Treatment of Depression in Primary Care

Family Medicine Review Course May 2010

Bill Elder, PhD Professor of Family Medicine University of Kentucky

Burden

2nd most common chronic condition

Leading cause of disability (and premature death) among people aged 18-44 worldwide

Financial burden:

\$83.1 billion dollars in 2000

Health service costs 50-100% greater

secondary to higher overall medical utilization



Primary Care Treatment

- PCPs provide majority of care
 - 65-70% who enter treatment
 - Prescribe 80% of antidepressants
- Diagnose < 50% (controversial)
- Effectively treat < 25%

Objectives

Increase treatment effectiveness for depression

- a. Discuss efficient screening patients for depression.
- b. Discuss the efficacy of specific treatment options.
- c. Identify effective management strategies.

Epidemiology

- Lifelong prevalence = 16.2%
- F>M 2:1
 - Point prevalence 8-10% in women, 3-5% in men
- · Peak onset in fourth decade of life
- Incidence and prevalence double in people aged 70-85
- · An episode usually resolves within a year but...
 - $-\;$ 10-30% of pts have residual sx
 - 20% of cases are persistent
 - Recurrence rates up to 90%

Epidemiology

Probably inherit predisposition to depression

- 76% chance of developing depression if identical twin has depression (67% chance if raised apart)
- 19% chance if twin is fraternal
- 1.5-3 times more likely to develop depression if found in first-degree relative
- 2-10 times more likely to develop depression if firstdegree relative has bipolar disorder

AHRQ

Practice Guideline

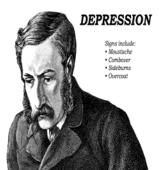
The U.S. Preventive Services Task Force (USPSTF) recommends screening adults for depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and follow-up

http://www.guideline.gov/summary/summary.aspx?doc_id=2605

USPSTF, Level of evidence: B. 2002. *Annals Intern Med.* 136(10): 760-764

Problem

• How to do the assessment efficiently?



Depression Screening

- Simple, inexpensive, and accurate screens works best.
- Most widely used and best-validated instruments in the primary care setting are the PHQ-2 and PHQ-9
- PHQ-2: 83-87% sensitivity, 78-92% specificity
- PHQ-9: 81% sensitivity, 92% specificity for major depressive d/o in primary care

Ebell MH. Screening instruments for depression. Am Fam Physician. 2008 Jul 15;78(2):244-6.

PHQ-2

- During the past month:
 - Have you often been bothered by feeling down, depressed, or hopeless?
 - Have you often been bothered by little interest or pleasure in doing thing?
- An affirmative answer to either question is a positive result
- A negative answer to both questions is a negative result.

PHQ=Patient Health Questionnaire, Copyright Pfizer Inc.

Most Efficient Strategy

- Best brief screening during a routine visit or annual physical: PHQ-2.
- In patients with a positive screen, have complete use the PHQ-9
 - to confirm diagnosis
 - to assess severity
 - to monitor response to therapy.

Ebell MH. Screening instruments for depression. Am Fam Physician. 2008. Jul 15:78(2):244-6.

Scoring a PHQ-9

SCORE	DEPRESSION SEVERITY
0-4	None
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

A score of ≥ 10 is an indication for initiation of therapy.

Diff Dx of Primary Mood Disorders

Depression Treatment

- Mild to moderate major depression: psychotherapy OR pharmacotherapy - equal efficacy
- Severe depression: pharmacotherapy
- Chronic or recurrent depression: psychotherapy AND pharmacotherapy

Source: Up To Date http://www.uptodate.com/online/content/topic.do?topicKey=psychiat/6836

Evidence: Grade 1A – Benefits clearly outweigh the risks based on RCTs

Psychotherapy

- Effective and has high patient satisfaction¹
- Meta Analysis²
- Primary care of adults
- 15 studies met inclusion criteria
- NNT 5.75
- Results significantly better if referred by physician rather than identified by systematic screening.

 - 1. Several Cochrane reviews 2. Cuijpers P. et al. Brit. J of General Practice, 2009. 59, (559).

