Current PSYCHIATRY

depression

Covering mood and vasomotor symptoms

Hormones, antidepressants, or psychotherapy—what would you recommend?

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Symptoms of perimenopausal depression are not inherently different from those of depression diagnosed at any other time in life, but they present in a unique context:

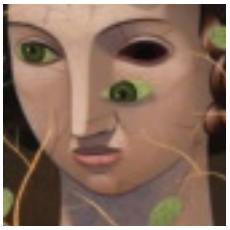
- Hormonal fluctuations may persist for a long duration.
- Women experiencing hormonal fluctuations may be vulnerable to mood problems.
- Psychosocial/psychodynamic stressors often complicate this life transition.

Managing perimenopausal depression has become more complicated since the Women's Health Initiative (WHI) studies found fewer benefits and greater risks with hormone replacement therapy (HRT) than had been perceived. This article discusses the clinical presentation of perimenopausal depression, its risk factors, and treatment options in post-WHI psychiatric practice.

Who is at risk?

Perimenopausal depression is diagnosed when onset of major depressive disorder (MDD) is associated with menstrual cycle irregularity and/or somatic symptoms of the menopausal transition.[1] Diagnosis is based on the overall clinical picture, and treatment requires a thoughtful exploration of the complex relationship between hormonal function and mood regulation.

Presentation. For many women, perimenopause is characterized by mild to severe vasomotor, cognitive, and mood symptoms *(Table 1, page 40).* Thus, in your workup of depression in midlife women,



Perimenopausal depression

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Evidence supports screening for perimenopausal depression even when primary complaints are vasomotor

Table 1

Vasomotor, cognitive, and mood symptoms of perimenopause

Vasomotor	Cognitive and mood
Hot flushes	Decreased concentration
Sweating	Anxiety
Heart palpitations	Irritability
Painful intercourse	Mood lability
Vaginal dryness and discomfort	Memory difficulty
Sleep disruption	
Headache	

document somatic symptoms—such as hot flushes, vaginal dryness, and incontinence—and affective/behavioral symptoms such as mood and sleep disturbances.

Explore psychiatric and medical histories of your patient and her close relatives. Ask about depression, dysthymia, hypomania, or mood fluctuations around hormonal events such as menses, pregnancy, postpartum, or starting/stopping oral contraceptives. In the differential diagnosis, consider:

- Is low mood temporally connected with hot flushes and disturbed sleep?
- Is low mood secondary to stressful life events?
- Does the patient have another medical illness (such as thyroid disorder) with symptoms similar to depression?
- Is low mood secondary to anxiety or another psychiatric disorder?

Screening. Menopause is considered to have been reached after 12 months of amenorrhea not due to another cause. Median ages for this transition in the United States are 47.5 for perimenopause and 51 for menopause, with an average of 8 years between regular cycles and amenorrhea.[2] Therefore, begin talking with women about perimenopausal symptoms when they turn 40.

Evidence supports screening perimenopausal women for depressive symptoms even when their primary complaints are vasomotor. The Greene Climacteric Scale[3] is convenient for quantifying and monitoring perimenopausal symptoms. It includes depressive symptoms plus physical and cognitive markers. The Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR)[4] questionnaire:

- takes minutes to complete
- is easy to score
- quantitates the number and severity of depressive symptoms ***(see Related Resources, page 50).***

