NEW TREND IN PSYCHOPHARMACOLOGY

Compared with men, women are at increased risk of depression, especially at several reproductive-related lifecycle points. This may be partially due to changing levels of estrogen, a hormone that can affect levels of neurotransmitters and neural proteins. As estrogen levels vary throughout the lifespan, risk of depression in women also varies, and not all treatments are appropriate or effective at all times. In adolescence, onset of depression may be associated with onset of puberty, but treating underage girls with antidepressants can risk suicidality. In females of childbearing age, mood disturbances associated with menstrual cycles signal a risk for later full-blown major depressive disorder. In depressed pregnant and postpartum women, risks of treatment versus risks of nontreatment are intricate and require case-by-case evaluation. In perimenopause, vasomotor symptoms may be harbingers of oncoming depression and also may signal the presence of dysregulated hormones and neurotransmitters. Relieving vasomotor symptoms may be a necessary dimension of treating depression. In postmenopause, response to selected antidepressants may depend on whether the patient is also taking hormone-replacement therapy. To attain optimal outcomes, modern psychopharmacologists must tailor treatment of depression to a woman's reproductive stage of life.

TRIMONOAMINE MODULATORS AND DEPRESSION

Clinicians often target the three neurotransmitters most implicated in depression—serotonin (5-HT), norepinephrine (NE), and dopamine (DA)—by using antidepressants to block reuptake at the respective neurotransmitter reuptake transporters. However, other agents can modulate all three neurotransmitters without
inhibiting their monoamine transporters. These “trimonoamine modulators”—such as thyroid hormone, lithium, L-methylfolate, and even psychotherapy—may be best utilized in combination with a monoamine reuptake inhibitor, rather than as a monotherapy. These trimonoamine modulators theoretically work by boosting ≥1 of the monoamines, which may be useful in augmenting the treatment of depressive episodes in patients who fail to remit with traditional antidepressants. Another trimonoamine modulator—perhaps not always given proper consideration in psychopharmacology—is estrogen. This hormone, whether endogenous or exogenous, can affect the incidence and treatment of depression across a woman’s lifecycle.

INCIDENCE OF DEPRESSION IN MEN AND WOMEN

Mood-altering hormones, such as estrogen and testosterone, can be found in men and women. However, women experience dramatic fluctuations in estrogen levels across their lifetime, which mirror an incidence of depression that is higher than in men (Figure 1), who do not experience similar fluctuations in testosterone (Figure 2). The risk of depression across the male lifespan rises in puberty and remains fairly constant throughout life, regardless of slowly declining levels of testosterone from 25 years of age forward (Figure 2). However, according to a study of 3,987 elderly men (71–89 years of age), those with levels of testosterone much lower than average (ie, those in the lowest quintile) are at a risk for depression nearly three times greater than men with higher levels of testosterone.

In contrast, the risk of depression in women is 2–3 times higher than in men during childbearing years; this may be due in part to fluctuating levels of estrogen. The National Comorbidity Survey of 8,098 United States residents showed that women are ~1.7 times more likely than men to report a history of a major depressive episode. The difference in prevalence between genders begins in early adolescence and persists until women are in their mid-50s. Another study of 9,792 British adults found that, from 16–54 years of age, depression was twice as likely in women than in men, but depression in postmenopause-aged females (55–64 years) returned to levels similar to males of the same age.

A more recent population-based study (N=3,481) demonstrated that women not only showed higher risk for onset of depression, but also experienced episodes that were ~20 weeks longer in duration and exhibited a nonsignificant tendency for higher risk of recurrence. Within this general lifetime trend, women also are at higher risk for depression at specific points in their life when reproductive hormones fluctuate: in puberty, when estrogen is first rising; in the premenstrual phase; in pregnancy or the postpartum period; in association with infertility, miscarriage, or perinatal loss; and/or in the perimenopausal period (Figure 3). Thus, men and women are only “equal” for risk of experiencing depressive episodes prior to puberty and in older age after women have experienced menopause.

