Detection and Management of Anxiety and Depressive Disorders in the Primary Care Setting

Heidi L. Combs, MD, MS
Professor, Psychiatry and Behavioral Sciences
Vice Chair of Education
University of Washington School of Medicine
Seattle, WA

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Disclosure

I have no financial interests or relationships to disclose.

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Objectives

- Identify the prevalence of anxiety and mood disorders and how they often present in a primary care setting
- Perform a quick screen for anxiety and mood disorders
- Apply general pharmacologic approaches to the treatment of anxiety and mood disorders

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What Percent of Patients with Depression and/or Anxiety Are Treated Solely in Primary Care?

A. 20-30%
B. 40-50%
C. 60-70%
D. 80-90%

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Anxiety Disorder Prevalence

- Anxiety disorders are the most common psychiatric diagnosis in the US with an estimated prevalence of 13.3%[1]
- Lifetime risk estimated at 29%[2]
- Kroenke found 19.5% of patients in primary care clinics had at least one anxiety disorder[3]

1.Kessler R. et al. Arch Gen Psychiatry 2005;62(6):617-27
2.Metzler DH, Mahoney D, Freedy, JR. Anxiety Disorders in Primary Care. Prim Care Clin Office Pract 43 (2016) 245–261.
3.Kroenke K e al. Ann Intern Med 2007;146(5):317-25

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General Considerations for Anxiety Disorders

- Often have an early onset- teens or early twenties
- Show ~2:1 female predominance
- There is significant familial aggregation for PD, GAD, OCD and phobias
- Waxing and waning course over lifetime
- **Comorbidities rule rather than exception!**

Metzler DH, Mahoney D, Freedy, JR. Anxiety Disorders in Primary Care. Prim Care Clin Office Pract 43 (2016) 245–261.

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Major Depressive Disorder (MDD) Prevalence

- Lifetime prevalence is 16%, 7% will have an episode in a year, 2X greater in women
- Incidence peaks in 20s but onset in late life not uncommon
- Higher prevalence is associated with chronic medical illness

Bromberger JT, Epperson, CN. Depression During and After the Perimenopause. Obstet Gynecol Clin N Am. 2018. 45:663-678.
Park LT, Zarate CA. Depression in the Primary Care Setting. N Engl J Med. 2019. 380;6:559-568

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Select the Correct Statement Regarding Risks of Having a Depressive Episode Reoccur:

A. Risk of having another episode:
   - ≥ 20% if one previous episode
   - ≥ 30% if two previous episodes
   - ≥ 40% if three previous episodes

B. Risk of having another episode:
   - ≥ 40% if one previous episode
   - ≥ 50% if two previous episodes
   - ≥ 60% if three previous episodes

C. Risk of having another episode:
   - ≥ 60% if one previous episode
   - ≥ 70% if two previous episodes
   - ≥ 90% if three previous episodes

Can We Explain These Differences with Sex Hormones?

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Not in Any Satisfying Way

- Estrogen and progesterone have been linked to the regulation of serotonin… in lots of different ways
  - No single, universal effects… or substantiated theories
- Additive estrogen treatment has been linked to improved responses to SSRIs in postmenopausal women
- Greater progesterone levels at the time of trauma may explain greater memory encoding and increased likelihood of developing PTSD
  - But testosterone has also been linked to increased anxiety and PTSD dx

Christiansen DM, Berke ET. Gender- and Sex-Based Contributors to Sex Differences in PTSD. Current Psychiatry Reports (2020) 22: 19.
LI SH, Graham BM. Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. Lancet Psychiatry. 2017;4:73-82.

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- Perhaps a Unifying Theory Is That Because Women Experience Significantly Greater Fluctuations in Sex Hormone Levels During Their Reproductive Years, They Are More Likely to Experience Mood and Anxiety Disorders.

Christiansen DM, Berke ET. Gender- and Sex-Based Contributors to Sex Differences in PTSD. Current Psychiatry Reports (2020) 22: 19.
LI SH, Graham BM. Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. Lancet Psychiatry. 2017;4:73-82.

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Impacts of Anxiety Disorders

- Similar to major depression and chronic diseases such as diabetes in functional impairment and decreased quality of life
- Suicide risk is higher with both acute and chronic anxiety disorders

Chartrand H, Sareen J, Toews M, Bolton JM
Depress Anxiety. 2012;29(3):172-179.

