mood states is the FSH and LH analog clomiphene which induced at least one case of mania identified after ovulation induction with gonadotropins [40]. The patient was a 34 year old woman with no previous personal or family history of psychiatric disorders. Several months after receiving clomiphene without result, she began ovulation induction with human chorionic gonadotropin and urofolitropin (FSH induction) from day 8-12 of her cycle, then HCG (LH induction) on days 13 and 14. Midway into a course of ovulation induction she had a 1 month manic episode associated with racing thoughts, heightened mood, bizarre activity, insomnia, hypersexuality. This manic state was followed by severe depression with suicidality successfully treated with sertraline 50 mg.

This information demonstrates the association of mood changes with the precipitous decline of serum estradiol similar to women who experienced surgical menopause after TAH/BSO. In addition, further support is offered for precipitous hormonal changes as triggers for CNS changes via the HPG axis.

III Brain Neurotransmitters and Mood

Changes in monoamines have been implicated in the etiologies of affective, anxiety and psychotic disorders [13]. Monoamine neurotransmitters in the brain are called biogenic amines and include the catecholamines, norepinephrine, epinephrine and dopamine and the indoleamine, serotonin [13]. The catecholamine
hypothesis suggests that depression is a result of deficient CA at important central adrenergic receptors and therefore play a role in stress and emotion.

Hormones which vary during the menstrual cycle, menopause, childbirth and oral contraceptive therapy perturb these central neurotransmitter and neuromodulator systems [41]. The potential effects of estrogen and progesterone include alterations of monoamine oxidase, dopamine, norepinephrine and serotonin turnover, and modulation of alpha adrenergic receptor density in the brain. Each of these CNS substances have been implicated in mood disorders [Fig 2].

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Neurotransmitters are stored within nerve terminals, released into the synaptic cleft and transfer messages via actions on pre- or post synaptic receptors. The monoamine system is regulated by enzymes within the nerve terminals. Specifically neurotransmitters are inactivated by the enzymes monoamine oxidase (MAO) and catechol-o-methyl-transferase (COMT) [13].

Several receptors are identified for each neurotransmitter. Both classes of adrenergic receptors: alpha and beta receptors are sensitive to norepinephrine, and beta receptors are sensitive to both epinephrine and norepinephrine [13].

A. Serotonin (5HT)

The monoamine, serotonin (5Hydroxytryptophan) is synthesized from the essential amino acid tryptophan with tryptophan hydroxylase as the rate limiting step in synthesis. Several subtypes of 5HT receptors have been identified.

The fact that changes in brain serotonergic activity underlies mood disorders is well replicated in the literature and reviewed by Mann et al.[42]. Tryptophan, the precursor of 5HT is reduced in the cerebrospinal fluid of depressed patients. The brains of suicide victims compared to victims of homicide show decreased 5HT levels, an acute reduction in 5HT receptor activity, and an increase in 5HT receptor numbers [41]. Thus, 5HT
binding is increased in the brains of suicide victims, in brains of depressed individuals postmortem and in platelets of depressed individuals obtained postmortem.

Serotonin may be found in other cells beside neurons such as the platelet [43]. The platelet is the peripheral model for the brain neuron because of its similar morphology and 5HT uptake sites. Levels of platelet 5HT correlate with those in the brain, making the platelet an accessible model for investigation of central monoamine function.

5HT is also involved in the activity of the HPA axis. Specifically, 5HT is implicated in the regulation of gonadotropins because 5HT neurons stimulate gonadotropin release through its interaction with 5HT receptors via projections to the median eminence [41]. 5HT axons also terminate on luteinizing hormone releasing neurons in the pre optic area.

Altered hormone states and 5HT levels have been implicated in premenstrual disorders [44]. Altered 5HT sensitivity is suggested by several mechanisms. Imipramine receptor binding in platelets, a reflection of 5HT activity is decreased in women with premenstrual depression. Cortisol response to tryptophan is blunted during the luteal phase of the cycle compared to the mid-follicular phase. Women with premenstrual disorder have decreased platelet 5HT uptake and diminished whole blood 5HT during the luteal phase.

Premenstrual symptoms may be disabling enough [45] to require pharmacotherapy. For these women, irritability, tension and depressed mood disrupt family, occupational and social functioning. Other than ovulation suppression, the serotonin specific uptake inhibitors (SSRIs) appear to be the most effective treatment for premenstrual dysphoric disorder (PMDD). Although this disorder occurs during normal hormonal shifts, the mechanism of symptoms appears to be due to changes in serotonergic function. 5HT uptake inhibitors [46] such as fluoxetine (Prozac) [47] and sertraline (Zoloft) [48] have demonstrated efficacy in controlled clinical treatment trials. Rapid relief of symptoms occurs with sub clinical doses of the SSRIs and supports these neurohormonal underpinnings [46].
B. Norepinephrine

Norepinephrine and epinephrine also belong to the class of neurotransmitters called catecholamines. CA are made from tyrosine, and released from the adrenergic nerve fibers or the adrenal medulla [15]. They bind to receptor molecules on the plasma membrane which transduce CA interactions into a physiological response. NE is found in highest concentrations in the hypothalamus.

The monoamine hypothesis postulates that noradrenergic (NE) deficiency in the brain also plays a role in the pathogenesis of some depression [49]. Knowledge of abnormalities in mood disorders result, in part from the fact that antidepressants decrease the number of central nervous system beta adrenergic receptors. Diminished beta receptor number is a genetically determined risk factor for mood disorders.

