

Managing menopause-related depression and low libido

“Anne” is distressed by hot flashes, depressive symptoms, and loss of sexual drive, and her marriage is suffering the strain. Her case illustrates an emerging strategy: use of psychotropics with or without hormones, including testosterone.

Practically overnight, the Women’s Health Initiative caused women and their physicians to think twice about estrogen and estrogen-progestin.^{1,2} Many are turning to psychiatric drugs that have been shown to improve both mood and hot flashes.

Unfortunately, many psychotropics used to treat hot flashes cause sexual side effects; among them are anorgasmia and low libido. Fine-tuning the drug regimen may be necessary to ensure improved mood without sacrificing sexual function.

In some cases, it may be advisable to consult with a psychiatrist, such as when psychotropics fail to ease symptoms or side effects become problematic.

This article presents the case of Anne, a woman struggling with menopause-related depression and low sexual desire, coupled with hot flashes. Treatment with psychotropic drugs or hormones, alone or in combination, is described. The recommendations here are based largely on clinical experience, though I also draw from randomized trials when possible.

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ANNE’S CASE

Irritable, no interest in sex

Anne, age 51, presents with complaints of depressed mood and low libido. She says she has become irritable and snaps easily at her 2 children and her husband. She has no interest in sex, no urge to masturbate, and has had no sexual intercourse for 6 months.

Anne also complains of fatigue, dry hair and skin, warm flushes, and painful joints.

She has no personal or family history of depression. She is not suicidal but she “really doesn’t want to live anymore if this is it.”

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KEY POINTS

- Depression is more likely when perimenopause exceeds 27 months and hot flashes are moderate to severe.
- All serotonin and norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors have sexual side effects, including anorgasmia and loss of libido. Gabapentin is the only psychotropic that improves hot flashes and mood without interfering with sexual function.
- If the patient complains of slow or no arousal, vaginal estrogen and/or sildenafil, 25 to 50 mg 1 hour before intercourse, may be beneficial.
- Women with androgen deficiency symptoms and low testosterone should at least be considered for testosterone replacement.

TABLE 1

What causes mood problems during menopause?

HYPOTHESIS	EXPLANATION
Psychodynamic	Onset of menopause is a critical life event and a readjustment of self-concept
Sociologic	Mood changes are caused by changing life circumstances at menopause (eg, "empty nest," aging parents, health changes)
Domino	Depressed mood is caused by hot flashes due to declining estrogen levels, which cause chronic sleep deprivation with subsequent irritability and memory and mood changes
Biochemical	Decreasing estrogen leads to neurochemical changes in the brain (serotonin, dopamine, cholinergic, gamma-aminobutyric acid, norepinephrine)

from a domino effect triggered by declining estrogen levels (TABLE 1).

Hot flashes increase risk of depression. Women with vasomotor symptoms such as hot flashes are at 4.6 times greater risk for depression than those who are hot flash-free.⁵

Hot flashes are moderate to severe for 40% of women who experience them and persist for 5 to 15 years. Moderate to severe hot flashes occur 4 to 10 or more times daily, last 6 to 10 minutes each, and often are preceded by anxiety, palpitations, irritability, nervousness, or panic.

Women with vasomotor symptoms are at 4.6 times greater risk for depression than those who are hot flash-free.

Hot flashes, prior depression linked to perimenopausal depression?

Women who first experience depression after age 50 do not fit the usual criteria for depression spelled out in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*. The Massachusetts Women's Health Study³ found that 52% of women who experience depressed mood in the perimenopause have never had depression. However, women who have had depression previously are 4 to 9 times more likely to have depressive symptoms during perimenopause than those who haven't.⁴

Depression more likely with prolonged perimenopause. This study also found a correlation between a longer perimenopause (more than 27 months) and increased risk of depressed mood. The increased mood symptoms may be related to psychodynamic, sociologic, or biochemical factors, or they may result

ANNE'S CASE

A marriage under stress

Anne says her husband is angry about the lack of sexual intercourse, and she feels the stress in their marriage. She also is worrying about her children leaving for college and about her mother's ill health.

She scores 20 on the Beck Depression Inventory, which indicates that she has mild to moderate depression. Her menstrual periods remain regular, but her cycle has shortened from 29 to 24 days. She reports that some hot flashes wake her at night, and says she hasn't had a good night's sleep in months.

Laboratory tests show follicle-stimulating hormone of 25 mIU/mL and inhibin B below 45 pg/mL. Her estradiol is 80 pg/mL—not yet in the menopausal range. Her thyroid-stimulating hormone is normal. Her shortened menstrual cycles suggest a diagnosis of perimenopause.