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Impacts of Depressive Disorders

- 11th leading cause of disability and mortality worldwide[1]
- Untreated episodes can last ≥ 4 months
- Up to **15% of patients** with severe MDD will kill themselves
- Suicide is now the 11th leading cause of death in the United States[2]

1. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2197.
2. 2. https://www.nimh.nih.gov/health/statistics/suicide

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If These Disorders Are So Common, Why Do We Miss Them?

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Time to Chat with Your Neighbor

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How Familiar Does This Sound?

- 38 yo female with a CC of fatigue and GI distress
- 25-50% of patients in primary care present with medically unexplained symptoms!

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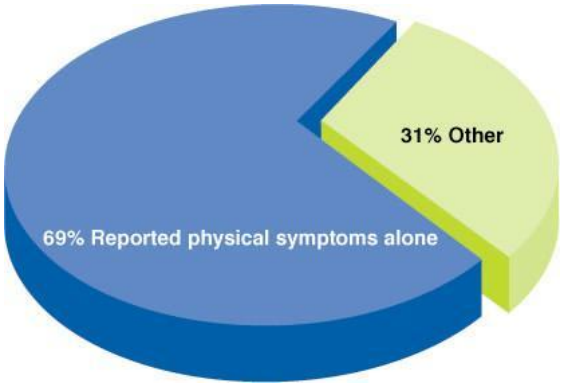
How Depressed Patients Often Present



Rijavec N, Grubic VN. Psychiatr Danub. 2012 Dec;24(4):346-52.

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How Anxious Patients Present

- Pts may report physical or psychologic distress including somatic complaints, pain, sleep disturbance and depression
- Wittchen found ~13% of GAD patients presented with CC of anxiety and ~47% presented with somatic concerns!
- Pts often don't know what they are experiencing is anxiety!

Nutt D et al. Eur Neuropsychopharmacol 2006;16(Suppl 2);S109-18
Wittchen H.et al. J Clin Psychiatry 2002;63(suppl 8);24-34

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How Do You Look for Anxiety and Mood Disorders?

- Screening tools?
- Screening questions?
- Some other way?

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Screening Questions

- How ever experienced a panic attack? (Panic)
- Do you consider yourself a worrier? (GAD)
- What is the worst thing that has ever happened to you? (PTSD)
- Do you get thoughts stuck in your head that really bother you or need to do things over and over like washing your hands, checking things or count? (OCD)
- When you are in a situation where people can observe you do you feel nervous and worry that they will judge you? (SAD)

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There Are Many Screening Tools That Are Very Helpful

But Only If You Use Them☺

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Anxiety Screening Tools

- GAD-7. Score of 10 or more-sensitivity 89%, specificity 82% Used to screen for GAD, PD and PTSD.
- GAD-2. Score of 3 has sensitivity of 86%, sensitivity of 83% for GAD.
- Panic module of Patient Health Questionnaire (PHQ)- had sensitivity 80%, specificity 99% for GAD, PD.

Spitzer R. et al. Arch Int Med 2006:166;(10)1092-7

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Depression Screening Tools

- PHQ-9[1]
  - Score ≥10= 0.88 sensitivity and specificity
  - Allows clinicians to track sx over time
- PHQ-2[2]
  - Score of ≥3 sensitivity for MDD = 80%
- Geriatric Depression Scale
  - Score >5 sensitivity 0.92, specificity 0.81
- Beck Depression Inventory
  - Cut off score of ≥4 Great sensitivity (0.97) and specificity (0.99) but $$

Park LT, Zarate CA. Depression in the Primary Care Setting. N Engl J Med. 2019. 380;6:559-568.
Kroenke K et al. J Gen Int Med 2001;16:606-13 Kroenke K et al Med Care 2003;41:1284-92

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So, You Have Made the Diagnosis Now What?