With reference to the HPA and HPG axis feedback mechanisms, disorders of the monoamine systems are predictive of disorders in hormone secretion of the anterior pituitary [49]. Inversely, disorders of the anterior pituitary can be indicative of disorders in the monoaminergic transmission in the hypothalamus. Release and concentration of hormones into the blood can therefore be regarded as a general indicator of neuronal activity in some monoamine systems.

One other mechanism which underlies the neuroendocrine hypothesis of depression is decreased luteinizing hormone (LH) in menopause which is understood as deficient noradrenergic activity in the hypothalamus (HT). This action supports the hypothesis that the anterior pituitary lobe is under monoamine control.

Clinical correlates of circulating catecholamines are demonstrated in the postpartum period. Specifically, women with one day of postpartum blues have significantly lower levels of noradrenaline and adrenaline on that day compared to surrounding days [50].
C. Dopamine

Dopamine, a catecholamine which is modulated by estrogen transmission is implicated in psychotic disorders. Dopamine originates from the amino acid precursor tyrosine [43].

The biochemical explanation for schizophrenia is derived from the observations that the only consistent feature among the antipsychotic drugs used to treat the disease is their ability to antagonize DA receptors. It is postulated that schizophrenia may be related to a relative excess of central dopaminergic neuronal activity [43].

Estrogen modulates the activity of DA, the neurotransmitter implicated in the onset of psychosis. GH is a measure of hypothalamic dopamine D2 receptor function in the brain and peripherally measured by apomorphine agonist activity. Wieck [20] studied this relationship in women with a history of psychosis.

Fifteen women with a history of psychosis and 15 control psychiatrically healthy women were injected with apomorphine. Seven of the 15 'at risk' women had a recurrence of psychosis after delivery while 8 'at risk' women remained well. The 8 women with recurrence of psychosis had an increase in GH response to apomorphine suggesting an increase in DA receptor activity in the hypothalamus while control women and those without recurrence did not.

In a similar study [51], McIvor et al. evaluated 14 women at 36 weeks gestation and 3 months postpartum. All had a history of depression. Five women relapsed in the postpartum period and demonstrated an increased sensitivity of DA receptor function. Both authors concluded that this increased DA activity in the postpartum period predicts depression and anxiety disorders and is likely due to estrogen's effects on DA transmission.
D. Gamma-amino-butyric acid (GABA)

GABA is an inhibitory amino acid neurotransmitter. It is at the GABA receptor where benzodiazepines exert anxiolytic, sedating and anticonvulsant effects [52,53].

The GABA-A receptor complex in the brain is the most prevalent of the two known GABA receptors in the mammalian CNS [43]. GABA-A has both agonist and antagonistic properties. Natural steroids interact with GABA which have physiological and pathological consequences [52,53].

GABA levels are low in the CSF of depressed subjects, and GABA agonists relieve depression.[52] In fact, antidepressants inhibit GABA uptake and stimulate its release. Steroid regulation of GABA activity is further evidence of their role in affective disorder. Further implication for affective change at various phases in the female life cycle are explained by these neuroendocrine relationships in the HPA and HPG axes.

IV. Catecholestrogens: the Estrogen Mediated System in the Brain

Neuroendocrine interaction is facilitated by catecholestrogens (CE) which are part of a major route of estrogen metabolism in the brain. Because they have the potential for interaction with both CA and E mediated systems, CES provide the mechanism by which estrogen effects mood. Catecholestrogens are 2 and 4 hydroxylated metabolites of estrogen and estradiol [54]. Three catecholestrogens which interact with the catecholamine system are thought to be mediators of estrogen metabolism. The interactions between steroids and brain monoamines is understood as the activity of these biological substrates along the HPA axis.

CES are mainly formed in the hypothalamus and the limbic system where they inhibit the synthesis, inactivation and degradation of catecholamines. This competitive inhibition occurs in a dose dependent manner at pharmacological doses because
physiological doses of CE are unable to compete with CA.

V. The Hypothalamic Pituitary Axes

Because many endocrinopathies present with mood symptoms the HPA axis has became an important area of research. Brain neurotransmitters linked to these disorders control peptides from the hypothalamus which regulate the release of pituitary hormones. These neurobiological mechanisms have encouraged the emerging area of study called psychoneuroendocrinology [13].

The function of the neuroendocrine system and mood is a complicated biological process. The cascade of events which begin in the brain and end in the target organ may be impaired at any level of the brain, hypothalamus or pituitary. The effects of any positive or negative feedback loop may be differentiated by this biological process [2].

A. The Hypothalamic Pituitary Adrenal (HPA) Axis

Early neuroendocrine studies in depressed subjects were focused on the HPA axis. These disturbances are demonstrated as consistently elevated plasma cortisol levels and the inability of dexamethasone to suppress cortisol activity [55]. This abnormal cortisol reaction is understood as a failure in normal negative feedback regulation of the HPA axis and results in fragmented secretory activity and higher plasma cortisol concentration.

Decreased monoamines (NE and DA) are correlated with high cortisol in depression. A significant negative correlation was found between the CSF norepinephrine levels and pre-dexamethasone cortisol level in depressed patients with a positive DST response. Pre-treatment data also showed cortisol had a significant negative correlation with dopamine in the cerebral spinal fluid.

Positive DST responders exhibit a negative response with treatment and recovery from illness. The nocturnal pattern of cortisol secretion also returns to that of normal age and sex
matched controls.

B. The Hypothalamic Pituitary Gonadal (HPG) Axis

Although less well studied, the increasing awareness of the relationship of mood with altered sex steroids has encouraged further investigation.

The gonadal hormones estrogen and progesterone influence a myriad of CNS processes. This complex system is vulnerable to numerous and diverse insults by stimuli which may influence specific steps in HPG functioning or the balance between hormone levels.

