

Depression in Primary Care

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Disclosures

- None

Objectives

- Define the prevalence and impact of depression on patients in primary care
- Review screening, monitoring, and treatment guidelines
- Review CPC + requirements
- Review common medications used in treatment
- Review gene testing to assist medication selection



CASE PRESENTATION

DSM 5 Criteria Major Depression

- Depressed mood and/or loss of interest or pleasure AND
 - Significant weight loss/gain
 - Insomnia/hypersomnia
 - Psychomotor agitation/retardation
 - Fatigue/loss of energy
 - Feelings of worthlessness, excessive guilt
 - Diminished concentration or ability to think
 - Recurrent thoughts of death or suicidal ideation

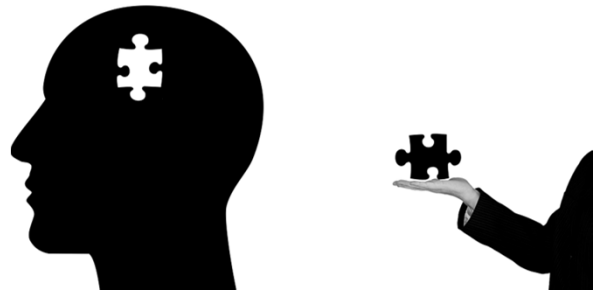
“There is no point treating a depressed person as though she were just feeling sad, saying, ‘There now, hang on, you’ll get over it.’ Sadness is more or less like a head cold—with patience, it passes. Depression is like cancer.”

--Barbara Kingsolver, The Bean Trees

Practice Guidelines

- US Preventive Services Task Force
- American College of Physicians
Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder: A Clinical Practice Guideline From the American College of Physicians

Link to Mood Disorders in Chronic Illness



IMPACT AND PREVALENCE

Impact of Depression

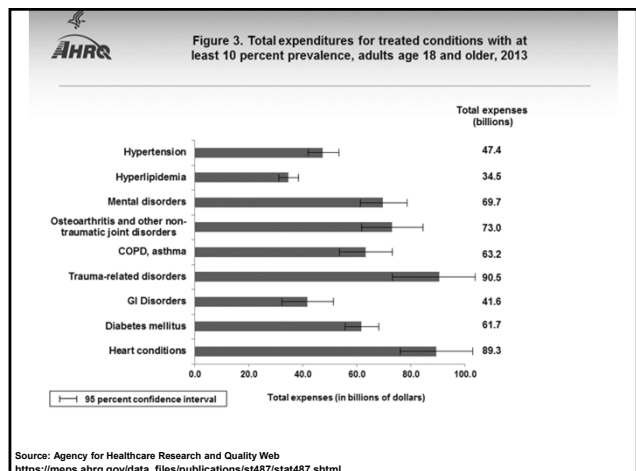
What percent of the US population suffers from depression?

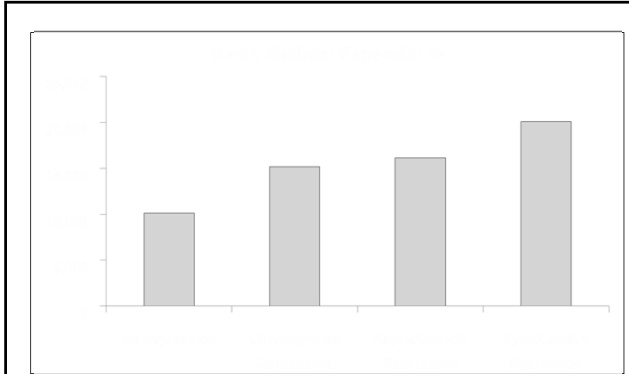
“The statistics on sanity are that one out of every four people is suffering from a mental illness. Look at you 3 best friends. If they’re ok then it’s you.”

