Psychoneuroendocrine Aspects of Temporolimbic Epilepsy

Part III: Case Reports

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Many reproductive steroids have neuroactive effects that can modulate neuronal excitability and influence emotions. Emotional disorders may result when 1) abnormal endocrine states interact with normal brain, 2) normal endocrine states interact with abnormal brain, and 3) abnormal endocrine states interact with abnormal brain. An understanding of these pathogenetic relationships and the potential therapeutic role of reproductive hormones should lead to a more effective and comprehensive management of women and men with anxiety and mood disorders.

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BRAIN, EPILEPSY, AND BEHAVIOR

Conceptualizations of mind have shifted from intangible to tangible. Based on the results of experimental animal and clinical brain ablation and stimulation investigations, many mental attributes that were previously ascribed to a soul or spiritual entity are now commonly referred to the brain. Attention, memory, perception, language, cognition, judgment, emotions, and behavior are considered to be functions that can be ascribed to the activity of 1) discrete brain areas, 2) systems of interconnected brain areas, and 3) parallel processing in brain systems.[1–5] Altered or disordered mental processes result from dysfunction or disconnection of brain areas or systems.[1–5]

Altered or disordered mental processes may also occur as a result of "sensory-limbic hyperconnectivity," that is, the association of perceptions with exaggerated emotional and motivational significance due to excessive limbic activity in the context of epilepsy.[6] Medial temporal lobe structures, especially the amygdala and hippocampus, are usually the sites of origin, or at least involvement, of epileptogenic discharges in partial seizures.[7] These regions form the part of the limbic system where emotions are thought to have representation.[3,8] Excessive activation of these regions by epileptogenic discharges can lead to seizures. Excessive activation may also lead to persistent or recurrent states of deepened or exaggerated affect and the association of perception with exaggerated emotional and motivational significance.[6] The resulting deepened emotional state may represent or contribute to at least some of the altered mood, personality, and behavior characteristics that are commonly known as the interictal features of temporal lobe epilepsy (temporolimbic epilepsy, TLE).[9] This syndrome includes intense affect, anxiety, depression, anger, rage, humorless sobriety, elation, feelings of personal destiny or grandiosity, obsessionalism, guilt, hypermoralism, religiosity, philosophical interests, hypergraphia, paranoid ideation, circumstantiality, tangentiality, viscosity, dependence, and altered sexual drives.

Altered mood and interictal personality features can cause functional impairment and distress in perhaps 30–50% of women and men with TLE.[10,11] Although these disorders may respond favorably to antiseizure medications,[10] treatment is often unsuccessful despite the achievement of good seizure control.[3] In some cases, worsening may occur.[3] This lack of success may be due to the fact

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that antiseizure medications typically act to prevent the spread of seizure discharges, but generally do not eliminate the epileptogenic focus or restore entirely normal physiologic function to the involved area, as evidenced by interictal electroencephalogram (EEG), single photon emission computed tomography (SPECT), and positron emission tomography (PET) data.[12] Antiepileptic drugs, moreover, may activate inhibitory mechanisms that could contribute to cognitive deficits and emotional changes.[10,11,13]

NEUROENDOCRINE ASPECTS OF SOME EMOTIONAL DISORDERS ASSOCIATED WITH EPILEPSY IN WOMEN

Agitated depression and anxiety disorders including anxiety, panic attacks, phobias, and obsessive compulsive disorder are frequent concomitants of TLE[9,13,14] that often show catamenial (i.e., menstrual cycle–related) patterns of exacerbation and favorable response to hormonal treatment with progesterone or clomiphene. These points are illustrated by the following cases.

Case 1. Bipolar Disorder

Ms. B. is a 29-year-old woman with depression, considered to be bipolar illness, dating back to her teens. For about 2 weeks before each menstrual period, she would become progressively more irritable, depressed, angry, argumentative, and aggressive. She would stay in her house, overeat and feel panicky, nervous, and sometimes suicidal. As menstruation approached, confusion, paranoid ideation, and other delusions developed, often to the point of frank psychosis. These symptoms improved dramatically on Day 2 of each cycle. Severity of her symptoms increased progressively over the years. Lithium exacerbated her confusion. Tricyclics increased the severity of the cycling. Olfactory and gustatory hallucinations, as well as premenstrual episodes of staring and unresponsiveness, raised the possibility of a seizure disorder. EEG showed epileptiform discharges and paroxysmal slowing over the left temporal region. Her daily medications, carbamazepine (1,400 mg) and clonazepam (5 mg), lessened her lapses but did not benefit the cyclic emotional deterioration that eventually required monthly hospitalization for psychosis and suicidal threats nor her staring episodes and auras.