The etiology of affective disorders related to the reproductive life cycle is likely represented in the biological cascade of events which begins in the cortex to influence feedback mechanisms [2]. Such activity includes stimulation of GnRH release in the hypothalamus. The pulsatile activity of GnRH influences FSH and LH secretion from the anterior pituitary which in turn cause ovarian secretion of estrogen, progesterone, androgens and inhibin. The feedback loops from these peripheral hormones influence higher level functions such as neurotransmitter activity, GnRH and gonadotropins.

During the reproductive years, GnRH is secreted in a pulsate fashion every 60-90 minutes resulting in normal levels of FSH and LH. This mechanism causes down regulation of GnRH receptor numbers and subsequent desensitization of pituitary gonadotrophs. The loss of endogenous ovarian gonadotropin stimulation causes a severe hypo estrogen state.[22].

In addition to PMS, GnRH analogs are used in gonadal hormone dependent conditions such as endometriosis, polycystic ovary syndrome, neoplastic diseases [37], and as adjuvant for in vitro fertilization. Clinical correlates of GnRH agonist previously described further attest to neuroendocrine regulation of mood and psychosis.
VI. Steroid Hormones: Mechanism and Modulation of Neuronal Effects

Steroid hormones provide feedback control over the HPA axis and the HPG axis by regulating the synthesis of respective trophic hormones and the induction and regulation of the synthesis of proteins, transmitters, hormones and receptors [56].

The adrenal cortical hormones are steroid hormones and produced by the adrenal cortex, the gonads and other reproductive structures such as the placenta. The hypothalamus [15] receives signals from the CNS and higher cortical systems via neurotransmitters. The HT then exercises control over hormone release by the pituitary, a structure which lies directly below the HT.

Fluctuations in the HPG axis cause perturbations in neurochemistry which in turn may induce behavioral changes. Because steroid hormones are lipid soluble, they easily cross cell membranes where they may regulate gene transcription for neuropeptides, for enzymes associated with neurotransmission, and structure and breakdown of synapses [56]. The mechanism of steroid actions on the brain have both fast and slow functions.

Fast steroid actions are nongenomic activities which occur over minutes to seconds. Hormones bind to membrane receptors causing changes in calcium channels, modulation of GABA receptors and changes in excitable membrane properties.

The slow reaction occurs inside of the cell via receptor mediated gene expression in the nucleus of enzymes and neurotransmitter receptors [41,52,53]. Inside of the cell hormones bind to the receptors which in turn become DNA transcription factors. Each transcription factor contains 3 main regions, a DNA binding site, a hormone binding region and a region for transcriptional regulation. The binding hormone induces a change in the receptor molecule which causes DNA binding and transcription of the gene. Over minutes to hours, steroids
regulate the gene transcription of neuropeptides, enzymes for neuronal transmission and factors for synapse regulation.

An example of steroid effects on neuronal excitability is the GABA_A receptor which regulates chloride conductance in neurons. This activity is enhanced by GABA agonists such as anxiolytics, hypnotics, anticonvulsant and anesthetics but reduced by convulsants. [52,53]. Bi-directional regulation of various steroids on GABA receptor function result in altered neuronal excitability. This mechanism provides important communication between body and brain integrating responses to external stimuli or internal signals.

This neuronal excitability was first described with the anesthetic action of IV injected cholesterol [53] and the rapid hypnotic effect of progesterone and deoxycorticosterone. In addition, cortisol provokes epileptogenic seizures and dramatic alterations in electroencephalograms [16].

Neuronal effects are also demonstrated by estrogen [57] These effects of transdermal estrogen replacement on EEG mapping were monitored in a double blind placebo controlled trial of 69 depressed menopausal women.

The women ranged in age from 45-60 years with no previous hormone replacement therapy (HRT). Each were randomly assigned to a 3 month treatment with transdermal oestradiol (Estraderm TTS; ETTS) 50 ug twice weekly or placebo. Menopause was defined as 6 months up to 5 years without menses, estrogen under 55 pg/ml and FSH >19 mu/ml. Surgically menopausal women were included if surgery was between 2 months to 5 years.

Estradiol increased and FSH decreased in the treatment group while those measures remained stable in the placebo group. Overall depressed mood improved and was associated with significant inter drug differences in brain function, particularly over the left temporal region. The ETTS patients demonstrated changes in brain wave activity, however no changes occurred in the placebo treated patients suggesting further evidence for estrogen's action on fluctuating CNS chemistry.
A. Estrogen

Estrogen is produced by the follicle and corpus luteum of the ovary and by the placenta in the second and third trimester of pregnancy [3]. The ovary secretes estradiol (E2) and estrone (E1) while the placenta produces both plus estriol (E3) [15].

Kendall [58] demonstrated the relationship of ovarian hormone secretion to the serotonin uptake system. Estrogen reduces 5HT2 receptor binding during prolonged imipramine (IMI) treatment in rat brain cerebral cortex, a mechanism which depends on the presence of sex steroids. This effect is blocked in ovariectomized rats and may be restored with estrogen administration.

Estrogen’s effect on platelet IMI binding sites, its displacement of tryptophan from binding sites on plasma albumin and degradation of monoamine oxidase (MAO) all support estrogen’s ability to increase brain neurotransmitters particularly at the site of the synapse.