- Rita Mae Brown

Impact of Depression

- Up to 8% of US residents suffer from depression resulting in 8 million visits per year
 - 4 million of these visits to primary care
- Cost of depression yearly \$83 billion including \$26 billion in health care costs and rest related to losses such as work absenteeism
- Comorbid depression increases risk of death from heart disease, respiratory disorders and stroke





Egede LE, Walker RJ, Bishu K, Dismuke CE. Trends in Cost of Depression in Adults with Diabetes in the United States: Medical Expenditure Panel Survey, 2004-2011. JGIM June 2016; 615-622.

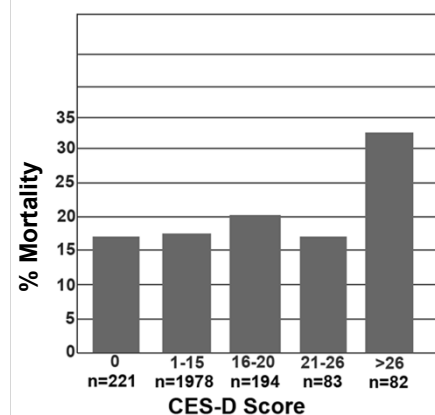
Morbidity and Mortality

- Increased functional impairment, decreased work productivity
- Decreases quality of life more than COPD, cancer, hypertension
- Barrier to positive productive relationships with providers and patients
 - PCP tend to rate depressed patients more difficult to treat
 - Depressed patients less satisfied with their pcp

Morbidity and Mortality

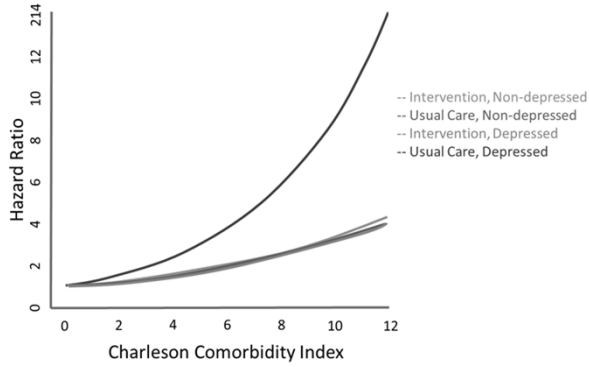
- Significant association with *hyperglycemia*
- Significant association with *complications of diabetes* (retinopathy, nephropathy, neuropathy, macrovascular complications) and *severity of those complications*
- Modest association with *all cause mortality*
 - Stronger association with *mortality resulting from cardiovascular disease*

Lustman PJ, Anderson RJ. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000; 23:434-42



Unutzer, Am Journal of Geriatric Psychiatry 10:5; Sept-Oct 2002

Adjusted relative hazard of all-cause mortality.



Gallo JJ, Gen Internal Med 2016 Apr;31(4):380-6.

Comprehensive Primary Care Plus

- Encourages practices to integrate behavioral health into practice or have priority access for its patients
- Co management—share records, treatment plans
- System capability
 - Standard screening tool, preferably integrated into EHR
 - Registries to track care of patients with behavioral health conditions
 - Monitor and assess treatment response, behavioral health outcomes
 - Share records between behavioral health and primary care

SCREENING

Screening Guidelines

- USPSTF (1/26/16, JAMA)
 - The USPSTF concludes with at least moderate certainty that there is a moderate net benefit to screening for depression in adults, including older adults, who receive care in clinical practices that have adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up after screening (grade B)

Siu AL, and USPSTF. Screening for Depression in Adults: US Preventive Services Task Force Recommendation. JAMA 2016; 315(4):38087. doi:10.1001/jama.2015.18392

Tools

- Tools
 - PHQ 9
 - Hospital Anxiety and Depression Scales
 - Geriatric Depression Scale
- Postpartum
 - Use Edinburgh Postnatal Depression Scale (EPDS)
- Bipolar
 - Use Mood Disorder Questionnaire (MDQ)