ESTROGEN MODULATES NEUROTROPHIC FACTORS, MONOAMINES, GLUCOSE USAGE, AND NEURAL STRUCTURE

Action via the Nuclear Estrogen Receptor

Incidence reports are not the only data supporting a role for estrogen in depression; basic science also suggests a relationship. When estrogen binds to and activates its nuclear receptors, it regulates gene products such as brain-derived neurotrophic factor, neurotransmitter-synthesizing enzymes, neurotransmitter-metabolizing enzymes,
and neurotransmitter receptors. Estrogen must penetrate both the neuronal membrane and the nuclear membrane to reach its receptors, which are located near the genes influenced by estrogen (Figure 4A). Activation of these genes, termed estrogen response elements (Figure 4B), requires receptor dimerization (ie, coupling of two copies of the estrogen receptor) upon estrogen binding to produce an active transcription factor that is able to cause expression of estrogen response elements. Once estrogen receptors are activated as transcription factors, they bind to estrogen response elements in the cell’s DNA and thus activate gene expression (Figure 4C). Estrogen theoretically exerts some of its mood-altering effects through estrogen receptors distributed in brain regions associated with symptoms of major depressive disorder (MDD). For example, the human brain contains estrogen receptors in the hippocampus and cerebral cortex, areas of the brain associated with the symptoms of depressed mood and cognitive dysfunction in MDD. In these brain regions, estrogen affects cellular spine density and related cognitive abilities. The human amygdala is especially rich in estrogen receptors. Anxiety is associated with the amygdala in humans and is a frequent symptom of MDD. Administration of estrogen to the amygdala of ovariectomized rats decreases anxious behaviors.

**Estrogen’s Trophic Properties Across the Menstrual Cycle**

Evidence of estrogen’s trophic properties can be seen in hypothalamic and hippocampal neurons in adult female animals across a single menstrual cycle. Early in the menstrual cycle, estradiol levels rise, causing dendritic spines to form on pyramidal neurons and in the ventromedial hypothalamus, which is observable in adult female rats. This spine formation is at its height when both estrogen and progesterone peak, just after the first half of the cycle. Once estrogen begins to fall and progesterone continues to rise, downregulation of these spines is triggered (Figure 5). The mechanism of this cyclical formation and subsequent loss of dendritic spines is shown in Figure 6. As a possible behavioral correlate of this biological cycle, along with fewer spines and falling estrogen levels, mood also can slip downward—in extreme cases, manifesting as premenstrual dysphoric disorder (PMDD).

**Estrogen and Serotonin**

Estrogen exerts generally positive effects on serotonergic raphe neurons and on their cortical postsynaptic targets (Figure 7). In ovariec
tomized animals, estrogen treatment increases protein levels of tryptophan hydroxylase, the key synthetic enzyme for 5-HT, and also increases the 5-HT content in raphe neurons. Normally, 5-HT1A autoreceptors in the raphe exert negative

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**FIGURE 2.**

Men’s risk of depression increases during puberty. Then it gradually decreases over the lifespan, regardless of the declining level of testosterone beginning at 25 years age.


**FIGURE 3.**

The risk of depressive symptoms in women is affected by several occurrences: puberty, menstrual cycles, postpartum period, and perimenopause.

PMS=premenstrual syndrome, ERT=estrogen-replacement therapy.

feedback on the firing activity of 5-HT neurons. In rats, withdrawing estrogen (ovariectomy) upregulated these inhibitory 5-HT₁A autoreceptors, while replacing estrogen downregulated them. The expected functional outcome of this has also been observed: estrogen treatment increases the firing rate of rat raphe neurons. In humans, radiolabel neuroimaging showed that 10 weeks of estrogen treatment increased 5-HT₃A receptors in the right prefrontal cortex of postmenopausal women and also improved verbal fluency and cognition.

