Basic Psychopharmacology of Antidepressants, Part 2: Estrogen as an Adjunct to Antidepressant Treatment

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Estrogen exerts profound effects upon behavior by interacting with neuronal estrogen receptors. Changes in estrogen levels over a woman's life cycle are linked not only to behavioral fluctuations, but potentially to the onset or recurrence of mood disorders. The modern psychiatric evaluation of women requires obtaining a complete reproductive history, including details of hormone treatments, while identifying reproductive events as triggers of affective disorder episodes. While guidelines for the use of reproductive hormones in psychiatry are just evolving, administration of estrogen as an adjunct to antidepressants is an exciting possibility for expanding the frontiers of psychiatry into the field of women's health. *(J Clin Psychiatry 1998;59[suppl 4]:15–24)*

Recent advances in neuroscience are strengthening the long-established links between reproductive hormones and behavior.[1] These new insights are impacting clinical psychopharmacology, as reproductive hormones are increasingly being seen as both exacerbators and mitigators of various psychiatric disorders. Appropriate knowledge of the female life cycle with its associated changes in reproductive hormones is increasingly necessary in order to optimize management of psychiatric disorders in women. Psychiatrists are being required more and more to understand the appropriate use of reproductive hormones as adjuncts to psychotropic medications. Primary care physicians and women's health specialists prescribe the majority of psychotropic medications for women and are called upon to recognize the differences between normal fluctuations in behavior and those requiring treatment with hormones, with psychotropic drugs, or both.

Here we discuss the impact which new understanding of the neurobiology of reproductive hormones is having in particular upon the recognition and treatment of depression. Disorders of cognition are also being impacted by this new neurobiology, but will be mentioned only briefly. This material is also presented as a continuing medical education lesson.[2]

ESTROGEN AND NEUROTRANSMITTERS

Estrogen exerts numerous physiologic effects upon several neurotransmitter systems in the central nervous system (CNS) with well-documented actions at serotonergic, adrenergic, and cholinergic neurons, pathways, and receptors[3,4] (Tables 1–3). These neurotransmitters have been shown to play key roles not only in the pathophysiologies of disorders of mood and cognition, but also in the mechanism of action of psychotropic drugs used to treat these disorders.[5,6] Thus, the actions of estrogen on monoamine neurotransmitter systems may explain estrogen's profound effects upon behavior as well as its role in various disorders of behavior and their treatments.[1–4,7,8] A partial listing of behaviors linked to ovarian steroids is given in Table 4. The specific actions of estrogen on monoamine neurotransmitter systems in the brain are too numerous to be reviewed in detail here. A number of key actions are summarized in Tables 1–3 and are reviewed elsewhere.[3,4]

Some of the most profound and important actions of estrogen in relationship to disorders of mood and their treatments may be exerted at serotonin systems.[9–12] Serotonin systems are widely hypothesized to be dysregulated in depression and to be the substrate for the actions of many antidepressants.[5] For example, down-regulation of serotonin receptors is a key observation following antidepressant treatment and has been linked extensively in the literature to the mechanism of delayed therapeutic action of antidepressants.[5]

Although almost all studies of serotonin receptor regulation have been performed in male rats, one key observa-

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Figure 1 reproduced with permission from Stahl SM. Essential Psychopharmacology. New York, NY: Cambridge University Press; 1996. The author expresses his appreciation to Uriel Halbreich, Vivien Burt, Bruce McEwen, Myrna Weissman, and Sheldon Preskorn for ideas for tables.

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Table 1. Effect of Estrogen on Serotonin*

Increases number of serotonin transporters
Decreases monoamine oxidase activity
Permissive for serotonin-2 receptor down-regulation by antidepressants
May normalize the blunted serotonin receptor responsiveness of postmenopausal women

*Based in part on references 27 and 63.

Table 2. Effect of Estrogen on Acetylcholine*

Enhances acetylcholine synthesis
Alters choline acetyl transferase activity
Alters muscarinic receptors in hypothalamus and preoptic area
Changes electrical firing response to acetylcholine in hypothalamus

*Based in part on references 27 and 63.

Table 3. Effect of Estrogen on Catecholamines*

Alters tyrosine hydroxylase activity
Alters norepinephrine turnover and plasma MHPG metabolite levels
Alters norepinephrine reuptake
Decreases monoamine oxidase activity
Alters catechol-o-methyl transferase activity
Changes α_2 receptor binding sensitivity
Changes β_2 receptor binding sensitivity
Alters sensitivity of D_2 dopamine receptors

*Based in part on references 27 and 63.

