Depression in Ambulatory Care and the Role of the Pharmacist

Megan Maroney, PharmD, BCPP
Clinical Assistant Professor
Ernest Mario School of Pharmacy at Rutgers University
Piscataway, New Jersey
Clinical Psychiatric Pharmacist
Monmouth Medical Center
Long Branch, New Jersey

Caitlin McCarthy, PharmD
Clinical Assistant Professor
Ernest Mario School of Pharmacy
Rutgers, the State University of New Jersey
New Brunswick, New Jersey
Director of Pharmacy Services
Henry J. Austin Health Center
Trenton, New Jersey

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Education Objectives
At the completion of this activity, the participant will be able to:
• Examine the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for major depressive disorder (MDD) and be able to recognize patients at risk
• Explore the Patient Health Questionnaire (PHQ-9) and other screening tools for MDD
• Discuss the medication and monitoring options for MDD to meet the goals of treatment
• Identify the role of the ambulatory care pharmacist as part of a team approach for the care of the MDD patient

Outline
• Introduction
  – Epidemiology
  – Diagnostic criteria
• Screening
• Treatment
• Monitoring
• Role of the Pharmacist

Epidemiology

• Affects over 300 million people worldwide
• Estimated lifetime prevalence: 19.2%
• US 12-month prevalence: 6.7% of adults
  – 7.6% of persons age 12 and older
  – 16.1 million adults
  • 8.5% females
  • 4.7% males
  – Up to 3% of children

Burden of Depression
• Second leading cause of disability worldwide
• Cost United States an estimated $210.5 billion in 2010
  – Direct health care costs
  – Suicide
  – Lost productivity
• Considered a moderate risk factor for early cardiovascular disease
• Increased risk for other mental illnesses
  – Anxiety disorders 36.6%
  – Mood disorders 13.3%
  – Substance use disorders 5.5%


DSM-5 Diagnostic Criteria
≥ 5 symptoms lasting at least 2 weeks; at least one in purple

Depressed mood
Loss of interest or pleasure

• Weight/appetite loss or gain
• Insomnia or hypersomnia
• Observable psychomotor agitation or retardation
• Fatigue/loss of energy
• Feelings of worthlessness or guilt
• Inability to concentrate or make decisions
• Recurrent thoughts of death or suicidal ideation


Differential Diagnosis
• Bipolar disorder
• Substance-induced mood disorder
• Attention-deficit/hyperactivity disorder
• Adjustment disorder with depressed mood
• Medical conditions
  – Hypothyroidism
  – Multiple sclerosis
  – Stroke


Risk Factors
• Family history
• Childhood trauma
• History of other mental health conditions
• Substance abuse
• Chronic health conditions
• Higher rates in
  – Females
  – Young and middle-aged adults
  – Nonwhite persons
  – Undereducated
  – Previously married
  – Unemployed


Screening Recommendations
• US Preventive Services Task Force (USPSTF) 2016 Recommendations for Primary Care
  – Depression screening recommended for general adult population and children age 12 and up
  – Including pregnant and postpartum women
  • Insufficient evidence to recommend screening for younger children
  • Adequate systems needed to ensure appropriate follow-up
  – Any positive screening should trigger a full assessment
  – Routine suicide risk screening not recommended in the general population

Screening Recommendations
Screening Tools

- Adults
  - Patient Health Questionnaire
  - Hospital Anxiety and Depression Scales
- Children and adolescents
  - Patient Health Questionnaire for Adolescents
  - Beck Depression Inventory – primary care version
- Older adults
  - Geriatric Depression Scale
- Postpartum
  - Edinburgh Postnatal Depression Scale