**Estrogen and Norepinephrine**

Estrogen positively modulates the NE network and its hypothalamic targets. In the locus coeruleus of female monkeys, an estrogen infusion increased the expression of messenger ribonucleic acid for tyrosine hydroxylase (the key synthetic enzyme for NE) and also caused dramatic release of NE into the hypothalamus. Hypothalamic NE is related to ingestive behavior and may therefore be related to the change of appetite in depressed patients. Activation

**FIGURE 5.**

In the early phase of the menstrual cycle, estradiol levels rise, inducing dendritic spine formation and synaptogenesis*

* Spine formation is greatest just after the first half of the menstrual cycle, when estrogen is at its highest and progesterone peaks as well. After this point, estrogen levels begin to fall while progesterone continues to rise. This leads to a downregulation of dendritic spines and removal of formed synapses by the end of the cycle.

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of hypothalamic $\alpha_1$ receptors in rats is associated with sexual receptivity$^{33}$ and sleep.$^{34}$ This is especially of interest because the hypothalamus of depressed patients is implicated in their loss of sexual interest and sleeping problems.$^{35}$ Moreover, administering estrogen to ovariectomized rats increased hypothalamic $\alpha_{1B}$ noradrenergic receptors.

**Estrogen and Dopamine**

Animal studies have demonstrated that DA release and reuptake in the nucleus accumbens fluctuates over the estrous cycle; as estrogen levels peak, DA release also is increased, indicating a possible role for estrogen in facilitating DA release.$^{36}$ Falling DA levels in the nucleus accumbens, a key pleasure-related area of the brain, are implicated in the loss of interest or pleasure experienced by depressed patients.$^{35}$ Moreover, estrogen can act like a reuptake inhibitor at the DA transporter$^{37}$ in a manner similar to certain antidepressants.

**Estrogen and Cellular Glucose Use**

Beyond the aforementioned specific changes to the brain regions, estrogen also affects the glucose metabolism of nearly the entire brain. In animals, estrogen treatment increases glucose uptake and utilization in 42 out of 60 anatomically discrete brain regions within 2 hours.$^{38}$ One way that estrogen exerts this effect is through the glucose transporter; estrogen increases expression of this transporter at the blood-brain barrier and on the membranes of neurons.$^{39,40}$ Thus, estrogen helps the brain to access and use glucose, enabling the brain to acquire energy.

**TREATING DEPRESSION IN WOMEN ACROSS THE REPRODUCTIVE LIFECYCLE**

It can be difficult to treat depressed females during adolescence, childbearing years, pregnancy, breast-feeding and the postpartum period, perimenopause, and menopause (Figure 8). A psychopharmacologist must weigh the risks and benefits of using antidepressants to treat a depressive episode during these stages versus the alternative: no treatment and potential increase in symptomatology.$^{1,3}$ Each of the stages summarized in Figure 8 is examined in the sections that follow.

**Treating Adolescent Onset of Depression**

The first episodes of depression experienced by some females can coincide with puberty, though these episodes are often unrecognized and/or untreated by clinicians. Treatment with antidepressants in adolescents has become increasingly difficult due to the heightened awareness of suicidality risk with antidepressants in those <25 years of age. Furthermore, documented efficacy of many antidepressants in adolescents <18 years of age is lacking. Antidepressants are generally not approved for use in girls <18 years of age and may be less than ideal when considering a benefit-to-risk ratio up to 25 years of age.$^{1,3}$ The American Academy of Child and Adolescent Psychiatry$^{41}$ recommends psychotherapy as the first line of treatment for adolescent depression and recommends reserving antidepressants for those with

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**FIGURE 6.**

Estrogen regulates spine formation in a cyclical pattern

- Initially, GABA inhibits pyramidal neurons, which are thus inactive. As the cycle continues, estrogen reduces GABA inhibition, leading to disinhibition of pyramidal neurons and a release of Glu. Glu acts on N-methyl-D-aspartate receptors that, when in a sustained-activation state, cause changes in the postsynaptic neuron, including formation of dendritic spines. As the cycle ends, estrogen levels fall, Glu neurons become inactive, and spine formation is downregulated.$^1$

GABA=$\gamma$-aminobutyric acid; Glu=glutamate.