Ms. B.'s past medical history was remarkable for learning difficulties as a child, a concussion during adolescence, irregular menstrual cycles, and hirsutism. The family history was remarkable for major mood disorder affecting her brother and both parents. Her mother was left handed.

On examination, she had a right hemihypoplasia and a vascular birthmark over the dorsal right forearm.

Daily progesterone using 200 mg lozenges tid during the second half of each cycle on Days 14–25 with subsequent gradual tapering and discontinuation of therapy over 4 days alleviated anxiety and staring episodes, as well as menstrually related exacerbations of agitated depression and psychosis. She required no further hospitalizations during the entire following year.

Comment: The syndrome of disabling mood changes and psychosis in relation to menses has been termed cyclic or periodic psychosis.[15,16] The psychosis is characterized by increasing psychomotor excitement for 7–14 days prior to menstruation, followed by psychomotor retardation during menstruation.[15] It is commonly associated with temporal lobe EEG abnormalities[15,17] and other markers of anomalous brain substrates.[17] Symptoms have been related to excessive estradiol[18] or diminished progesterone[15,19] influence on the brain. ECT and psychotropic medications are often of limited value.[15] Cyclic psychosis has been effectively treated by various forms of oral and parenteral reproductive hormones that eliminate menses, reduce estrogenic effects, or increase progestin levels.[17,20–22] In the case of Ms. B., substantial improvement occurred with the cyclic use of progesterone and was contingent on a gradual taper of progesterone premenstrually.

Case 2. Panic Disorder

Ms. F. is a 31-year-old woman with irregular cycles and infertility, who, beginning in the second month of attempted ovulation induction with chorionic gonadotropin, developed severe panic attacks with a type-3 pattern of catamenial exacerbation. She also experienced milder daily symptoms of fear, sweatiness of her palms, palpitations, nausea, and occasionally terrible foul smells.

Ms. F. was the product of an almost 10-month gestation with very difficult labor and forceps delivery. Her father and sister were left handed. Her mother developed seizures as an adult.

Ms. F. had abnormally heightened deep tendon reflexes. Her EEG showed paroxysmal epileptiform discharges in both temporal regions. During the hyperventilation phase of her EEG, she experienced a very high level of anxiety, fear, cold sweats, rapid heart rate, and breathing difficulty. A CT scan of her head was normal.

Ms. F.'s symptoms were refractory to antiepileptic drugs and benzodiazepines. The addition of progesterone (200 mg tid) during the second half of each cycle eliminated her severe attacks entirely and permitted her to return to her full-time occupation.

Comment: Concomitant panic attacks and paroxysmal temporal lobe EEG abnormalities are now well recorded in the medical literature.[23–28] Symptoms and manifestations of fear and anxiety are among the commonest auras of TLE.[3] They may also occur, however, in the setting of EEG abnormalities alone, that is, in the total or relative absence of other clinical seizure manifestations, sometimes known as atypical panic at-

tacks.[27] A causal relationship between epilepsy and panic attacks has been suggested in some cases by the demonstration of a temporal association between the occurrence of paroxysmal temporal lobe EEG discharges and panic attacks.[28] In Weilburg and associates' series, EEG telemetry demonstrated focal paroxysmal EEG changes in 45% of subjects who had captured attacks. The effective use of progesterone in management has not been previously reported.

Case 3. Depression and Obsessive-Compulsive Disorder

Ms. G. is a 23-year-old woman who had cyclic exacerbation of her major unipolar depressive mood disorder and obsessive-compulsive disorder (OCD) in relation to her menstrual cycle. Irritability developed in the second week. Angry thoughts with episodic rage became progressively more prominent after Day 14. During the third week, malicious intent was perceived in everyone around her. She became confused, hyper-religious, read the Bible constantly and smelled unpleasant things. Her generally intermittent and minor obsessions about religious and moralistic themes became constant and overwhelming. They reached the point that she would continuously feel a great need to confess. Ms. G. carried out rituals all day, organizing religious materials around her room. These activities helped to control her high level of anxiety. Recurrent thoughts about cutting her wrists with a knife kept her from sleep at night. These thoughts and rituals remained prominent during the fourth week along with agitation, depression, emotional lability, and paranoid ideation. By the second day of menstruation, she felt much improved.

