Depression: Partnering With Patients to Achieve Better Outcomes

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Faculty:
Thomas L. Schwartz, MD

Educational Partner: Neuroscience Education Institute
Session 4: Depression: Partnering With Patients to Achieve Better Outcomes

Learning Objectives
1. Use screening tools to identify patients with depression.
2. Provide initial evidence-based depression treatment that is specifically suited to the individual patient’s need.
3. Monitor patients with depression over time in order to track treatment adherence, response, and side effects.
4. Make evidence-based treatment adjustments to address residual symptoms and side effects.

Faculty

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Thomas L. Schwartz, MD, associate professor of psychiatry, director of adult outpatient services, and assistant director for psychiatric residency training at SUNY Upstate Medical University, Syracuse, New York, completed his MD and residency from SUNY. Dr Schwartz directs the Depression & Anxiety Disorders Research Program. He provides resident supervision, lectures, and directs CME events for the psychiatry department. Dr Schwartz maintains a private practice and consults for the Indian Health Service, pharmaceutical companies, and associated industries. He has been recognized with the Marc H. Hollander, MD, Psychiatry Award, Teacher of the Year, and Mentor of the Year awards from SUNY Upstate; Nancy Roeske, MD, Irma Bland, Certificates of Recognition for Excellence in Medical Student and Resident Education from the APA, the SUNY Upstate President’s Award and Chancellor’s Awards for Teaching. He has served as principal investigator on clinical trials, authored Depression: Treatment Strategies and Management, 2nd ed., published articles in medical journals, and served as peer reviewer for U.S. and international journals.

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The presenting faculty reports the following:

Dr Schwartz has received grants and/or does research for Cephalon, Inc.; Cyberonics; Forest Laboratories, Inc.; Forest Pharmaceuticals, Inc. He is a consultant/advisor for Pamlab, L.L.C. He also serves on the speakers’ bureau for AstraZeneca Pharmaceuticals LP (divested); Pfizer Inc (divested); and Wyeth Pharmaceuticals (divested).

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Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
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<tr>
<td>EP</td>
<td>Education Partner</td>
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<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
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<tr>
<td>NDRI</td>
<td>norepinephrine reuptake inhibitor</td>
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<tr>
<td>NRI</td>
<td>norepinephrine reuptake inhibitor</td>
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<td>PHQ-9</td>
<td>Patient Health Questionnaire</td>
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<td>SERT</td>
<td>serotonin transporter</td>
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<tr>
<td>SNRI</td>
<td>serotonin norepinephrine reuptake inhibitor</td>
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<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
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<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
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</table>
Suggested Reading List


Depression: Partnering With Patients to Achieve Better Outcomes

Drug List

- Generic  
  - TK-301 N/A  
  - NEU-11 N/A  
  - agomelatine Not in U.S.
- Generic Trade  
  - amitriptyline Elavil  
  - amoxapine Asendin  
  - bupropion Wellbutrin
- Generic Trade  
  - citalopram Celexa  
  - clomipramine Anafranil  
  - desipramine Norpramin
- Generic Trade  
  - desvenlafaxine Pristiq  
  - doxepin Sinequan  
  - duloxetine Cymbalta
- Generic Trade  
  - escitalopram Lexapro  
  - eszopiclone Lunesta  
  - fluoxetine Prozac
- Generic Trade  
  - fluvoxamine Luvox  
  - gabapentin Neurontin  
  - imipramine Tofranil
- Generic Trade  
  - isocarboxazid Marplan  
  - maprotiline Ludiomil  
  - melatonin melatonin
- Generic Trade  
  - milnacipran Savella  
  - mirtazapine Remeron  
  - modafinil Provigil
- Generic Trade  
  - nefazodone Serzone  
  - nortriptyline Pamelor  
  - paroxetine Paxil
- Generic Trade  
  - phenelzine Nardil  
  - pregabalin Lyrica  
  - protriptyline Triptil
- Generic Trade  
  - reboxetine Not in U.S.  
  - selegiline EMSAM  
  - sertraline Zoloft
- Generic Trade  
  - tranylcypromine Parnate  
  - trazodone Desyrel  
  - trimipramine Surmontil
- Generic Trade  
  - venlafaxine Effexor  
  - vilazodone Viibryd  
  - undefined

Learning Objectives

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- Provide initial evidence-based depression treatment that is specifically suited to the individual patient's need
- Monitor patients with depression over time in order to track treatment adherence, response, and side effects
- Make evidence-based treatment adjustments to address residual symptoms and side effects

Pretest

Do you think screening tools for depression are valuable in a primary care practice?

