



Depression: A Primary Care Approach to Assessment and Intervention

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Edgar Degas (1834-1917). *Melancholy*, late 1860s, French. Oil on canvas. Courtesy of The Phillips Collection, Washington, DC. © 2010 Fitzgerald Health Education Associates, Inc.



Efficacy of Depression, Anxiety Therapies

- Pharmacologic therapy
 - 80% Rx written by primary care providers
 - All prescription antidepressants +/- equally effective if taken in therapeutic doses for sufficient length of time
 - Under dosing
 - Too short a treatment interval

Hosp Pract. 2000;35:77-84. Available at: <http://www.hosprract.com/issues/2000/07/feld.htm>, accessed 7.30.10.

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What are the clinical and cost considerations?

- What does what?
 - What does the patient need for a clinical response?
 - Will a given medication provide that help?
 - What depression, anxiety, disorders thought, symptoms respond best to medication?

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What are the clinical considerations?

- What is the drug's adverse effect profile?
- What is the risk of the medication in overdose?
- What medication is affordable and accessible?

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What does what in the maintenance of mood?

- Serotonin
 - AKA 5-hydroxytryptamine or 5-HT
 - Similar in structure to norepinephrine and dopamine
 - Modulates mood, emotion, sleep, appetite, keeps the motor of life running smoothly
 - Source- www.biopsychiatry.com/serotonin.htm, accessed 5.24.10.

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What does what in the maintenance of mood? (continued)

- Norepinephrine
 - Associated with focused attention, elevated energy, motivation to win a reward
 - Source- http://www.acnp.org/Docs/G5/CH4_47-58.pdf, accessed 5.10.10.



What does what in the maintenance of mood? (continued)

- Dopamine
 - In part, helps with the joy of life, attention, pleasure
 - Also contributes to disinhibition, euphoria
 - Source- www.acnp.org/default.aspx?Page=5thGenerationChapters, accessed 5.15.10.



Hormone Effects: Presence of Estrogen

-
- ↑ Catecholamines*
 - ↑ Serotonin function and transport[†]
 - ↓ Monoamine oxidase[‡]
-

* Fink et al. *Cell Mol Neurobiol.* 1996;16:325.
[†] Aylward and Maddock. *Lancet.* 1973;1:936.
[‡] Luine et al. *Brain Res.* 1975;86:293.



How to Choose a Therapeutic Agent for the Treatment of Depression

- What has worked in the past?
 - Use the tried and true if safe and reasonable
- What has worked for relatives?
 - May be related to similar action of receptor sites, neurotransmitter activity



How to Choose a Therapeutic Agent for the Treatment of Depression (continued)

- Are these antidepressants?
 - Anxiolytics?
 - Psychoactive, psychotherapeutic agents



How to Choose a Psychotherapeutic Agent

- What is the most bothersome sx?
 - Vegetative
 - Energized
 - Anxious
- Drug's T_{1/2}
- Drug's adverse effects
- Potential drug interactions



Most psychotropic medications used in the treatment of depression work via manipulation of serotonin, norepinephrine and/or dopamine.



Commonly Prescribed Psychotropic Medications

- SSRIs (selective serotonin or serotonin specific reuptake inhibitors)
 - Inhibit reuptake of serotonin (5-HT)
 - Net result is more serotonin at synaptic cleft
 - Citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft)
 - Source-Stringer (2007)



Comparing Psychotropic Medications (Katzung, 2007, Goldberg, 2007)

Drug	Sedation or activation?	Anticholinergic	Serotonin	NE	Dopamine
Citalopram, escitalopram	+ sedation + / ++ activation	0	+++	0	0
Fluoxetine	+ sedation + / ++ activation	+	+++	0/+	0/+
Paroxetine	++ sedation + activation	++	+++	0	0
Sertraline	0 sedation + / ++ activation	0	+++	0	0



Commonly Prescribed Psychotropic Medications

- Venlafaxine (Effexor), duloxetine (Cymbalta), desvenlafaxine (Pristiq)
 - Inhibits reuptake of 5-HT, NE
- Bupropion (Wellbutrin)
 - Inhibits reuptake of NE, dopamine



Commonly Prescribed Psychotropic Medications (continued)

- Mirtazapine (Remeron)
 - Blocks presynaptic α_2 -adrenergic autoreceptor; blocks 5-HT₂, 5-HT₃
 - Net effect, enhance serotonin and NE activity



Comparing Psychotropic Medications (Katzung, 2007, Goldberg, 2007)