While these substrate effects maintain estrogen’s bioavailability for central nervous system function, clinical studies show conflicting effects of estrogen on psychological function. For example, in a placebo controlled clinical treatment trial Ditkoff et al.[59] administered conjugated equine estrogen (0.65 and 1.25 mg) for 3 months to postmenopausal women. While no subject had major depressed mood, the estrogen treated group showed significant improvement on the Beck Depression Inventory [60] compared to controls, findings which were not dose related. Although this trial does not support estrogen as treatment for depression, its antidepressant properties are demonstrated in this postmenopausal sample of women.

In animal studies, ovarian steroids demonstrate a complex effect on the serotonergic system. The acute effect of estrogen exposure causes an immediate reduction of 5HT receptor density throughout the brain. However a delayed effect of 48-72
hours caused a selective increase in brain regions which contain estrogen receptors [18].

Early work of Biegon and McKewen [18] demonstrated the aforementioned bimodal mechanism of estrogen on 5HT function in the female rat brain. Estrogen's rapid effects on brain membranes occur by modifying 5HT receptor availability. Slower change on the same receptors occur via interaction with intracellular estrogen receptors and DNA transcription.

The effects of estradiol on serotonin receptors in brains of ovariectomized female rats in vivo and in vitro were investigated. Initially, ovariectomized female rats were injected with estradiol while control animals were injected with a control substance. Both were sacrificed after one hour.

In a second experiment, the animals were sacrificed after 48 and 72 hours. Steroid hormones were added directly to the serotonin assay tubes and tissue from the whole forebrain or cortex was pre incubated in steroid containing buffer for 2 hours.

The study demonstrated estradiol's biphasic effect on serotonin receptors i.e. estradiol's ability to decrease the concentration of 5HT1 receptors within 1-2 hours of injection [Figure 3a & 3b] followed by delayed (72 hour) effects in 5HT2 receptor. Estrogen exposure acutely effected all areas of the brain while the delayed effects occurred only in estrogen containing areas such as the amygdala, the medio basal hypothalamus and pre optic area.

In sum, this animal model of estrogen modulation effects on the 5HT system demonstrates support for the affective changes in women who are susceptible to rapidly changing hormone levels.

Biegon and McKewen=figure insert

1. Estrogen, Mood and Reproduction

The clinical application of Biegon and McKewen's work to postnatal depression is demonstrated by by Hamilton and Sichel
[61]. For some women, the postpartum period may be a time of acute sensitivity to the rapid decline in estrogen. However, postpartum depression is treated with the standard psychopharmacological interventions used for nonpuerperal conditions.

If the immediate postpartum hormonal decline is a risk factor, a logical preventive intervention might be to halt the neurohormonal cascade by interfering with steps in this event. Hamilton administered estrogen prophylactically to postpartum women at risk for recurrence.

In 50 women with past histories of moderate to severe postpartum mood disorders, a single injection of a long-acting estrogen was given immediately after delivery, followed by a taper of oral conjugated estrogen over 14 days. Statistically the risk of postpartum recurrence is 30-50%, however there were no postpartum recurrences in these at risk patients. Although there were no instances of thromboembolic events, this adverse effect at high doses of estrogen must be considered.

In a subsequent study, Sichel et al. [62] administered high dose oral estrogen as the first dose at delivery, supplemented by subcutaneous heparin and followed by transdermal estrogen patches. Seven women with a history of postpartum psychosis and 4 with a history of postpartum depression were treated with high dose oral estrogen (10 mg) daily administered in decreasing doses over 4 weeks. Heparin 5000u subcutaneously was administered twice daily for the first week.

Only one patient had a postpartum recurrence. All others required no psychotropic medications for the first year after delivery, an effect which is likely due to replacing the rapid loss of hormone at a critical time in the puerperium.

This preliminary data demonstrates the antidepressant properties of estrogen in postpartum depressed women. In view of the risk of thromboembolysis and other adverse events, prophylactic use of estrogen for recurrent postpartum affective disorder remains experimental. Data is insufficient and further research is warranted [62].
One mechanism of action which explains the antidepressant effects is estrogen's interference with the enzymatic degradation of norepinephrine accomplished by the catecholestrogen metabolites of estradiol. When catecholestrogens competitively inhibit catechol O methyl transferase (COMT), the action of NE is potentiated. In addition, estrogen's inhibition of monoamine oxidase (MAO) makes NE more available for synaptic action in adrenergic neuron.

2. Estrogen, Mood and Menopause

Klaiber et al. [63] administered estrogen to pre and post-menopausal women to determine its effect on depression and central adrenergic function. Twenty three subjects who failed two years of antidepressant treatment were given large doses of conjugated estrogen in double blind fashion. Ten women had psychotic symptoms associated with the affective disorder. Placebo was administered to 17 women with comparable illness.

The treatment cycle for pre-menopausal patients was 3 menstrual cycles and 12 weeks for non-cycling women. After a 2-3 week placebo washout, the treatment groups received oral conjugated estrogen begun at 5 mg/day titrated up to 25 mg/d as tolerated. Weekly Hamilton Depression Rating Scales [38] were administered and twice weekly blood samples were drawn for MAO activity.

On day 21 of treatment, pre menopausal women were given 2.5 mg of methoxyprogesterone for 5 days, then estrogen and progestin were discontinued to allow menstruation. After 3 months the treatment group demonstrated a significant decline in the Hamilton scores compared to the control group indicating clinical improvement. However, overall scores remained fairly high.

As predicted, estrogen decreased plasma MAO activity in the depressed subjects while that of the placebo group increased for unclear reasons. Therefore, this study supports the antidepressant effects of estrogen, and clinically demonstrates the underlying biological mechanism for these effects.
Although the risks of large doses for a long duration must be considered, estrogen may be a good adjunctive treatment for partial response to antidepressant medication. Such adverse events include thromboembolic events and endometrial hyperplasia and therefore warrant caution.