Fewer hot flashes, better mood?

Until July 2002, estrogen or estrogen-progestin was standard treatment for controlling hot flashes in patients such as Anne. Then the Women's Health Initiative (WHI) reported that the health risks of estro-

gen-progestin—heart attack, stroke, breast cancer, and blood clots—exceeded potential benefits during 5 years of therapy.

Although the estrogen-only arm found an elevated risk for stroke, but not for breast cancer or heart disease, fewer women want to take estrogen,⁶ and many physicians are advising patients to get through menopause without hormones if they can.

For mild hot flashes (1 to 3 per day) only vitamin E, 800 U daily, may be needed, plus deep relaxation breathing to “rev down” the sympathetic nervous system when a hot flash occurs. Although vitamin E is unproven, some experts recommend it along with lifestyle changes.⁷ I suggest it only when a patient with mild hot flashes wants to take something “natural.”

For moderate to severe hot flashes (4 to 10 or more per day) estrogen is the most effective therapy. Estradiol, 1 mg daily, reduces hot flashes by 80% to 90%.⁸ Many small studies have shown that mood often improves as estrogen reduces hot flashes.⁹ The WHI quality-of-life study, however, reported that estrogen plus progestin did not improve mood in women aged 50 to 54 with moderate to severe vasomotor symptoms, even though hot flashes were reduced and sleep may have improved.¹⁰

New drugs of choice. Because of estrogen’s efficacy in reducing hot flashes, some women and their Ob/Gyns decide to use it briefly (18 to 24 months). For others, psychotropics are becoming the drugs of choice for depression with moderate to severe hot flashes.

The serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine, 75 or 150 mg daily, has been shown to reduce hot flashes by 60% to 70%.¹¹ A new trial is investigating whether duloxetine also reduces hot flashes. Duloxetine is an SNRI awaiting approval by the US Food and Drug Administration (FDA).

Other agents that have been shown to reduce hot flashes by 50% or more include:

- **selective serotonin reuptake inhibitors (SSRIs):** paroxetine CR, 12.5 to 25 mg daily¹² (see “Controlled-release paroxetine reduces

hot flashes,” page 12); citalopram, 20 to 60 mg daily¹³; and fluoxetine, 20 mg daily¹⁴

- **gabapentin**, 900 mg daily¹⁵

Consider SNRI, SSRI sexual side effects. For moderate to major depression, try an SNRI or SSRI first (see the algorithm on page 34), but consider the possible effects on sexual function. All SNRIs and SSRIs have sexual side effects, including anorgasmia and loss of libido in women and men.

Among psychotropics that improve hot flashes and mood, gabapentin is the only one that does not interfere with sexual function.

ANNE’S CASE

Mood improves, but still no libido

You and Anne decide to try the SNRI venlafaxine, 75 mg daily, to treat her hot flashes and depression. Four weeks later, she is having only half as many hot flashes and her mood has improved (Beck Depression Inventory score of 10). She feels much better and wishes to continue the antidepressant.

She and her husband attempted intercourse once during the past month, although she wasn’t very interested. She did not achieve orgasm, despite adequate vaginal lubrication, and she did not enjoy the experience. “I still have no libido—zero, or even less,” she says.