Symptoms in Primary Care

- >5/year medical visits
- Multiple unexplained symptoms
- Work/relationship dysfunction
- Dampened affect
- Poor behavioral follow through with treatment recommendations
- Weight gain or loss
- Sleep disturbance
- Fatigue
- Memory/cognitive complaints
- IBS
- “stress”
- **POORLY CONTROLLED CHRONIC ILLNESS**

Special Population

- Adolescents
 - Poor school performance
 - Poor attendance
 - Somatic complaints (fatigue, headaches, abdominal pain)
- LGBTQ
 - Particularly high rates of depression
 - High rate of suicide
 - leading cause of death

Selected Medications Associated with Depressive Symptoms

- Clonidine
- Contraceptives (progesterone)
- Beta blockers
- Interferons
- Isotretinoin
- Reserpine
- Corticosteroids
- Benzodiazepines, sedative hypnotics
- Barbituates
- Varenicline
- Topiramate
- Levetiracetam
- Tamoxifen

Patten SB, et al. J Psychiatry Neurosci 1993; 18(3): 92-102
Rogers D, et al. Psychiatry 2008; 5(12): 28-41.
VA/DOD Guidelines 2016

MONITORING

Monitoring Guidelines

- **Proactive Followup Contact**
 - First followup within 30 days
 - Several visits in first 6 months of therapy
- **Monitor and management tool (PHQ 9)**
 - Full Remission is PHQ 9 <5
 - Response is defined as 50% reduction in symptoms
- **Collaboration with mental health**

Depression in Primary Care

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TREATMENT

Acute Phase Treatment Modalities				
Modality				
Severity of illness	Pharmacotherapy	Depression-Focused Psychotherapy	Pharmacotherapy in Combination With Depression-Focused Psychotherapy	Electroconvulsive Therapy
Mild to Moderate	Yes	Yes	May be useful for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring Axis II disorder	Yes, for certain patients
Severe Without Psychotic Features	Yes	No	Yes	Yes
Severe With Psychotic Features	Yes, provide both antidepressant and antipsychotic medication	No	Yes, provide both antidepressant and antipsychotic medication	Yes
Recommended Modalities for Acute Phase Treatment of Major Depressive Disorder				
Source: APA Major Depressive Guidelines 2010 http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd-guide.pdf				

Psychotherapy and Alternative Treatment

- ## Psychotherapy
- Cognitive behavioral therapy
 - Interpersonal psychotherapy
 - Psychodynamic therapy
 - Problem-solving therapy
 - Other types
 - Little data on optimal duration and frequency
 - Most clinical trials consisted of 12-16 weekly sessions
 - Integrative medicine

- ## Other treatment modalities
- Physical Activity
 - Integrative medicine (insufficient evidence to recommend)
 - Acupuncture while pregnant
 - Yoga
 - St Johns Wort, SAM-E (insufficient evidence, medication interactions)
 - Saffron (ongoing research)
 - Link between depression and deficiencies (magnesium, zinc, omega 3 fatty acids)
 - Cannabis (insufficient evidence)
 - Light therapy 10,000 lux for 30 minutes each am

Pharmacotherapy for Depression

Antidepressants in 2010 APA Guidelines

- Selective serotonin reuptake inhibitors (SSRI)
- Selective norepinephrine reuptake inhibitors (SNRI)
- Tricyclic antidepressants (TCA)
- Bupropion
- Mirtazapine
- Trazodone/Nefazodone
- Monoamine oxidase inhibitors (MAO-I)

Antidepressants in 2010 APA Guidelines

- | | |
|----------------|------------------|
| • SSRI | • SNRI |
| • Citalopram | • Duloxetine |
| • Escitalopram | • Desvenlafaxine |
| • Fluoxetine | • Venlafaxine |
| • Fluvoxamine | |
| • Paroxetine | |
| • Sertraline | |