Halbreich et al. [64] investigated the mechanism of estrogen replacement on serotonergic activity. The serotonin agonist meta-chlorophenylpiperazine (m-CPP) was administered to postmenopausal women. Cortisol and prolactin responses to m-CPP are indicative of serotonergic activity. A blunted response indicates diminished serotonergic activity.

Eighteen normal postmenopausal women, 11 of whom were also treated with estrogen transdermal patches (estraderm 0.1 mg) were compared to 15 normal women of reproductive status. Menopause was determined by the absence of menses for 2 years, absence of menopausal symptoms for 1 year and no detection of progesterone. Without estrogen, the prolactin and cortisol responses to m-CPP were blunted in postmenopausal women compared to control reproductive women. Estrogen replacement increased the hormonal responses.

The diminished 5HT response in postmenopausal women likely contributes to affective vulnerability, and may explain the mood enhancing effect of estrogen. This finding further suggests that damaged receptors may be an important factor in the inhibition of steroid effects.

The unpredictable nature of this finding is suggested by variable mood states induced by ERT. Oppenheim [65] described the mood altering effects of estrogen in a case of rapid cycling mood. Although rapid cycling is a direct complication of antidepressant medication, estrogen induced the state in a 72 year old woman who had a partial response to antidepressant treatment. Oral conjugated estrogen (Premarin) was added at 0.625 mg/day and increased to 4.375 mg/day over 30 days. By day 5 of treatment her moods cycled from elation and hypomania to depression every 1 to 3 days. Hypomania was demonstrated as elation, aggression, and over activity associated with impulsivity and shopping sprees.
Other cases of induced hypomania have been reported. [66].

An interesting caveat was Chouinard's [67] clinical case report of the mood stabilization effects of combined estrogen and progesterone in 2 women with bipolar disorder resistant to lithium and/or tryptophan.

Schneider and colleagues [68] combined estrogen with antidepressant medication in a randomized double blind trial of elderly depressed women on fluoxetine 20 mg/day. Seventy two patients received estrogen replacement therapy (ERT) compared to 286 who did not. Patients on ERT and fluoxetine had a 40.1% greater mean Hamilton improvement than 17% of patients on ERT and placebo. This combination provides a reasonable alternative for elderly depressed outpatients who fail to respond to monotherapy.

The particular response in women on ERT may best be explained by an inadequate to response to SSRIs because of a chronic hypoestrogenic state. Because 5HT2 receptor binding appears to be estrogen dependent, some elderly depressed women may fail SSRIs because of inadequate estrogen modulation of receptor activity. In sum, estrogen appears to improve mood in non-depressed post-menopausal women, but appears to be ineffective in women with major depression.

B.Progesterone

The female sex hormones accumulate and are metabolized in the brain where CNS activity is increased by estrogen and decreased by progesterone. Because progesterone opposes effects of estrogen on monoamine function, it has opposite effects on mood. Depressogenic effects of progesterone are attributed to its action on MAO [2]. In contrast to estrogen, progesterone decreases the degradation of monoamine oxidase. The subsequent increase in the enzymatic breakdown of monoamines makes these neurotransmitter substrates less available at the site of the synapse. As previously described, negative mood is sometimes induced by progesterone and attenuated by a higher estrogen to progesterone dose ratio.

Progesterone and deoxycorticosterone are major hormones
released by the adrenals and ovaries which contain enzymes capable of forming "barbiturate-like" substrates from inactive hormones. These metabolites of progesterone (3α-5α tetrahydropregesterone; THP) and deoxycorticosterone (3α-5α tetrahydrodeoxycorticosterone; THDOC) are allosteric agonists of the GABA<sub>A</sub> receptor [24,52,53]. THP which is increased during the luteal phase and in pregnancy acts as a sedative, anxiolytic, anticonvulsant and pro anesthetic. However, pregnenolone sulfate (PS) and dehydroepiandrosterone sulfate (DHEA) are antagonists with antidepressant properties.

The substantial amounts of steroids in the CNS, their fast turnover and alterations during physiological states once again implies their active role in CNS functions.

1. Progesterone, Mood and Reproduction

Although progesterone appears to be depressogenic, it has been studied as a potential prophylactic agent for postpartum depression. Dalton [69] administered inter muscular progesterone at delivery to 27 women with prior postpartum depressions then daily for 7 days. This was followed by progesterone suppositories two times per day for 60 days. Six months after delivery, none of the women had developed postpartum depression. Because of major methodological problems such as lack of double blind condition, these data remain inconclusive. Other trials of progesterone prophylaxis [70] dispute Dalton's results.

Further support was provided when Harris et al.[71] queried the relationship of puerperal mood, progesterone and cortisol. In a prospective study of 120 primiparous women, saliva was collected twice daily from 2 weeks antepartum to 35 days postpartum to determine cortisol and progesterone levels. Seven women developed major depression. Decreased evening cortisol levels in the immediate peripartum period were associated with postnatal depression, however no relationship of mood to progesterone was detected. Similar to other reports, this provides no support for a treatment strategy of progesterone augmentation after delivery.
2. Progesterone, Mood and Menopause

Progesterone induced depressive states cause considerable non-compliance in clinical populations of post-menopausal women on hormone replacement therapy. It is not well known that a relationship between mood symptoms is reported with progestins. Consequently, the patient may be categorized as postmenopausal onset of depression. Specifically concerns over non-compliance include the risk of cardiovascular disease, osteoporosis and GI cancer [9].