Table 4. Actions Linked to Ovarian Steroids*

Motor activity
Epilepsy (catamenial)
Premenstrual syndrome
Depression
Pain
Cognitive functions (verbal memory, spatial memory)
Dementia

*Based in part on reference 27.

tion in female rats is stunning: that is, ovariectomized rats treated with antidepressants are unable to down-regulate their serotonin receptors following chronic treatment with antidepressant agents.[9] However, this action of antidepressants is restored by the addition of estrogen to antidepressant treatment.[9] Could this explain the apparent synergy of antidepressants with estrogen in some depressed women? Does this suggest that depressed women unresponsive to antidepressant agents may become responsive after addition of estrogen to their therapeutic regimen?

A related observation in women is the apparent desensitization of serotonin receptors in normal postmenopausal women not receiving hormone replacement therapy.[13] When these women were given estrogen replacement, their serotonin responsiveness normalized.

Some of the most profound and important actions of estrogen in relationship to disorders of cognition and their treatments may be exerted at acetylcholine systems (Table 2), hypothesized to be deficient in disorders of memory and cognition, such as Alzheimer's disease, and the substrate for the actions of cognitive enhancers that block the enzyme acetylcholinesterase.[4,14–16]

Unfortunately, too little is known about how estrogen interacts with neurotransmitter systems such as those of serotonin or acetylcholine, or about how estrogen impacts the ability of antidepressants or cognitive enhancers to regulate neurotransmitter systems and their receptors. One hint about how the actions of estrogen and antidepressants in the brain may be linked comes from the observation that both agents ultimately exert their biological actions on neurons via transcription factors, which alter the expression of different genes.

In other words, the delayed actions of antidepressants are hypothesized to be mediated ultimately through the transfer of a message from neurotransmitter receptors on the neuronal membrane, which produces an intracellular transcription factor. This transcription factor in turn alters the genetic machinery in the cell nucleus. This action results in changing gene expression, ultimately altering cellular functioning to effect an antidepressant response (see Figure 1).[5]

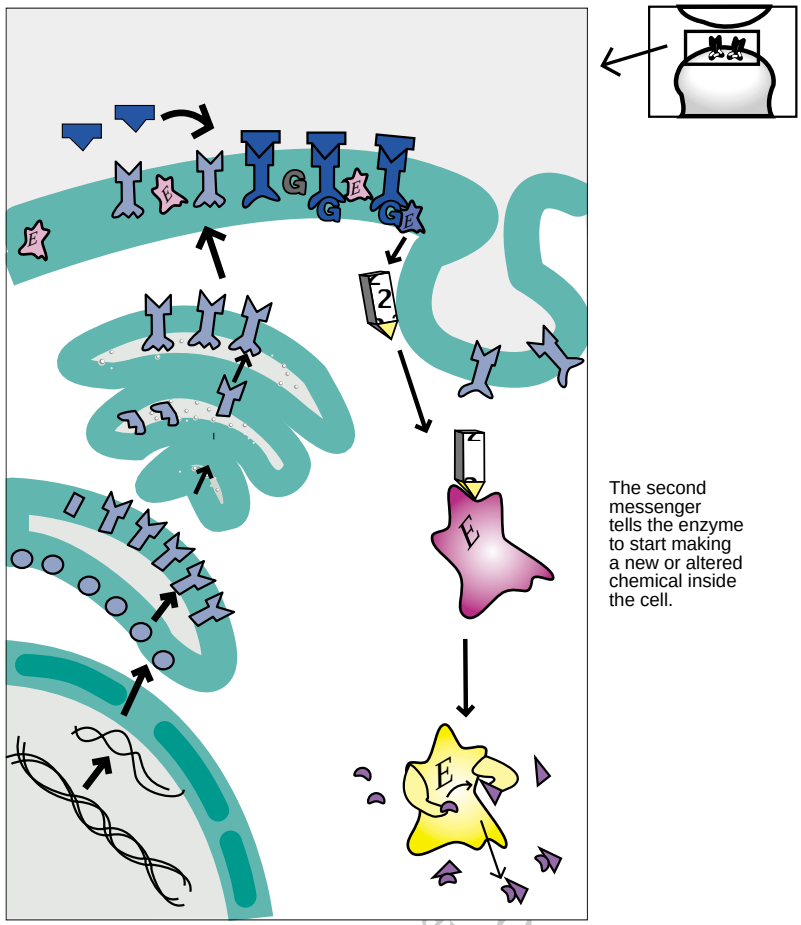
Estrogen is itself a transcription factor.[17] Thus, it travels directly to its receptors, which in fact are located right in the cell nucleus itself.[18–22] Once there, estrogen alters gene expression. This results in the physiologic effects of estrogen in various tissues, including the brain as well as bone, reproductive organs, and other tissues.[18] The actions of estrogen in brain may synergize with various psychotropic agents, be permissive for certain biological responses to drugs, or be necessary but not sufficient gene regulators for a psychotropic drug to effect a therapeutic response. Just as various estrogens have differing effects in different peripheral tissues such as uterus versus breast, so might various estrogens have differing effects in brain versus peripheral tissues.