Antidepressants in 2010 APA Guidelines

- | | |
|-----------------|-------------------------|
| • TCA | • Other Antidepressants |
| • Amitriptyline | • Bupropion |
| • Clomipramine | • Mirtazapine |
| • Desimpramine | • Nefazodone |
| • Doxepin | • Trazodone |
| • Imipramine | • MAO-I |
| • Nortriptyline | • Isocarboxazid |
| | • Phenelzine |
| | • Selegiline |
| | • Tranylcypromine |
| | • Moclobemide |

Antidepressant Adverse Effects						
	SSRI	SNRI	TCA	MAO-I	Bupropion	Mirtazapine
Gastrointestinal	X	X			X	
Activation/Insomnia	X	X		X	X	
Sexual dysfunction	X	X	X	X		
Weight Gain	Paroxetine		X			X
Increased HR and BP		X		With tyramine	X	
Headache	X	X		X	X	
Seizures			In overdose		X	
Anticholinergic			X			X
Cardiovascular ADE/Prolonged QTc			X			
Sedation			X			X
Orthostatic hypotension			X	X		
Hyperlipidemia						X
Bleeding	X					
BBW for suicidal ideation	X	X	X	X	X	X

APA Major Depressive Guidelines 2010

New Antidepressants

Vilazodone (Viibryd®)

- **Combined SSRI and 5-HT_{1A} partial agonist**
 - ✓ Serotonin partial agonist-reuptake inhibitor (SPARI)
- **Dosing: 20-40 mg once daily with food**
- **Adverse Effects**
 - ✓ Most common ADE: diarrhea, nausea, headache
 - ✓ No impact on QTc interval, LFTs, or BP
- **Contraindications/Precautions**
 - ✓ Use with monoamine oxidase inhibitor
 - ✓ Seizure disorder?

McCormack PL. Drugs. 2015; 75: 1915-23.

Vilazodone (Viibryd®)

- **Four phase 3/4 placebo-controlled RCTs**
 - 8-10 weeks in duration
 - Significant improvement in MADRS score
 - As soon as 1 week in 1 trial
- **One open-label, non-comparative 52 week study**

Rickels K, et al. J Clin Psychiatry. 2009; 70(3): 326-33.
 Khan A, et al. J Clin Psychiatry. 2011; 72 (4): 441-7.
 Croft HA, et al. J Clin Psychiatry. 2014; 75(11): e1291-8.
 Mathews M, et al. Int Clin Psychopharmacol. 2015; 30(2): 67-74.
 Robinson DS, et al. J Clin Psychopharmacol. 2011; 31(5): 643-6.

Vilazodone's Potential Benefits

- Potential benefits of 5-HT_{1A} activation
 - Greater efficacy than traditional antidepressants
 - Not proven in clinical trials
 - More rapid onset of action
 - Not proven in clinical trials
 - May be limited due to necessary dose titration
 - Mitigation of sexual ADE
 - Sexual dysfunction high at baseline in trials
 - Sexual function improved with vilazodone and placebo
 - Unclear how vilazodone compares to other antidepressants

Robinson DS, et al. J Clin Psychopharmacol. 2011; 31(5): 643-6
McCormack PL. Drugs. 2015; 75: 1915-23.
Mathews M, et al. Int Clin Psychopharmacol. 2015; 30(2): 67-74.

Vortioxetine (Trintellix™)

- SSRI/multimodal serotonin modulator
 - 5-HT_{1A}, 5-HT_{1B}, 5-HT₃, 5-HT₇, SERT
- Dosing 10 – 20 mg once daily
- Long half-life
 - Low risk for discontinuation symptoms – taper still recommended
- Adverse Effects
 - Nausea, vomiting, constipation
 - No significant change in vitals, weight, QTc, or labs
- Contraindications/Precautions
 - Use with monoamine oxidase inhibitor

Connolly KR, et al. Expert Opin on Pharmacol. 2016; 17(3): 421-31.