1. Yes, they are important.
2. No, they take too much time.
3. No, they are the psychiatrist's responsibility.
4. No, they are unimportant.

Pretest

A 24-year-old woman states that she has no appetite, she's always tired, and she feels generally unwell and unmotivated to do anything. Initial physical exam is not significant. She is asked to complete the Patient Health Questionnaire; her score is 15, indicating moderate depression. Based on this, which of the following would be an appropriate treatment recommendation?

1. Watchful waiting
2. Antidepressant medication
3. Psychotherapy
4. 1 or 3
5. 2 or 3
6. Unsure

Pretest

Do you establish and monitor "markers" for patients who are being treated for major depression?

1. Yes, for all patients who are/have been treated for depression
2. Yes, for patients who have not yet responded to antidepressant treatment
3. No, I do not use markers
A 36-year-old married woman with depression has shown a partial response to venlafaxine XR after 8 weeks. However, she now complains of sexual dysfunction; specifically, she states that she has no desire for sex and it is affecting her marriage. Despite her depression, she and her husband had a satisfactory sex life before she began treatment and thus she attributes her lack of desire to her treatment. Which of the following would be an appropriate treatment strategy for this patient?

1. Switch to bupropion or vilazodone
2. Switch to citalopram or escitalopram
3. Add a phosphodiesterase-5 inhibitor
4. Unsure

Guidelines for Identification and Assessment

• U.S. Preventive Services Task Force recommends universal screening when systems are in place to ensure accurate diagnosis, psychotherapy, and follow-up
• Relying solely on voluntary disclosure → false negatives
• Relying solely on self-report checklists → false positives and false negatives

Risk Factors

• Problems in psychosocial functioning
• Personal and/or family history of
  – Depression
  – Bipolar disorder
  – Suicide-related behaviors
  – Substance abuse
  – Other psychiatric illness
  – Significant psychosocial stressor

Major Depressive Disorder in Adults

Screening and Diagnosis

Over the LAST 2 WEEKS, have you been bothered by

Feeling down, depressed, or hopeless……………….Yes No

Little interest or pleasure in doing things………...Yes No

From MEDCOM form 779

PHQ-9 Symptom Checklist

1. Over the last two weeks have you been bothered by the following problems?

   a. Little interest or pleasure in doing things
   b. Feeling down, depressed, or hopeless
   c. Trouble falling or staying asleep, or sleeping too much
   d. Feeling tired or having little energy
   e. Poor appetite or overeating
   f. Feeling bad about yourself, or that you are a failure . . .
   g. Trouble concentrating on things, such as reading . . .
   h. Moving or speaking so slowly . . .
   i. Thoughts that you would be better off dead . . .

2. ... how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

   Subtotal:

   TOTAL:

   Not at all
   Somewhat
   Very
   Extremely
When to Refer

- Unclear diagnosis
- Severe depression with significant impairment in functioning
- Psychotic or manic features, or history of psychotic/manic symptoms
- Comorbid psychiatric disorders
- Family history of suicide
- Suicidal ideation, plan, or intent
  - Active suicidality may warrant hospitalization
- Failure to respond to initial interventions within 6–8 weeks
- Other complicating factors or concerns

Guidelines for Management

- EDUCATE the patient about depression, management options, and the limits of confidentiality
- DEVELOP a treatment plan with the patient that includes specific treatment goals in key areas of functioning (home, work, and social settings)
- ESTABLISH relevant collaboration with mental health resources
- ESTABLISH a safety plan
  - Especially important at diagnosis and during initial treatment

Medication vs. Psychotherapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Psychotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe loss of pleasure</td>
<td>• Severe negative thinking</td>
</tr>
<tr>
<td>• Overwhelming neurovegetative symptoms</td>
<td>• Life crisis</td>
</tr>
<tr>
<td>• Interpersonal therapy</td>
<td></td>
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</tbody>
</table>
Comparative Efficacy and Acceptability of 12 New-Generation Antidepressants

- Multiple-treatments meta-analysis
- Results/interpretation:
  - Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine, fluoxetine, fluvoxamine, paroxetine, and reboxetine
  - Escitalopram and sertraline showed the best profiles of acceptability and therefore the lowest rates of discontinuation (significant vs. duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine)
  - Sertraline may be the best choice when initiating treatment for moderate to severe major depression: best balance between benefits, acceptability, and cost

The efficacy and acceptability of bupropion, milnacipran, and citalopram were at intermediate values that were not significantly different from the other 9 agents. Note: Reboxetine and milnacipran are not approved to treat depression in the U.S.