severe depression. In such cases, fluoxetine is the only antidepressant with documented efficacy and Food and Drug Administration approval for use in adolescents; its use should be coupled with careful monitoring and psychotherapy.41

**Treating Premenstrual Dysphoric Disorder During the Fertile Years**

Once women experience the onset of menstruation, some may be susceptible to PMDD.134 This disorder manifests primarily as irritability (or depressed mood, anxiety, or mood swings) during the late luteal phase just prior to menstrual flow and can potentially be incapacitating. Additionally, this end-of-cycle worsening of symptoms may actually be unmasking an underlying mood disorder that may be present the entire cycle but only becomes more obvious during “menstrual magnification.” Women who experience PMDD and/or menstrual magnification may be at increased risk for future onset of full-blown MDD14; therefore, symptomatic and preventive treatment are important. Two pharmacologic options have demonstrated efficacy for PMDD and are approved by the FDA: selective serotonin reuptake inhibitors (SSRIs), three of which are approved for PMDD, or a low-dose oral contraceptive pill containing estrogen and progestin.42 Due to the unique pathophysiology of the disorder, SSRIs can be effectively administered intermittently, with dosing limited to the luteal phase of the cycle (2 weeks prior to menses).42 Dopaminergic or noradrenergic agents have not shown efficacy against PMDD, but GABAergic treatments, such as benzodiazepines, may be efficacious for PMDD.42

**Treating Depression During Pregnancy**

Pregnant women requiring treatment for depression pose a unique situation: the benefit-to-risk ratio must include consideration of the fetus (Table). Some antidepressants may be harmful to the fetus, especially when administered during the first trimester, whereas others may be more harmful if taken during the third trimester. Risks to the fetus include prematurity, low birth weight, long-term neurodevelopmental

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**FIGURE 7.** Estrogen exerts generally positive effects on serotonergic raphe neurons and on their cortical postsynaptic targets*

* TpH is the key synthetic enzyme for 5-HT.


**FIGURE 8.** Over the course of the female lifespan, appropriate pharmacotherapy use, including antidepressants and/or estrogen, may vary by age or by reproductive status3

E2=estradiol; SNRI=serotonin-norepinephrine reuptake inhibitor; ERT=estrogen-replacement therapy.


abnormalities, and fetal withdrawal symptoms after birth. However, lack of treatment to the mother is not without its own risks—untreated depression may result in poor self-care, potential self-harm, or progressive worsening of symptoms. In women with a history of depression, those who discontinue antidepressant treatment during pregnancy are at much higher risk for relapse than those who continue medication. In mild cases, psychotherapy may be sufficient; in severe depression, the benefits of treating the mother may outweigh the risks. Women of child-bearing age should be educated on the risks of becoming pregnant while on an antidepressant and can be given the option of contraception during this time if so desired.

Treating Depression During the Postpartum Period

During pregnancy, estrogen levels skyrocket to much higher levels than even the peak of the cycle of estrogen in nonpregnant women of child-bearing age; after parturition, estrogen levels dramatically plummet, which is considered a risk factor in the development of postpartum depression. Regular hormonal cycles do not resume until after a woman stops nursing. Approximately 90% of postpartum depression episodes occur within the first 4 weeks after delivery. Women with any history of depression are twice as likely as never-depressed women to experience postpartum depression. Women with a history of postpartum depression have a 63% risk of recurrence, whereas only one tenth of that risk exists if such patients take antidepressants.

Treating depression during this postpartum period, when the mother may be breast-feeding the infant, may also be difficult and is considered high-risk. Nursing women who take antidepressants can pass some of the drug to the infant via breast milk. Thus, the key question for this particular subgroup is not whether to treat, but whether to breast-feed. Estrogen, fluoxetine, sertraline, and venlafaxine supplementation all have been found effective against postpartum depression, and thyroid levels also should be checked to see whether that system, which is susceptible to changes in pregnancy, needs treatment. The relative hypercoagulative state of pregnant women may complicate treatment with estrogen in the immediate postpartum period, especially for women with thrombotic risks. For women who choose to remain medication-free, preferring the ability to breast-feed, psychotherapy in the postpartum period also has efficacy against depression.

