Identifying & treating Mood disorders

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Goals & Objectives

- Identify the differences between unipolar depression & bipolar disorder
- Explain the medication treatment options for unipolar depression & bipolar disorder
- Explore the use of antipsychotics in the treatment of unipolar depression & bipolar disorder

No current or previous pharmaceutical company affiliations

Alice

- 35yo married Caucasian female reports sadness with associated sleep disturbance, low energy, problems with concentration, and appetite changes since her pet dog died about one month ago. She has had difficulties functioning at work as well as keeping up with household tasks. She reports feeling embarrassed by her degree of grief as others "have it a lot worse".

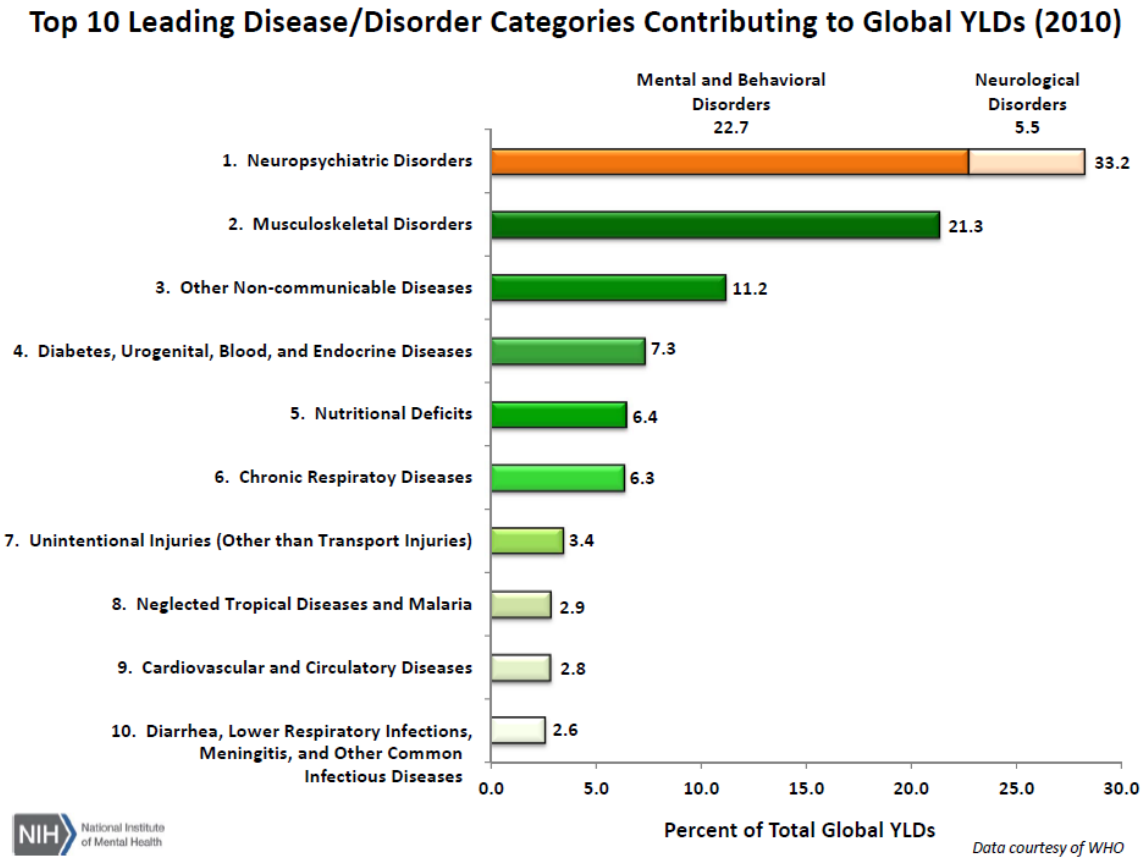
Major Depressive Disorder

- Lifetime prevalence around 15%
- Approximately 21 million (6.7%) US adults symptomatic annually
- Average age of onset 32yo
- Incidence in primary care practices about 10%
- Women 70% more likely than men to experience MDD in their lifetime
- Hispanics and African Americans 40% less likely than non-Hispanic Caucasians to experience MDD in their lifetime
- Accounts for significant cause of disability