The symptoms had their onset in adolescence and became progressively more pervasive and severe during adolescence and her early twenties. They necessitated repeated hospitalizations for psychosis and suicide attempts, generally in the fourth week of each cycle. At the time of referral, she was spending more time in the hospital than at home.

Her past medical history was remarkable for perinatal anoxia and irregular cycles with menometrorrhagia and prolonged menstrual intervals of about 40 days. Fluid retention up to 10 or 15 lbs and breast tenderness were prominent premenstrually. She had excessive hair growth but no galactorrhea. Pelvic ultrasound showed multiple ovarian cysts. Major mood disorder and left handedness were prominent on both sides of her family. Her mother had a history of irregular menstrual cycles and ovarian cysts.

Medications were ineffective including monoamine oxidase inhibitors, methylphenidate, haloperidol, prolixin, lithium, and ECT. Desipramine and amitriptyline increased her cycling. She had a major motor seizure while on fluoxetine and also following ECT. The possibility of TLE was raised. EEG showed paroxysmal left temporal (sphenoidal) sharp and slow activity. Subsequent EEGs showed independent bitemporal paroxysmal epileptiform activity in one of four studies.

She improved marginally with antiepileptic drugs. An attempt to cycle her with conjugated estrogen and medroxyprogesterone resulted in the occurrence of seizures and extremely severe agitated depression during the estrogen phase. Treatment with natural progesterone alone during the second half of each cycle, however, was associated with the elimination of psychosis and overt seizures, a dramatic stabilization of her mood, a marked lessening in her obsessive thoughts and compulsive rituals, and the elimination of paranoid features. Attempts to stop her progesterone treatment were associated with florid recurrences of symptoms.

Case 4. Obsessive-Compulsive Disorder and Panic Attacks

Ms. P., a 31-year-old left-handed woman, was referred for evaluation of OCD, panic attacks, and phobias that developed 5 years earlier, 3 months after the birth of her daughter. Her symptoms were much more severe in the second half of each menstrual cycle, especially premenstrually. Hypochondriacal traits were noted as early as 5 years of age. She had anorexia and amenorrhea as a teen and later developed infrequent episodes of confusion and incoherent speech without subsequent recollection. Cycles always had irregular intervals ranging between 24 and 36 days. Her brother was hospitalized on two occasions for depression, obsessive-compulsive behavior, and hypochondriacal traits. Depression affected a number of family members on her father's side. A maternal grandfather was left handed.

On exam, there was a notable skeletal asymmetry with the left hand being larger than the right, decreased smell perception on the right side, and a mild speech articulation disturbance. The EEG showed paroxysmal epileptiform temporal lobe discharges, predominating on the right side.

Trials of tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants during her twenties did not agree with her. Her mood responded well to carbamazepine and her cycle became regulated for the first time. While on carbamazepine, she became pregnant. This occurred despite several years of infertility. She did very well during the pregnancy and delivery. Within 3 months after delivery, however, her obsessive and compulsive symptoms developed and increased to a disabling level despite psychotherapy and carbamazepine. A second pregnancy 4 years later was again associated with a marked improvement in her symptoms. She elected not to breastfeed her baby. She had moderately severe postpartum depression. This was replaced after 1 month by anxiety, agitation, panic attacks, phobias, obsessions, and compulsive behavior, which became progressively more severe and pervasive. Three months after delivery and endocrine documentation of inadequate luteal phase cycles, progesterone therapy was started using 200 mg lozenges three times daily on Days 14–25 of each cycle followed by tapering and discontinuation by Day 28. During the next 6 months, she had regular cycles. She felt relaxed. Panic attacks were eliminated and OCD features were described as a lot better by the patient, her husband, and her therapist. Progesterone was discontinued. Her cycle then became irregular with periods occurring every 2–3 weeks. She experienced, moreover,

a recurrence of panic attacks, severe worsening of obsessions, rituals and phobias, and episodes of incoherence without recollection of events. Re-institution of progesterone regulated her cycle and markedly benefited her symptoms again.