Since most basic science studies of estrogen utilize estradiol and most clinical studies use Premarin (ultimately a mixture of estrone and equilin as well as estradiol), results in animals may not be predictive of results in humans. Also, binding properties of various estrogenic compounds, including specific estrogen receptor modulators (SERMS) such as raloxifene, may alter gene expression in brain differently than do other estrogenic compounds,[18] and may have profoundly different effects in pathologic conditions or in the presence of a psychotropic agent. Clearly, much more research on the interplay between estrogen and psychotropic drugs is required in order to understand the potential synergy of such agents in disorders of mood.

PROGESTERONE AND NEUROTRANSMITTERS

Even less is known about the actions of progesterone upon monoamine neurotransmitter systems in the CNS

Figure 1. Production of Transcription Factors*



*Reprinted with permission from reference 5. Receptor occupancy at the neuronal membrane by a neurotransmitter or drug (top of diagram) can lead to chemical instructions by intracellular enzymes, which ultimately produce a transcription factor (bottom of diagram). Shown here is a neurotransmitter-induced cascade (icons at top) leading to second messenger formation (designated "2"), and then second messenger activating an intracellular enzyme (E), which in turn has triggered yet another intracellular enzyme to produce a transcription factor (shaped like an arrowhead). This particular transcription factor targets that part of the neuron's DNA (lower left of diagram) which controls the expression of the neurotransmitter receptor (designated by arrows pointing up).

Table 5. Effect of Progesterone on Neurotransmitters*

Partial agonist at allosteric benzodiazepine or neurosteroid sites on the $GABA_A$ receptor/chloride channel complex

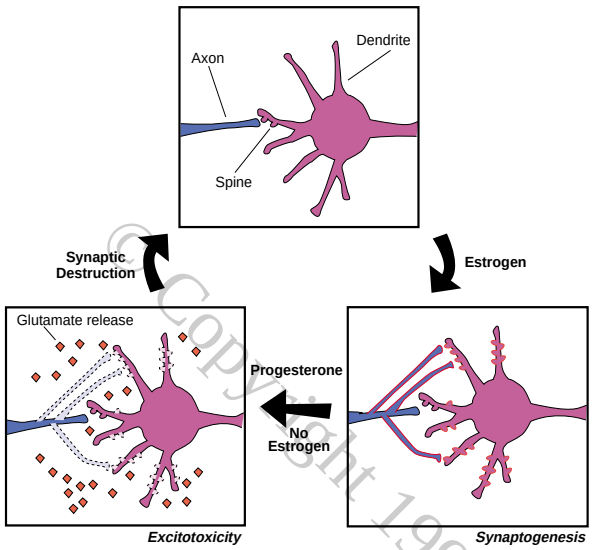
*Based in part on reference 27.

than is known about the actions of estrogen. One well-known action is a sort of alprazolam-like effect of progesterone on GABA receptors (Table 5).[1,3] That is, progesterone acts as a weak allosteric modulator of GABA's ability to increase chloride conductance through the $GABA_A$ receptor complex. Such observations have led some to speculate that progesterone may therefore be a calming or anxiolytic agent.[1,3,23,24]

Perhaps a more important observation is how progesterone appears to mitigate the actions of estrogen in CNS neurons analogous to its actions in mitigating estrogen effects in other tissues, such as uterus.[1–4,8] Thus, it is a common observation that the administration of exogenous progesterone can have a mood-destabilizing effect in women and mitigate some of the mood-stabilizing or even antidepressant-facilitating actions of estrogen in certain women.[1–4,24] This may underlie the development of various strategies to counter the undesired actions of progesterone in some women receiving estrogen replacement therapy by the hormone replacement regimens discussed later in this article.

One profound action of progesterone is its ability to dismantle synapses at the end of the menstrual cycle that were erected by estrogen at the beginning of the cycle (Figure 2).[8,17,21,26,27] Estrogen's trophic effects on certain synapses may also underlie its apparent ability to enhance cognitive function in postmenopausal women and perhaps to prevent or delay the onset of Alzheimer's disease.[14,15,28]

Figure 2. Effect of Estrogen on Synapses During the Menstrual Cycle*



*Reprinted with permission from reference 17. An axon innervating a dendrite at the beginning of the menstrual cycle (top) sprouts to innervate more dendrites under the influence of estrogen (right). Removal of estrogen plus the presence of progesterone dismantles these synapses, possibly via an excitotoxic mechanism through glutamate release.