TREATING DEPRESSION IN WOMEN AFTER THE REPRODUCTIVE LIFECYCLE

Perimenopause, Vasomotor Symptoms, and Perimenopausal Depression

Perimenopause can be a time of chaotic change
for a woman’s body and mind. Some changes are easily observed, starting around 47 years of age: first a woman’s period changes in length, and then whole cycles are skipped. Vasomotor symptoms, such as hot flashes and night sweats, mark these transitional years, particularly late perimenopause and early postmenopause. Around 51 years of age, a woman’s final menstrual period occurs, although she cannot know it was her last until 1 year after the fact. The duration of each stage and age during occurrence are different for each woman. Whenever they occur, however, the hormonal fluctuations driving these physiological changes can put a woman at risk for depression. Some women are at greater risk than others, including midlife women with a history of depression, postpartum depression, or premenstrual syndrome. However, even a woman with no history of depression is almost twice as likely to experience an onset of MDD when she enters perimenopause than women of the same age who remain premenopausal. Diagnosis of perimenopausal MDD can be complicated due to the high degree of symptom overlap between perimenopause and depression (Figure 9).

Vasomotor symptoms and depression are linked neurobiologically and clinically. Clinically, perimenopausal women with vasomotor symptoms are four times more likely to be depressed than perimenopausal women without vasomotor symptoms. The elevated risk seems to subside in postmenopause, when estrogen levels are low and when vasomotor symptoms also subside. This agrees with observations that risk for depression and for vasomotor symptoms correlate with hormonal fluctuations, not absolute levels. Neurobiologically, both vasomotor symptoms and depression are regulated.

**FIGURE 9.**
The symptoms of depression and perimenopause often overlap due to similar neurobiological links between these two conditions

![Figure 9](image)

**FIGURE 10.**
Fluctuating levels of estrogen can lead to dysregulation of monoamines, leading to depressive symptoms via mood circuits (upper figure) and vasomotor symptoms via hypothalamic circuits (lower figure)

![Figure 10](image)
Trends in Psychopharmacology

Therefore, dysregulation of the monoaminergic neurotransmitter systems can lead to depression when the dysregulation occurs within mood-related circuits and can lead to vasomotor symptoms when the dysregulation occurs within the hypothalamic thermoregulatory centers (Figure 10). Vasomotor symptoms are mediated via hypothalamic thermoregulatory centers, which are the homeostatic control sites for regulating internal core body temperature and integrating peripheral signals with vascular and neurochemical signals. Two key thermoregulatory signals are noradrenergic and serotonergic input to the hypothalamus; in monkeys, injecting 5-HT into the hypothalamus causes core body temperature to rise, and injecting NE into the hypothalamus causes internal body temperature to fall. Since estrogen fluctuations can cause dysregulation of both noradrenergic and serotonergic circuits, it is not surprising that estrogen fluctuations could lead to both vasomotor symptoms and depression, with substantial overlap in presentation.

Due to the association of vasomotor symptoms with the onset or recurrence of a major depressive episode, experts now debate whether prescribers should identify and treat vasomotor symptoms as well as the traditional symptoms of depression in perimenopausal women. Actually, the treatments for these two conditions overlap. Treating vasomotor symptoms could theoretically prevent a major depressive episode in vulnerable women. Furthermore, failure to treat vasomotor symptoms in a perimenopausal woman who also has a major depressive episode may stand in the way of full remission of the major depressive episode or of sustaining...
that remission in the long run. That is, remission of the classic symptoms of depression while vasomotor symptoms persist is a likely signal that fluctuating estrogen levels are still affecting the brain and may continue to create vulnerability for relapse. Ongoing research seeks to determine whether targeting vasomotor symptoms in women with depression or who are at risk for depression will achieve better outcomes.