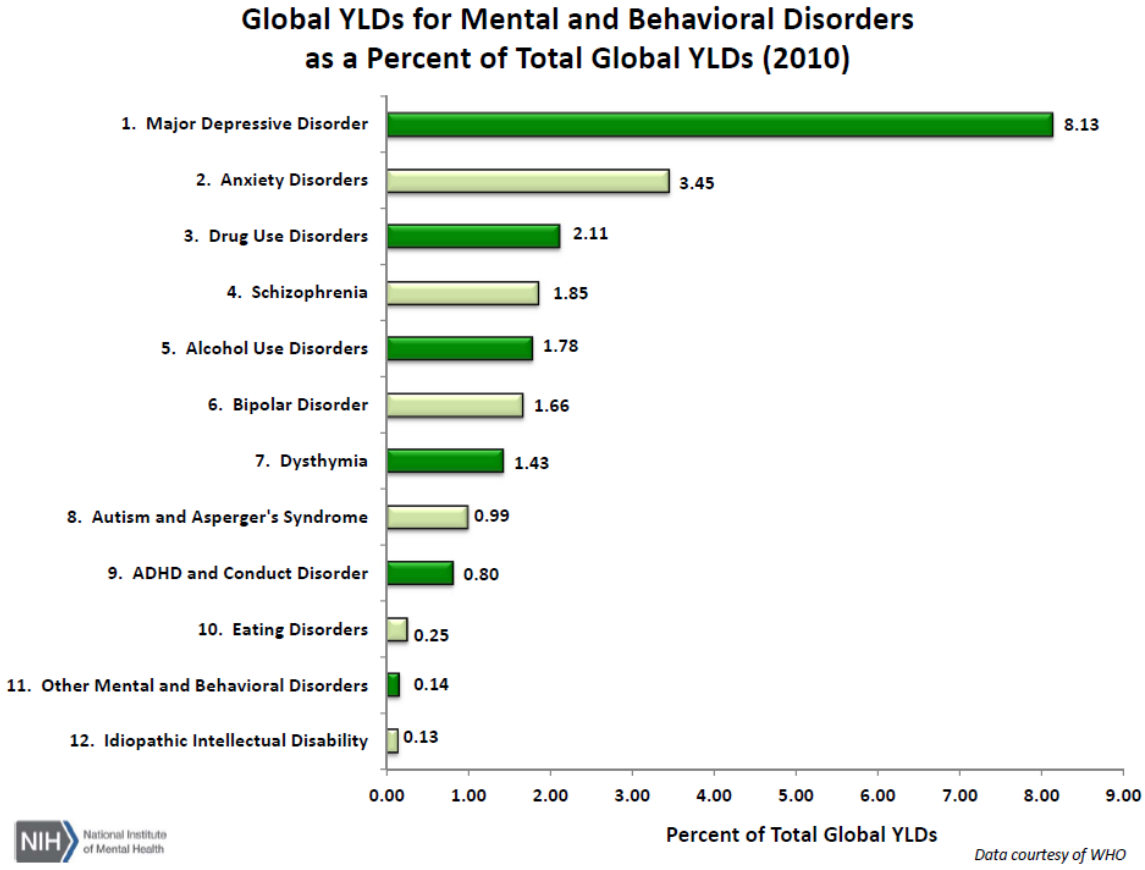
Major Depressive Disorder
DSM-5 Criteria

- SYMPTOMS
  - Depressed mood*
  - Anhedonia*
  - Appetite or weight changes
  - Sleep disturbance
  - Psychomotor activity change
  - Low energy
  - Beliefs of worthlessness or guilt
  - Concentration difficulties or indecisiveness
  - Thoughts of death or suicidal ideation
- Symptoms cause distress or impaired functioning