Vortioxetine (Trintellix™)

- 6 of these RCTs conducted in US, 6-8 weeks duration
 - 3 had significant reduction in MADRS/other score
 - 3 had no significant reduction in MADRS/other score
- One 24-week continuation RCT
 - Vortioxetine dose of 5-10 mg/day
 - Lower relapse rate at 24 weeks vs. placebo
- Three open-label 52 week extension trials

Connolly KR, et al. Expert Opin on Pharmacol. 2016; 17(3): 421-31.
Katona C, et al. Int Clin Psychopharmacol. 2012;27(4):215-23.
Jain R, et al. J Neuropsychopharmacol. 2013;16(2):313-21.
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Jacobsen PL, et al. J Clin Psychiatry. 2015;76(5):575-82.
Mahableshwarkar AR, et al. Psychopharmacology. 2015;232(12):2061-70.
Mahableshwarkar AR, et al. J Clin Psychiatry. 2015; 76(6):583-91.

Vortioxetine (Trintellix™)

- Potential benefits
 - Sexual dysfunction
 - RCT: impact of vortioxetine vs. escitalopram on rate of sexual dysfunction
 - Cognition

Connolly KR, et al. Expert Opin on Pharmacol. 2016; 17(3): 421-31.
Pearce EF, et al. Ann Pharmacother. 2014; 48(6): 758-65.
Jacobson PL, et al. J Sex Med. 2015; 12: 2036-48.

Levomilnacipran SR (Fetzima®)

- Serotonin norepinephrine reuptake inhibitor
- More potent inhibition of NE vs. 5-HT
- Dosing: 40 – 120 mg daily

Bruno A, et al. Current Neuropharm 2016; 14: 191-99.
Asnis GM, et al. Neuropsych Dis Treat 2015; 11:115-25.
Palmer EC, et al. Ann Pharmacother 2014; 48(8): 1030-39.

Levomilnacipran SR (Fetzima®)

- Adverse effects
 - Nausea, vomiting, constipation
 - Sexual dysfunction (dose-related)
 - Cardiovascular effects
 - Mean +3.9 mmHg SBP, 3.1 mmHg DBP
 - Mean +7 bpm HR
 - LFT elevations
- Contraindications/Precautions
 - Use with monoamine oxidase inhibitor
 - Seizures?
 - Chronic liver disease

Bruno A, et al. Current Neuropharm 2016; 14: 191-99.
Asnis GM, et al. Neuropsych Dis Treat 2015; 11:115-25.
Palmer EC, et al. Ann Pharmacother 2014; 48(8): 1030-39.

Levomilnacipran SR (Fetzima®)

- Five RCTs, 8-10 weeks duration
 - Four trials – decrease in MADRS score vs. placebo
 - One trial – no statistically significant decrease in MADRS score
- One open-label trial, 48-week duration
 - Lower MADRS score at week 48 vs. week 0
 - No placebo comparison
- One continuation RCT, 24 week duration
 - Lower relapse rates vs. placebo (not statistically significant)

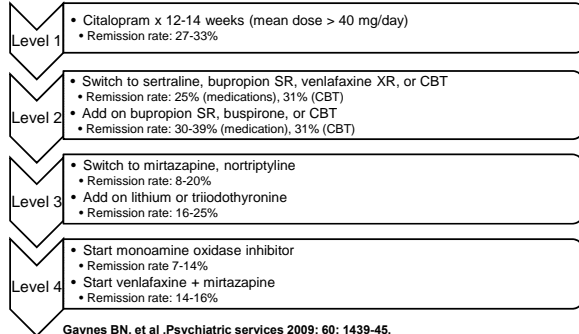
Bruno A, et al. Current Neuropharm 2016; 14: 191-99.
Asnis GM, et al. Neuropsych Dis Treat 2015; 11:115-25.
Palmer EC, et al. Ann Pharmacother 2014; 48(8): 1030-39.