Table 6. Modern Myths About Mood, Reproductive Hormones, and the Female Life Cycle

Mood fluctuation means mood disorder
Menopause causes depression
Treatment of mood disorders with reproductive hormones is not a psychiatrist's job

Much more remains to be investigated about these dramatic changes in synapse formation by estrogen and destruction by progesterone. Harnessing the profound actions of reproductive hormones on synaptogenesis may enhance the ability to treat disorders of both mood and cognition and to use these hormones appropriately to optimize the actions of psychotropic agents,[29] especially antidepressants and cognitive enhancers such as procholinergic drugs.

Estrogen's effects on cholinergic neurons is better studied than are progesterone's and include alterations both in acetylcholine synthesis and in acetylcholine receptor regulation (see Table 2).[1–4,8,21] As the cholinergic system is thought to underlie not only important cognitive functions but also the mechanism whereby cognitive enhancers such as tacrine and donepezil (cholinesterase inhibitors) improve memory in Alzheimer's disease,[5] better characterization of how estrogen and progesterone impact the cholinergic system can help guide the appropriate concomitant use of these agents in postmenopausal women.

Table 7. Is It Mood Fluctuations or a Mood Disorder?*

Postpartum blues or postpartum depression/postpartum psychosis?
Perimenopausal hot flushes, sleep disturbance, and mood fluctuation or perimenopausal major depression?
Premenstrual magnification of mood fluctuations or PMS?
Oral contraceptive–induced magnification of mood fluctuations or precipitation of major depression?
Cyclical estrogen administration causing estrogen withdrawal syndrome with magnification of mood fluctuations or with precipitation of major depressive episode?
Progestin-induced magnification of mood fluctuations or precipitation of major depressive episode?

*Based in part on reference 65.

MOOD, REPRODUCTIVE HORMONES, AND THE FEMALE LIFE CYCLE

Several myths exist in psychiatry regarding mood, reproductive hormones, and the female life cycle (Table 6). The first discussed here is that mood fluctuation equals psychiatric disorder. Another is that mood disorders rise predictably after menopause. And a third is that a psychiatrist does not need to take a gynecological history or to record, understand, and guide the prescription of hormones such as oral contraceptives or hormone replacement therapy. We will deal with each of these in turn.

Myth #1: Mood Fluctuation Means Mood Disorder

There is no doubt that estrogen, or the lack of it, can impact mood.[1–4,23,30–41] Women frequently report changes in mood during the late luteal phase of the menstrual cycle,[1–4,42,43] following childbirth,[1–4,44,45] when taking oral contraceptives,[37] when entering menopause,[1–4] and when taking hormone replacement therapy postmenopausally.[14,23,28,33,40–42] On the other hand, it is important to recognize when such changes are normal and when they are psychiatric disorders (Table 7). Setting the threshold too low essentially pathologizes the normal female life cycle. Setting the threshold too high explains away disabling and treatable disorders of mood as part of the normal female life cycle.

Most mood changes in women, in fact, are fluctuations that fail to surpass the threshold for a full-fledged DSM-IV psychiatric disorder of mood. That does not mean that such fluctuating mood symptoms cannot be inconvenient, uncomfortable, or worthy of eliminating by appropriate interventions. In such cases, the intervention can often be manipulation of reproductive hormones.[1–4] Antidepressants play a well-documented role only in full-blown disorders of mood with actual social and/or occupational impairment.[5]

Estrogen is much better documented to improve mood and well being in normal peri- and postmenopausal women than it is to have a robust and proper antidepressant action in women with full-criteria major depressive disorder.[1–4,7,23,24,28–36,38,39,41–46]

Table 8. Definition of Menopause

Final cessation of menses
Median age 51
Secondary amenorrhea of 12 months' duration in a woman older than 45 confirms menopause
Follicle-stimulating hormone (FSH) above 40 IU/L is consistent with menopause. If irregular cycling, check level on Day 2 or 3 of cycle (Note: FSH may be normally elevated during midcycle surge)

Table 9. Definition of Perimenopause

Interval between regular ovulatory menstrual cycles and complete cessation of ovarian function
Typically 5–7 years prior to menopause

Table 10. Do Women Have an Increase in Episodes of Major Depressive Disorder Around Periods of Endocrine Shifts?*

Period of Endocrine Shift	Evidence
Puberty	Strong
Postpartum	Strong
Perimenopause	Highly suggestive
Menopause	Not convincing

*Based in part on reference 49.

Table 11. Kindling for Vulnerable Women?*

Women who suffer from affective disorders following one reproductive event are at increased risk for recurrences at other reproductive events

*Based in part on reference 45.