**Estrogen Treatment for Perimenopausal Depression and Vasomotor Symptoms**

Vasomotor symptoms are the clinical indication that estrogen levels are fluctuating irregularly and are increasingly recognized as the harbinger of onset or relapse of major depression during perimenopause. Fluctuating estrogen levels can theoretically create monoaminergic dysfunction in the brain; when this dysregulation of monoaminergic control occurs in the hypothalamic thermoregulatory centers, vasomotor symptoms could occur (Figure 11). In patients whose fluctuating estrogen levels are causing vasomotor symptoms via dysregulation of (≥1) monoaminergic hypothalamic thermoregulatory center(s), estrogen may restore monoamine function and thereby relieve vasomotor symptoms (Figure 11). However, many women are not willing to take estrogen for vasomotor symptoms, and most prescribers are not willing to treat long-term with estrogen due to concerns over health risks. This has created the need for a nonhormonal treatment for vasomotor symptoms.

Because estrogen-replacement therapy is the recognized treatment option for vasomotor symptoms of perimenopause, estrogen may seem a natural therapeutic choice for perimenopausal depression as well (Figure 12). However, no type of hormonal therapy is yet approved for

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*(continued from page 655)*

![Figure 13](image1.png)

**FIGURE 13.** Treatment of vasomotor symptoms with SSRIs has provided inconsistent results as to their efficacy in improving vasomotor symptoms.

SSRIs = selective serotonin reuptake inhibitors.


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![Figure 14](image2.png)

**FIGURE 14.** Treating vasomotor symptoms with an SNRI may be more efficacious than other forms of treatment.

*SNRIs for Vasomotor Symptoms?

- Overactivation
- Normal
- Baseline
- Hypoactivation

SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors.


* It is possible that actions on both serotonergic and noradrenergic systems are required to achieve hypothalamic thermoregulator control, necessitating an SNRI or an SSRI with some noradrenergic activity (paroxetine).
the treatment of perimenopausal depression, and the multitude of available formulations has long obscured any clear results, even in experimental literature. Low dosages (oral estrogen/progestin, 5 µg/1 mg/day, a formulation commonly given for the alleviation of vasomotor symptoms) are insufficient against perimenopausal depression. A high dosage of transdermal estradiol (100 µg/day) is effective against MDD in perimenopausal women but not in postmenopausal women. Add to this confusion the constantly changing and controversial reports about risk-benefit ratios of estrogen therapy, and a physician is left with an unapproved and uncertain therapy as well as possibly an unwilling patient.

**FIGURE 15.**
Treating depressive symptoms with SSRIs is generally considered efficacious, but results may differ when treating postmenopausal women not taking estrogen-replacement therapy

SSRIs for Perimenopausal or Postmenopausal Depression?

* Overactivation
* Normal
* Baseline
* Hypoactivation

SSRIs=selective serotonin reuptake inhibitors; NE=norepinephrine; VMPFC=ventromedial prefrontal cortex; 5-HT=serotonin; DA=dopamine.


* It is suggested that the presence of estrogen may boost the efficacy of SSRIs and the absence of estrogen may reduce the efficacy of SSRIs in some women.\\n
**FIGURE 16.**
SNRIs appear to be efficacious in treating depressive symptoms in women, irrespective of the presence of estrogen

SNRIs for Perimenopausal Depression?

* Overactivation
* Normal
* Baseline
* Hypoactivation

SNRIs=serotonin-norepinephrine reuptake inhibitors; NE=norepinephrine; VMPFC=ventromedial prefrontal cortex; 5-HT=serotonin; DA=dopamine.


**Antidepressant Treatment for Perimenopausal Depression and Vasomotor Symptoms**

SSRIs show inconsistent benefit for relief of vasomotor symptoms (Figure 13), although there are some positive results reported for paroxetine, a compound that may, in fact, have some noradrenergic activity, making it a weak serotonin-norepinephrine reuptake inhibitor (SNRI). In contrast, full-fledged SNRIs may show a clearer benefit for relief of vasomotor symptoms (Figure 14), although such agents are not approved for this use. Under investigation is whether SNRIs have the same effect size as estrogen and whether the benefits versus the risks of SNRIs justify their use in treating vasomotor symptoms in perimenopausal women.