Table 2

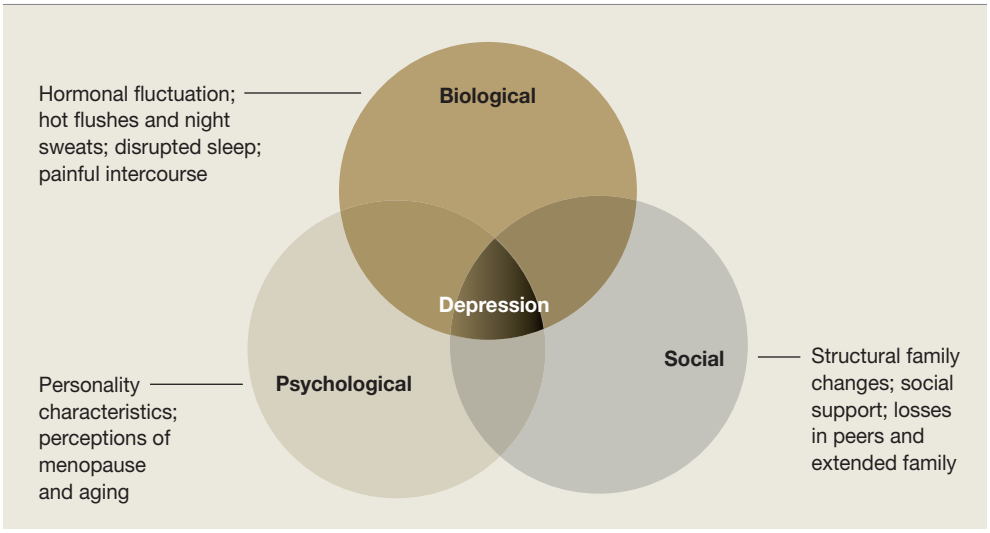
Risk factors for depression in women

Predictive over lifetime	High risk during menopausal transition
History of depression	History of PMS, perinatal depression, mood symptoms associated with contraceptives
Family history of affective disorders	Premature or surgical menopause
Insomnia	Lengthy menopausal transition (≥27 months)
Reduced physical activities	Persistent and/or severe vasomotor symptoms
Weight gain	Negative attitudes toward menopause and aging
Less education	
Perceived lower economic status	
Perceived lower social support	
Perceived lower health status	
Smoking	
Stressful life events	
History of trauma	
Marital dissatisfaction	

PMS: Premenstrual syndrome

Figure

Biopsychosocial milieu of depression during perimenopause



Psychosocial factors can predict depression at any time in life, but some are specific to the menopausal transition ***(Table 2)***.[5] The "empty nest syndrome," for example, is often used to explain depressive symptoms in midlife mothers, but no evidence links mood lability with the maturation and departure of children. What may be more stressing for women is supporting adolescents/young adults in their exit to independence while caring for aging parents.

Sociocultural beliefs about sexuality and menopause may play a role in how your patient experiences and reports her symptoms. In some cultures, menopause elevates a woman's social status and is associated with increased respect and authority. In others, such as Western societies that emphasize youth and beauty, women may view menopause and its physical changes in a negative light.[6]

Therefore, give careful attention to the psychosocial context of menopause to your patient and the social resources available to her. Questions to ask include:

- Has your lifestyle changed recently?
- Have your husband, family members, or close friends noticed any changes in your functioning?
- Is there anyone in your life that you feel comfortable confiding in?

Explaining the complexity of this life transition may ease her anxiety by normalizing her experience, helping her understand her symptoms, and validating her distress.

What might be the cause?

Although the exact pathophysiology of perimenopausal depression is unknown, hormonal changes,[7] general health, the experience of menopause,[8] and the psychosocial context[2] likely work together to increase vulnerability for depressive symptoms ***(Figure)***.

Hormonal fluctuation. The estrogen withdrawal theory[7] explains depressive symptoms as resulting from a sustained decline in ovarian estrogen in tandem with spiking secretions of follicle-stimulating hormone by the pituitary. The finding that women with surgical menopause have a higher incidence of depressive symptoms than women with natural menopause supports this hypothesis.

Mood disorders occur across various female reproductive events, and increased risk appears to be associated with fluctuating gonadal hormones. Thus, declining estrogen may be less causative of perimenopausal depression than extreme fluctuations in estradiol activity.[9,10]

Estrogen interacts with dopamine, norepinephrine, beta-endorphin, and serotonin metabolism. In particular, estrogen

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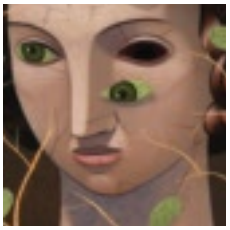
No evidence supports the 'empty nest syndrome,' linking mood lability with the maturation and departure of a woman's children



Perimenopausal depression

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FDA on HRT for menopausal symptoms: Use the lowest effective dose for the shortest time necessary

facilitates serotonin delivery to neurons across the brain. These findings—and the success of selective serotonin reuptake inhibitors (SSRIs) in treating mood disorders—support the theory that fluctuating estrogen affects the serotonergic system and may cause depressive symptoms.

'Domino theory.' Others have hypothesized that depressive symptoms are the secondhand result of somatic symptoms of perimenopause. In a "domino effect," hot flushes and night sweats disrupt women's sleep, bringing fatigue and impaired daytime concentration, which lead to irritability and feelings of being overwhelmed.[8]

This theory, which incorporates perimenopausal hormone changes, is supported by elevated levels of depression in women who report frequent and intense vasomotor symptoms persisting >27 months.[2]

The psychosocial theory suggests that depression results from increased stress or adverse events.[2] Midlife women with depressive symptoms report many possible sources of stress:

- demanding jobs
- family responsibilities
- dual demands of career and family
- little time for self
- poverty or employment stressors
- not enough sleep
- changing social relationships.