Patient Health Questionnaire: PHQ-9

- 9-item self-report questionnaire
- Over the past 2 weeks, how often have you been bothered by...
  - Little interest or pleasure in doing things
  - Feeling down, depressed or hopeless
  - Trouble sleeping or sleeping too much
  - Feeling tired or having little energy
  - Poor appetite or overeating
  - Feeling bad about yourself or that you are a failure
  - Trouble concentrating
  - Moving or speaking slowly or being fidgety and restless
  - Thoughts of hurting yourself
- Rated not at all (0 points), several days (1), more than half the days (2), or nearly every day (3)
- Total score of ≥ 10 has high sensitivity and specificity for major depressive disorder (MDD)

Patient Health Questionnaire: PHQ-2

- Contains the first 2 questions of the PHQ-9
  - Over the past 2 weeks, how often have you been bothered by...
    - Little interest or pleasure in doing things
    - Feeling down, depressed or hopeless
  - Total score ≥ 3 has high sensitivity and specificity for MDD

Depression Screening By Pharmacists

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Number of Participants</th>
<th>Screening Tool</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>50% of participants felt “very comfortable” completing the screening</td>
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<td></td>
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<td>Depression screening implemented thereafter</td>
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<tr>
<td>O’Reilly CL, et al. Res Soc Adm Pharm. 2015;11(3):364-81.</td>
<td>20 pharmacies in 12 community pharmacies</td>
<td>41 out of 75 approached</td>
<td>BeyondBlue Depression Checklist, PHQ-9, WHO-5</td>
<td>PHQ-9 was most popular tool amongst pharmacists</td>
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<td>Mean interaction time of 16 minutes</td>
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<td>70% were referred to a primary care or mental health specialist</td>
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<td>25% referred to physician</td>
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<td>5 patients referred for urgent treatment due to suicidal thoughts</td>
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Goals of Treatment

- Acute
  - Response – clinically significant improvement in depressive symptoms (usually ≥50%)
  - Remission – absence of symptoms
- Intermediate
  - Recovery – sustained remission
  - Eliminate residual symptoms
  - Restore prior level of functioning
- Long-term
  - Maintenance to prevent recurrence
Phases of Treatment

- **Acute**
  - 4-10+ weeks
- **Continuation**
  - 6-9 months
- **Maintenance**
  - Usually 2 years or more
  - History of ≥ 3 prior episodes or other risk factors
  - Residual symptoms
  - Early age of onset
  - Family history
  - Patient preference

Non-Pharmacologic Treatment

- Cognitive Behavioral Therapy
- Interpersonal Therapy
- Mindfulness-based Cognitive Therapy
- Electroconvulsive Therapy (ECT)
- Transcranial Magnetic Stimulation

Antidepressants

- **SSRIs**
  - Fluoxetine
  - Citalopram
  - Sertraline
  - Paroxetine
  - Fluvoxamine
  - Escitalopram
- **SNRIs**
  - Venlafaxine
  - Duloxetine
  - Desvenlafaxine
  - Levomilnacipran
- **MAOIs**
  - Phenelzine
  - Tranylcypromine
  - Transdermal selegiline
- **TCAs**
  - Amitriptyline
  - Nortriptyline
  - Clomipramine
  - Imipramine
  - Doxepin
  - Desipramine
- **Miscellaneous**
  - Bupropion
  - Mirtazapine
  - Trazodone/nefazodone
  - Vilazodone
  - Vortioxetine

Medication Choice

- Overall, all available antidepressants considered equally effective
- First-line – SSRI, SNRI, mirtazapine, or bupropion
  - Canadian guidelines now recommend vortioxetine as an option
- TCAs and MAOIs usually restricted to non-responders due to unfavorable risk/benefit ratio
  - Adverse effects
  - Drug/food interactions

Individualizing Treatment

- **Balance risk vs benefit**
- **Medication Factors**
  - Adverse effect profile
  - Pharmacokinetics
  - Drug interactions
  - Half-life
  - Cost
- **Patient factors**
  - Patient preference
  - Age – risk of certain adverse effects
  - Suicidality in children and young adults
  - Anticholinergic effects in elderly
  - Prior response to medication
  - Family member response to medication
  - Co-occurring medical and psychiatric disorders
  - Type of depression – specific symptoms
  - Patient’s adherence history