Choosing Pharmacotherapy

- Response in prior major depressive episodes
- Family history of response
- Anticipated side effects/comorbidities
 - Safety and tolerability
- Pharmacological properties
 - Half-life
 - Drug interactions
 - Disease state interactions
- Cost
- Patient preference
- Pharmacogenomics

APA Major Depressive Guidelines 2010

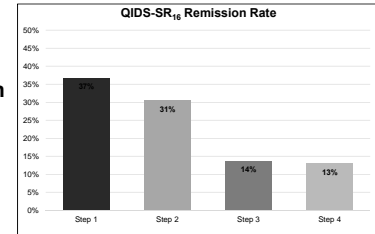
STAR*D Trial



Gaynes BN, et al. *Psychiatric services* 2009; 60: 1439-45.
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 Rush AJ, et al. *N Engl J Med* 2006; 352(12): 1231-42.
 Trivedi, et al. *N Engl J Med* 2006; 354(12): 1243-52.
 Fava M, et al. *Am J Psychiatry* 2006; 163(7): 1161-72.
 McGrath PJ, et al. *Am J Psychiatry* 2006; 163(9): 1531-41.

STAR*D Take Home Points

- Rate of remission after 2 medication trials decreases substantially
- Cumulative remission rate after 4 levels of treatment ~ 67%
- No clear 2nd line treatment choice
- Augmentation and switching therapy appropriate



Rush AJ, et al. *Am J Psychiatry* 2006; 163: 1905-17.
 Gaynes BN, et al. *Psychiatric services* 2009; 60: 1439-45

Partial or Nonresponse to Pharmacotherapy

- ENSURE ADEQUATE TREATMENT DURATION
 - 4-8 weeks duration
- Confirm correct diagnosis
- Determine presence of clinical barriers
 - Medical conditions, drug interactions, substance abuse
- Confirm adherence to medication
 - Including treatment emergent side effects

APA Major Depressive Guidelines 2010

Partial or Nonresponse to Pharmacotherapy

- Change to different antidepressant
- Increase dose of antidepressant
- Augment with psychotherapy
- Augment with antidepressant
 - SSRI/SNRI + bupropion
 - SSRI/SNRI + mirtazapine
- Augment with non-antidepressant medication

APA Major Depressive Guidelines 2010

Pharmacogenomics and Antidepressant Use

- CYP2D6 involved in metabolism of 25% of medications
- CYP2C19 also involved in metabolism of some antidepressants
- Functional variations in gene coding
 - Poor metabolizer
 - Intermediate metabolizer
 - Extensive metabolizer (60-85% of Caucasians)
 - Ultra-rapid metabolizer
- Limited data on impact of genetic testing on patient outcomes and cost of care
- Some third party payers are covering cost of testing
- Combinatorial pharmacogenomics decision support available

Perlis RH. Clin Chem. 2014; 60(1): 53-9.

Duration of Pharmacotherapy

- Continuation phase: 4-9 months
- Maintenance phase: > 1 year
 - ≥ 3 major depressive episodes
 - Residual symptoms
 - Ongoing psychosocial stressors
 - Early age at onset
 - Family history of mood disorders
- Other considerations
 - Patient preference
 - Presence of side effects
 - Probability of recurrence
 - Frequency and severity of prior episodes
 - Suicide/psychosis

APA Major Depressive Guidelines 2010

Summary

- Antidepressant therapy is a recommended first line treatment in depression
- Antidepressants typically considered equally effective
- In partial/non-response situations switching to another agent or augmenting treatment is recommended
- Pharmacogenetic testing available to guide drug therapy decisions
- Antidepressant discontinuation is based on risk for relapse; medications should typically be tapered

Depression in Primary Care

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Potential Changes in Practice

- Screen for depression in chronic illness
- Measure severity with standardized tool
- Followup frequently and escalate therapy if not working (use standardized tool to measure)
- Integration of Behavioral health providers into the primary care office (CPC+)
- Cognitive Behavioral Therapy

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