Treating low interest in sex

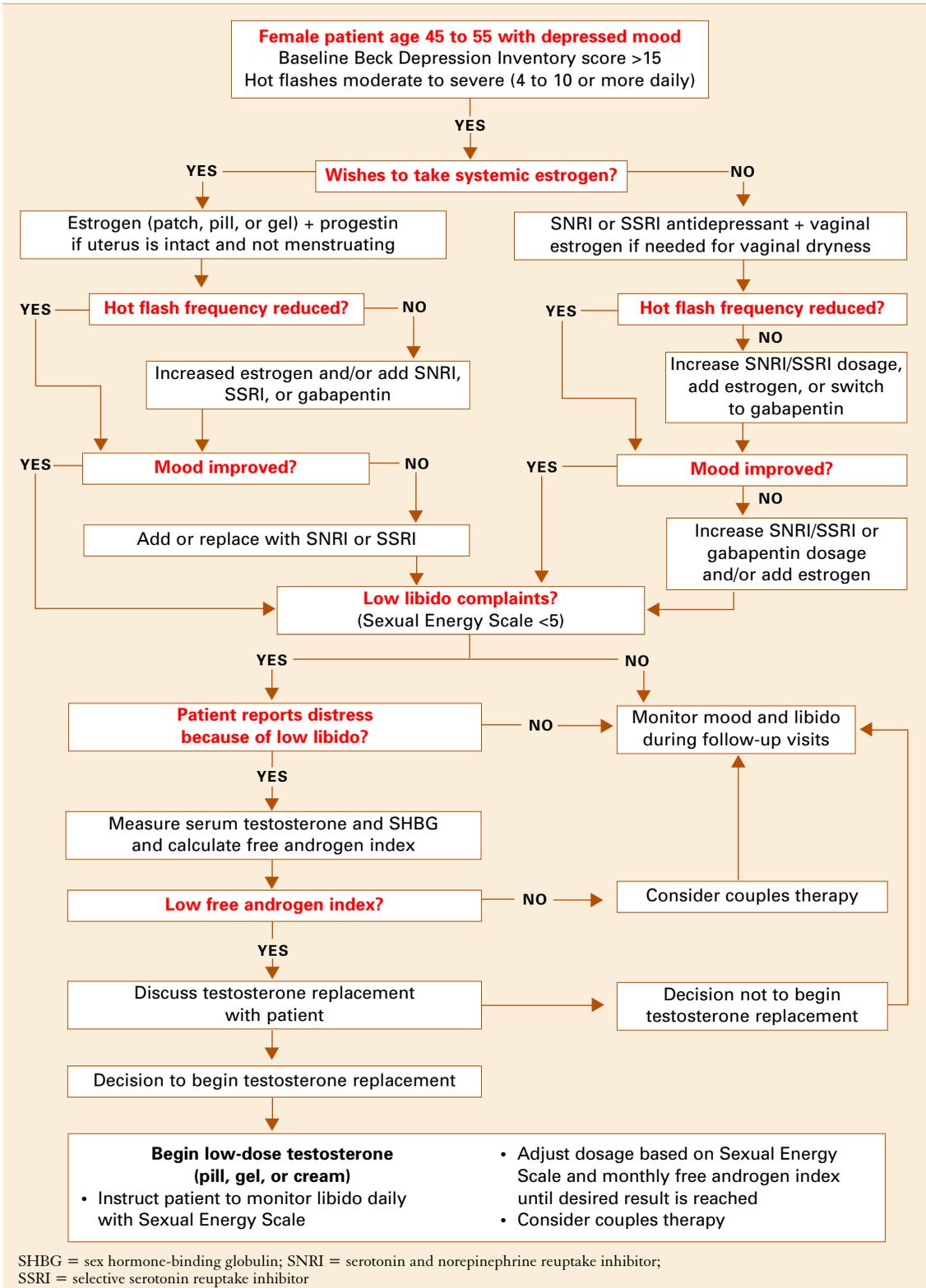
Being angry with one’s partner is the number one reason for decreased sexual desire in all studies. Therefore, consider couples therapy for any woman complaining of loss of interest in sex. In addition, eliminate—if possible—any medications she may be taking that have known sexual side effects, such as SSRIs or beta blockers.

If the patient complains of slow or no arousal, vaginal estrogen and/or sildenafil, 25 to 50 mg 1 hour before intercourse, may be beneficial.¹⁶ Other agents the FDA is reviewing for erectile dysfunction may help.

Consideration of how hormones affect female sexual desire may suggest what advice to give Anne and how to coordinate her care with a psychiatrist, if necessary. For example, CONTINUED

FIGURE

Managing mood and libido problems during perimenopause



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the psychiatrist might treat her sexual complaints and relationship problems while the Ob/Gyn manages gynecologic symptoms.

How androgens affect sexual desire

Testosterone is the hormone of sexual desire in men and women. Other female androgens are androstenedione, androstenediol, 5 α -dihydrotestosterone, dehydroepiandrosterone (DHEA), and its sulfate (DHEA-S).

Premenopausal women produce testosterone in the ovaries (25%), adrenal glands (25%), and peripheral tissues (50%); DHEA and DHEA-S are produced in the adrenal glands (95%).

Get the cardiologist's clearance before giving testosterone to a woman with heart disease or an HDL below 45 mg/dL.

Average daily serum testosterone concentrations decline in women between ages 20 and 50. When values in women aged 20 to 29 were compared with those in women 40 to 49, they were 195.6 g/dL and 140.4 g/dL, respectively, for DHEA-S; 51.5 ng/dL and 33.7 ng/dL, respectively, for serum testosterone; and 1.51 pg/mL and 1.03 pg/mL, respectively, for free testosterone.¹⁷

Lower levels also are seen with estrogen replacement therapy, oral contraceptives, lactation, anorexia nervosa, and conditions that reduce ovarian function. Total hysterectomy with bilateral oophorectomy induces a sudden 50% loss of testosterone and an 80% decline in estradiol.¹⁸

Regularly menstruating women in their 40s and early 50s can have very low testosterone levels—at least 50% lower in the first 5 to 7 days of their cycles—compared with what they had when in their 30s.¹⁹

The percentage of women reporting low libido increases with age until menopause: 30% at age 30 to 50% at age 50. The rate declines to 27% in women aged 50 to 59.²⁰

Female androgen deficiency syndrome.