Comment: Manifestations of OCD are common features of interictal personality among individuals who have temporal lobe seizures.[6] They may also occur, as in Ms. G. and Ms. P., in the setting of temporal epileptiform discharges without prominent evidence of seizures, show catamenial patterns of exacerbation, and respond favorably to progesterone therapy.[29]

A reproductive hormonal influence on OCD manifestations is consistent with popular structural and chemical neurological hypotheses of etiology and pathogenesis. As of yet, there is no established basis for OCD. It is frequently reported to occur, however, in the setting of neurological disorders, in particular, those that involve the limbic system or basal ganglia. These include, for example, temporolimbic epilepsy,[6,9] encephalitis lethargica,[30–35] Sydenham's chorea,[36,37] Tourette syndrome,[38] tumors in the region of the cingulate gyrus, and lesions of the caudate nucleus.[39,40] Cingulotomy, moreover, has been reported to benefit patients.[41–44] This distribution of lesions is relevant because the neuronal activity of the basal ganglia, like the limbic system, are modulated by gonadal steroids.[45,46]

Case 5. Polycystic Ovarian Syndrome and Depression

Ms. D., a 40-year-old wife, mother, and gospel singer, came to see me because she felt that she had exhausted local medical resources and felt hopeless. She had polycystic ovarian syndrome (oligomenorrhea, hirsutism, ultrasound demonstration of multiple follicular cysts, and increased ovarian stroma), irritable bowel syndrome, personality disorder, OCD, agoraphobia, and depression. She had been refractory to a large number of antidepressant and anxiolytic drugs and experienced little improvement while attending psychiatry, allergy, and premenstrual clinics. An EEG, prompted by the episodic nature of her symptoms, showed paroxysmal sharp and slow waves in the left frontotemporal region. Carbamazepine provided significant relief from her usual episodes, lasting minutes to hours, of "unreality," "black depression," and "uncontrollable crying." She was once again able to sing masses at local churches. However, she continued to have fears and obsessions. Her menstrual periods were very irregular, and basal body temperature charts gave no indication of ovulation. For the next 3 months, she took clomiphene (50 mg daily) on Days 5–9 of her menstrual cycle and enjoyed a period of unparalleled well-being. She had no further episodic symptoms. She lost her fears and obsessions. She was able to perform at local churches. She chose, however, to stop doing this. She had an extramarital "affair" and kept a chart that showed 20/30 "good days" per month. The clomiphene was stopped in mid-October because of an episode of severe pelvic pain. Subsequently, she continued to ovulate regularly for 2 months, but in December, January, and February she once again developed irregular cycles, became depressed, obsessed about premenstrual syndrome, and had only 5/30 "good days" per month.

Comment: Ms. D.'s history of oligomenorrhea, hirsutism, and ovarian cysts was diagnostic of PCO. PCO is commonly associated with TLE, depression, and migraine.[47,48] The anovulatory cycles of PCO expose temporal lobe limbic structures to a constant estrogen effect without normal luteal phase elevations of progesterone and thereby heighten seizure activity and likely contribute to agitated depression and mood instability. Clomiphene therapy corrects the endocrine abnormalities of PCO, normalizes the menstrual cycle, and lessens seizure discharges.[18] Normalization of the menstrual cycle and luteal phase progesterone secretion generally also benefits the catamenial exacerbation of agitated depression and OCD in the setting of TLE.

Case 6. Cumulative Hormonal Effects on Anxiety, Mood, and Psychosis

Ms. S., a 36-year-old left-handed woman with prenatal diethylstilbesterol (DES) exposure, presented with severe anxiety, widely fluctuating moods, and intermittent psychosis. She had been very well until 2 years earlier when she required a total hysterectomy and bilateral oophorectomy for an infection that she acquired during tests for infertility. She did well on conjugated estrogen (0.625 mg daily for 3 months). Subsequently, however, Ms. S. began to develop increasing amounts of anxiety, agitation, irritability, and mood lability. Her anxiety, at times, would build to levels where she would physically shake, experience palpitations, and become only loosely tied to reality. Over the course of 2 years she was seen by several psychiatrists and was variably labeled as having a major mood disorder or anxiety disorder. Minor tranquilizers produced excessive sedation and depression with regular use. Antidepressants increased her agitation. Major tranquilizers were poorly tolerated. Discontinuation of estrogen replacement left her depressed and without energy. Increased estrogen dosage aggravated her anxiety.

As a child, Ms. S. walked late, between 2 and 3 years of age, and required elocution lessons for articulation difficulties. She had green eyes and blonde hair, a short stature, just under 5 feet in height, and a notable skeletal asymmetry with the right foot being between one-half to one shoe size bigger. There were no elementary neurological findings aside from the above-mentioned minimal dysarthria. She was agitated and labile. An EEG showed bitemporal paroxysmal sharp waves and slowing, especially on the left side.

