Navigating Depression in the Metabolic Syndrome Patient

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Disclosures

- NONE.
  I receive all my income from the University of Colorado SOM.

Learning Objectives:

- Identifying Depression
- How to Start the Conversation
- Considering Differential & Comorbidities
- Patient Engagement & Education
- Initiating Management
- Consider a Team Approach: Innovative Consults & Referrals
Mrs. Feeling Blue presents to your office today….

- What are the signs, symptoms and risk factors that alert you that she is struggling with a depressive disorder/illness?
- Why is it important to treat?
- Do you feel adequately comfortable talking about depression so that you can help her open up and get treatment?
- Does part of you want to focus on the “real” medical problems or concerned that you do not have time to talk about depression?
- What treatments will you recommend? Can you provide full medication consent?

My hope is that you will have more confidence, comfort, and competence to recognize & discuss depressive symptoms and know how to think about diagnosis, initiate management, or consider novel referral services.

_The goal is to build on your current skill set and not to make you mental health experts in 35 minutes._
Multiple Complex Mechanisms

- Depression has been positively associated with central obesity, chronic inflammation, and insulin resistance, which are underlying etiological mechanisms for MetS.
- Depression has known neuroendocrine effects (e.g., dysregulation of the hypothalamic-pituitary-adrenocortical axis and sympathetic nervous system activation), which could influence MetS risk by affecting abdominal fat accumulation, glucose metabolism, and blood pressure regulation.
- Third, depressed individuals tend to have poor diet and sleep disturbance and engage in less physical activity, and these behaviors are known risk factors for the development of MetS.
- Fourth, conventional medication treatment for depression may exert direct effects on various components of MetS and partially explain the observed association.
Depression Overview

**Common**
- The lifetime prevalence of MDD is 20.6%
- The 12-month prevalence of MDD is 10.4%
- Most common psychiatric disorder in primary care
- Under-recognized: 30-70% percent missed
- Inadequately "treated": Less than 50% receive adequate treatment

**Significant**
- Without adequate treatment often becomes chronic and recurrent
- Results in 2-3 fold increase in medical utilization
- Increased morbidity and mortality
- Leading cause of disability worldwide (World Health Organization 2016)

Almost 60% of People with Any Mental illness Do Not Receive Any Mental Health Services

**Why is Mental Health Untreated in Our Country?**

Answer:
- Shortage of Mental Health Providers
- Access
- Cost & Fragmented Reimbursement Structures
- Stigma Pervades
- The Culture of Medical Systems and Training
Diagnosis Can Be Difficult

**Only Through Clinical Examination**

- Astute evaluation
- Constellation of signs and symptoms
- Impact on functioning and/or high distress
- Enduring for Specified Period of Time

- *Highly Heterogeneous
- Many comorbidities

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MDD Diagnosing

At least **5 Symptoms** should be present for a period of **2+ weeks** and represent a change from previous functioning.

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Causes of Depressive Disorders

**Complex interactions of biologic, psychologic, social & wellness factors**

**Highly Heterogeneous Illness**

- **Biologic**
  - Genetics: Family History, Propensity, Epigenetics, female 2x
  - Medications: IFN, beta-blockers, steroids, amethyldopa, L-dopa, OCPs, opiates
  - Diseases: HIV, Lyme, Hypothyroidism, Porphyria, Uremia, Cushings Dz, Liver disease, Huntington’s, MS, Lupus, L-MCA stroke, hyperparathyroidism, cancer…
  - Substances: ETOH, cocaine/amphetamine withdrawal
- **Exposures:** Lead Toxicity
Causes of Depressive Disorders

Complex interactions of biologic, psychologic, social & wellness factors
Highly Heterogeneous Illness

- **Psychologic**
  - History of abuse/trauma (ACE score)
  - Early parent loss
  - Bullying
  - Trust, Safety, Security
  - Esteem
  - Attachment, Relatedness, Intimacy

- **Social / SDOH**
  - Poor Social Support
  - Economic hardship
  - Food insecurity
  - Housing insecurity
  - Acute Stress or Life Change
    - Job loss - in men
    - Relationship loss - in women
  - Care taking responsibilities
  - Marital status: Unmarried men and married women

- **Wellness**
  - Sleep
  - Nutrition
  - Exercise
  - Sunlight Exposure
  - Stress Management
  - Relationships
Step 1: Identify Depression

COMMON PRESENTATIONS:

- Multiple persistent physical symptoms with no clear cause
- Low energy, fatigue, sleep problems
- Persistent sadness or depressed mood, anxiety
- Loss of interest or pleasure in activities that are normally pleasurable

Patient Case:

Charles is a 58-year-old married man seen by his primary physician for scheduled care of diabetes. Diagnosed 4 years ago with type 2 diabetes, he is mildly obese (5 feet, 11 inches, 218 lb, body mass index 30.4 kg/m²) and hypertensive (blood pressure 165/92 mmHg), but otherwise has no evidence of coronary heart disease or other complications of diabetes. He uses insulin and has insufficient control of hyperglycemia (recent hemoglobin A₁c [A1C] concentrations range from 10 to 11.5%). He does not perform blood glucose testing.

- Six months ago, the patient started having difficulty falling and staying asleep. As a result, he felt tired and fatigued most of the time.
- When he presented to your office, he had gained 12 lbs in 3 months.
- When asked, he adamantly denied depression or feeling sad.
- Now what?
Option 1:
You have 20 minutes.
Evaluate the insomnia and treat with sleep hygiene and Trazodone 25-50mg PO QHS PRN.
Optimize plan for diabetes management.
Identify your concern for exacerbation and have a close follow-up in 1 week.
Note to self: Have PHQ-9 administered at the start of next visit (or in between visits) and discuss.

Option 2:
You have 20 minutes. You decide to evaluate further potential depression.
Reflect & Summarize:
You are having some difficulty with your diabetes management. You are having some difficulty with sleep. I hear you are not feeling depressed or sad.
Clarifying Questions?
Tell me what have you enjoyed the last 2 weeks? What do you usually enjoy? Have you noticed that lately it is more difficult to engage in the things you used to enjoy?

If patient reports decreased pleasure/interest/motivation, utilize PHQ-9 or another tool to further evaluate symptoms of Major Depressive Disorder.
Consider if Charles has at least 4 of the following additional symptoms for at least 2 weeks to meet the criteria for MDD??

- Disturbed sleep or sleeping too much
- Significant change in appetite or weight (decrease or increase)
- Beliefs of worthlessness or excessive guilt
- Fatigue or loss of energy
- Reduced concentration
- Indecisiveness
- Observable agitation or physical restlessness
- Talking or moving more slowly than usual
- Hopelessness
- Suicidal thoughts or acts

Charles shares the following:

Due to fatigue, he stopped exercising and then felt bad about the 12 lb weight gain. For the last 6 weeks, he gradually stopped socializing and eventually lost interest in most things, including sexual activity. He continued to work but has trouble concentrating, frequently forgets things, and feels impatient, irritable, and frustrated. For the past month, the constellation of symptoms has been persistent and interfering. No SI or psychosis.

Reflect and Summarize:

I hear your sleep is disturbed, you are fatigued, you don’t enjoy the things you used to, you are struggling with concentration at work, you don’t feel good about the weight gain, and your relationships have been strained. And this has been going on for several weeks. Did I hear that right?

R/O: anemia, hypothyroidism, substance abuse and medication side-effects
Step 2 is Psychoeducation: Educate & Engage The Patient

Because of all these symptoms, I am concerned that you have a depressive disorder. It is very common. Up to 1 in 4 patients with diabetes can have depression.

You don't always have to feel sad or depressed especially for men.

Depression is an illness that affects the brain and there are many treatment options.

It is imperative that we treat so it does not become chronic and because your diabetes will likely exacerbate if we do not.

Provide a handout on symptoms of Major Depressive Disorder and see if he agrees that he meets many of these criteria.

Ask if he has questions or concerns?


Pending Time:

Query past depressive episodes, family history, past safety concerns, past manic episode?

Step 3 Brief Determination of Severity

This patient is not severe or an emergency.

He is not suicidal or psychotic.

He has no past suicide attempts.

He does not have substance disorder.

He is married and still working.

You have a good rapport with him.

You trust he will come in for follow-up.
Step 4: Initial Management for MDD

1. Provide psychoeducation to the person and their primary supports.
2. Reduce stress and strengthen social supports.
3. Promote functioning in daily activities and community life.
4. A course of psychotherapy is just as effective as medication treatment in mild/moderate depression. Consider interpersonal therapy (IPT), cognitive behavioral therapy (CBT), and behavioral activation.
5. *Consider antidepressants.*

mhGAP Intervention Guide WHO 2016

Promoting Mental Health Treatment in Non-Specialized Health Settings

*Key Tips from WHO*

Psychosocial Interventions are Part of Every Depression Management Plan

Assess for and try to reduce acute stressors. (acute loss of finances, relationship, health, housing, food, trauma)

Reactivate the person’s previous social support.