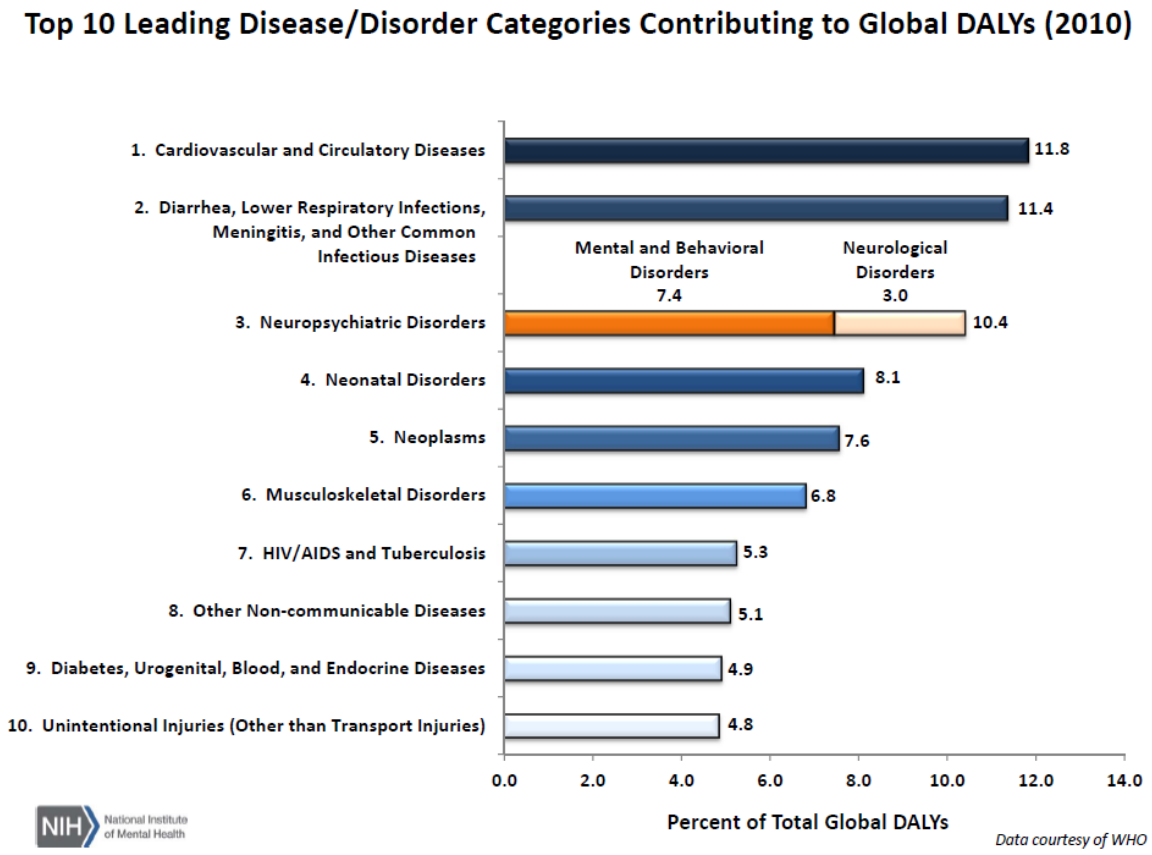
Measuring Burden of Disease
Global Years Lived with disability