Negative interpretations of aging or the menopausal transition also have been implicated in cross-cultural studies.[6] The predictive nature of psychosocial issues for depression during perimenopause supports this theory.

Evidence-based treatment

HRT. Research and clinical reports suggest that estrogen may have antidepressant effects, either alone or as an adjunct to antidepressant medication.[11] Before the WHI studies, expert consensus guidelines on treating depression in women recommended HRT as first-line treatment for patients experiencing a first lifetime onset of mild to moderate depression during perimenopause.[12] WHI findings since 2002 that associated HRT with increased risk of stroke, deep vein thrombosis, and pulmonary embolism—without clear protection against coronary heart disease or cognitive decline—have left HRT a controversial option for treating perimenopausal depression. In the WHI trials:

- 10,739 postmenopausal women age 50 to 79 without a uterus received unopposed conjugated equine estrogens, 0.625 mg/d, or placebo for an average 6.8 years.[13]
- 16,608 postmenopausal women age 50 to 79 with an intact uterus received combination HRT (conjugated equine estrogens, 0.625 mg/d, plus 2.5 mg of medroxyprogesterone), or placebo for an average 5.6 years.[14]

The study using combination HRT found increased risks of breast cancer, ischemic stroke, blood clots, and coronary heart disease.[15] A follow-up study showed that vasomotor symptoms returned in more than one-half the women after they stopped using combination HRT.[15]

A companion WHI trial found that estrogen, 0.625 mg/d—given unopposed or with a progestin—did not prevent cognitive decline in women age 65 to 79 and may have been associated with a slightly greater risk of probable dementia.[16,17]

The FDA recommends that women who want to use HRT to control menopausal symptoms use the lowest effective dose for the shortest time necessary.[18]

Antidepressants. SSRIs may be more useful than estrogen for producing MDD remission in perimenopausal women.[19] SSRIs and other psychotropics may reduce perimenopausal vasomotor symptoms in addition to addressing depressive symptoms ***(Table 3)***. When choosing antidepressant therapy, consider the patient's dominant presenting perimenopausal symptoms and side effects associated with treatment.[20]

Nonpharmacologic interventions are viable options for women who are reluctant to begin HRT or psychotropics.

Psychotherapy. Interpersonal psychotherapy (IPT) and cognitive-behavioral therapy (CBT) have been recommended to address psychosocial elements of perimenopausal mood lability.[21] For women with climacteric

Table 3

Nonhormone medications for perimenopausal depression: Evidence-based dosages and target symptoms

Medication	Dosage effective for perimenopausal depression	Symptoms assessed
SSRIs		
Citalopram[a]	40 to 60 mg	Depressive and vasomotor
Escitalopram[b,c]	5 to 20 mg	Depressive and vasomotor
Fluoxetine[d]	20 to 40 mg	Depressive and vasomotor
Paroxetine[e,f]	12.5 or 25 mg	Depressive and vasomotor
Sertraline[g]	100 mg	Depressive and vasomotor
Other antidepressants		
Duloxetine[h]	60 to 120 mg	Depressive and vasomotor
Venlafaxine[i]	75 to 225 mg	Depressive and vasomotor
Mirtazapine[j]	30 to 60 mg	Severe depressive symptoms; used as an adjunct to estrogen
Hypnotics		
Eszopiclone[k]	3 mg	Depressive and vasomotor; insomnia
Zolpidem[l]	5 to 10 mg	Insomnia
Anticonvulsant		
Gabapentin[m]	300 to 900 mg	Vasomotor

SSRIs: selective serotonin reuptake inhibitors
Source: For reference citations, see this article on CurrentPsychiatry.com

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If a patient has had a good response with an antidepressant in the past, consider starting with that medication

depression, IPT focuses on role transitions, loss, and interpersonal support, whereas CBT focuses on identifying and altering negative thoughts and beliefs.

Although no randomized trials have examined psychotherapies for perimenopausal depression, a pilot open trial provided group CBT—psychoeducation, group discussion, and coping skills training—to 30 women with climacteric symptoms. Anxiety, depression, partnership relations, overall sexuality, hot flushes, and cardiac complaints improved significantly, based on pre- and post-intervention surveys. Sexual satisfaction and the stressfulness of menopausal symptoms did not change.[22]

Integrative medicine. Plant-based substances and herbal remedies such as phytoestrogens, red-clover isoflavones, black cohosh, and evening primrose oil have been included in a few research investigations, and the evidence is equivocal. Because of potential interactions between alternative therapies and medications, inquire about their use. Although a comprehensive review of integrative medicine for perimenopausal symptoms is beyond the scope of this article, see suggested readings (***Box, page 49***).