Drug	Sedation or activation	Anti-cholinergic	Serotonin	NE	Dopamine
Bupropion	Sedation 0 Activation +++	+	0	+	+++
Venlafaxine desvenlafaxine	Sedation + Activation + / ++	0	+++	+ / ++	0
Duloxetine	Sedation + Activation + / ++	0	+++	+++	0
Mirtazapine	Sedation ++++ Activation 0	+	0	0	0



Commonly Prescribed Psychotropic Medications (continued)

- Nefazodone (Serzone), trazodone (Desyrel)
 - Inhibits reuptake of 5-HT; blocks 5-HT_{2A}
 - Anxiety receptor site
- Tricyclic antidepressants (TCA)
 - Block reuptake of NE, 5-HT
 - Amitriptyline, imipramine, desipramine, nortriptyline, clomipramine

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Comparing Psychotropic Medications (Katzung, 2007, Goldberg, 2007)

Drug	Sedation or activation	Anti-cholinergic	Serotonin	NE	Dopamine
Amitriptyline	Sedation +++ Activation 0	++++	+++	++	0
Desipramine	Sedation +/- Activation 0	++	0/+	+++	0
Nortriptyline	Sedation ++ Activation 0	++	+++	++	0
Trazodone	Sedation +++ Activation 0	0	0/+	0	0
Nefazodone	Sedation +++ Activation 0	+++	+	0	0

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Common Adverse Effects with Select Psychotropic Medications

- Serotonin reuptake inhibition
 - GI disturbance (often loose stools)
 - Sexual dysfunction
 - Extrapyramidal symptoms

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Common Adverse Effects with Select Psychotropic Medications (continued)

- Norepinephrine (NE) reuptake inhibition
 - Tremor
 - Tachycardia
 - Erectile and ejaculatory dysfunction

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Common Adverse Effects with Select Psychotropic Medications (continued)

- Dopamine reuptake inhibition
 - Psychomotor activation
 - Antiparkinsonian effect

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Potential Adverse Effects from Medications with Anticholinergic Effect

- Dry mouth, skin
- Blurred vision
- Urinary retention
 - Usually w BPH
- Sedation
- Agitation
- Tachycardia
- Hyperpnea
- Mydriasis
- Flushing
- Psychosis
- Seizure
- Coma
- Hyperthermia

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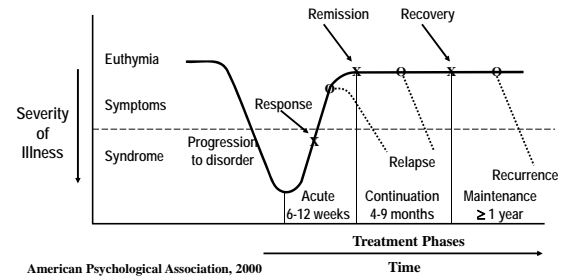
Or...

- Dry as a bone (dry mouth)
- Red as a beet (flushing)
- Mad as a hatter (confusion)
- Hot as a hare (hyperthermia)
- Can't see (vision changes)
- Can't pee (urinary retention)
- Can't spit (dry mouth)
- Can't (something that rhymes with spit {constipation})



Treatment of Depression

Course of Illness and Phases of Treatment



American Psychological Association, 2000



Evaluating Response to Therapy per AHCPR

- At four weeks, should be
 - = >25% reduction in symptoms
- If not found but some reduction noted
 - Increase antidepressant dose and reevaluate at 4 weeks



Evaluating Response to Therapy per AHCPR (continued)

- At 4 weeks, no improvement with adherence and adequate dose
 - Watch and wait, particularly if patient not worse and minimal vegetative symptoms
 - Vegetative symptoms include altered sleep, sex drive, appetite, etc.
 - Might be slow responder
 - Prudent course with elder with up to 10 weeks needed prior to clinical response



Depression: Recurrence Risks



Source- Maxmen, J., Ward, N. (2002) Psychotropic Drug Facts Fast (3d. Ed.) New York: W.W. Norton.