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STAR*D Algorithm

Level 1: Citalopram
Level 2: SER BUP VEN CT CIT + BUP BUS CT
Level 2a: BUP VEN
Level 3: Mirt Nortr Augmentation: Li vs. T3 SER BUP VEN CIT
Level 4: TCP VEN+MIRT

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STAR*D: Percent Response and Remission by Levels

- The further along treatment goes, the less change actually occurs


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STAR*D Relapse Rates

- The New and the Under-Used


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Things to Tell Your Patients About Antidepressants

- Antidepressants only work if taken every day
- Antidepressants are not addictive
- Benefits from medication appear slowly; some symptoms may take longer to resolve than others
- Mild side effects are common, happen early (before therapeutic effects), and usually improve with time
- Notify you of any late-developing or persistent side effects—may require treatment adjustment
- Antidepressants should still be taken even after symptoms abate
- Stopping antidepressant treatment abruptly is dangerous
- Sometimes it takes a few tries to attain remission

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Treating Depression in Adults

The New and the Under-Used
The New: Vilazodone

- Vilazodone is a 5HT1A partial agonist and a 5HT transport inhibitor
- Like combining an SSRI with buspirone, except
  - Vilazodone’s effects at 5HT1A receptors are equal or more potent than its effects at 5HT transporters
  - Buspirone is much weaker at 5HT1A receptors
- The combined action downregulates presynaptic 5HT1A autoreceptors over time, eventually increasing 5HT release into postsynaptic receptors and causing antidepressant effects
- However, due to the predominance of 5-HT1A actions, vilazodone has the low incidence of sexual dysfunction associated with selective 5-HT1A partial agonists

Note: buspirone is not approved to treat depression

Immediate Actions of Vilazodone

Delayed Actions of Vilazodone: Part 1

Delayed Actions of Vilazodone: Part 2

Vilazodone: Clinical Data

Vilazodone Tips and Pearls

- Usual dose: 40 mg once daily with food
- Minimally effective dose not established
- Metabolized by CYP450 3A4
- Relative lack of sexual dysfunction and weight gain
- Consider for patients with comorbid anxiety
- Not well studied, but can consider 50–80 mg/day for treatment-resistant depression/OCD/anxiety

The Under-Used: Tricyclic Antidepressant (TCA) Tips and Pearls (1)

- Can monitor plasma drug levels of many TCAs, especially nortriptyline, amitriptyline, desipramine, imipramine, clomipramine/desmethylclomipramine.
- Most TCAs are CYP2D6 substrates so lower the dose in genetic poor metabolizers (can now genotype patients for CYP2D6).
- Also, lower the dose if used concomitantly with 2D6 inhibitors (e.g., fluoxetine, paroxetine, many others).
- Tertiary TCAs are metabolized to secondary TCAs by CYP1A2 (e.g., amitriptyline to nortriptyline; imipramine to desipramine; clomipramine to desmethylclomipramine) which can be inhibited by 1A2 inhibitors such as fluvoxamine.

Note: clomipramine is not approved to treat depression.

The Under-Used: Tricyclic Antidepressant Tips and Pearls (2)

- TCAs can be sedating, so usually given in a single dose at bedtime.
- Doxepin most highly antihistaminic, even at 1-10 mg.
- In fact, a low-dose formulation of doxepin is now available for treating insomnia.
- TCAs may be the best treatment for depression in Parkinson’s disease.
- Desipramine, nortriptyline, maprotiline are more noradrenergic.
- Some TCAs have 5HT2A and 5HT2C antagonist properties that contribute to their antidepressant action.