Clinical recommendations

Explore options with your patient; discuss side effects, risks, and expected minimum duration of treatment. Antidepressants, hormonal therapies, psychotherapy, and complementary and alternative treatments each might have a role in managing perimenopausal depression. A patient's preferences, psychiatric history, and depression severity help determine which options to consider and in what order. How she responded to past treatments also can help you individualize a plan.

HRT may be appropriate for women who express a preference for HRT, have responded well to past hormone therapy, and have no personal history or high-risk

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factors for breast cancer. Based on the WHI findings, we consider a history of breast cancer in the patient or a first- or second-degree relative a contraindication to HRT.

Estrogen can be used alone or with an antidepressant. Studies support 17β-estradiol, 0.1 to 0.3 mg/d, for 8 to 12 weeks.[11,23] Concomitant progesterone may be indicated to offset the effects of unopposed estrogen in women with an intact uterus. This option calls for an informed discussion with the patient about risks and benefits.

No data support long-term use of estrogen for recurrent or chronic depression. Because HRT's risks and benefits vary with the length of exposure, individualize the extended use of estrogen solely to augment treatment for depression. Because vasomotor symptoms may recur when HRT is discontinued,[15] we recommend that women make an informed decision in consultation with a gynecologist or primary care physician.

Antidepressants that have serotonergic activity—such as SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs)—appear most promising for treating comorbid depressive and vasomotor symptoms. If a patient has had a good response to an antidepressant in the past, consider starting with that medication.

Common antidepressant side effects are difficult to assess in perimenopausal patients with MDD because the symptoms attributed to antidepressant side effects—such as low libido, sleep disturbance, and weight changes—also can be caused by mood disorders and hormonal changes. Therefore, inquire about these symptoms when you initiate antidepressant therapy and at follow-up assessments.

Psychotherapy. We recommend that all women who present with perimenopausal depression receive information about psychotherapy. Psychotherapy alone often is adequate for mild depression, and adding psychotherapy to antidepressant treatment usually enhances recovery from moderate and severe depression episodes. In addition, patients who engage in psychotherapy for depression may have a lower rate of relapse.[24]

Box

Integrative medicine treatments for perimenopausal symptoms: Suggested resources

- Albertazzi P. Non-estrogenic approaches for the treatment of climacteric symptoms. *Climacteric* 2007;10(suppl 2):115-20.
- Blair YA, Gold EB, Zhang G, et al. Use of complementary and alternative medicine during the menopause transition: longitudinal results from the Study of Women's Health Across the Nation. *Menopause* 2008;15:32-43.
- Freeman MP, Helgason C, Hill RA. Selected integrative medicine treatments for depression: considerations for women. *J Am Med Womens Assoc* 2004;59(3):216-24.
- Mischoulon D. Update and critique of natural remedies as antidepressant treatments. *Psychiatr Clin North Am* 2007;30:51-68.
- Thachil AF, Mohan R, Bhugra D. The evidence base of complementary and alternative therapies in depression. *J Affect Disord* 2007;97:23-35.
- Tremblay A, Sheeran L, Aranda SK. Psychoeducational interventions to alleviate hot flashes: a systematic review. *J North Am Menopause Soc* 2008;15:193-202.

Individual psychotherapy can help patients with perimenopausal depression:

- accept this life transition
- recognize the benefits of menopause, such as no need for contraception
- develop awareness of personal potential in the years ahead.

Because depression often occurs in an interpersonal context, consider including family members in psychotherapy to improve the patient's interpersonal support.

Integrative therapies. A full evaluation and consideration of standard treatment options is indicated for all women with MDD. Integrative medicine appeals to many patients but has not been sufficiently studied for perimenopausal depression. Supplemental omega-3 fatty acids and folate are reasonable adjuncts to the treatment of MDD[25-27] and deserve study in perimenopausal MDD.

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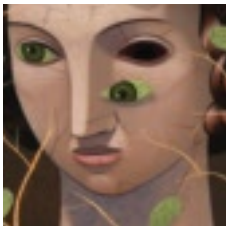
We recommend that all women who present with perimenopausal depression receive information about psychotherapy



Perimenopausal depression

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Integrative medicine appeals to many patients but has not been sufficiently studied in perimenopausal depression