Magos et al. [72] reproduced this state in a placebo controlled prospective study in 58 postmenopausal hysterectomized women who were treated with subcutaneous estradiol (150 mg) and testosterone (100 mg) implants (Orgeron). Norethisterone (19-nor steroid progestagen) 2.5 and 5 mg/day was given for 7 days and placebo for 2 periods of 7 days. Psychological, physiological and behavioral variables were assessed.

Seventy women with an average age of 48.3 years had hysterectomies for non-malignant conditions within the previous 22 years. Asymptomatic women were judged to be postmenopausal either by a history of bilateral salpingo-oophorectomy or by a plasma FSH measurement of >20 IU/l before HRT with estradiol and testosterone. There was a 5 period design, each representing 7 days. The first and last periods were used as baseline and were tablet free. Norethisterone or an identical placebo were allocated during the middle three periods.

A total of 58 women completed the study, thirty nine treated with 5 mg and 19 with 2.5 mg. A significant increase in psychological symptoms such as depression, anxiety, irritability and several variables such as pain, concentration and water retention showed worsening of 5 mg/day of the progestagen. While there was a trend in some variables at low doses, there were no statistical differences between the drug and placebo. The dose relationship suggests that it may be advantageous to prescribe
minimum dosages of progestational agents to achieve effects. The author addresses the similarity of norethisterone induced behavioral change to the complaints of premenstrual syndrome and suggests that PMS is a model for this condition.

In order to determine if a relationship exists between a history of PMS and adverse response to progesterone, oral medroxyprogesterone acetate was given in conjunction with transdermal estrogen [73] to two groups of women with TAH BSO. Twenty four women with a history of PMS and 24 with no history received estrogen 100 ug on days 1 through 25 and oral medroxyprogesterone acetate 10 mg daily or placebo 12-25 days in a random double blind cross over design.

A history of PMS did not predict a difference in mood or physiological symptoms between groups. The authors suggest that using a single cycle may be a limiting factor, and further investigation should include several cycles of therapy.

Alternatively, Siddle et al. [74] found no mood changes associated with progesterone. Equine estrogen 1.25 mg/d was administered continuously to two groups of subjects who were subsequently randomized to dydrogesterone 20 mg/d for 12 days each month for 3 months. then 10 mg in the same fashion for subsequent 3 months. Group 1 followed this protocol while group 2 received the hormone regimen in reverse order. There were no significant differences in mood or anxiety symptoms when either dydrogesterone doses were administered. The authors refer to previous unpublished findings in which they found 10-20% of women experienced a PMS syndrome induced by progestins and suggests that this syndrome is therefore limited to a subsection of women.

Klaiber et al. [75] addressed the varied outcome of positive mood states with estrogen, and reversal of these effects with the addition of progestin. The author posited that the opposite steroid effects may relate to their opposite action on the adrenergic and serotonergic function. In menopause, these opposite effects do not occur in all women, but may be caused by other variables.

This receptor modulation was clinically demonstrated
by comparing the role of estrogen therapy in women with a short duration of menopause (12.9 months + 6.1) to women with a long duration of menopause (76.6±52.3). ERT is associated with improved mood in post-menopausal women, but may not always exert the expected physiological and behavioral effects. Because the duration of menopause determines estradiol levels, lower levels are found in women with a longer duration of menopause.

Klaiber et al [76] followed 38 psychiatrically healthy menopausal women between 45 and 65 with no menses for 6 months and FSH > 50 mIU/ml. In a double blind cross over design, the women were studied over five 28 day cycles using two randomly assigned groups (A & B). After a 28 day placebo entry (Phase I), Group A received estropipate 1.5 mg./day for two 28 day cycles (Phase II) then crossed over to placebo treatment for Phase III. Norethindrone 1 mg./day was administered for 10 days of each cycle to both groups during the ERT cycle. Group B received placebo for Phases I and II, then ERT for Phase III. Hormones were assayed and mood monitored by the Hamilton Depression Rating Scale [38].

Pre treatment variables included the duration of menopause, age and serum levels of estradiol, testosterone and FSH. The adrenergic/serotonergic variable was platelet MAO activity.

The short duration group had higher mean pre treatment estradiol levels than the long duration group. However the short duration group had lower mean estradiol levels during treatment. Both groups showed a significant improvement in mood when estrogen was administered alone.

Differences in mood response occurred when estrogen and progestin were administered. The short duration group had no significant decline in mood symptoms compared to controls when progestin was administered. The long duration group tended to loose mood improvement gained with estrogen when progestin was added. The long duration group had higher estrogen levels on hormone replacement therapy (HRT), and more dysphoric mood on progestin.

Women characterized by short menopausal duration, high pre treatment serum estradiol and testosterone levels and low pre
treatment serum FSH levels were less adversely affected by the estrogen/progesterone combination that women with long menopausal duration, low pre treatment serum estradiol and testosterone levels and high pre treatment serum FSH levels.

In contrast to women in menopause for a long duration, women in menopause for a short duration had higher circulating pre treatment estradiol levels, unimpaired receptors and a higher density of estradiol receptors. Therefore addition of progestin and reduction in estradiol receptor density may not be sufficient to adversely affect mood states.

Higher serum estradiol levels were associated with decreased MAO activity during HRT. As expected, high estradiol levels in the long duration group did not protect against dysphoric mood during progestin treatment, yet the short duration group had no mood changes on progestin despite lower mean estradiol. It appears that higher pre treatment estradiol levels in the short duration group were protective against depressive mood changes induced by a progestin.

In euthymic patients, decreased MAO is a marker of adrenergic and serotonergic function and correlates positively with DA and 5HT metabolites in the CSF. Women with functional adrenergic and serotonergic function have a less negative mood response to progestins. A reasonable conclusion for estrogen's inability to sustain positive mood changes in the presence of high estradiol levels in the long duration group is likely due to impaired receptors.