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Tx: General Framework

Pharmacologic

- **Thoughtful choice of agent**
- **Optimize single agents**
  - **Have EXTRA patience**
- **Augmentation**
- **Switching agents**

Nonpharmacologic

- Clarify dx
- Screen for other disorders
- Psychotherapy
- Psychoeducation
- Sleep optimization
- Psychosocial interventions
- Lifestyle optimization

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Anxiety Disorders: Crank Up the Serotonin

- Cornerstone of treatment for anxiety disorders is increasing serotonin
- Any SSRIs or SNRIs can be used

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How to Use SSRIs/SNRIs in Anxiety Disorders

- Start at ½ the usual initial starting dose for depression
- WARN THEM THEIR ANXIETY MAY GET WORSE BEFORE IT GETS BETTER!!
- May need to use an anxiolytic while initiating and titrating the antidepressant

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Anxiolytics

- Propranolol
  - Often used in treatment of performance anxiety
  - No risk of physiologic dependence
- Hydroxyzine
  - Wide dose range (12.5-100mg per dose)
  - Anticholinergic side effects
- Buspirone-For GAD- 60mg daily
- Benzodiazepines
  - Excellent efficacy
  - Risk of tolerability and dependence limit long term use

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Benzodiazepine Pearls

- Set expectations around use early
- Alprazolam has a very short half-life and can lead to rebound anxiety
- Clonazepam and lorazepam are often preferred agents
- Be very warry of concurrently prescribing opiate and benzos
- When it comes time to taper:
  - Taper no faster than 25% per week
  - Consider transitioning to a longer acting agent prior to down titrating

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Anticonvulsants

- Valproic acid 500-750 mg bid (ending dose)
- Carbamazepine 200-600 mg bid (ending dose)
- Gabapentin 900-2700 mg daily in 3 divided doses (ending dose)

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Prazosin and PTSD

- Prazosin can be very effective in treating PTSD related nightmares
  - Though there are some conflicting trials
  - Start at 1 mg dose
  - Gradually uptitrate until nightmares stop or side effects become problematic
  - Some patients need > 20 mg at night
  - Daytime dosing can also be effective for daytime arousal symptoms

Raskind M et.al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry. 2013 Sep;170(9):1003-10.
Raskind M et.al. Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans. N Engl J Med. 2018. 378;6:507-517.

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Depression Tx: Antidepressants

First generation

- TCAs
- MAOIs

Second generation

- SSRIs
- SRNIs
- Serotonin Modulators
- Atypical Antidepressants
- New Kids on the block

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SSRIs

Table 1
Selective serotonin reuptake inhibitor adverse effects

Side Effects	Citalopram	Escitalopram	Fluoxetine	Fluvoxamine[a]	Paroxetine	Sertraline
Sexual dysfunction	++	++	++	++	+++	++
Weight gain	+	+	+	+	++	+
GI toxicity	+	+	+	+	+	++
QTc prolongation	+	+	+	+	+	+
Orthostatic hypotension	+	+	+	+	++	+
Insomnia	+	+	++	+	+	++
Drowsiness	±	±	±	+	+	±

Abbreviations: ±, none to minimal; +, mild; ++, moderate; +++, severe; GI, gastrointestinal; QTc, corrected QT interval.

[a] Only approved to treat obsessive compulsive disorder.

Data from Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved. Available at: http://www.wolterskluwercdi.com/lexicomp-online/.

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SNRIs

Table 2
SNRI adverse effects

Side Effects	Desvenlafaxine	Duloxetine	Milnacipran[a]	Venlafaxine
Sexual dysfunction	+++	+++	±	+++
Weight gain	±	±	±	±
GI toxicity	++	++	++	++
QTc prolongation	±	±	±	+
Orthostatic hypotension	±	±	±	±
Insomnia	++	++	±	++
Sedation	+	±	+	+

[a] Approved for the treatment of fibromyalgia.

Data from Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved. Available at: http://www.wolterskluwercdi.com/lexicomp-online/.

Prim Care Clin Office Pract 43 (2016) 327–340

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Serotonin Modulators and Atypical Agents

Table 3
Serotonin modulator (trazodone and vilazodone) and atypical agent (bupropion and mirtazapine) adverse effects

Side Effects	Trazodone	Vilazodone	Bupropion	Mirtazapine
Sexual dysfunction	+	++	±	+
Weight gain	+	±	±	+++
GI toxicity	+++	+++	+	±
QTc prolongation	++	±	+	+
Orthostatic hypotension	+++	±	±	±
Insomnia	±	++	++	±
Sedation	+++	±	±	+++

Data from Lexicomp Online. Copyright © 1978-2015 Lexicomp, Inc. All Rights Reserved. Available at: http://www.wolterskluwercdi.com/lexicomp-online/.