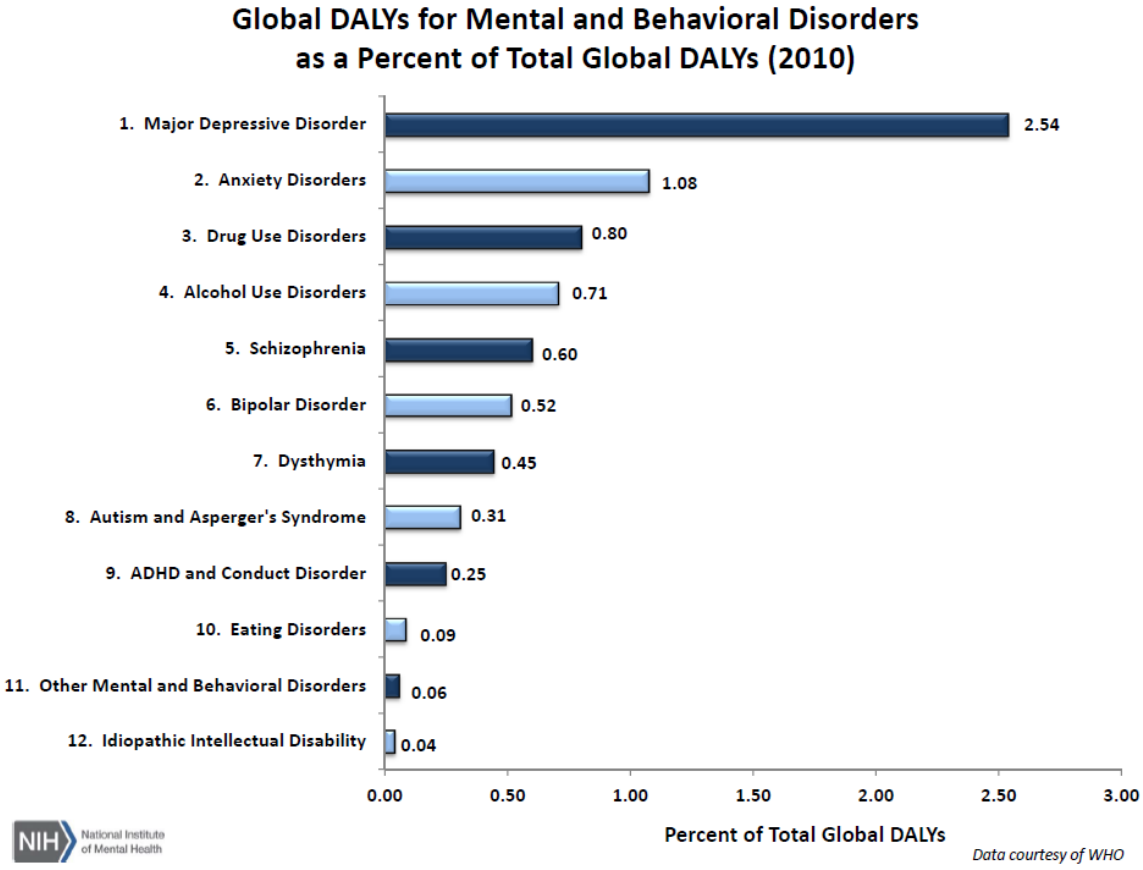
Measuring Burden of Disease
Global Years Lived with disability



Measuring Burden of Disease
Global Disability adjusted Life years



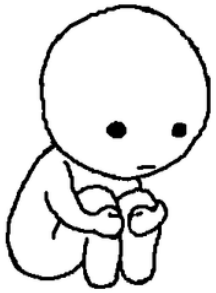
Measuring Burden of Disease Global Disability adjusted Life years



Alice

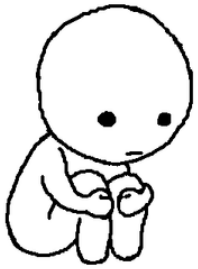
- She admits to wishing for her death at times in recent days. While she does admit to considering to overdose on over the counter sleeping pills, she denies intent to follow through with these thoughts. She reports her Catholic faith and children would prevent her from attempting suicide. She has never previously attempted suicide.