New Antidepressants: Vilazodone

- **Efficacy**
  - Response rates 40-72% vs 28-55% with placebo
  - Number needed to treat (NNT) = 8
- **Mechanism of Action:** SSRI and 5-HT1A partial agonist
- **Dosing:** 10 mg daily titrated at weekly intervals to target dose of 20-40 mg daily
  - Titration necessary to avoid GI adverse effects
  - Dose adjustment required with CYP 3A4 inhibitors or inducers
- **Pharmacokinetics**
  - Half-life 25 hours
  - Should be given with food to enhance absorption
- **Adverse effects**
  - Diarrhea: 26-29%
  - Nausea: 22-24%
  - Headache: 15%
  - Insomnia: 10-16%
  - Dry mouth: 13-16%
  - Increased sweating: 6-8%
New Antidepressants: Vortioxetine

- **Efficacy**
  - Response rates 37.5-68.1% vs 23.0-46.9% with placebo
  - NNT = 9
  - Possible benefit in cognitive functioning
- **Mechanism of Action:** SSRI, 5-HT\(_1\) and 5-HT\(_2\) agonist
- **Dosing:** 10 mg daily titrated to 20 mg daily
  - Dose adjustment recommended with CYP inducers or CYP 2D6 inhibitors
  - 5 mg dose available for those unable to tolerate higher doses
- **Pharmacokinetics**
  - Half-life 66 hours
- **Adverse Effects**
  - Sexual dysfunction: self-report 1-5%, rating scale-based 16-34%
  - Nausea: 21-32%, females > males

New Antidepressants: Levomilnacipran

- **Efficacy**
  - Response rates 38.4-59.1% vs 29.1-42.2% with placebo
  - NNT = 10
- **Mechanism of Action:** SNRI
- **Dosing:** 20 mg daily titrated to 40-120 mg daily
- **Pharmacokinetics**
  - Half-life 12 hours
- **Adverse Effects**
  - Nausea: 17%
  - Cardiovascular effects: orthostatic hypotension, tachycardia, palpitations, hypertension

When Initial Therapy Fails

- Roughly 55-65% of patients will continue to have symptoms despite treatment
- Chance of response decreases if no improvement seen by 4 weeks
- Re-evaluate
  - Diagnosis
  - Adequacy of treatment (dose, duration)
  - Adherence to treatment
  - Comorbid medical and psychiatric diagnoses
- Treatment options
  - Increase dose of current antidepressant (AD)
  - Minimal adverse effects
  - Some improvement
  - Switch to a different AD
  - Adverse effects
  - No improvement
  - Combine or augment with a second medication (adjunctive medication)
  - Partial response and good tolerability

Adjuvative Medication Strategies

<table>
<thead>
<tr>
<th>Medication</th>
<th>First-Line</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>aripiprazole, quetiapine, risperidone</td>
</tr>
<tr>
<td>Second-Line</td>
<td>brexpiprazole, bupropion, lithium, buspiroine, mirtazapine, modafanil, olanzapine, T(_3)</td>
</tr>
<tr>
<td>Third-Line</td>
<td>lamotrigine, stimulants, TCAs, ziprasidone</td>
</tr>
<tr>
<td>Experimental</td>
<td>ketamine</td>
</tr>
<tr>
<td>Not recommended</td>
<td>pindolol</td>
</tr>
</tbody>
</table>

FDA-approved Adjunctive Options

- **Adjunctive with antidepressants**
  - Aripiprazole 2-5 mg/day titrated up to 15 mg/day
  - Quetiapine XR 50 mg/day titrated to 150-300 mg/day
  - Brexpiprazole 0.5-1 mg/day titrated up to 2-3 mg/day
- **Treatment-Resistant Depression**
  - Olanzapine/fluvastatin 6 mg/25 mg OHS titrated to usual max dose of 18 mg/50 mg