Prim Care Clin Office Pract 43 (2016) 327–340

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Dosing Recommendations

Agent	Starting dose	Usual maintenance dose (daily)
Citalopram	20mg	20-40mg
Escitalopram	5-10mg	10-20mg
Paroxetine	20mg	20-40mg
Sertraline	50mg	100-200mg
Fluoxetine	20mg	20-60mg
Fluvoxamine	50mg	50-200mg
Venlafaxine	75mg	225-375mg
Desvenlafaxine	25mg	50mg
Duloxetine	30mg	60mg
Bupropion	75mg	300mg
Mirtazapine	15mg	45-60mg
Trazodone	25-50mg BID	150-400mg

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New Kids on the Block

- Levomilnacipran (Fetzima)-Is an SNRI with comparatively more active inhibition of norepinephrine reuptake than serotonin reuptake, particular at lower doses[1].
- Vortioxetine (Trintellix) – Novel mechanism functioning as an SSRI with additional activity as various neuroreceptors.[2] In clinical trials, it has demonstrated lower incidence of sexual side effects and weight gain, when compared to traditional SSRIs[3].

1. Bruno A, et al. The Role of Levomilnacipran in the Management of Major Depressive Disorder: A Comprehensive Review. *Curr Neuropharmacol*. 2016;14(2):191-199.
2. Wagner G,et. al. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: A systematic review and network meta-analysis. *J Affect Disord*. 2018;228:1-12.
3. Stahl SM. *Prescriber's Guide: Seventh Edition.* Cambridge University Press; 2021.

37

New Kids on the Block

- Bupropion plus dextromethorphan (Auvelity)- increases release of glutamate from interneurons in the brain, which is theorized to be dysfunctional in patients with depression.[1,2]

1. Akbar D, et al. Dextromethorphan-Bupropion for the Treatment of Depression: A Systematic Review of Efficacy and Safety in Clinical Trials. *CNS Drugs*. 2023;37(10):867-881. doi:10.1007/s40263-023-01032-5
2. Marwaha S, et. al. Novel and emerging treatments for major depression. *Lancet*. 2023;401(10371):141-153. doi:10.1016/S0140-6736(22)02080-3

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Is Newer Better?

- There are no large, robust, multiagent comparator trials comparing these agents to the efficacy of older SSRI and SNRI agents.
- Metanalyses of smaller comparator and non-inferiority trials offer some insight, but only demonstrate non-inferiority[1,2].

1. Cipriani A,, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357-1366. doi:10.1016/S0140-6736(17)32802-7
2. Wagner G, et al.. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: A systematic review and network meta-analysis. *J Affect Disord*. 2018;228:1-12. doi:10.1016/j.jad.2017.11.056

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Antidepressant Pearls

- Efficacy is very similar (~70% overall, ~50%-60% for each)
- So, select based on:
  - Previous trials- effective? not effective? Patient interest/willingness
  - Family member treated for same disorder?
  - What are the target sx?
  - Side effect profile to match the patient
  - Cost
  - Pregnant? (see later talk)

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Antidepressant Pearls

- h/o Seizure disorder or active eating disorder
  - No bupropion
- High risk for suicide or h/o suicide attempt
  - no TCAs
- Difficulty with med compliance
  - Avoid meds with short half-lives, no MAOIs

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Antidepressant Pearls

- Concurrent anxiety disorder?
  - SSRI or SNRI
- Comorbid ADHD?
  - bupropion, venlafaxine
- Low BMI and/or hx of GI upset?
  - mirtazapine
- Concurrent insomnia severe?
  - mirtazapine, trazodone

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Optimizing

- ↑ dose of the initial antidepressant after verifying adherence and lack of drug-drug interactions
- Continue until maximum dose reached, symptoms abate, or side effects become excessive
- 8-12 weeks is an adequate trial for most agents if the patient can tolerate a moderate dose
  - Subset of patients need 16-20 weeks
    - Particularly co-occurring anxiety disorders

Park LT, Zarate CA. Depression in the Primary Care Setting. N Engl J Med. 2019. 380;6:559-568.