SUICIDE



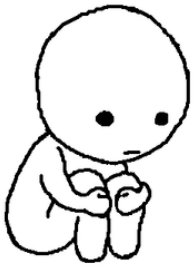
- About 9 million (3.9%) US adults will experience suicidal thoughts annually
- About 1.3 million (0.6%) US adults will attempt suicide annually
  - 494,169 ER visits in 2013 for treatment of self-inflicted injuries at $10.4 billion dollars in medical and work loss cost
- 13/100,000 US adults complete suicide annually
  - Men account for nearly 78% of suicides
- 13 US adults will complete suicide daily
  - $44 billion dollar cost in medical and work loss costs

Suicide



- Cause of US death
  - 7th for men; 14th for women
  - 2nd cause in 15-34yo
  - 4th cause in 35-54yo
  - 8th cause in 55-64yo
  - 17th cause over 65yo
- Firearms most common method of completion
  - More than 50% of suicides involved firearm
- Suffocation & poisoning 2nd and 3rd methods of completion

Suicide



- *Risk Factors*
  - Previous attempt
  - Access to firearm
  - Mood disorders
  - Psychotic disorders
  - Personality disorders
  - Addictions
  - Medical conditions
  - Family history
  - Poor support system
  - Money/housing problems
  - Legal problems
- *Protective Factors*
  - Commitment to others
  - Religious beliefs
  - Pregnancy
  - Good support system
  - Engagement in treatment

IMMINENT SUICIDE RISK

Application for Emergency Admission - ***PAGE 1 of 2*** **in accordance with Section 5122.10 ORC**

TO: The Chief Clinical Officer of _____ _____
(Facility Name) (Date)

The undersigned has reason to believe that:

_____
(Name of Person to be Admitted)

1. is a mentally ill person subject to hospitalization by court order under division B of Section 5122.01 of the Revised Code, i.e. this person

   ☐ (1) Represents a substantial risk of physical harm to himself as manifested by evidence of threats of, or attempts at, suicide or serious self-inflicted bodily harm;

   ☐ (2) Represents a substantial risk of physical harm to others as manifested by evidence of recent homicidal or other violent behavior, evidence of recent threats that place another in reasonable fear of violent behavior and serious physical harm, or other evidence of present dangerousness;

   ☐ (3) Represents a substantial and immediate risk of serious physical impairment or injury to himself as manifested by evidence that he is unable to provide for and is not providing for his basic physical needs because of his mental illness and that appropriate provision for such needs cannot be made immediately available in the community; or

   ☐ (4) Would benefit from treatment in a hospital for his mental illness and is in need of such treatment as manifested by evidence of behavior that creates a grave and imminent risk to substantial rights of others or himself..

2. Represents a substantial risk of physical harm to himself or others if allowed to remain at liberty pending examination.

Therefore, it is requested that said person be admitted to the above named facility.

STATEMENT OF BELIEF

Must be filled out by one of the following: a psychiatrist, licensed clinical psychologist, licensed physician, health or police officer, sheriff, or deputy sheriff.

(Statement shall include the circumstances under which the individual was taken into custody and the reason for the person's belief that hospitalization is necessary. The statement shall also include a reference to efforts made to secure the individual's property at his residence if he was taken into custody there. Every reasonable and appropriate effort should be made to take this person into custody in the least conspicuous manner possible.)

Alice

- Alice declines need for psychiatric hospitalization but expresses interest in treatment including medication for her depression. She denies any history of impairing mood symptoms. She has never taken an antidepressant. She has no chronic medical conditions with her medications consisting of only a multivitamin daily and ibuprofen as needed. She is not pregnant or considering future pregnancy. Her alcohol use is reported to be infrequent and minimal.

Antidepressant therapy
Alice should understand . . .