References

1. Schmidt PJ, Rubinow DR. Reproductive ageing, sex steroids and depression. *J Br Menopause Soc* 2006;12(4):178-85.
2. Rasgon N, Shelton S, Halbreich U. Perimenopausal mental disorders: epidemiology and phenomenology. *CNS Spectr* 2005;10(6):471-8.
3. Greene JG. Constructing a standard climacteric scale. *Maturitas* 1998;29(1):25-31.
4. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54(5):573-83. Erratum in: *Biol Psychiatry* 2003;54(5):585.
5. Feld J, Halbreich U, Karkun S. The association of perimenopausal mood disorders with other reproductive-related disorders. *CNS Spectr* 2005;10(6):461-70.
6. Avis NE, Stellato R, Crawford S, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med* 2001;52:345-56.
7. Campbell S, Whitehead M. Oestrogen therapy and the menopause syndrome. *Clin Obstet Gynecol* 1977;4:31-47.
8. Schmidt PJ, Rubinow DR. Menopause-related affective disorders: a justification for further study. *Am J Psychiatry* 1991;48:844-52.
9. Soares CN. Menopausal transition and depression: who is at risk and how to treat it? *Expert Rev Neurother* 2007;7(10):1285-93.
10. Prior JC. The complex endocrinology of menopausal transition. *Endocrinol Rev* 1998;19:397-428.
11. Rasgon N, Altshuler LL, Fairbanks LA, et al. Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *J Clin Psychiatry* 2002;63(suppl):45-8.
12. Altshuler LL, Cohen LS, Moline ML, et al. The Expert Consensus Guideline Series. Treatment of depression in women. *Postgrad Med* 2001 Mar;(Spec No):1-107.
13. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12.
14. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
15. Ockene JK, Barad DH, Cochrane BB, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005;294:183-93.
16. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 2004;291:2947-58.
17. Shumaker SA, Legault C, Rapp SR. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. The Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* 2003;289:2651-62.
18. FDA approves new labeling and provides new advice to postmenopausal women who use or who are considering using estrogen and estrogen with progestin [FDA Fact Sheet, January 8, 2003]. Available at: http://www.fda.gov/oc/factsheets/WHI.html. Accessed September 11, 2008.
19. Soares CN, Arsenio H, Joffe H, et al. Escitalopram versus ethinyl estradiol and norethindrone acetate for symptomatic peri- and postmenopausal women: impact on depression, vasomotor symptoms, sleep, and quality of life. *Menopause* 2006;13(5):780-6.
20. Cohen LS, Soares CN, Joffe H. Diagnosis and management of mood disorders during the menopausal transition. *Am J Med* 2005;118(suppl 12B):93-7.
21. Kahn DA, Moline ML, Ross RW, et al. Depression during the transition to menopause: a guide for patients and families. *Postgrad Med* 2001 Mar;(Spec No):110-1.
22. Alder J, Besken KE, Armbruster U, et al. Cognitive-behavioural group intervention for climacteric syndrome. *Psychother Psychosom* 2006;75(5):298-303.
23. Soares CN, Almeida OP, Joffe H, Cohen LS. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: a double-blind, randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2001;58(6):529-34.
24. Otto MW, Smits JA, Reese HE. Combined psychotherapy and pharmacotherapy for mood and anxiety disorders in adults: review and analysis. *Clinical Psychology: Science and Practice* 2005;12:72-86.
25. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomized, placebo controlled trial. *J Affect Disord* 2000;60:121-30.
26. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry [American Psychiatric Association subcommittee report]. *J Clin Psychiatry* 2006;67:1954-67.
27. Otto MW, Church TS, Craft LL, et al. Exercise for mood and anxiety disorders. *J Clin Psychiatry* 2007;68:669-76.

Related Resources

- Greene Climacteric Scale. www.menopausematters.co.uk/greenescale.php.
- Quick Inventory of Depressive Symptomatology. www.ids-qids.org.
- National Center for Complementary and Alternative Medicine. National Institutes of Health. http://nccam.nih.gov.

Drug Brand Names

Citalopram • Celexa
Duloxetine • Cymbalta
Escitalopram • Lexapro
Estradiol • various
Eszopiclone • Lunesta
Fluoxetine • Prozac
Gabapentin • Neurontin
Medroxyprogesterone • Provera
Mirtazapine • Remeron
Paroxetine • Paxil
Sertraline • Zoloft
Venlafaxine • Effexor
Zolpidem • Ambien

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Dr. Freeman receives research support from GlaxoSmithKline, Forest Pharmaceuticals, and Eli Lilly and Company. She was associate professor of psychiatry at the University of Texas Southwestern Medical Center at Dallas when this article was written and is now on the faculty at Harvard Medical School and Massachusetts General Hospital, Boston.

Bottom Line

Screen women over age 40 for coexisting depressive and vasomotor symptoms. No data support the long-term use of HRT for recurrent or chronic depression. Antidepressants with serotonergic activity appear to be the most promising treatment. Make collaborative decisions based on the patient's medical and psychiatric history, psychological characteristics, and psychosocial supports.