Psychotherapy and Psychosocial Interventions

- Interpersonal psychotherapy
 - · Dysfunctional relationships
- Cognitive-behavioral therapy (CBT)
 - · Irrational thinking
- Mindfulness-based psychotherapies
 - · Ruminations
- Self help strategies
 - Feeling Good by David Burns, MD (also When Panic Attacks)



Pharmacotherapy

- The use of antidepressants has DOUBLED in the US between 1995 and 2002
- The number of medication choices has also grown
- Antidepressants improve depression sx in adults compared to placebo [A]



Selective Serotonin Reuptake Inhibitors (SSRIs)

- Most popular class of medications to treat depression since fluoxetine was introduced in 1986
- Mech: inhibit presynaptic serotonin reuptake



Side Effects of SSRIs

- Agitation, insomnia, GI upset (nausea, diarrhea, 3.6-fold risk of GI bleed), sexual dysfunction, weight gain
- P450: multiple potential drug interactions
 - Benzos, antipsychotics, antiarrhythmics, phenytoin
 - Interactions most likely for fluoxetine, paroxetine, and fluoxamine

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

- Mech: inhibit serotonin and norepineprine reuptake, also dopamine at high doses
- Venlafaxine (Effexor)
- First and most commonly used SNRI
- Duloxetine (Cymbalta)
 - Also indicated for neuropathic pain
- SE: dizziness, nausea/vomiting, high DBP, drowsiness, headache, changes in appetite, vivid dreams, sexual dysfunction
- · Interactions: TCAs, ciprofloxacin

Buproprion (Wellbutrin)

- Mech: inhibition of presynaptic uptake of dopamine and norepinephrine
- Lowers sz threshold (dose-dependent)
- Rare sexual SE, wt loss, helps with smoking
- SE: insomnia, headache

Second-Generation Antidepressants

- Mech: Block of 5-HT2A and 5-HT2C serotonin receptors
- Trazodone (brand was Desyrel)
- Mirtazapine (Remeron)
 - Faster onset than SSRIs, less sleep disturbance, more weight gain
- Nefazodone (brand was Serzone)
 - Rare SE: fulminant liver failure, check LFTs q6mo

Tricyclic Antidepressant (TCAs)

- Mech: exert effect on serotonin, norepinephrine, and/or dopamine neurotransmitter receptors
- SE: wt gain, sedation, constipation, dry mouth, orthostasis, tachycardia
 - Higher risk of CV events with ischemic heart dz
 - Highly lethal in overdose
- · P450 metabolism

Monoamine Oxidase Inhibitors (MAOIs)

- · Restricted to non-responders
- · Potent antidepressants
- Significant dietary restrictions (tyramine +++; tryptophan++)
- Potential for fatal drug-drug interactions
- · Selegiline (Emsam)-patch



http://www.dr-bob.org/tips/maoi.html#avoid

St John's Wort

Hypericum perforatum

- RCTs of pts with mild-mod depression:
 - Conflicting results
 - Very small benefits over placebo, if any
 - High variability of bioactive components
- Considerable potential for drug interactions (cytochrome P450)





Where Do You Start?

- Fluoxetine (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS))
- Paroxetine (Paxil, Seroxat, Sereupin, Aropax, Deroxat, Rexetin, Xetanor, Paroxat)
- Sertraline (Zoloft, Lustral, Serlain)
- Citalopram (Celexa, Cipramil, Dalsan, Recital, Emocal, Sepram, Seropram)
- Escitalopram (Lexapro, Cipralex, Esertia)
- Fluvoxamine (Luvox, Fevarin, Faverin, Dumyrox, Favoxil, Movox)
- Zimelidine (Zelmid, Normud)
- Dapoxetine (no trade name yet; not yet approved by the FDA)

http://en.wikipedia.org/wiki/Selective_serotonin_reuptake_inhibitor

Pharmacological Management

- Little variation in antidepressant efficacy [A]
 Newer medications: fewer side effects
 - Tricyclics NNT 4; NNHarm 5-11
 - SSRIs NNT 6; NNHarm 21-94
- Pick initial medication(s) based on:
 - Previous medication history
 - Safety including anticipated SE
 - Cost: formulary guidelines, insurance status, \$\$

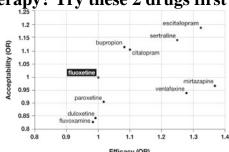
Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression. Am Fam Physician. 2008 Mar 15;77(6):785-92.