Myth #2: Menopause Causes Depression

This commonly held belief arises out of observations that mood and sexual functioning can indeed change in many women when entering menopause.[1–4,29–41] Also psychoanalytic notions may portray menopause as the "empty nest syndrome," causing depression on a psychodynamic basis due to the woman's reaction to transitioning from a child-rearing role to other activities. The reality suggested by new epidemiologic studies seems, however, to be much different.

Recent epidemiologic studies reveal that for most women, mental health is not adversely affected by the menopausal transition.[1–4,47–49] Specifically, natural menopause alone does not increase the odds that a woman will become depressed. The Epidemiology Catchment Area (ECA) study of depression in men and women in the United States appears to abolish the myth that menopause is associated with increases in depression.[49]

For men, the incidence of major depression rises during puberty and thereafter stays relatively stable throughout the life cycle. Interestingly, the rate of major depression in women is the *same* as in men not only before puberty, but also after menopause. The rate for women, however, rises dramatically above that for men during and after puberty, with two peaks, and then actually falls after menopause. Those peaks are firstly during the childbearing years, and then secondly during the perimenopausal transition. Interestingly, the rates of depression in women across their life cycle roughly track the plasma levels of estrogen across their life cycle. This association is very provocative, but there is not yet sufficient proof that estrogen in fact drives these rates of depression across the life cycle.

Thus, the focus for women is changing from menopause to the perimenopausal period. In order to understand this changing focus, it may be useful to define these terms (see Tables 8 and 9).[1–4,25,50] Recent research shows that new onset of major depression in a woman is therefore moderately associated with *peri*menopause, is related to length of perimenopause, and, in fact, if anything, remits at menopause.[1–4,47–49] Thus, menopause is associated with a *reduction* in the incidence of depression, not an increase as has been so popularly believed. What appear to be key associations are therefore those between various shifts in reproductive endocrine functioning across the female life cycle (Table 10) and increases in incidence of depression. Such shifts occur specifically at puberty, after childbirth, and during perimenopause.[1–4,47–49]

Not only is perimenopause a risk factor for new-onset depression, it is also a time when women with a prior major depressive episode are at increased risk for a recurrent episode.[1–4,45,47–49] In fact, there is the notion that depressive episodes in association with an endocrine shift "kindle" that individual for a subsequent depressive episode in association with a subsequent endocrine shift later in the female life cycle (Table 11).[45] Specifically, data from postpartum depression suggest vulnerability to recurrence after a subsequent pregnancy and may also predict vulnerability to recurrence in the perimenopausal transition.[45]

Finally, sexual functioning can change during menopause. However, not all sexual dysfunction is related to depression. Neither is all sexual dysfunction related to reproductive hormones.[1–4,23] Thus, it is important to ask "Is it primary sexual dysfunction, or is it a mood disorder?"

Changes in sexual functioning that occur in the peri- and postmenopausal periods can include decreased libido, decreased lubrication and swelling/arousal, delayed orgasm or anorgasmia, and postmenopausal sex organ changes such as vaginal atrophy. Urogenital atrophy itself has possible consequences on sexual functioning including dyspareunia, decreased frequency of intercourse, and a subjective sense of diminished sensitivity and responsiveness.[25,49] Other factors to be assessed in the differential diagnosis of sexual dysfunction in the perimenopausal period include not only the obvious possibility of major depressive disorder, but the potential side effects of antidepressant drugs themselves.[1–4,51] In addition, sexual functioning can be compromised by a number of other factors requiring assessment, including

Table 12. Treatment Considerations for Women With Mood Symptoms*

Is the patient premenopausal, perimenopausal, or postmenopausal?
Age
Characterize cycling
Vasomotor symptoms?
Sleep pattern
Hormone levels (FSH, estradiol)

*Based in part on reference 65.

Table 13. Assessing Mood Changes in Mid-Aged Women*

Ascertain patient's views on approaching or reaching childbirth, menopause, aging
Ask about physical changes:
Vasomotor
Sexual
Mood changes: is it mood fluctuation or is it major depressive disorder?

*Based in part on reference 65.

Table 14. Mood Changes in Women*

Correctly identify where the patient is in the reproductive life cycle
Evaluate for past history of mood disorders, especially in relation to reproductive life events
Assess health and social circumstances
If woman is mid-aged, use estrogen replacement therapy in peri- and postmenopausal period both for:
Physical symptoms
Mood symptoms
Treatment of major depressive episode with antidepressants and/or psychotherapy

*Based in part on reference 65.