Per Maxmen and Ward

- Slowly DC antidepressant p 4-6 month maximum improvement
 - 1st episode MDD
 - Family's 1st depression
- Treated = >9-12 months
 - Repeat episode
 - Strong family hx depression



Antidepressant Use in Adjustment Disorder with Depressed Mood

- If depression is with stressor
 - Agent will work well initially
 - Less well as time goes on if stressor continues
- If stressor stops, drug will resume its initial efficacy



Depression as Part of Bereavement

- Indications
 - Severe acute bereavement (<4 mo post event)
 - Moderate to severe chronic bereavement



Depression as Part of Bereavement (continued)

- Anticipated effect of medications
 - Improves vegetative symptoms
 - No real effect on normative mood fluctuation of grief
 - Maxmen & Ward (2002)



45 Year-old Woman

- Presents with nausea and headache X 3 days
 - Headache better with ibuprofen but this worsens GI upset
 - On day 7 of fluoxetine therapy for depression
- "The medicine is not helping. In fact, I feel pretty lousy."



Depression

- A chronic disease where people generally want a quick recovery
- Need a realistic time frame of
 - Onset of therapeutic action of the antidepressant
 - Management of common early use side effects



SSRI Side Effects Take 3-4 weeks to resolve

- Nausea
 - Take with food and adequate water
 - Use at bedtime
 - Consider adding a short course of H2RA but not cimetidine (Tagamet)



SSRI Side Effects

Take 3-4 weeks to resolve
(continued)

- Headache
 - Usually controlled with acetaminophen
 - Keep well hydrated
 - GI SE worsened at times with NSAID, ASA



SSRI Side Effects

Take 3-4 weeks to resolve
(continued)

- Sedation
 - Take at bedtime
 - Most likely with paroxetine, not with fluoxetine
- Anorexia
 - Small initial loss then gain
 - Most likely with fluoxetine, unlikely with paroxetine



SSRI Side Effects

Take 3-4 weeks to resolve
(continued)

- Diarrhea
 - Take with food
 - All but paroxetine
- Agitation
 - Reduce dose by 25% and gradual reintroduce
 - Trazodone to help with sleep
 - Sedating antidepressant
 - Low abuse potential
 - Onset of action= ½-1 h



SSRI Onset of Action

- 4-7 days
 - Energy improved
- 7-10 days
 - Improved mood and concentration
- 8-10 days
 - Less diurnal variation in mood



SSRI Onset of Action (continued)

- 8-9 days
 - If libido not impaired by the drug, begins to improve
- 10-14 days
 - Hopelessness, helplessness fade
- 12-16 days
 - Dysthymia, suicidal thoughts, excessive guilt



SSRI Withdrawal Syndrome

- Seen with
 - Use greater than 5 weeks
 - Rapid discontinuation of all products with shorter T ½



SSRI, TCA Withdrawal Syndrome

- Dizziness
- Paresthesia
- Anxiety
- Nausea
- Sleep disturbance
 - Insomnia
 - Nightmares



SSRI	T ½
Paroxetine (Paxil)	26 h
Fluvoxamine (Luvox)	16 h
Sertraline (Zoloft)	25- 65 h
Citalopram (Celexa)	24-48 h
	Metabolites= 2 d & 4 d
Fluoxetine (Prozac)	24-72 h
	Metabolite= 4-16 d



Paroxetine Withdrawal

- Known to produce a particularly severe withdrawal syndrome
- Why?



Avoiding SSRI Withdrawal Syndrome

- Taper dose over 4 weeks
- Reduce ~25% per week
- Depression relapse may occur
- Increase gradually to original dose



You see a 52 year-old woman...

- ...With valvular heart disease who is taking warfarin. She also is seeking treatment for a longstanding depression.
- What should you consider in prescribing an SSRI?



Warfarin A Racemic Compound

- R-warfarin
 - Substrate= CYP 1A2, 2C19
- S-warfarin
 - Substrate= CYP 2C9

CYP450 Isozyme Inhibition by the SSRIs (*in vitro**)

	CYP Isoenzymes				
	1A2	2C9	2C19	2D6	3A4
Escitalopram	0	0	0	0	0
Citalopram	+	0	0	+	0
Fluoxetine	+	++	+ to ++	+++	++
Paroxetine	+	+	+	+++	+
Sertraline	+	+	+ to ++	+	+

0 = minimal or weak inhibition; +, ++, +++ = mild, moderate, or strong inhibition
 * Clinical significance of *in vitro* data is unknown
 There are limited *in vivo* data suggesting a modest CYP 2D6 inhibitory effect for escitalopram 20 mg/day.
 von Moltke et al., 2001; Greenblatt et al., 2002; Greenblatt et al., 1998

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You see a 42 year-old woman...

- ...Who is being treated with sertraline 50 mg qd for the past 6 months for major depressive disorder. She states, "I feel a little better but still have no energy. It's OK, I can get by like this."