Discontinuation of estrogen produced a rapid, dramatic reduction in anxiety and agitation. After 3 days of feeling well off estrogen, however, she developed rapidly increasing asthenia. She could not get out of bed and felt hopelessly depressed. The reintroduction of conjugated estrogen resulted in marked improvement within hours. She became animated and lively. After 4 days of therapy, however, she became racy, agitated, panicked, disorganized, and very concerned about "losing her mind." Progesterone lozenges (100 mg tid) were added. After 1

hour, she became calm and organized. She did very well for 4 days. By the 5th day, however, she once again could not get out of bed and felt asthenic and hopeless. Both hormones were discontinued with resulting improvement for 2 days, followed by recurrence of low energy and mood. At this point, she was placed on a cyclic 10-day regimen of estrogen for 4 days, estrogen plus progesterone for the next 4 days, and then no hormone for 2 days. On this unusual 10-day cycle, she has done very well. She has been able to establish a new business and return to her former community activities.

Comment: Hormonal effects on emotional behavior are often exaggerated in the setting of abnormal or anomalous temporolimbic substrates.[17,19] Hormones, however, can also have a progressive, cumulatively increasing effect on behavior. Ms. S. presents an extreme example of this phenomenon. Both types of responses are especially notable in the setting of temporolimbic epileptiform discharges, as in this case.[19] These effects may represent progressively increasing neuronal sensitivity and reactivity to continuous hormonal exposure. Two mechanisms may be involved: 1) estradiol can progressively increase dendritic branching and surface excitatory synapses,[49] as well as its own specific cytoplasmic receptors;[50] 2) the epileptogenic influence of estradiol exerts a kindling effect over time on limbic structures.[51] Estrogen effects are limited in both instances by progesterone. Progesterone reduces dendritic branching and excitatory synapses,[49] as well as the number of estradiol receptors.[52] It also inhibits kindling and epileptiform activity.[53] In the case of Ms. S., the energizing effects of estrogen became pathologically exaggerated after a few days of exposure, leading to anxiety and agitation. The sedating effects of progesterone effectively resolved the situation acutely but, after a few days, produced exaggerated effects of its own. The build up of both types of undesirable effects was prevented by a short cycle.

HORMONAL THERAPY OF SOME EMOTIONAL AND SEXUAL DISORDERS ASSOCIATED WITH EPILEPSY IN MEN

Testosterone Therapy

Testosterone replacement is the most common form of therapy for sexual dysfunction resulting from hypogonadism. Its efficacy in men with epilepsy, however, is not proven. In our experience with 12 men who had diminished sexual interest and reduced potency in the setting of TLE and antiepileptic drug use, biweekly 400-mg im injections of depotestosterone enanthate were associated with normalization of serum free testosterone levels and moderate improvement in sexual interest and potency scores in all 12 men. Seizure frequency showed no significant change.[54,55]

Therapy With Testosterone and Aromatase Inhibitor

Testosterone therapy in our experience has been only moderately effective in restoring reproductive and sexual function. Moreover, testosterone has not lessened seizures despite some reports of its anticonvulsant properties in experimental animals.[56] One possible explanation is that antiepileptic drugs that induce increased enzyme synthesis may enhance the conversion of testosterone to estradiol by aromatase.[57] Estradiol lowers male sexual interest and function[58] and increases seizure discharges[59,60] and anxiety. The addition of testolactone (300–500 mg daily), an aromatase inhibitor, and depotestosterone (400 mg biweekly) to baseline antiepileptic drug therapy produced clinically and statistically significantly better effects on sexual interest and function as well as on seizure frequency and anxiety than treatment adding testosterone alone.[55] This is illustrated in a 52-year-old hypogonadal man with intractable seizures on baseline carbamazepine therapy (Table 1).[61] A possible anxiogenic effect of estradiol in men as well as women is supported by the apparent association between estradiol and anxiety levels as indicated by anxiety scores in the Profile of Mood States.

Clomiphene Therapy

Clomiphene dramatically benefited sexual interest, potency, and seizure control in one case report of a man with complex partial seizures and hypogonadotropic hypogonadism.[62] Seizures were eliminated during clomiphene use in another case with epilepsy and oligospermia.[63] It offered no benefit, however, for a man who had complex partial seizures and hypergonadotropic hypogonadism, that is gonadal failure.[62] Total and free antiseizure medication levels were not affected. The mechanism of clomiphene action on seizure activity is conjectural but may involve either the normalization of the serum testosterone level or direct antiestrogenic effects on epileptogenic limbic structures that have high-density estradiol receptors. An effect of clomiphene on sexual interest and function as well as competitive drive is suggested by the following case.