- Medication not “addictive”
- Medication will need to be taken daily at about the same time
- Beneficial effects will not be noticed until at earliest 2 weeks but more likely closer to 4 weeks
- Benefits of medication are limited
- Some side effects short-lived while others often lasting
- Avoid alcohol use as may worsen depression and/or cause additional side effects
- Medication should be continued for some time even once feeling better
- Discuss discontinuation with provider as tapering of medication likely

Antidepressant therapies

- SSRI
  - Fluoxetine (Prozac®)
  - Paroxetine (Paxil®)
  - Sertraline (Zoloft®)
  - Citalopram (Celexa®)
  - Escitalopram (Lexapro®)
  - Vortioxetine (Brintellix®)
  - Vilazodone (Viibryd®)
- SNRI
  - Venlafaxine (Effexor®)
  - Duloxetine (Cymbalta®)
  - Desvenlafaxine (Pristiq®)
  - Levomilnacipran (Fetzima®)
- Other
  - Bupropion (Wellbutrin®)
  - Mirtazapine (Remeron®)
  - TCAs
  - MAOIs

	Starting Dosage	Usual Target Dosage
Fluoxetine (Prozac®)	10-20mg daily	20-80mg daily
Paroxetine (Paxil®)	IR: 10-20mg daily CR: 12.5mg daily	IR: 20-60mg daily CR: 25-75mg daily
Sertraline (Zoloft®)	25-50mg daily	100-200mg daily
Citalopram (Celexa®)	10-20mg daily	20-40mg daily
Escitalopram (Lexapro®)	5-10mg daily	10-20mg daily
Vortioxetine (Brintellix®)	10mg daily	10-20mg daily
Vilazodone (Viibryd®)	10mg daily	20-40mg daily
Venlafaxine (Effexor®)	IR: 18.75mg BID XR: 37.5mg daily	IR: 75-375mg daily in BID XR: 75-225mg
Duloxetine (Cymbalta®)	30mg daily	60-120mg daily
Desvenlafaxine (Pristiq®)	50mg daily	50-100mg daily
Levomilnacipran (Fetzima®)	20mg daily	40-120mg daily
Bupropion (Wellbutrin®)	IR: 75mg BID SR/XL: 100-150mg daily	IR: 300-450mg daily in BID-TID SR: 300-400mg daily; XL: 300-450mg daily
Mirtazapine (Remeron®)	15mg daily	15-45mg daily

Antidepressant Therapy *How to choose???*

- Keeping in mind antidepressant effectiveness is generally comparable within and between classes, determine choice by considering . . .
  - Patient preference
  - Prior response
  - Side effect profile
  - Drug interactions
  - Comorbities
  - Cost

Antidepressant sample availability should generally NOT guide medication choice!

Antidepressant Therapies
Side effects

- Anytime serotonin is increased, potentially . . .
  - Nausea
  - Diarrhea
  - Headache
  - Insomnia
  - Anxiety
  - Weight gain*
  - Sweating*
  - Sexual dysfunction*
  - Easy bruising/abnormal bleeding*

- When norepinephrine is increased, potentially . . .
  - Increased blood pressure and pulse

Antidepressant Therapies
Pearls from facts & my experiences . . .

- Long-half life of fluoxetine (Prozac®) helps with adherence
- Fluoxetine (Prozac®) and paroxetine (Paxil®) seem to cause sexual dysfunction more often & have more drug interactions than other SSRIs
- Bupropion (Wellbutrin®) and mirtazapine (Remeron®) least likely to cause sexual dysfunction
- Weight gain and sedation significant with paroxetine (Paxil®) and low dose mirtazapine (Remeron®)
- Venlafaxine (Effexor®) and bupropion (Wellbutrin®) with minimal weight gain

Antidepressant Therapies
Pearls from facts & my experiences . . .

- Citalopram (Celexa®) and escitalopram (Lexapro®) probably carry same QT prolongation risk
- Sertraline (Zoloft®) seems to cause more GI distress than other SSRIs
- Paroxetine (Paxil®) more anticholinergic than other SSRIs
- Vilazodone (Viibryd®) needs to be taken with food
- SNRIs seem to cause sweating more often than SSRIs
- All SNRIs seem to help with pain syndromes
- Duloxetine (Cymbalta®) associated with constipation and dry mouth
- Bupropion (Wellbutrin®) monotherapy typically not very effective for MDD

Antidepressant Therapies
Pearls from facts & my experiences . . .