But

- Meta-analysis of 117 randomized controlled trials involving 25,928 participants with major depression.¹
- Compared 12 second-generation antidepressants
- Main outcomes were the proportion of patients who responded to, or dropped out of, the allocated treatment.
- Intention-to-treat basis.
- Main weakness: Study was of acute phase of treatment. Not long term outcomes

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373:746-758

"Initiating antidepressant therapy? Try these 2 drugs first"



Strength of Recommendation A
Priority Updates from the Research Literature in the July 2009. JFP
http://www.ifponline.com/pages.asp?AID=7678

Black Box Warning

- · Applies to all antidepressants
- · Monitor for suicidal ideation and balance risk/benefit
- · Inform patient and family of danger signs
- · Have plan for how to respond

Ongoing Management Strategies [C]

- Monitor patients taking antidepressants for:
 - Effectiveness (use PHQ-9)
 - Side effects
 - Suicidality
- · Watch for Serotonin Syndrome
- · Avoid SSRI Discontinuation Syndrome

Serotonin Syndrome

Usually within hours of starting or changing meds

- · Akathisia
- · Anxiety
- Clonus
- Delirium
- Dilated pupils
- · Muscular rigidity
- · Renal failure
- Rhabdomyolysis
- Seizures
- · Sweating
- · Tachycardia
- Tremor

Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression Am Fam Physician. 2008 Mar 15;77(6):785-92.

SSRI Discontinuation Syndrome

if withdrawal of SSRI or SNRI is not tapered (paroxetine and venlafaxine are the worst offenders)

- · Anxiety
- Ataxia
- Diarrhea
- · Dizziness, vertigo, or light-headedness; feeling "faint"
- Fatigue
- Headache
- Insomnia

- · Irritability
- Nausea
- Paraesthesias or "electric shock" sensations
- Tremor
- Visual disturbances
- · Vomiting

Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression. Am Fam Physician. 2008 Mar 15;77(6):785-92.

Effectiveness: Monitoring the patient

- The U.S. Preventive Services Task Force (USPSTF) recommends screening adults for depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and follow-up
- Use staff support to ensure follow-up
- · Establish a monitoring schedule
 - Mild Depression = monthly
 - Moderate = every 2 weeks Severe = weekly
 - When stable, every 1-3 months
- Office systems and QI methods available from Macarthur Initiative on Depression and Primary Care:http://www.depression-primarycare.org/

Ongoing Management Strategies

- · Approximately half of primary care patients respond partially to medications (=25% reduction in sx)
- One third of patients who are treated with a single medication achieve complete remission after 3 mo
- · One half of responders need 8+ weeks
- Treat depression at adequate doses for 4-8 wks before considering medication regimen as ineffective. [C]

Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression. Am Fam Physician. 2008 Mar 15;77(6):785-92.

Ongoing Management Strategies

- Consider a change in antidepressant medication regimen if no improvement after 4-12 wks. [B]
- For partial or non-responders, try:
 - Different medication from same class
 - Pts who do not respond to one SSRI/TCA have a 70% chance of responding to another med in the same class
 - Medication from a different class
 - Augmentation with a second agent [B]

Treatment Length

- · Terminate treatment based on pt's risk of recurrence
- · Guidelines for length of medication treatment:
 - First episode: 6-12 months
 - Second episode: 3 years
 - Third episode or second episode with complicating factors: lifetime therapy
- Treat longer if:
 - Comorbid psychiatric disorder

Tips for Improving Compliance

- 40% stop meds after < 1 mo
 - Predictors include lower education and SES
- Use SE to your advantage
 - Use paroxetine or mirtazapine to gain weight
 - Use fluoxetine or buproprion to lose weight
- Use concomitant benzos for a few weeks (2001 Cochrane review)
- Add psychotherapy to pharmacotherapy
- Continued contact with treating physician
 - 2001 RCT involving 2 visits and 3 calls
- · Be sure to address cultural factors

Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression. Am Fam Physician. 2008 Mar 15;77(6):785-92.

Other Effective Treatment Modalities

- · Exercise: yes, effective
 - 30 min 3x/wk equal to sertraline in 1 RCT
- Light Therapy (2004 Cochrane review)
 - Yes, effective vs. SAD
 - No, not effective for non-seasonal depression
- ECT: yes, effective but...
 - Treatment effects do not last
 - SE: Cognitive impairment
 - Reserved for refractory cases

Maurer D, Colt R. An evidence-based approach to the management of depression

Other Treatment Modalities

- Limited evidence to support the use of these therapies for treatment-resistant depression:
 - Lithium (best choice)
 - Anticonvulsants
 - Thyroid hormone
 - Stimulants (2008 Cochrane review)
 - DHEA
 - SAMe (AHRQ)

Maurer D, Colt R. An evidence-based approach to the management of depression. Prim Care. 2006 Dec;33(4):923-41, vii.