Monitoring Patients

- 46% of patients stop medication before the chance of response.
- A large portion who do respond discontinue once they “feel better.”
- Use 10-minute phone calls to identify patients:
  - With intolerable side effects
  - Who are not responding or have residual symptoms
  - Who have discontinued their medication
  - Who relapse.
- Focus on tracking most troublesome symptoms rather than depressed mood per se.

Monitoring for Response/Remission and Relapse: Markers

Options to Avoid/Address the Most Troublesome Side Effects

Monitoring for Response, Adherence, and Side Effects

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- A large portion who do respond discontinue once they “feel better.”
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  - With intolerable side effects
  - Who are not responding or have residual symptoms
  - Who have discontinued their medication
  - Who relapse.
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**Most Troubling Antidepressant Side Effects**

**Short-term**
- Nausea
- Headache
- Activation

**Longer-term**
- Sedation
- Sexual dysfunction
- Weight gain


**SSRI-Induced Activation**

- SSRIs can be activating upon initiation, causing agitation and/or increasing anxiety
  - fluoxetine > sertraline > citalopram/esctalopram/paroxetine

- Side effects usually subside in first few weeks of treatment
  - Discontinuing or changing dose can prevent stabilization of therapeutic effects
  - Therapeutic effects can take several weeks to stabilize
  - Adding a benzodiazepine short-term can be useful


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**Sedation**

<table>
<thead>
<tr>
<th>Sedating</th>
<th>Non-Sedating</th>
</tr>
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<tbody>
<tr>
<td>bupropion</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>citalopram</td>
<td>mirtazapine</td>
</tr>
<tr>
<td>escitalopram</td>
<td>doxepin</td>
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<tr>
<td>fluoxetine</td>
<td>desvenlafaxine</td>
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<tr>
<td>sertraline</td>
<td>doxepin</td>
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<tr>
<td>vilazodone</td>
<td>trazodone</td>
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<tr>
<td>fluvoxamine</td>
<td>trazodone</td>
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<tr>
<td>mirtazapine</td>
<td>maprotiline</td>
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<tr>
<td>amoxapine</td>
<td>trimipramine</td>
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<td>nefazodone</td>
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<td>amitriptyline</td>
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<td>paroxetine</td>
</tr>
<tr>
<td>desvenlafaxine</td>
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</table>

Note: clomipramine, fluvoxamine, milnacipran, and low-dose doxepin formulation are not approved to treat depression.


**Addressing Sedation**

- Dose at night or take larger dose at night
- Switch to a nonsedating antidepressant
- If patient is responding and otherwise tolerating current treatment, can consider adding modafinil/armodafinil


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**Sexual Dysfunction**

<table>
<thead>
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<tr>
<td>maprotiline</td>
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</tbody>
</table>

Note: clomipramine, fluvoxamine, and milnacipran are not approved to treat depression.


**Addressing Sexual Dysfunction**

- Assess sexual function before starting medication
- Don’t rely on self report
- Add high-dose (60 mg/day) buspirone
- Switch to agent with less likelihood of sexual dysfunction (bupropion, vilazodone)
- Add phosphodiesterase 5 (PDE-5) inhibitor (e.g., sildenafil, vardenafil, tadalafil)
  - Do not increase desire
- For women, consider estrogen creams

Weight Gain

<table>
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<th>Drug</th>
<th>Weight Gain</th>
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<tr>
<td>Paroxetine</td>
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<tr>
<td>Amisulpride</td>
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<tr>
<td>Clozapine</td>
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<tr>
<td>Quetiapine</td>
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<tr>
<td>Ziprasidone</td>
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<tr>
<td>Trazodone</td>
<td></td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td></td>
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<tr>
<td>Mirtazapine</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
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</tbody>
</table>

Note: Clomipramine, Fluvoxamine, and Milnacipran are not approved to treat depression in the U.S.

Short-Term Weight Gain: Meta-Analysis

Addressing Weight Gain

- In meta-analysis, average weight with medications is small
  - A few patients may gain most of the weight, related to their own genetic predispositions and other factors
- Large weight gain typically occurs gradually over many months
- Monitor patients for weight gain, appetite changes, and metabolic parameters
- If significant weight gain occurs, consider switching to an agent with less risk of weight change

Residual Symptoms

Options for Partial/Lack of Response

When Does it Make Sense to Increase the Dose?
Case: Charles

Charles is a 45-year-old man who suffers from MDD. He is currently taking sertraline, and his depressive symptoms are fairly well (but not completely) controlled.