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Evaluating Nonresponder

- Has there been an adequate medication trial?
 - Adequate dose
 - Adequate length of therapy
 - Adherence

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Evaluating Nonresponder (continued)

- Consider coexisting health issues
 - Medications
 - Clonidine, beta blockers, HCTZ
 - Metabolic issues
 - DM, thyroid
 - Substance abuse
 - Stress, life events

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Evaluating Nonresponder (continued)

- Consider drug-drug interactions
- Reevaluate initial diagnosis
- Is the class of drugs correct?
 - Serotonin vs. NE vs. dopamine
 - Source- Preston & Johnson (2002) Clinical psychopharmacology made ridiculously simple. Miami: MedMaster, Inc.

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Medication Augmentation for Nonresponder

- Maximize dose of original medication if some response
- Add a second agent
 - SSRI plus buspirone
 - SSRI plus bupropion
 - SSRI plus mood stabilizer (LD lithium)
 - SSRI plus low dose stimulant
 - Preston & Johnson (2002)

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If these fail...

- Try meds with different activity
 - Mirtazapine (Remeron)
 - Nefazodone (Serzone)
 - Uncommonly used due to rare but random risk of liver toxicity
 - Venlafaxine (Effexor), desvenlafaxine (Pristiq)
 - Duloxetine (Cymbalta)
 - Liver toxicity risk with heavy alcohol use



If these fail... (continued)

- Psycho-pharmacology consult
 - Does the psycho-pharm person also provide psychotherapy?



Evaluating Relapse

- Substance abuse
- Sleep disturbance
- Adherence
- Stress
- Medical and metabolic issues
- Psychotropic medication tolerance



Bupropion-SR, Sertraline, or Venlafaxine-XR after Failure of SSRIs for Depression

Rush et al.

NEJM, Volume 354:1231-1242

March 23, 2006 Number 12



Rush et al. Method

- 727 adult outpatients with a nonpsychotic major depressive disorder who had no remission of symptoms or could not tolerate the SSRI citalopram to receive one of the following drugs for up to 14 weeks:



Rush et al. Method (continued)

- Sustained-release bupropion (239 patients) at a maximal daily dose of 400 mg
- Sertraline (238 patients) at a maximal daily dose of 200 mg
- Extended-release venlafaxine (250 patients) at a maximal daily dose of 375 mg



Rush et al. Conclusion

- After unsuccessful treatment with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant. Any one of the medications in the study provided a reasonable second-step choice for patients with depression.



Medication Augmentation after the Failure of SSRIs for Depression

NEJM Trivedi et al.
Volume 354:1243-1252
March 23, 2006 Number 12



Trivedi et al. Method

- 565 adult outpatients who had nonpsychotic major depressive disorder without remission despite a mean of 11.9 weeks of citalopram therapy (mean final dose, 55 mg per day) to receive sustained-release bupropion (at a dose of up to 400 mg per day) as augmentation, 286 to receive buspirone (at a dose of up to 60 mg per day) as augmentation.



Conclusion

- Augmentation of citalopram with either sustained-release bupropion or buspirone appears to be useful in actual clinical settings. Augmentation with sustained-release bupropion does have certain advantages, including a greater reduction in the number and severity of symptoms and fewer side effects and adverse events.



45 Year-old Woman

- Long-standing anxiety disorder
 - Ran out of benzo this AM
 - “I need it for my nerves.”
- Primary provider is out-of-town
 - Was given BuSpar by covering MD



Pharm Fun Facts: BZD True or False?

- The use of a BZD does not help in decreasing the worry associated with anxiety but is helpful in reducing disease-associated vigilance.
- BZD abuse is rare in the absence of substance abuse.



Benzodiazepine Tolerance

- 2440 NJ Medicaid patients who had received Rx's for benzo > 2 y continuously
 - Overall incidence of dosage escalation: 1.6%

Soumerai SB et al. *Psychiatry Serv.* 2003;54:1006-1011.

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Benzodiazepine Tolerance (continued)

- Higher risk of dose escalation:
 - Also prescribed antidepressants
 - Prescribed lorazepam
 - Younger and NOT disabled
 - Filling duplicate prescriptions at different pharmacies

Soumerai SB et al. *Psychiatry Serv.* 2003;54:1006-1011.