Brexiprazole

- Also approved for treatment of schizophrenia
- **Efficacy for MDD**
  - Response rates of 23.0-23.4% vs 14.3-15.7% with placebo
  - NNT ≤ 11-13
- **Mechanism of action:** partial agonist at D\(_2\) and 5-HT\(_1\)\(_A\)
- **Pharmacokinetics**
  - T\(_{1/2}\) = 91 hours
  - Metabolized by CYP 3A4 and 2D6
- **Adverse effects**
  - Akathisia – 6-14%
  - Weight gain
  - 30% gained clinically significant levels of weight (≥ 7%) in long-term studies
Adverse Effects

- Cardiovascular
  - Hypertension – SNRIs, bupropion
  - Hypertensive crisis – MAOIs
  - Orthostatic hypotension – TCAs, trazodone, MAOIs
  - Arrhythmias – TCAs, citalopram
- Anticholinergic – TCAs
- Neurologic
  - Headache – SSRIs, SNRIs, bupropion
  - Seizures – TCAs, bupropion
- Anticholinergic
  - TCA
- Sexual dysfunction
  - Both sexes
  - Less frequent with bupropion, mirtazapine, nefazodone, vilazodone?, vortioxetine?
  - May be more frequent with paroxetine and escitalopram
- Mental status changes
  - Serotonin syndrome
  - Tramadol
  - Meperidine
  - Antipsychotics
  - Dextromethorphan
  - Linezolid
- QTc prolongation
  - Especially citalopram and escitalopram

Drug Interactions

- Pharmacodynamic
  - Serotonin syndrome
  - Hypertensive crisis
  - Blood pressure
  - QT, Prolongation
- Pharmacokinetic
  - CYP 450
  - Impaired absorption

Monitoring for Adverse Effects

- Symptom/adverse effect diary
- Open dialogue with physicians about adverse effects
  - Some will go away on their own
  - Some can be mediated by careful titration or changing time of day
- Hypertensive crisis
  - Throbbing headache
  - Palpitations
- Serotonin syndrome
  - Mental status changes
  - agitation
  - Myoclonus and hyperreflexia
  - Fever and diaphoresis
  - Shivering
  - Ataxia
  - Diarrhea

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  - Shivering
  - Ataxia
  - Diarrhea
**QTc Prolongation With Citalopram and Escitalopram**

- Citalopram – FDA warning
  - Maximum dose lowered to 40 mg/day
  - Maximum dose 20 mg/day
  - Age ≥60 years
  - Hepatic impairment
  - Concurrent use of moderate-strong CYP2C19 inhibitors
  - CYP2C19 poor metabolizers

- Escitalopram – Medicines and Healthcare Products Regulatory Agency (UK) warning
  - Maximum dose 10 mg/day for those ≥65 years

**Drug Interactions**

- Hypertensive crisis (MAOIs)
  - Tryptamine-containing foods
  - Pseudoephedrine
  - Phenylephrine
  - Dextromethorphan

- Bleeding (SSRIs, SNRIs)
  - Anticoagulants
  - Antiplatelets
  - NSAIDs

**Pharmacokinetic Drug Interactions: CYP 450**

<table>
<thead>
<tr>
<th>Minimal/Low Potential</th>
<th>Moderate Potential</th>
<th>High Potential</th>
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<tbody>
<tr>
<td>Citalopram</td>
<td>Aniprazole (2D6, 3A4 substrate)</td>
<td>Fluoxetine (2D6, 2C19 inhibitor)</td>
</tr>
<tr>
<td>Dvoretaline</td>
<td>Bupropion (2D6 inhibitor)</td>
<td>Fluvoxamine (1A2, 2C19, 3A4 inhibitor)</td>
</tr>
<tr>
<td>Eslicaropram</td>
<td>Duloxetine (2D6 inhibitor, 1A2 substrates)</td>
<td>Paroxetine (2D6 inhibitor)</td>
</tr>
<tr>
<td>Mitrazapine</td>
<td>Levothiapropan (3A4 substrates)</td>
<td>Quetiapine (3A4 substrate)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Olanpipazine (1A2 substrate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sarineline (2D6 inhibitor)</td>
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</tr>
<tr>
<td></td>
<td>Vilaadime (3A4 substrate)</td>
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</tr>
<tr>
<td></td>
<td>Vortioxetine (2D6 substrate)</td>
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</tr>
</tbody>
</table>