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Ketamine

- Has been found to be effective treatment for short-term, maintenance, or prolonged treatment.[1,2]
- Rapid onset of efficacy with improvement seen within days[1,2]
- Esketamine (Spravato) is a nasal spray used under strict medical supervision

1. Daly EJ, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry*. 2019;76(9):893-903
2. Marwaha S, et. al Upthegrove R. Novel and emerging treatments for major depression. *Lancet*. 2023;401(10371):141-153.

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ECT/rTMS

ECT

- **One of our oldest and most effective treatments**
  - **Efficacy is 70-90% in studies of treatment resistant depression**
- **Limited availability**
- **Cognitive side effects**

rTMS

- **Substantial efficacy**
- **Treatment modality still advancing**
- **Decreased cognitive impacts compared to ECT**
- **Greater availability than ECT**

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New Old Kids on the Block

- Psilocybin-In trials, participants receive doses of psilocybin during sessions with therapists providing nondirective, supportive therapy. Small, open-label trials have been encouraging, larger trials are needed to better evaluate the efficacy.[1]
- MDMA AKA "ecstasy"- Small trials of MDMA assisted psychotherapy have been encouraging. Inadequate data to draw generalized conclusions. Further study is needed.[1]

1. Reiff CM, Richman EE, Nemeroff CB, et al. Psychedelics and Psychedelic-Assisted Psychotherapy. *Am J Psychiatry*. 2020;177(5):391-410.

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If Things Aren't Working, Should I Switch Agents or Augment?

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- Augmentation strategies also appear to be more beneficial than switching within or between classes of antidepressants
- Augmentation with an agent with a different mechanism of action may accelerate response to antidepressant therapy

Rafeyan R, Papakostas GI, Jackson WC, et al. Inadequate response to treatment in major depressive disorder: augmentation and adjunctive strategies. J Clin Psychiatry. 2020;81(3):OT19037BR3

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If You See Even a Little Benefit, Consider Augmenting First

- First choices of augmentation agents (based on side effects/risk:benefit ratios):
  - Bupropion-(may need to reduce SSRI dose given bupropion is an inhibiter of 2D6)
  - Mirtazapine

Connolly KR, Thase ME. If at first you don't succeed: A Review of the Evidence for Antidepressant Augmentation, Combination and Switching Strategies. Drugs 2011; 71 (1): 43-64.
Park LT, Zarate CA. Depression in the Primary Care Setting. N Engl J Med. 2019. 380;6:559-568.

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Other Augmenting Options

- Lithium- at >600mg/day see 30-60% response rate[1]
- Thyroid-hormone- T3 at doses of 25-50mcg/day-helpful in approximately ½ of studies[1]
- Buspirone-10-30mg/day-effectiveness mixed-did help with sexual side effects[2]
- Second generation antipsychotics

1. Nierenberg AA. et al. Am J Psychiatry 2006;163(9):1519-30
2. Trivedi MH. Et al. J Eng J Med 2006;354(12):1243-52

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Second Generation Antipsychotics and Depression

- Aripiprazole- several trials have found significant benefit as an adjunctive tx. NNT 5-10 depending on the study.
- Olanzapine+fluoxetine combination- received FDA approval based on 5 studies
- Quetiapine XR- Has FDA approval for adjunctive therapy for MDD. NNT ~8
- Risperidone- two studies found significant benefit in first 4 weeks but not sustained so not currently recommended.
- **The data is limited** and see increased side effects, but rapid responses

Connolly KR, Thase ME. If at first you don't succeed: A Review of the Evidence for Antidepressant Augmentation, Combination and Switching Strategies. Drugs 2011; 71 (1): 43-64.
Chen J Curr Opin Psychiatry 2011 24;10-17

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Weight Gain Associated with Antipsychotics

- Early weight gain associated with greater propensity to gain more weight
- Step 1- reevaluate if really need med
- Step 2- diet, exercise
- Step 3- Metformin
  - 500mg daily X 2weeks ->500mg BID for 2 weeks. IF needed ->850mg BID
  - GI distress- slow your roll or use slow-release formulation
  - If no benefit after 16 weeks d/c
  - If wait too long does not help!