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Benzodiazepine Withdrawal

- Quickest onset
 - Short T $\frac{1}{2}$ drugs
 - Likely most severe symptoms
- Slow onset
 - Longer T $\frac{1}{2}$ drugs
 - Likely less severe symptoms



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BZD Pharmacokinetics

	Dose equivalent	Half-life in hours
Alprazolam (Xanax)	0.5	6-20
Chlordiazepoxide (Librium)	10	30-100
Clonazepam (Clonidine)	0.25	18-50
Clorazepate (Tranxene)	7.5	30-100
Diazepam (Valium)	5	30-100
Lorazepam (Ativan)	1	10-20
Oxazepam (Serax)	15	8-12

Source- Arana & Rosenbaum (2000) Handbook of Psychiatric Drug Therapy.

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Benzodiazepine Dependence

- Reduce dose by 25% per week
- Rapid withdrawal
 - Tremors
 - Hallucinations
 - Seizures
 - DT-like picture

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Buspirone (BuSpar)

- Non benzo
- Action likely at 5-HT_{1A} receptor site
 - Agonist
- Possible D₂ dopamine receptor activity
 - No activity at GABA binding sites

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If anxiety is disabling...

- ...Add short term benzo while awaiting other agent's action
- ...Inform that duration of use may be limited



Combining Antidepressants with Benzodiazepines

- Provide rapid anxiolysis during antidepressant lag
- Decrease early anxiety associated with the initiation of antidepressant
- Treat residual anxiety with antidepressant therapy



Combining Antidepressants with Benzodiazepines (continued)

- Better prevention and treatment of depression compared to benzodiazepine monotherapy



Buspirone (BuSpar)

- Initial therapeutic effect at 2 weeks
 - Full effect may take 4-6 weeks
- No
 - Effect on performance, nonsedating
 - Tolerance, withdrawal syndrome
 - Potentiation with alcohol
 - Will not be helpful in alcohol withdrawal



Provider BuSpar Misuse

- Give as PRN rx
- Rx as a sleep aid only
- Rx to "cover" benzo withdrawal
- Failure to
 - Inform patient of length time needed before onset of therapeutic effect
 - Write for sufficient number of tablets
 - Raise dose adequately



Janice

- 52 year-old woman
 - Taking SSRI for MDD X 6 weeks
- Feeling better with less diurnal variation in mood, "clearer thoughts"
 - Improved libido but difficulty achieving orgasm



Sexual Adverse Effects with Psychoactive Medications

- Impaired erection, inhibited orgasm
 - Serotonin, especially at 5HT2 receptor
- Reduced intensity of orgasm
 - Dopamine, norepinephrine
- Anticholinergic
 - Impaired erection
- Antihistamine
 - Loss of libido, impaired erection

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Observed Rates of Sexual Dysfunction with Antidepressants

- SSRIs
 - 40%
- Venlafaxine (Effexor)
 - ~40%
- Mirtazapine (Remeron)
 - ~40%
- Bupropion (Wellbutrin)
 - ~22%

Freedman, S., Rosenbaum, J., Antidepressant-Induced Sexual Dysfunction and Its Management, available at <http://cme.medscape.com/viewarticle/457164>, accessed 5.25.10.

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AD Side Effects Long Term, Unlikely to Resolve

- Sexual dysfunction
 - Erectile problems
 - Decreased libido
 - Inability to achieve orgasm
 - Delayed orgasm

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AD Related Sexual Dysfunction

- Hold dose for day prior to sexual activity with shorter acting agents
 - May lead to serotonin withdrawal symptoms
 - Likely not effective with fluoxetine

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AD Related Sexual Dysfunction (continued)

- Switch to or initiate therapy with less effect
 - Nefazodone, bupropion, venlafaxine (?), TCA

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To Reverse or Attenuate SSRI-related Sexual Adverse Effects

- Most helpful with anorgasmia
 - Buspirone
 - 10-20 mg BID
 - Bupropion
 - Up to 225 mg qd
- Help with ED
 - Sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis)

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Sildenafil (Viagra), Vardenafil (Levitra), Tadalafil (Cialis)

- Mechanism of action
 - Identical in the drug class
- Onset of action
 - For all= 30 to 60 min
- T_{1/2}
 - Sildenafil, vardenafil= T_{1/2} =4 to 5-h
 - Tadalafil= T_{1/2} =17 to 20-h



Ginkgo Biloba

- Reversal of SSRI-related sexual side effects
 - 100 patients with 84% efficacy
 - Other study in conflict with these findings
- Dose
 - 40 mg Ginkgo leaf extract per capsule
 - 40-80 mg TID
 - www.prescribersletter.com, accessed 7.10.08.



Conclusion

- Understanding the science behind prescribing medications in depression will help you and your patients to choose the best treatment option.



End of Presentation!
Thank you for your time and attention.

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