*Promote daily functioning:
- Even if it is difficult, encourage the person to try to do as many of the following as possible:
  - Try to start an activity that was previously pleasurable.
  - Try to maintain regular sleeping and waking times.
  - Try to be as physically active as possible.
  - Try to eat regularly despite changes in appetite.
  - Try to spend time with trusted friends and family.
  - Try to participate in community and other social activities as much as possible.

*These are all part of behavioral activation to promote mood*
American Psychiatric Association (APA) Practice Guidelines: Importance of Patient Engagement

- Solicit patients understanding of their own depression
- Validate the difficulty & Importance of Treatment
- Educate about depression
- Discuss treatment options
  - Therapy, Wellness, Behavioral Activation, Medication
- Solicit preferences about treatment
- Discuss and set self-management goals
- Support empowerment
- Interrupt catastrophizing and distorted thinking


Initial Management for Charles' Depression

- Evaluate and treat known comorbidities
  - For CD, evaluate and treat for insomnia
  - CBT for insomnia, Sleep Hygiene, Trazodone 25-50mg PO QHS PRN
- Engage his wife, obtain ROI
- Assess for and try to reduce acute stressors
- Have him Commit to improving one aspect of daily functioning - Behavioral Activation, exercise if he is willing
- Offer referral to CBT or IPT - Psychology Today is an effective tool
- *Consider Medication
- Close Follow-Up (1 week, RN call in between visits)

RECOMMENDATIONS ON FREQUENCY OF CONTACT

» Schedule the second appointment within 1 week.

» Initially maintain regular contact via telephone, home visits, letters, or contact cards more frequently, e.g. monthly, for the first 3 months.
Step 5: Patient Alignment with Medication Treatment

- Combination Psychotherapy and Medications most efficacious for all MDD
- Strongly Recommend Medication in severe or recurrent MDD

Little evidence to support one medication vs. another in the population

Comparative Efficacy and Acceptability of 12 New-generation Antidepressants (LANCET’s meta-analysis)*

<table>
<thead>
<tr>
<th>Most Efficacious</th>
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<tbody>
<tr>
<td>Mirtazapine, Escitalopram, Sertraline</td>
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</table>

<table>
<thead>
<tr>
<th>Most Tolerated</th>
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<tbody>
<tr>
<td>Escitalopram, Sertraline</td>
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</table>

*small differences
*concomitant illnesses may not have been accounted for, not “real world”

Cipriani et al. LANCET 2009;373:746-58.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

- Largest prospective clinical trial of treatment of major depressive disorder
- NIH Funded
- 2,876 “real-world” patients with treatment-resistant depression
- Fewer exclusion criteria
- Followed a 4 step algorithm for treatment

STAR*D Study Results

- No specific medication had better results than another
- Time to achieve remission ~ 7 weeks
- Max effectiveness up to 12-14 weeks
  - Step 1: 33% achieved Remission
  - Step 2: 20% (cumulative remission 53%)
  - Step 3: 6-7% (cumulative remission 60%)
  - Step 4: 6-7% (cumulative remission 67%)

American Psychiatric Association (APA) Practice Guidelines:
Patient Centered Medication Choice

- Nature of prior response to medication
- Indications
- Co-occurring psychiatric or general medical conditions
- Safety
- Tolerability and anticipated side effects
- Potential drug interactions
- Half-life
- Cost

- Patient Preference Supports Placebo and Adherence
Treating Comorbidities: FDA Indications for Antidepressants

Table 1. FDA-Approved Indications for the Use of Antidepressants Medications in Adults

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Indication</th>
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<tbody>
<tr>
<td>Unipolar depression</td>
<td>(continued)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>(continued)</td>
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<tr>
<td>Generalized anxiety disorder</td>
<td>(continued)</td>
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<tr>
<td>Obsessive-compulsive disorder</td>
<td>(continued)</td>
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<tr>
<td>Bulimia nervosa</td>
<td>(continued)</td>
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<tr>
<td>Premenstrual dysphoric disorder</td>
<td>(continued)</td>
</tr>
<tr>
<td>Seasonal affective disorder</td>
<td>(continued)</td>
</tr>
<tr>
<td>Smoking Cessation</td>
<td>(continued)</td>
</tr>
<tr>
<td>Post Traumatic Stress Disorder</td>
<td>(continued)</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>(continued)</td>
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</tbody>
</table>

STAR-D, the largest NIH study on Major Depressive Disorder (MDD) Treatment, along with American Psychiatric Association Practice Guidelines teach us to choose an initial medication for a patient with MDD based on the following: (Choose all that are correct.)