Aripirazole

- · Adjunctive Treatment in adults w/ MDD
- Atypical Antipsychotic
 - Mech > agonist of D₂ and 5-HT_{1A}; antagonist of 5-HT_{2A}
 - Mood stabilization, reduce anxiety and agitation, decrease
- 2-5 mg/day initial, 5-10 mg day recommended, available IM
- SE: akathisia, restlessness, insomnia, constipation, fatigue, blurred vision. Neuroleptic malignant syndrome.
- · Interacts w/ ketoconazole and fluxoxetine.
- Do not use w/ elderly patients w/ dementia related psychoses. Not evaluated in pediatric patients

STAR*D Study¹

- Purpose: Assess effectiveness of pts w/ MDD in primary and specialty care
- · Longest and largest study
- 4041 patients from 41 sites
- · 2876 patients entered study
- Questions: How adequate is a level of treatment?

1. Rush et al., Am j Psychiatry 2003, 2006

Sequenced Treatments

80 to 88% reach remission

- Citalopram 12-14 wks 33% remission, 10-15% respond
- Switch to cognitive therapy, sertraline, burprorpion or venlafaxin 25% remission

Augment with: buproprion or buspirone 33% remission

- 3. Switch to mirtazapine or nortryptyline 12-20 % remission
 - Augment with lithium or T3 (only with buproprion, sertraline, venlafaxine) 20% remission
- 4. Switch to MAOi or combination of venlafaxine and mirtazapine 7-10% remission

Suicide Risk

- Patients with depression have a suicide risk that is 20x normal.
- Up to 15% of patients suffering from severe major depression commit suicide.
- Short-term risk of suicide is not necessarily decreased and may even be increased by antidepressants in adult patients.
 - Increased suicide risk with SSRIs (2005 Cochrane review)
 - No increased suicide risk (2005 meta-analysis)

Three important questions

Ideation---Intent---Plan---Lethality

- Do you ever feel hopeless or that life is not worth living?
- Have you thought of taking your life?
- How would you end you life?

Consider Risk Factors

- Age > 65*
- · White or Native Amer
- Unemployed
- FH of suicide
- · Drug or alcohol use
- Panic attacks/anxiety
- Hopelessness
- · Psychotic/hallucinations · Recent exposure-suicide
- · Post partum stress
- · Lack of social support

- · Male sex
- · Unmarried 0 children
- · History of psychiatric admission
- · Prior suicide attempts
- · Stressful life event
- · Severe physical illness · Access to guns, etc
- · Specific plan
- · Females attempt Males complete

Acute high risk for suicide

- 56% of suicides occur on first attempt
- In addition to factors described before, look for comorbid affective, substance abuse or anxiety disorders.
- Prospective study of 954 patients w/ affective d/os:
 - Severity of ideation, past attempts, hopelessness associated with suicide
- Severe psychic anxiety, panic attacks, severe insomnia, severe anhedonia, recent onset of alcohol abuse associated with suicide within one year • Study of 100 suicide attempts, 90% anxiety, 70% panic, 40%
- Study of 76 inpatient suicide, 77% had 2 or more days of anxiety or agitation.

Fawcett, JA. Suicide and bipolar disorder, Medscape Psychiatry and Mental Health, 2005; 10(2)

Questions?

Many thanks to Julie Taylor, MD, Kathy Mariani, MD and Frank Domino, MD

Depression in Special Populations

Pediatrics



Reproductive women



Adolescent Patients (Screen, Dx)

- Identification of depression in highrisk youth
- · Systematic assessment procedures
- · Patient and family psychoeducation
- Establishing relevant links in the community
- · Safety planning

Zuckerbrot RA, Cheung AH, Jensen PS, Stein RE, Laraque D; GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): I. Identification, assessment, and initial management. Pediatrics. 2007 Nov;120(5):e1299-312.



Adolescent Patients (Rx, Manage)

- Active monitoring of mildly depressed youth
- Medication and psychotherapy
- Monitoring for adverse effects
- Consultation and coordination of care
- · Tracking outcomes

Cheung AH, Zuckerbrot RA, Jensen PS, Ghalib K, Laraque D, Stein RE; GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II.

Treatment and ongoing management. Pediatrics. 2007 Nov;120(5):e1313-26... 2008 Jan;121(1):227.

Adolescent Patients

- FDA BLACK BOX WARNING for suicidal ideation and behaviors in children, adolescents, and young adults (18-24 yo) treated with antidepressants.
- Fluoxetine is the only SSRI approved for pediatric use



 $http://www.fda.gov/cder/drug/antidepressants/antidepressants_label_change_2007.pdf$

Post-Partum Depression

- Prevalence is 13%
- Dx: onset of depression sx within 4-6 weeks after delivery (can be up to 6 mo)
- Diff dx includes "blues" and psychosis
 - "Blues" affects 30% of women
 - Psychosis 1 in 1000 deliveries (1 in 2 for bipolar or hx of puerperal psychosis)

Musters C, McDonald E, Jones I. Management of postnatal depression. BMJ. 2008 Aug 8;337:a736. doi: 10.1136/bmj.a736.