SSRIs have long been the first-line therapy for treatment of depression, and in young women,
SSRIs may often be a good choice. In women less than ~40 years of age, depression is more responsive to SSRIs than to a tricyclic antidepressant or to a norepinephrine reuptake inhibitor. However, this advantage of SSRIs never exists in men of any age and is lost in women past ~44 years of age, which suggests the mode of action of SSRIs may benefit from the presence of estrogen (Figure 15). In contrast, SNRIs seem to be more efficacious for the treatment of depression across all ages and genders, including perimenopausal women, and also offer the aforementioned efficacy against vasomotor symptoms (Figure 16). Venlafaxine, an SNRI, was more effective than SSRIs (fluoxetine, fluvoxamine, and paroxetine) against depression in women both younger and older than 50 years of age. Similarly, duloxetine demonstrated consistent efficacy for depressed women in all age groups (<40, 40–55, and >55 years of age). Desvenlafaxine, a new SNRI, is approved for the treatment of depression and has been well studied but not yet approved for vasomotor symptoms. When tested specifically in perimenopausal and postmenopausal women, these three SNRIs not only improved mood, but also relieved vasomotor symptoms. Since vasomotor symptoms are a risk factor for (or marker of) perimenopausal depression, it is perhaps unsurprising that drugs effective against this particular kind of depression are also effective against vasomotor symptoms.

Treatment Depression in Postmenopausal Women

Menopause is the final stage in the female lifecycle and can involve estrogen deficiency or, in some women, use of estrogen-replacement therapy. During this stage, the risk for depression is lower than during perimenopause. Although estrogen no longer fluctuates, vasomotor symptoms are often still experienced. These vasomotor symptoms may arise from insufficient numbers of brain glucose transporters due to the lack of estrogen to induce their expression. The resultant inefficient transport of glucose to the brain would be detected by hypothalamic centers, which would react by triggering a noradrenergic and vasomotor response to increase blood flow to the brain and to generate a compensatory increase in brain glucose transport. In women with diabetes and pre-diabetes, this situation could be exacerbated. Because SSRIs may work better in the presence of estrogen, which is diminished in menopause, SSRIs may not be as effective in postmenopausal women. However, SSRIs may be more effective in patients taking estrogen-replacement therapy than in those who are not. In contrast, SNRIs appear to offer consistent efficacy against MDD, regardless of estrogen level or estrogen-replacement therapy, age, or gender. Therefore, when choosing a treatment for depression in postmenopausal women, clinicians should consider presence of vasomotor symptoms and/or use of estrogen-replacement therapy and should consider SNRIs as a first-line treatment.

Conclusion

Compared with men, women are at an increased risk of developing depression, especially at several reproduction-related lifecycle points. This may partially be due to changing levels of estrogen, a hormone that can affect levels of neurotransmitters and neural proteins, which, theoretically, can result in symptoms of depression. As estrogen levels vary throughout the lifespan, risk of depression in women also varies, and not all treatments are appropriate or effective at all times. Thus, tailoring treatment to a woman’s reproductive stage of life aids in determining the best treatment option. SSRIs are beneficial in treating depression in younger women, but risks should be considered in pregnant women and in adolescents, and breast-feeding should be avoided in postpartum women if antidepressant pharmacotherapy is utilized. Psychotherapy may be more appropriate for youths and for pregnant or postpartum women. Hormonal control can sometimes offer relief of PMDD and postpartum or perimenopausal depression (and its comorbid vasomotor symptoms). SNRIs are currently the most efficacious nonhormonal treatment for vasomotor symptoms and also can effectively address depressive symptoms in older women, in whom SSRIs may be less efficacious. Clinicians who are aware of the varying risk levels for development of depression over the lifespan, as well as the risks and benefits of utilizing various therapies, can offer tailored and maximally effective treatments to bring their depressed female patients to remission of symptoms.