A: The antidepressant that is proven to be most effective and efficacious
B: Side Effect Profile
C: Comorbidities
D: Cost
E: Patient Preference

B, C, D, & E are correct

Medication Consent:

Discuss with the person and decide together whether to prescribe antidepressants. Explain that:

- Antidepressants are not addictive.
- It is very important to take the medication every day as prescribed.
- Some side effects may be experienced within the first few days but they usually resolve.
- It usually takes several weeks before improvements in mood, interest, or energy is noticed.
- Antidepressant medications usually need to be continued for at least 9-12 months after the resolution of symptoms.
- Medications should never be stopped just because the person experiences some improvement.

mhGAP Intervention Guide WHO 2016
SSRI Side Effects

Acute
- Drowsiness 17%
- Insomnia 11%
- Dizziness 11%
- Headache 10%
- Dry Mouth 7%
- GI Distress/Nausea 6%
- Activation/Anxiety 11% (go slow)
- Often Transient

Delayed Onset
- Sexual dysfunction 17% - 30%
- Weight gain 12%
- Cognitive or Affective blunting
- SIADH (rare)

Acute Side Effects Decrease Over Time

<table>
<thead>
<tr>
<th>% of Patients</th>
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<tbody>
<tr>
<td>Weeks</td>
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</table>


SSRI’s Effects on Weight

<table>
<thead>
<tr>
<th>Percent with &gt;7% Weight Gain</th>
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APA: Items to Monitor Throughout Treatment

- Symptomatic Status
- Functional Status
- Risk/Safety Assessments
- Signs of switch to mania
- Side effects
- When patient is taking medicine
- Adherence
- Patient acceptability
- Other mental disorders, including alcohol and drug disorders, anxiety

Refine and Understand Your Goals of Treatment and Follow-Up

Three Phases of Treatment

- Acute Phase 3 months
- Continuation 4-9 months
- Maintenance years

*Response
> 50% STOP Rx

65 to 70%
STOP Rx

Remission

Recurrence


Oxman, 2001 TX
• Almost 30 Million people receive a prescription for an antidepressant in a given year
• 20-30% drop out of treatment too early
• 25-50% stay on ineffective treatments for too long

Goals of Therapy
► Complete remission (100% reduction of symptoms)
► Maintaining level of improvement (no relapse or recurrence)

► Maintain all individuals on Medication 6-9 months after initial response
► Maintenance Dose should be at full Dose
► Make a Relapse Prevention Plan before slowly discontinuing
► Treat those at high risk for recurrence for 2 years or longer
Non-adherence of antidepressant medications has been documented as high as 60% to 70% in some studies and contributes to the pervasive undertreatment of mental Major Depressive Disorder (MDD). Adherence to medications is supported by the following steps: (Choose all that are correct.)

A: Choosing the most effective medication on the market
B: Doctor-Patient Alignment
C: Managing Stigma
D: Educating patients that antidepressants are not addictive & reviewing common side effects
E: Setting expectation on treatment course including dose, adequate trial, and maintenance treatment with goal of remission

B, C, D & E are all correct

References: Importance & Management of Antidepressant Medication Adherence

Options when patients fail to respond to an initial antidepressant trial

- Reconsider Diagnosis & Comorbidities (Trauma, Anxiety, Substance abuse)
- Optimize Current Medication: Push dose
- Augment antidepressant
- Switch to a different antidepressant
- Combine 2 or more antidepressants
- Consult or Refer

Optimizing Antidepressant Dosage

- If Tolerating

Pushing up specific antidepressants:
- Fluoxetine: 60-80 mg/d
- Paroxetine: 60-80 mg/d
- Escitalopram: 30-40 mg/d
- Sertraline: 250 mg/d
- Venlafaxine: 300 mg 450 mg/d
- Duloxetine: 120 mg/d
- Mirtazapine: 60 mg/d

Don’t push:
- Tetracyclines: risk of toxicity, cardiac arrhythmias
- Citalopram: 40 mg/d. The FDA has issued a warning to not exceed 40 mg/d in adults < 60, and not to exceed 20 mg/d in adults > 60, due to risk of QT prolongation
- Bupropion: increased risk of seizures at doses > 450 mg of IR and XL or 400 mg SR

Partial Response (Optimize/Augment)

Vs.