Table 15. Treatment Considerations: Group 1*

Mild to moderate mood swings
Perimenopausal
No past psychiatric history
Prominent vasomotor symptoms
Consider estrogen replacement therapy
If no response in 6 weeks, reevaluate psychiatric condition
Then consider standard antidepressants and psychotherapy

*Based in part on reference 65.

chronic health problems, interpersonal difficulties (new or ongoing), and partner sexual dysfunction.[25,50]

Myth #3: Treatment of Mood Disorders With Reproductive Hormones: Not a Psychiatrist's Job

The third myth to be discussed here is that since psychiatrists are not primary care physicians or women's health specialists, they do not need to take a gynecological history or to record, understand, and guide the prescription of hormones such as oral contraceptives or hormone replacement therapies in order to adequately treat mood disorders in women. The fact that the majority of patients treated by many psychiatrists are women and that many if not most of them are in the high-risk period of the female life cycle (i.e., between puberty and menopause) should be sufficient to debunk this third myth. That profound links between both endogenous and exogenous reproductive hormones and mood as well as links between shifts in reproductive hormone status and onset or recurrence of mood disorder exist is another powerful argument for psychiatrists to take a crash course in gynecological endocrinology and to modify the manner in which they may be taking histories.

Specifically, treatment considerations for a female patient in a psychiatrist's practice might now include asking whether the patient is premenopausal, perimenopausal, or postmenopausal (Table 12). This could be amplified by asking about the age of the patient during episodes of mood disorder, probing for any cyclic symptomatology, asking about vasomotor symptoms and sleep patterns, and obtaining relevant hormone levels such as follicle-stimulating hormone (FSH) and estradiol.

These items can be collected while also ascertaining the patient's views on approaching or reaching childbirth, menopause, or aging; asking about physical changes in urogenital tissues and about sexual changes; and, most importantly, deciding whether mood changes are a mere depressive syndrome or a major depressive episode (Tables 7 and 13).

Having correctly identified the patient's reproductive time of life, the psychiatrist can then look not only for a past history of mood disorder, but especially for whether there is any relationship of a past episode of depression to reproductive events or endocrine shifts. Obviously, health and social circumstances must also be assessed (Table 14).

The bottom line here is that proper consideration should be made about treating mood changes in mid-aged women that do not meet criteria for a major depressive episode with estrogen replacement therapy when there are troublesome physical symptoms, such as hot flushes and insomnia, and mood symptoms (Table 15).[1–4,25,50] On the other hand, no matter where in the life cycle a woman might be, treatment of major depressive disorder itself continues to require antidepressants and/or psychotherapy (Tables 16 and 17). Specific treatment recommendations for hormone preparations and antidepressants are considered below.

IMPACT OF REPRODUCTIVE HORMONES ON TREATMENT OF MOOD DISORDERS WITH ANTIDEPRESSANTS

The advent of these new insights into the role of reproductive hormones in mood and its disorders is definitely changing the use of reproductive hormones with or without antidepressants. Treatment considerations for three major groups of perimenopausal women are shown in Tables 15–17. Firstly, for mild to moderate depression in

Table 16. Treatment Considerations: Group 2*

Major depression
Perimenopausal
No prior psychiatric history
Standard therapy with antidepressants and/or psychotherapy
Consider estrogen replacement therapy for vasomotor symptoms and for long-term treatment of postmenopausal complications

*Based in part on reference 65.

Table 17. Treatment Considerations: Group 3*

Major depression
Perimenopausal
History of recurrent major depressive episodes
Standard therapy for depression with antidepressants and/or psychotherapy
Use history of prior responses to previous antidepressant treatments as a guide for best treatment
Consider estrogen replacement therapy for vasomotor symptoms and for long-term treatment of postmenopausal complications

*Based in part on reference 65.

a perimenopausal woman with no past psychiatric history and prominent vasomotor symptoms, one might consider estrogen replacement therapy first. If, however, there is no response in 6 weeks, it would seem prudent to reevaluate the psychiatric condition and consider standard antidepressants and psychotherapy (Table 15).

On the other hand, for an episode of major depressive disorder in a perimenopausal woman with no prior psychiatric history, it may be best to consider standard therapy with antidepressants and psychotherapy first (Table 16). However, one might also consider estrogen replacement therapy, not so much for the mood disorder as for vasomotor symptoms and long-term treatment of postmenopausal complications such as bone fractures and heart disease.

Finally, for a major depressive episode in a perimenopausal woman with a history of recurrent major depressive episodes, one might not only consider standard antidepressants and psychotherapy first, but use history of prior responses to previous antidepressant treatments as one guide to suggest the possible best treatments (Table 17). Use of estrogen replacement therapy for vasomotor symptoms and long-term complications could also be considered.