His chief complaint is that he is unable to sleep. He has difficulty falling asleep, and he wakes up several times during the night. He is very tired during the day, and his daytime fatigue is starting to affect his job as a forklift operator.

Charles is not taking any other medications at this time.
Chronotherapies:

**Bright Light Therapy**
- Exposure to light alters circadian rhythms and suppresses melatonin release
- 10,000 lux (bright light) for 30 min/day
- Must be timed with patient’s circadian phase of melatonin secretion
  - Administer light 7.5-9.5 hrs after evening melatonin secretion
  - Approximation of melatonin secretion can be determined using the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ)
- Useful as a non-pharmacological intervention during pregnancy


**Bright Light Therapy for Depression**
- Rapid onset of antidepressant action
- Hastens the effects of antidepressant drugs
- Antidepressant effects mediated through eyes
  - Extracocular administration shows no antidepressant benefits
- Good for bipolar depression but may precipitate mania
- Dawn simulation therapy
  - Slow incremental light signal at the end of the sleep cycle
- Side effects are rare
  - Headaches, eyestrain, nausea, and agitation


**Sleep Deprivation Therapy**
- 36 hrs of deprivation
- Antidepressant effects within hours
- Decreases activity of 5-HT2C receptors
- Response rates are similar to antidepressants (50-80%)
  - Response is influenced by some of the same polymorphisms
    - 5-HTTR (serotonin transporter), 5-HT7, COMT, GSK-3β
- Improvement doesn’t last unless combined with:
  - Other chronotherapies
  - Lithium
  - Antidepressants
- Contraindicated for patients with epilepsy
- Sleep deprivation increases risk of seizures in patients with epilepsy


**Sleep Phase Advance Therapy**
- Advances timing of sleep-wake cycle
- Synchronizes sleep with other biological rhythms
- Improves effects of antidepressants
- Also effective as monotherapy


Treating Residual Symptoms:

**Fatigue and Concentration**

![Image](101.png)


Other Common Residual Symptoms of Depression

![Image](102.png)

Switching Options for Lack of Response

- No evidence supporting preference for one agent or one class over another
- Switching within the same class or to another class are both options
- Commonly used: another SSRI/SNRI, bupropion, mirtazapine
- Under-used: tricyclic antidepressant (TCA), monoamine oxidase inhibitors (MAOIs)
- New: vilazodone

Summary

- Screen every patient for depression using a universal screener
- Many treatment options are available; customize treatment selection based on the patient’s symptoms and concerns
- Establish markers and use brief follow-up phone calls to monitor patients for response, side effects, and adherence
- Adjust treatment by switching or augmenting to address side effects and residual symptoms

Posttest

Do you think screening tools for depression are valuable in a primary care practice?

1. Yes, they are important.
2. No, they take too much time.
3. No, they are the psychiatrist’s responsibility.
4. No, they are unimportant.

Posttest

A 24-year-old woman states that she has no appetite, she’s always tired, and she feels generally unwell and unmotivated to do anything. Initial physical exam is not significant. She is asked to complete the Patient Health Questionnaire; her score is 15, indicating moderate depression. Based on this, which of the following would be an appropriate treatment recommendation?

1. Watchful waiting
2. Antidepressant medication
3. Psychotherapy
4. 1 or 3
5. 2 or 3
6. Unsure

Posttest

Do you now plan to establish and monitor “markers” for patients who are being treated for major depression?

1. Yes, for all patients who are/have been treated for depression
2. Yes, for patients who have not yet responded to antidepressant treatment
3. No, I do not use markers

Posttest

A 36-year-old married woman with depression has shown a partial response to venlafaxine XR after 8 weeks. However, she now complains of sexual dysfunction; specifically, she states that she has no desire for sex and it is affecting her marriage. Despite her depression, she and her husband had a satisfactory sex life before she began treatment and thus she attributes her lack of desire to her treatment. Which of the following would be an appropriate treatment strategy for this patient?

1. Switch to bupropion or vilazodone
2. Switch to citalopram or escitalopram
3. Add a phosphodiesterase-5 inhibitor
4. Unsure