Platelet MAO activity in long duration women negatively correlate with serum estradiol levels during HRT suggesting that menopausal women with a higher level of serum estradiol during HRT have poor adrenergic and serotonergic function.

Klaiber concluded that these effects may involve the adrenergic and serotonergic neural system by the following mechanism. Because estradiol increases the density of adrenergic and serotonergic receptors, estrogen plus progesterone reportedly decreased the concentration of adrenergic and CNS estradiol receptors induced by estrogen deprivation. Progestin may adversely
affect mood states by reducing the effects of estradiol on CNS adrenergic and serotonergic function.

Because MAO activity is a genetic marker of adrenergic and serotonergic activity, Klaiber inquired about enzyme activity. Findings illustrated that estrogen’s mood elevating effects in women with low pre treatment platelet MAO activity and impaired pre treatment mood states had improved mood on estrogen alone, but addition of progesterone impaired mood. Women with higher platelet MAO activity were resistant to the negative effects of progestin on mood. Women whose platelet MAO activity increased during HRT had less adverse mood response on progestin then those with decreased MAO.

In summary, impaired CNS adrenergic and serotonergic function make non depressed menopausal women vulnerable to the antiadrenergic and antiseroptonegic effect of the estrogen/progesterone combination, whereas optimal adrenergic and serotonin function may protect against the adverse response of progesterone/estrogen. These biological mechanisms support the thesis that steroid hormones have profound effects on female mood states.

C. Androgens

Androgens are produced in the Leydig cells of the testes in men and adrenals in both sexes. The main secretory product from the testes is testosterone. Attempts to determine a relationship between testosterone and mood are varied. Testosterone has been implicated in PMS [77] and synthetic derivatives of testosterone have been implicated in depression.

Erikson et al. [77] measured serum levels of free testosterone and found them significantly higher throughout the menstrual cycle in subjects with PMS. However, Danazol, a synthetic derivative of 17 a ethyl testosterone suppresses ovarian activity and has been implicated in the treatment of PMS [78]. In a randomized double blind cross over controlled trial, 16 women who were treated with Danazol experienced relief of severe PMS symptoms when compared
to the 12 on placebo. Seven (43%) of the Danazol group had responses in the asymptomatic range on 200 mg B.I.D. compared to 8.3% on placebo.

Another relationship between sex steroid hormones and mood was illustrated with a precursor of testosterone and estrogen, Dehydroepiandrosterone (DHEA). Because DHEA and its sulfate DHEA-S decrease with aging, Wolkowitz [79] recruited six middle aged and elderly patients with major depression and low basal plasma hormone levels and administered DHEA for 4 weeks. When dosing was adjusted for levels in the normal range for younger healthy patients, depression and memory improved significantly and directly correlated with plasma levels of the steroid.

The author suggests two possible mechanisms for improved mood; the return of youthful levels as well as DHEA’s action as a precursor for testosterone and estrogen which appear to have mood elevating effects.

Seidman and Rabkin [80] demonstrated an open case series of testosterone replacement in men with refractory depression and low normal serum T levels. After 2 months of ineffective treatment with SRI, each of 5 men received a 400 mg injection of testosterone enanthate every 2 weeks for 8 weeks. There was a significant improvement in Hamilton Depression Rating Scales from entry week through week 8. The authors suggest that testosterone should be administered with caution in men with abnormal prostate examination or elevated prostate specific antigen levels. While the study is limited by the number of subjects and the absence of a control group it provides support for further study.

1. Androgens, Mood and Reproduction

The relationship of T to menopause has been a recent focus of study. The profound decrease of estrogen during natural menopause is a consequence of ovarian follicle depletion. Testosterone levels increase with LH secretion which causes ovarian hyperplasia, therefore testosterone levels may vary. Estrogen and testosterone are depleted after TAH-BSO while women with natural
menopause produce testosterone until the fifth menopausal year [35].

2. Androgens, Mood and Menopause

In an attempt to clarify effects of HRT, Sherwin and Gelfand [81] administered estrogen and androgen in a prospective, double blind cross over design to healthy surgically menopausal women. All subjects anticipated a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) for benign disease. During the pre-operative period, 12 patients were randomly assigned to the estrogen-androgen (EA) group, 11 to an estrogen (E) group, 10 to an androgen (A) group and 10 in the placebo (PBO) group. Ten hysterectomy controls without oophorectomy comprised the fifth group (CON). Intramuscular hormones were administered monthly for 3 months of the post-operative year.

While the study found correlations with hormone levels and improved mood in depressed women, Sherwin cautions against generalizing to the clinical populations because of the induction of physiological hormone levels and the absence of objective criteria to measure mood.

Sherwin and Gelfand [35] investigated the administration of HRT with androgens in order to determine if the affective status of surgically menopausal women treated with estrogen alone would differ from those treated with an estrogen-androgen (EA) combination.

Subjects were healthy women without psychiatric history, matched for age and socioeconomic status. All subjects were at least 2 years post-op TAH-BSO. The study population was separated into 3 groups. Group 1 received EA I.M. every month for the entire postoperative period. Group 2 was composed of women who were given a monthly injection of estrogen (E) alone while a control group 3 (CON) received no hormonal intervention.

All subjects had a hormone washout 8 weeks prior to baseline. The E-A group received 1 ml of estrogen / androgen combined drug (Climactron) while E group received Delgestrogen.
Objective mood scales and hormone samples were evaluated at intervals in 44 subjects; 22 in EA, 11 in E and 11 in CON.