Risk Factors for Post-Partum Depression

- Depression or anxiety during pregnancy
- Hx of other psychiatric conditions
- Recent stressful life events
- Poor social support, especially from FOB



Musters C, McDonald E, Jones I. Management of postnatal depression. BMJ. 2008 Aug 8;337:a736. doi: 10.1136/bmj.a736.

Treating Post-Partum Depression Stepped care approach

- Psychological and psychosocial interventions including self help strategies, peer support, non-directive counseling, CBT, and psychotherapy are effective
 - 2007 Cochrane meta-analysis of 10 post-partum trials
- Indications for antidepressants:
 - If a woman declines therapy
 - If counseling does not work
 - Is she has severe depression

Musters C, McDonald E, Jones I. Management of postnatal depression. BMJ. 2008 Aug 8;337:a736. doi: 10.1136/bmj.a736.

Which Antidepressants are Safe in Pregnancy?

Pregnancy risk categories

- · No antidepressants are A
- Buproprion and maprotiline: B
- · Most medications: C
- Paroxetine, imipramine, and nortriptyline: D
- No antidepressants are X

Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression Am Fam Physician. 2008 Mar 15;77(6):785-92.

Which Antidepressants are Safe in Breastfeeding Women?

- Pooled analysis of 57 trials measuring concentrations of antidepressants in breastfeeding infants, primarily SSRIs
- SSRIs of choice: sertraline and paroxetine
 - undetectable levels in infant serum
- SSRIs to avoid: fluoxetine and citalopram
 - highest concentrations in infant serum

Musters C, McDonald E, Jones I. Management of postnatal depression. BMJ. 2008 Aug 8;337:a736. doi: 10.1136/bmj.a736.

Outcomes for Women with Post-Partum Depression

- Research is difficult to interpret across such a wide range of diagnoses (from mild subclinical depression to psychosis)
- Average episode lasts 3-6 mo, some > 1 yr
- Most women recover completely if treated but are at risk for further episodes of depression (both post-partum and non)
 - Discreet adversity lowers the risk of future episodes
 - Early onset, severe sx, bipolar d/o or psychosis raise the risk of future episodes

Musters C, McDonald E, Jones I. Management of postnatal depression. BMJ. 2008 Aug 8;337:a736. doi: 10.1136/bmj.a736.

PMHx

- Past history of mood disorders
 - $-\ Treatments, hospitalizations, suicide\ attempts$
- Other medical conditions
 - Thyroid conditions
- · Current medications
 - Glucocorticoids and reserpine
- Previous psychiatric medications
- Family history of depression and bipolar d/o

Differential Diagnosis

- · Bipolar disorder
- Bereavement
- · Adjustment disorder
- PTSD
- Dementia/delirium
- · Substance abuse/withdrawal
- · Medical condition or medication

Depression Resources: Screening

- Ebell MH. Screening instruments for depression. Am Fam Physician. 2008 Jul 15;78(2):244-6.
- · Dejesus RS, Vickers KS, Melin GJ, Williams MD. A system-based approach to depression management in primary care using the Patient Health Questionnaire-9. Mayo Clin Proc. 2007 Nov;82(11):1395-402.

Depression Resources: **Special Populations**

- Zuckerbrot RA, Cheung AH, Jensen PS, Stein RE, Laraque D; GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): I. Identification, assessment, and initial management. Pediatrics. 2007 Nov;120(5):e1299-312.

 Cheung AH, Zuckerbrot RA, Jensen PS, Ghalib K, Laraque D, Stein RE; GLAD-PC Steering Group. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): II. Treatment and ongoing management. Pediatrics. 2007 Nov;120(5):e1313-26.
- Musters C, McDonald E, Jones I. Management of postnatal depression. BMJ. 2008 Aug 8;337:a736. doi: 10.1136/bmj.a736.
- Skultety KM, Rodriguez RL. Treating geriatric depression in primary care. Curr Psychiatry Rep. 2008 Feb; 10(1):44-50.

Depression Resources: Treatment

- · Halfin A. Depression: the benefits of early and appropriate treatment. Am J Manag Care. 2007 Nov;13(4 Suppl):S92-7.
- · Maurer D, Colt R. An evidence-based approach to the management of depression. Prim Care. 2006 Dec;33(4):923-41, vii.
- Adams SM, Miller KE, Zylstra RG. Pharmacologic management of adult depression. Am Fam Physician. 2008 Mar 15;77(6):785-92.