**Role of the Pharmacist**

- Identifying those at risk
- Providing patient education
- How to take it
- What to expect (time to onset of effect, adverse effects)
- Emphasize value of early treatment and importance of adherence
- Provide depression symptom checklist/rating scale
- Collaboration and communication with providers
- Increase awareness of the pharmacist’s role

**APhA Foundation White Paper on Pharmacist Role in Depression Management**

- Identifying those at risk
- Providing patient education
  - What the medication is used for
  - How to take it
  - What to expect (time to onset of effect, adverse effects)
  - Emphasize value of early treatment and importance of adherence
  - Provide depression symptom checklist/rating scale
- Collaboration and communication with providers
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**What Do Patients Want to Know?**

- Balance of benefit and harm information
- Written information largely focuses on negative effects
- Information about
  - Indications
  - Benefits
  - Likely duration of treatment
  - At least 4-6 months after symptom resolution
  - Adverse effects
Optimizing Medication Adherence

- Non-adherence to antidepressants 50-75%
- Adherence and discontinuation associated with amount of information given to patient
- Patients more likely to adhere to medication regimens if clinicians ask about adverse effects and medication-related concerns


Drug Knowledge
Attitudes
Adherence

Optimizing Medication Adherence

- Rickles, et al.
  - 63 patients presenting with new AD prescription
  - 3 monthly telephone calls from pharmacists
  - Results
    - Patients who gave more feedback to RPh had:
      - Better AD knowledge (P ≤ .05)
      - More positive AD beliefs (P ≤ .05)
      - More positive perceptions of progress (P ≤ .001)


Improving Medication Attitudes

- Most ADs work by increasing availability of certain chemicals in the brain (serotonin, norepinephrine, dopamine)
- 60-70% of patients respond to the first AD they try
- ADs take at least 3-4 weeks to achieve full therapeutic benefit
- Patients should continue taking their AD for at least 6-9 months to minimize risk of relapse


Treatment Expectations

- Don’t stop taking your antidepressants or change the dose on your own
- Depression may return if ADs are stopped too soon
- Discontinuation symptoms
  - Flu-like symptoms (headache, chills)
  - Insomnia
  - Nausea
  - Imbalance/dizziness
  - Sensory disturbances (paresthesias, “electric shock-like” sensations)
  - Hyperarousal
  - Others: anxiety, irritability, lightheadedness


Project ImPACT: Depression, Asheville North Carolina
- 130 patients in 2 ambulatory care clinics
- Face-to-face visits with pharmacist care manager once per month-quarterly for a year
- Intake interview to obtain medical history
- Formulated treatment plan and communicated to primary care physician
- Educated patient and assessed for adherence
- PHQ-9 completed at baseline and each follow-up visit
- Results
  - 80% had a decrease in PHQ-9 scores
  - 68% considered responders
  - 58% achieved remission
  - Annual medical costs decreased
  - Employers continued to offer the program after the study ended


Pharmacist Medication Management
Conclusion

- Major depressive disorder is a common and debilitating illness
- Multiple screening tools exist to aid in identifying patients in need of treatment
- Pharmacists can be implemental in screening for this disorder, recommending appropriate pharmacotherapy and monitoring for treatment response

References

- StataCorp. Stata/SE 14: Reference Manual. College Station, TX: StataCorp LP; 2015.
- StataCorp. Stata/SE 14: Reference Manual. College Station, TX: StataCorp LP; 2015.