After natural menopause, luteinizing hormone (LH) continues to stimulate the ovarian hilar cells and interstitial cells to produce androgens, which is why many women at age 50 have adequate testosterone levels to sustain sexual desire. Oral estrogen reduces bioavailable testosterone by 42% on average, which can induce androgen deficiency in menopausal women.²¹ The increased estrogen inhibits pituitary LH and decreases stimulation of the androgen-producing cells in the ovary.²²

▪ **Symptoms.** Diagnosis of female androgen deficiency syndrome²³ requires symptoms of thinning pubic and axillary hair, decreased body odor, lethargy, low mood, diminished well-being, and declining libido and orgasm, despite adequate estrogen but low levels of testosterone and DHEA.

Usually, this occurs in perimenopausal or menopausal women but it can also occur in otherwise healthy premenopausal women.²⁴

Value of testosterone replacement

Replacing testosterone can improve mood, well-being, motivation, cognition, sexual function related to libido, orgasm, sexual fantasies, desire to masturbate, and nipple and clitoral sensitivity.²⁵ Muscle and bone stimulation and decreased hot flashes also are reported.²⁶

Women with androgen deficiency symptoms and low testosterone at menopause should at least be considered for physiologic testosterone replacement.

Potential disadvantages. Patients should be informed that testosterone may lower levels of beneficial high-density lipoprotein (HDL) cholesterol. Get the cardiologist's clearance before you give testosterone to a woman with heart disease or an HDL cholesterol level below 45 mg/dL.

A meta-analysis of 8 clinical trials found no changes in liver function in menopausal women taking 1.25 to 2.5 mg daily of methyl testosterone. Liver toxicity has been reported in men using 10-fold higher testosterone doses.²⁷

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Simple tools to measure depression and libido

The Beck Depression Inventory-II

The questionnaire assesses level of depression by having the patient rate 21 psychological attributes. She chooses 1 of 4 graded statements for each attribute, which are assigned 0 to 3 points. The points are tallied at the end of the test for an overall view of the patient's depression—or lack thereof.

For details, see:

<http://marketplace.psychcorp.com/PsychCorp.com/Cultures/en-US/default.htm>

The Sexual Energy Scale

This 1-10 scale is designed to identify and follow-up patients with sexual dysfunction due to a general

Data from Warnock et al^{33,34}

medical condition or substance-induced sexual dysfunction. It can be given at every visit, including at baseline, to evaluate a patient's sexual energy level and response to therapy. In this assessment, the term "sexual energy" includes ease of arousal, sexual pleasure, orgasms, interest in sex, sexual fantasies, and sexual fulfillment.

Instructions to the patient are: "On a scale of 1 to 10, with 1 being the lowest sexual energy level you have experienced in your adult life, and 10 being the highest sexual energy level you have experienced in your adult life, rate your current energy level."

At the normal level of testosterone, darkening and thickening of facial hair are rare in light-skinned, light-haired women but can occur in dark-skinned, dark-haired women. Increased irritability, excess energy, argumentativeness, and aggressive behavior have been noted if testosterone levels exceed the physiologic range.

Controlled, randomized studies are needed to assess the effects of long-term use (more than 24 months) of testosterone replacement in women.

Monitoring progress. Depending on the patient's progress through menopause, after 12 to 24 months, it may be possible to reduce the testosterone dose or to give it only 2 to 4 times per week. As estrogen levels drop off through menopause, free testosterone may rise and the increased LH drive to the ovary may increase production of ovarian testosterone.

Challenges in measuring testosterone levels. Serum free testosterone is the most reliable indicator of a woman's androgen status, but accurately measuring testosterone levels is tricky:

- Only 2% of circulating testosterone is unbound and biologically active; the rest is

Serum free testosterone is the most reliable indicator of a woman's androgen status, but accurately measuring testosterone is tricky.

bound to sex hormone-binding globulin (SHBG) or albumin.

- In ovulating women, serum testosterone levels are higher in the morning than later in the day and vary greatly within the menstrual cycle.
- Levels of androgens and estrogen are highest during the middle third of the cycle—on cycle days 10 to 16, counting the first day of menstrual bleeding as day 1.²⁸
- Oral contraceptives decrease androgen production by the ovary and can result in low libido in some women.²⁹

Tests developed to measure testosterone levels in men are not sensitive enough to accurately measure women's naturally lower serum concentrations, let alone even lower levels characteristic of female androgen or testosterone deficiency.