Case 7. Effect of Clomiphene on Sexual Interest and Function

Mr. W., a 36-year-old man with left-sided sensorimotor and secondary generalized seizures of 16 years' duration, was referred for evaluation of refractory epilepsy and infertility. His treatment regimen consisted of carbamazepine (200 mg five times daily) and primidone (250 mg four times daily). Neurological examinations were remarkable for variable mild left hemiparesis. EEGs were mildly abnormal because of bilateral

paroxysmal temporal theta slowing. A pneumoencephalogram showed dilation of the right temporal horn. His personality showed great depth of feeling, excessive attention to detail, unassertive, placid demeanor, and diminished sexual interest. For several years, he had reproductive dysfunction consisting of insufficient erection for penetration and no ejaculation. The sexual and reproductive dysfunction seriously threatened his marital life. External genitalia and testicular ultrasound were normal.

Reproductive endocrine profile showed decreased serum luteinizing hormone and testosterone. Semen analysis in 1986 showed a normal sperm count but decreased motility values. After 1 month on 25 mg of clomiphene daily, the patient and his wife reported that he demonstrated a more assertive attitude, competitive drive, and increased sexual desire. He could achieve sexually functional erections. His luteinizing hormone and testosterone levels normalized. She became pregnant after 3 months and delivered a healthy baby boy after 9 months. He remained on clomiphene therapy for a total of 6 months. During the entire treatment period, he had no seizures. After clomiphene was discontinued, seizures recurred on a weekly basis and he resumed his more unassertive, placid, hyposexual demeanor.

CONCLUSION

The temporolimbic structures of the brain that subserve emotional representation are highly epileptogenic and play an important role in the modulation of hormonal secretion and mediation of hormonal feedback. Estrogen is highly epileptogenic and exerts energizing and antidepressant effects. Excessive estrogen influence produces anxiety, agitation, irritability, and lability. It can promote the development of anxiety manifestations (e.g., panic, phobias, and obsessive-compulsive disorder). Progesterone and its metabolites inhibit kindling and seizure activity. They have potent anxiolytic effects, possibly by virtue of their GABAergic activity. Excessive progesterone influence produces sedation and depression. Testosterone has two major metabolites: estradiol, which can exacerbate seizures, and dihydrotestosterone, which blocks NMDA-type glutamate transmission and may be responsible for antiseizure effects. Testosterone has energizing effects and increases sexual desire in both men and women. In excess, however, it may promote aggressive, impulsive, and hypersexual behavior.

Temporolimbic dysfunction can produce altered hypothalamopituitary regulation of gonadal steroid secretion, which can lead to abnormal hormonal influences on emotional behavior. Hormonal effects, moreover, tend to be exaggerated or idiosyncratic in the setting of an abnormal or anomalous temporolimbic substrate, especially temporolimbic epilepsy. In this particular setting, hormones can also have a progressive, cumulatively increasing effect on emotional behavior, such that the normal physiological emotional effect of a hormone becomes transformed over days or weeks of continuous unopposed exposure, into a pathological emotional state. This may reflect progressively increasing or kindled neuronal responsivity to continuous hormonal exposure perhaps by virtue of changes in the number of dendritic spines and receptors. Finally, there is reason to believe that repeated episodes of psychosocially triggered emotional stress may utilize the limbic kindling paradigm to promote more spontaneously occurring recurrent mood and anxiety disorders. Such a kindling process could also play an important role in the frequent association of reproductive dysfunction with anxiety and mood disorders in both men and women.

Emotional disorders may result when abnormal endocrine states interact with normal brain, when normal endocrine states interact with abnormal brain, and when abnormal endocrine states interact with abnormal brain. An understanding of these relationships and the therapeutic role of reproductive hormones should lead to a more effective and comprehensive management of women and men with anxiety and mood disorders.

TABLE 1. Testosterone versus testosterone-testolactone effects on sexual interest, potency, and seizure frequency

	Sexual Function (score/20)	Seizures per week	Testosterone (ng/ml)	E2 (pg/ml)	Anxiety (score/32)
Normal range	>16		300–1,200	10–40	
Carbamazepine	10*	2	191*	41*	20
+ Testosterone	14*	2	1,210	70*	26
+ Clomiphene	14*	0	527	34	18
+ Testolactone and testosterone	18	0	1,214	22	8

*Abnormal value.
Note: Sexual function: score on standardized inventory of sexual interest and potency. Anxiety: score on anxiety scale of Profiles of Mood States.

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