- Seizure risk with bupropion (Wellbutrin®) dose related and more likely with IR forms
- Lower doses of mirtazapine (Remeron®) cause more sedation and appetite stimulation than higher doses
- Mirtazapine (Remeron®) has 5HT3 receptor antagonism which eliminates serotonin-mediated nausea
- Paroxetine (Paxil®) and venlafaxine (Effexor®) require very slow discontinuation
- Most antidepressants are pregnancy category C
- Paroxetine (Paxil®) is pregnancy category D due to association with congenital cardiac malformations

Antidepressant Therapies

- **$4/month generics**
  - Fluoxetine (Prozac®)
  - Paroxetine (Paxil®)
  - Citalopram (Celexa®)
- **Generics**
  - Sertraline (Zoloft®)
  - Escitalopram (Lexapro®)
  - Venlafaxine (Effexor®)
  - Duloxetine (Cymbalta®)
  - Bupropion (Wellbutrin®)
  - Mirtazapine (Remeron®)
- **No generics**
  - Vortioxetine (Brintellix®)
  - Vilazodone (Viibryd®)
  - Desvenlafaxine (Pristiq®)
  - Levomilnacipran (Fetzima®)

Alice

- After extended discussion regarding potential benefits and risks of antidepressant therapy, Alice agrees to start sertraline (Zoloft®) at 25mg daily with a plan to increase to 50mg daily on 10th day of dosing. She also accepts contact information for a local counselor. She is instructed to call the office with any questions or concerns before her follow-up appointment which is scheduled for about one-month from today.

Alice

- Alice calls the office the next morning as her best friend told her she has heard that antidepressants like sertraline (Zoloft®) may make her more suicidal. She is unwilling to start it without discussing this reported risk.

Antidepressants & Suicide

- **WARNING:** Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger in short term studies. Monitor closely for clinical worsening and emergence of suicidal thoughts and behaviors.

  - Placed in October 2004 when FDA review found increase in the suicidal thoughts and behaviors of children treated with SSRIs. Warning applied to SSRIs & SNRIs.
    - Out of 2,200 treated children, 4% (88) displayed increase compared to 2% of treated with placebo
    - No actual suicides!
  - Subsequent studies suggest benefits of antidepressant therapy outweighs this risk

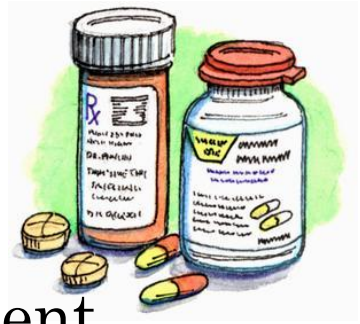
Antidepressant Therapy *Treatment Guidelines*

- Treatment goal is remission of symptoms
- Treat for sufficient duration
- Treat at sufficient dosage
- Make treatment modification when no symptomatic improvement after about 4 weeks
- Monitor for adherence
- Consider augmentation when at least partial response achieved
- Consider medication change to different agent when less than partial response achieved at maximized therapy

Alice

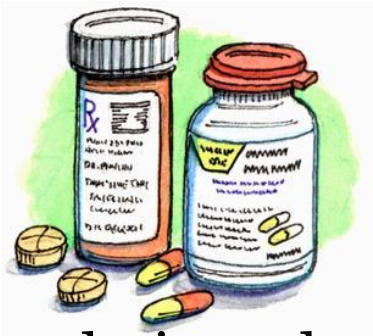
- At her one-month follow-up, Alice reported tolerating 50mg sertraline (Zoloft®) daily with minimal improvement reported. Her regimen was increased by 50mg every 4 weeks until she reached a daily dosage of 150mg daily. She also started engaging in individual counseling. At her 3 month follow-up, Alice reported a 75% improvement overall with issues with energy and concentration persisting. She also reported problems with anorgasmia which frustrated both her and her husband.