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Switching

- Within a class.
  - STAR*D trial showed ~50% of nonresponders to an SSRI will benefit from a second SSRI[1]
  - Second switch less likely to help
- Can also consider switching to a different class
- Approximately 30-60% will respond to a medication switch

1. A John Rush et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin 2004 Feb;25(1):119-42 Trials

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How to Switch

- Two options:
  - Cross-tapering typically occurs over a two-to-four- week period. If patient sensitive to side effects or discontinuation symptoms, cross-tapering is extended over three to four weeks.
  - Immediate Switch to equivalent dose of new antidepressant- see more when moving within a class

Keep an eye on drug drug interactions!!!

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Antidepressant Withdrawal

- At minimum therapeutic doses there is ~80% serotonin transporter occupancy.[1]
- Risk factors[2]
  - Potent serotonin reuptake inhibition
  - Short half-life
  - Limited low dose availability
  - Long term treatment (> 6 mo)
  - High doses

1. Shapiro B. Psychopharmacology 2018;235:2779-2781
2. Shapiro B, Cohrs D. Antidepressant Withdrawal. Psychiatric News Sept 2025:19-25

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Tx: General Framework

Pharmacologic
- Thoughtful choice of agent
- Optimize single agents
- Augmentation
- Switching agents

Nonpharmacologic
- **Clarify dx**
- **Screen for other disorders**
- **Psychoeducation**
- **Psychotherapy**
- **Sleep optimization**
- **Psychosocial interventions**
- **Lifestyle optimization**

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Psychotherapy

- Many forms are effective including **Cognitive Behavior Therapy, Interpersonal Psychotherapy**, Behavioral Activation Therapy, Problem-solving Therapy
- Choose based on availability and patient preference
- Benefits often persist after therapy unlike meds in which benefits are often lost after med discontinuation.

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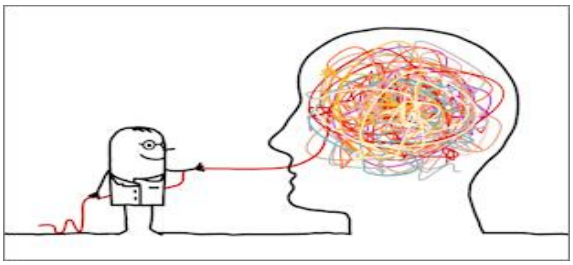
- RCTs found combination of pharmacotherapy and psychotherapy, more effective than either of these treatments alone



Cuijpers P, et al. Psychotherapy versus the combination of psychotherapy and pharmacotherapy in the treatment of depression: a meta-analysis. Depress Anxiety 2009; 26:279.

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Other Therapy Resources

- Smartphone apps are amazing:
  - Mindfulness
  - CBT-I
  - ACT coach
  - PE and PTSD coach
  - CPT Coach
  - Virtual hope box
  - Move Forward (which is problem solving therapy)
  - And many more…
- Though there is limited clinical data comparing apps

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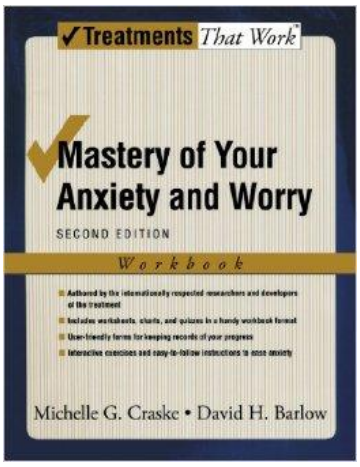
Other Therapy Resources



- There are a number of other tools that patients can use themselves:
  - Workbooks
  - Online courses
  - Community course
  - Clinic courses

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Sleep Disturbance and Mental Health

Insomnia is an independent risk factor for development of depression and anxiety

Sleep disturbance is a VERY common sx of depression

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- Aggressively treat insomnia
- Many non-pharmacologic interventions! Do these first!

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Wrapping It Up

- Anxiety and mood disorders are common and often present with somatic manifestations

- There is a huge amount of suffering associated with these illnesses!
- Screening questions can help identify diagnosis

- There are many effective treatments including psychotherapy and psychopharmacology

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