There was no difference in basal hormone levels between the groups. Women receiving either hormone preparation had higher E levels associated with improved mood, and felt more elated and energetic than the CON group. Mood covaried with the physiological range of estrogen and supra physiological levels of T. The T group had the most improved mood scores most likely due to the very high levels. All symptoms improved when E and T levels were high.

The hormone treated groups had lower depression scores than the placebo group which corresponded to their higher levels of circulating E and T. Heightened hostility was detected in the androgen treated group.

In conclusion, because of slow T metabolism, T remained at supraphysiological levels. Therefore, conclusions only apply to high T levels, but cannot predict mood at physiological levels.

The mechanism by which estrogen maintains higher serotonin levels is by decreasing MAO activity in the amygdala and hypothalamus. While the mechanism of androgen action is not well understood, it may be aromatized to estrogen to provide added antidepressant effect.

Because individual responses to HRT (particularly T) are difficult to predict, the same authors [82] measured levels of bound and unbound steroid. Both steroids bind to sex hormone binding globulin (SHBG). In plasma, E increases while T decreases SHBG. Only the free unbound portions of circulating T are presumed biologically active.

The study aimed to determine the SHBG profile induced by chronic administration of an estrogen-androgen preparation. Ten healthy women in the 2nd postoperative year after TAH BSO received 1 ml estrogen/androgen drug IM every 28 days for 2 years [82]. After an 8 week washout period, baseline blood samples were drawn. A combined hormone injection was followed by psychometric tests and steroid hormone levels.

High circulating hormone levels corresponded with improved mood in women with normal affective states. T levels
remained fairly high and stable. E levels decreased after 2 days. However 1 subject had abnormally increased SHBG levels associated with dysphoric mood and 1 had abnormally low levels which were associated with improved depression score.

Sherwin suggests that total plasma hormone levels are altered by SHBG, and provide insufficient information. Levels of HSBG may be important to understanding mood and clinical response in some women thereby providing additional information when dosing.

Conclusion

Thus far, several researchers report mood enhancing effects of HRT, while others fail to demonstrate this pattern. Generalizations from data of HRT such as biological outcomes and psychological variables are difficult to make. Recent studies have addressed the inconsistent methodology in menopause research. Evaluation of outcome must consider qualitative measures and pre-existing variables such as natural vs. surgical menopause, history of depressed mood and duration of menopause.

In order to aggregate data, Zwiefel et al. [83] performed a meta-analysis to examine the effectiveness of HRT upon menopausal depressed mood. Methodologies and existing variables were addressed.

This systematic evaluation addressed variables such as sample size, level of depression, reliability of depression rating scales, type and dose of HRT and length of treatment.

Studies were obtained from literature searches (1974 to 1995) and correspondence with major contributors of research. Inclusion criteria for the twenty six studies were the use of valid measures of depression and administration of hormone therapy.

The average number of subjects per study was 47.15 (SD=28.94). Study variables included types of design, assignment to groups, application of double or single blind conditions, recruitment procedures and demographics. Most studies did not provide demographic information such as level of education,
socioeconomic status, income, urban or rural location, marital status and race.

While most studies included postmenopausal women, few used perimenopausal women or both. In addition, menopause was determined by various measures such as TAH-BSO, FSH levels, amenorrhea for 12 months, estrogen levels and presence of menopause symptoms. Mechanisms of menopause were classified as TAH-BSO, natural menopause, TAH without BSO while others did not specify. Hormones varied by dose, route of administration and type of steroids. Some utilized progesterone or testosterone. Most studies included subjects who were either not depressed or experiencing only mild levels of depression.

Most studies included in the meta-analyses used adequate sample sizes, controlled research designs, random assignment and valid, reliable outcome measures for depression.

Overall results of the meta-analyses demonstrated that depressed mood scores decreased from pre treatment to post treatment for estrogen vs. estrogen plus progesterone comparison treatment. Estrogen was a more effective treatment. Significant effect scores were associated with HRT. The average treatment subject had lower levels of depressed mood than control subjects. Estrogen plus progesterone reduced the effect of ERT on depressed mood. The androgen alone and androgen plus estrogen treatment yielded a large effect size.

The results of this meta-analysis suggest that estrogen reduces depressive symptoms in non-clinically depressed women, while progesterone alone and in combination with estrogen is associated with smaller reductions in depressed mood. Androgen alone and in combination with estrogen was associated with improved mood.

In summary, there were a variety of methodological approaches in the use of study design, depression measures and length of treatment, all associated with variation in effect size.

Further issues which must be addressed include optimal combination of hormones, dose response relationships, effectiveness of HRT across demographic variables such as race and
socioeconomic economic status, and treatment outcomes as a function of menopausal status, type of menopause and severity of symptoms. Several suggestions were made to improve further studies such as improved reporting of demographic information and report of effective dose of hormones.

In this author's experience, the onset of mood and anxiety symptoms associated with HRT remain underdiagnosed and undertreated. Non-compliance with HRT may have serious implications for the post-menopausal woman, and thereby cautions the prescribing physician to inquire about mood in women who may hesitate to report depressive symptoms and therefore discontinue HRT.

In addition, particular attention should be given to women with existing mood disorders such as chronic depression, bipolar mood disorders or previous history of puerperal psychiatric illness.

The developing field of perinatal and reproductive psychiatry encourages liaison between the field of mental health and reproductive events. Improved communication between the Psychiatry and Obstetrics and Gynecology may increase awareness of mood disorders induced by endogenous or exogenous steroids. Standard psychopharmacology intervention easily provides treatment for those women in need of intervention.
REFERENCES


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