New measurements and standardization of normal reference ranges have been developed for women complaining of low libido.³⁰

Tests for androgen deficiency include

TABLE 2

Free androgen index values in women, by age

TO CALCULATE THE FREE ANDROGEN INDEX:	
Total testosterone in nmol/L (total testosterone in ng/mL x 0.0347 x 100), divided by sex hormone-binding globulin in nmol/L	
AGE	NORMAL RANGE
20 to 29	3.72 to 4.96
30 to 39	2.04 to 2.96
40 to 49	1.98 to 2.94
50 to 59+	1.78 to 2.86

Data from Guay et al³¹

Restoring bioactive testosterone to the normal free androgen index range may improve low libido.

total testosterone, free testosterone, DHEA, and DHEA-S. Measuring SHBG helps determine the free, biologically active testosterone level and helps in calculating the free androgen index in women (TABLE 2).³¹

ANNE'S CASE

A candidate for testosterone therapy?

Now that Anne's mood, sleep, and hot flashes have improved with venlafaxine, she wants help with her lack of sexual interest. You measure her testosterone and SHBG levels and find that her free androgen index is very low at 0.51 nmol/L (normal range, 1.78 to 2.86).

You and Anne decide to start testosterone replacement therapy. You prescribe Androgel, starting at one seventh of a 2.5-mg foil packet (about 0.35 mg daily of testosterone) and instruct her to rate her sexual energy daily, using a Sexual Energy Scale (see page 39).

Testosterone choices for women

Restoring a woman's bioactive testosterone level to the normal free androgen index range for her age group may improve low libido. Some low-dose testosterone replace-

ment options that I use clinically include: **Methyl testosterone** sublingual pills, 0.5 mg daily, made by a compounding pharmacy or reduced dosages of oral pills made for men. If you prescribe methyl testosterone, routine lab tests will not accurately measure serum testosterone levels unless you order the very expensive test that is specific for methyl testosterone.

Two percent vaginal cream, applied topically to increase clitoral and genital sensitivity. It may increase blood levels moderately through absorption.

Androgel, a topical testosterone approved for men. As in Anne's case, start with 0.35 mg daily or one seventh of the 2.5-mg packet (ask the pharmacist to place this amount in a syringe). Instruct the patient to apply the gel to hairless skin, such as inside the forearm. Effects last about 24 hours, and you can measure serum levels accurately after 14 days. Vaginal throbbing—a normal response—may occur within 30 minutes of testosterone application.

The FDA is considering other testosterone preparations, including a testosterone patch for women and a gel in female-sized doses.

Research is warranted to evaluate the benefits and safety of longer-term interventions with these therapies in women because of the large numbers of women experiencing diminished sexual interest and declining general well-being during their late reproductive years.³²

Using the Sexual Energy Scale. At every visit, monitor therapeutic response with the Sexual Energy Scale—a scale numbered 1 to 10.^{33,34} Instruct her to define "10" as the time in life when she had the most fulfilling sexual life, was the most easily aroused, had the most sexual pleasure, and the best orgasms. Conversely, "1" would be when she felt the worst sexually and had the least desire.

Supplemental estrogen, progestin. If you prescribe estrogen plus testosterone (Estratest), start with Estratest HS (0.625 mg esterified estrogens and 1.25 mg of methyl testosterone). Add a progestin if the patient is

■ Menopause-related depression and low libido

postmenopausal with an intact uterus.

A vaginal lubricant is not enough to defeat age-related vaginal atrophy, which can make intercourse difficult or impossible. Women with vaginal dryness need estrogen that can be applied vaginally.

ANNE'S CASE

Libido improves somewhat

Anne returns in 4 weeks with gradually improving sex drive (Sexual Energy Scale score is now 5). She had sexual intercourse twice in the past month and didn't "dread" it, but did not enjoy it or reach orgasm. You have told her that venlafaxine may slow or prevent orgasm, but she wants to keep taking it. She reports that her marital relationship is improving.

You order repeat testosterone and SHBG blood levels and find her free androgen index has improved to 1.10, which is still low.

You increase the Androgel dosage to one fifth of a 2.5-mg packet (0.5 mg daily) and continue to monitor her Sexual Energy Scale ratings at monthly visits. She has set a Sexual Energy Scale rating of 7 to 8 as her target. Anne says she appreciates your help with—as she puts it—"this embarrassing problem." ■

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