Gender Psychopharmacology: A New Consideration

Historically, most antidepressants have been studied first in healthy men, then in men with depression, and then in women who do not have childbearing potential.[1–4,51–53] Only relatively late in drug development are women included from all stages of the life cycle. Gathering data in this manner can lead to distortions in our understanding of drug doses and effects with a bias to treating women as if they responded to antidepressants in the same ways that men do. Although this is often the case, there has been recent awakening to the unique psychopharmacologic considerations about how administration of antidepressants may need to be modified in some women.[1–4,52–57]

Table 18. Gender Psychopharmacology: Women*

Less gastric acid secretion
Decreased gastrointestinal transit times
Increased adipose tissue
Decreased hepatic blood flow and hepatic metabolism
Cyclic levels of reproductive hormones
Increased drug half-lives
Increased plasma drug levels
Increased drug side effects
Menstrual- or pregnancy-related variations in efficacy

*Based in part on reference 64.

Specifically, questions now arise that have never been adequately addressed in the past, including whether the dose of some medications should be adjusted during the menstrual cycle; whether different doses should be used in the immediate postpartum interval; and whether antidepressants affect reproductive functioning. Although there are few answers to such questions, it is already an advance to see that the questions are now being asked.

There is also increased recognition that gender can affect the pharmacokinetics of antidepressants in women (Table 18).[1–4,46,52,53] For example, failure to address gender differences in body size, daily dose requirement, and relative percentage of adipose tissue could have the potential consequence of higher drug levels and longer residual plasma half-lives in women than in men taking the same dose. Also, reproductive hormones affect the cytochrome P450 system such that drug half-lives and levels are altered with potential changes in drug efficacy, tolerability, and/or safety. This may not be unimportant, for women may be more prone to specific adverse effects of antidepressants or to their consequences, as when orthostatic hypotension occurs in elderly women with osteoporosis who are vulnerable to hip fractures. Gender differences in pharmacokinetics caused by reproductive hormone effects on drug levels and half-lives may cause menstrual- or pregnancy-related variations in side effects or in efficacy.

Gender pharmacokinetics include the following differences in women[1–4,46,52,53]: less gastric acid secretion, decreased gastrointestinal transit times, increased adipose tissue, decreased hepatic blood flow and metabolism, and cycling levels of reproductive hormones. The consequence of decreased hepatic blood flow and decreased gastrointestinal transit time could be greater absorption and slower clearance, leading to higher drug levels.

Since so few studies have taken these factors into account, it is not yet possible to determine whether any of these factors are significant influences on the use of antidepressants by women. Future studies may ultimately change the way we administer antidepressants—by gender and by presence of endogenous and exogenous reproductive hormones as we already do by age.

Table 19. Estrogen as an Adjunct for Refractory Depression?

Few studies
Fewer than 30 cases
High doses of estrogen
Pre-, post-, and perimenopausal women combined
Conflicting data
No clear antidepressant augmentation shown
Induction of mania/rapid cycling

Table 20. General Health Benefits of Estrogen Replacement Therapy in Postmenopausal Women*

Reduces cardiovascular risk
Decreases bone resorption, osteoporosis, and fractures
Reduces aging effects, particularly of sex organs and urinary tract
Alleviates vasomotor symptoms

*Based in part on reference 63.

Table 21. Health Risks of Estrogen Replacement Therapy*

Endometrial hyperplasia
Exacerbation of endometriosis
Increased risk of uterine cancer
Increased risk of breast cancer? (controversial)
Destabilizing mood, especially with supplemental progesterone
Increased risk of gall bladder disease
Breakthrough bleeding
Thrombophlebitis
Nausea, abdominal cramps, bloating, and water retention
Breast tenderness, enlargement, or secretion

*Based in part on reference 63.

ESTROGEN AS AN ADJUNCT FOR REFRACTORY DEPRESSION

One logical extension of the information presented here is the possibility that clever and appropriate use of reproductive hormones along with antidepressants might convert depressed women with inadequate treatment responses into full responders when both reproductive hormones and antidepressants are coadministered.[29] As obvious as this proposal might seem, there is precious little investigation of this possibility. The use of estrogen to supplement ongoing antidepressant treatment to enhance antidepressant responsiveness has been studied generally with the older tricyclic antidepressants and not with modern antidepressant agents such as the serotonin selective reuptake inhibitors (SSRIs) (Table 19).[30–32,34] Also, the type of estrogen varies from study to study (synthetic versus others), often in supra-physiologic replacement doses, and study of dose-response effects is lacking.

There are fewer than a half dozen reports of a few dozen cases selected from uncontrolled studies in which estrogen was used to augment antidepressant treatment.[1–4,29–34] Incredibly, studies mixed efficacy analyses of premenopausal women with those of perimenopausal women and with those of postmenopausal women. There was also no confirmation of life-cycle stage with appropriate hormone levels.

Table 22. Contraindications for the Use of Estrogen*

Breast cancer (relative contraindication)
Estrogen-dependent neoplasia
Undiagnosed abnormal uterine bleeding
Active thrombophlebitis or thromboembolic disorders, particularly during prior estrogen use
Known or suspected pregnancy

*Based in part on reference 63.