No Response (Switch)
Exercise for MDD

- Inflammatory cytokines are elevated in depressed patients
  - Interleukin-6 (IL-6)
  - Tumor necrosis factor α (TNF-α)
- ATD-Treatment (SSRIs) decreases some inflammatory cytokines
  - IL-1β, IL-6, TNF-α
- Elevated baseline TNF-α and IL-6 correlated with treatment failure with SSRIs

Rationale/Mechanism of Action

- 4 potential mechanisms
  - B-endorphins linked to neurogenesis, and during exercise
  - Vascular endothelial growth factor (VEGF) increases during exercise & linked to hippocampal neurogenesis in rats.
  - BDNF during exercise
  - Exercise’s tryptophan hydroxylase, needed for 5HT synthesis
- Level I, Grade A evidence, large effect size (0.8)
Recommendations for Prescription of Exercise for MDD

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Modality</td>
<td>Aerobic &gt; resistance training</td>
</tr>
<tr>
<td>Session frequency</td>
<td>3-5 exercise sessions/week</td>
</tr>
<tr>
<td>Session duration</td>
<td>45-60 minutes</td>
</tr>
<tr>
<td>Exercise intensity</td>
<td>50-85% max HR (aerobic) or 80% 1-RM (resistance)</td>
</tr>
<tr>
<td>Intervention duration</td>
<td>At least 10 weeks</td>
</tr>
</tbody>
</table>

Consider a Team Approach: Innovative Psychiatric Consults & Referrals

"2/3 of primary care providers report they are unable to get their mental health patients into outpatient mental health services"

Peter Cunningham (2009)

If they are not coming to us, tele-psychiatry helps us come to them.

"If the patient is not coming to us, tele-psychiatry helps us come to them."

How do we virtually embed psychiatric providers into a primary care clinic?

University of Colorado School of Medicine
AF Williams
Large Family Medicine Clinic
NCQA PCMH
Residency Training (18)
Behavioral Health & IH Team

Primary Care Physicians (40 PT)
Residency Training (18)
Behavioral Health & IH Team

19,000 patients
30,000+ visits per year

University of Colorado School of Medicine

Depression Center
Large Mental Health Outpatient Clinic
NNDC

6 Part Time Psychiatrists
2 Psychiatric NP
4 PhD Psychologists
2 LCSW
Program Design: Stepped Model of Available Services

Technology: Cloud-based virtual telemedicine platform, real-time, video-based (Vidyo/Zoom platforms)

1) E-consults: Staff message through EPIC EHR for brief questions/chart review
2) Provider-to-Provider Consultations: Scheduled or brief curbsides with PCP and/or BH
3) Co-Consultations: Provide Consultations with PCP, Patient, and sometimes BH to develop a plan together
4) Psychiatric Evaluation: Initiate plan, document recommendations for continued management
5) Interdisciplinary Team Meetings: Discuss patients with high medical complexity
6) Didactic Education

Take Away Points

- Shared Patients: Bilateral Relationship Between Depression & Metabolic Syndrome
- Common, Leading Cause of Disability
- Correlated with High Medical Complexity, Comorbidity, and Mortality
- Correlated with Excess Costs and ED Utilization
- Potential to become Chronic illness
- Asking patients about depression is the first step toward treatment and it takes all health professionals to meet this challenge
- Physicians who ask about depression help reduce stigma and encourage treatment (not just PHQ)
- Many Medication Options, SSRI is First Line, No one medication has proven superior effectiveness
- Keep Patient Centered, Encourage Adherence to Adequate Medication Trial, Remission is Goal
- Psychotherapy with Medications Improves Outcomes
- Wellness & Exercise
- Consider Novel Team Approaches
Case: We received a consult concerning a 59-yo male with a previous history of major depressive disorder (MDD) who achieved remission on Venlafaxine 225 mg PO QM many years ago but who recently re-presented with return of “depression”. Because he had been tried on several antidepressants in the past with either significant adverse effects or lack of efficacy, we were asked for additional medication options.

Evaluation: Upon further questioning during our telepsych patient evaluation, we learned that the patient’s father had passed away a few months ago, the patient was feeling resentment and guilt due to their fractured relationship, and that he recently increased his alcohol use to 3-4 drinks every day to manage these difficult feelings. While this patient had clear risk for a recurrent MDD episode, and it is obviously important to consider medications, the ultimate focus of his treatment was on grief counseling, psychotherapy, and cessation of alcohol use.