Results of combining estrogen with antidepressants are largely negative in terms of improving treatment outcome of the mood disorder and even include the possible adverse consequence of inducing mania or rapid cycling in some women. Although these findings are not encouraging in terms of suggesting a synergy between estrogen and antidepressants in treatment-refractory peri- and postmenopausal depressed women, much further work is required before the utility of this approach can be adequately assessed.

One promising preliminary observation suggesting that there is a positive effect of the combination of antidepressants and estrogen on antidepressant treatment response comes from a provocative but as yet unpublished report from an NIMH workshop reporting the results from a multicenter study of fluoxetine in 658 patients over 60 years of age with major depression. Overall, the efficacy of fluoxetine was 32% compared with a placebo rate of 18%. However, among women who had been receiving estrogen replacement therapy, the difference between drug and placebo was three times greater. As this study was merely observational, it calls for a randomized study examining the effects of interactions between antidepressants and estrogen supplementation on depression.

REPRODUCTIVE HORMONE ADMINISTRATION AND THE PSYCHIATRIST

The risks, benefits, and contraindications of estrogen replacement therapy for general health purposes are shown in Tables 20–22.[25,50,58–62] Several types of reproductive hormones used for hormone replacement therapy are shown in Tables 23 and 24. Various types of estrogen-containing oral contraceptives are sometimes useful for women of childbearing age and especially for women at the beginning of perimenopause, when anovulatory cycles may disrupt mood. In such patients, regularization of the menstrual cycle may be desired and may require the more potent doses of hormone provided by oral contraceptives to accomplish this. As progestin-only contraceptives may destabilize rather than improve mood in some patients, a combination agent with a low dose of both an estrogen and a progestin may be more effective for this therapeutic application in such patients.

Finally, the art of combining estrogen and progestins from a psychiatric perspective may occasionally require the elimination of the progestin (thus necessitating uterine bi-

Table 23. Some Estrogen Replacement Products

Brand Name (Estrogen)
Premarin (conjugated estrogens)
Estrace (micronized estradiol)
Estraderm and other transdermal patches (estradiol)
Estratab, Menest (esterified estrogen)
Ogen, Ortho-Est (estropipate)
Various oral contraceptives containing estrogen/progestin combinations

Table 24. Some Progesterone Replacement Products

Brand Name (Progestin)
Provera, Cycrin, Amen (medroxyprogesterone acetate)
DepoProvera (depot medroxyprogesterone acetate)
Aygestin, Micronor, Nor-Q D (norethindrone acetate)
Micronized progesterone
Various progestin-only oral and implantable contraceptives

Table 25. Principles Underlying Use of Progestins With Regimens of Estrogen Replacement Therapy*

Progesterone counteracts some effects of estrogen
Progesterone can have adverse mood and cognitive effects
Cyclic administration of progesterone can mimic PMS

*Based in part on reference 63.

opsies) or a switch from cyclical to continuous administration (Tables 25 and 26). Few if any controlled clinical studies document the utility of such approaches, but numerous anecdotes from observant patients and clinicians suggest that such manipulations may be very useful in various individuals and justify further objective and controlled study.

SUMMARY

A new era in understanding the role of reproductive hormones in the CNS has begun to clarify how such hormones affect neurotransmitter systems. This in turn is starting to have an impact upon our understanding of disorders of mood and behavior, and therefore upon how women with these disorders are evaluated and treated by psychiatrists as well as women's health physicians (Table 27). Translating these advances into clinical medicine is beginning to guide the rational use of reproductive hormones as adjuncts to psychotropic agents such as antidepressants and cognitive enhancers. However, we are only beginning to understand how to do this. Much more research is required to adequately integrate these exciting new concepts into the practice of psychiatry, but evolving data promise to point to ways to improve the treatment of disorders of mood and cognition.

Drug names: donepezil (Aricept), estradiol (Estrace and others), estrogen (Premarin and others), estropipate (Ogen, Ortho-Est), medroxyprogesterone (Amen and others), norethindrone (Micronor and others), norethindrone acetate (Aygestin).

Table 26. Regimens for Estrogen and Progestin Replacement Therapy*

Cyclic administration of estrogen and a progestin
Continuous administration of estrogen and cyclical administration of progestin
Continuous combined administration of both estrogen and progestin
Cyclic administration of estrogen with no progestin
Cyclic or continuous administration of estrogen and androgen

*Based in part on reference 63.

Table 27. Summary: Modern Psychiatric/ Psychopharmacologic Evaluation of Women*

Complete reproductive history
Collect details of hormone treatments, oral contraceptives
Survey for reproductive events as triggers or kindling
Advocate appropriate hormone use

*Based in part on reference 65.

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