Antidepressant Therapy
Augmentation strategies



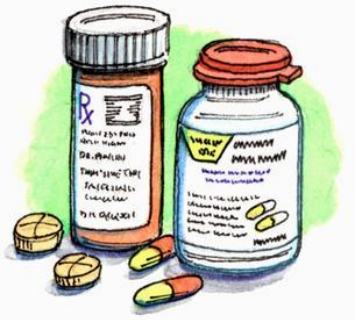
- Augmenting agent should have different mechanism of action
- Most commonly, SSRI/SNRI therapy augmented with bupropion (Wellbutrin®) or mirtazapine (Remeron®)
- Other augmenting agents with a modest evidence base include atypical antipsychotics, lithium, and thyroid hormone
  - Aripiprazole (Abilify®), brexpiprazole (Rexulti®), quetiapine XR (Seroquel XR®), and olanzapine in combination with fluoxetine (Symbyax®) only ones with FDA indications
- Augmenting agents with limited supporting evidence include anticonvulsants, psychostimulants, omega-3 fatty acids, and folate

Antidepressant Therapy
Augmentation Strategies
How To Choose???



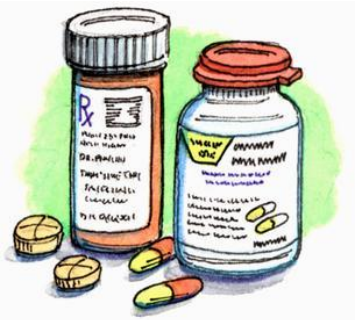
- Bupropion (Wellbutrin®) reasonable choice when residual symptoms include lack of energy and concentration difficulties
- Bupropion (Wellbutrin®) helpful in reducing sexual dysfunction related to SSRI/SNRI therapy
- Mirtazapine (Remeron®) reasonable choice when residual symptoms include low appetite and sleep onset difficulties
- Combination of high dose venlafaxine (Effexor®) and high dose mirtazapine (Remeron®) considered regimen for treatment resistant depression

Antidepressant Therapy Augmentation Strategies How To Choose???



- Decision to use atypical antipsychotic increases acute and long-term side effect burden
  - Extrapyramidal symptoms including NMS & TD
  - Metabolic syndrome
- Consider aripiprazole (Abilify®) when residual symptoms failed to remit with bupropion (Wellbutrin®) or when bupropion not tolerated or contraindicated
  - Starting dose between 2-5mg daily
  - Increase by 5mg or less on a weekly basis
  - 15mg daily maximum dose

Antidepressant Therapy Augmentation Strategies How To Choose???



- Consider quetiapine XR (Seroquel XR®) when residual symptoms failed to remit with mirtazapine (Remeron®) or mirtazapine not tolerated or contraindicated
  - Starting dose 50mg daily
  - Increase to 150mg daily on day 3 of dosing
  - 300mg daily maximum dose
  - Take on empty stomach or with light meal
- Role of olanzapine/fluoxetine (Symbyax®) limited
  - Combinations ranging from 3/25mg to 12/50mg
- Role of brexpiprazole (Rexulti®) unclear
  - Starting dose 0.5-1mg daily
  - Increase by 1mg weekly to maximum dose of 3mg daily

Alice

- The decision was made to augment Alice's sertraline (Zoloft®) regimen with bupropion SR (Wellbutrin SR®) 100mg daily. She also planned to continue individual counseling. At her follow-up appointment in 6 weeks, she reported resolution of her depressive symptoms with her daily functioning back to baseline. Alice also reported her anorgasmia had essentially resolved. She inquires how long she should remain on antidepressant treatment.

Antidepressant Therapy

Length of Treatment Recommendations

- Continue medication regimen at same dosage(s) used to achieve remission for at least 4 months
- Discuss risk of recurrence before attempting discontinuation
  - About 20% experience recurrence within 6 months of remission
  - At least 50% will experience another episode of MDD in his/her lifetime
  - Earlier age of onset, severity of episode, presence of other psychiatric conditions and/or chronic medical condition, and ongoing psychosocial stressors are risk factors for recurrence
- Consider maintenance medication therapy in patients with 3 or more prior episodes of MDD

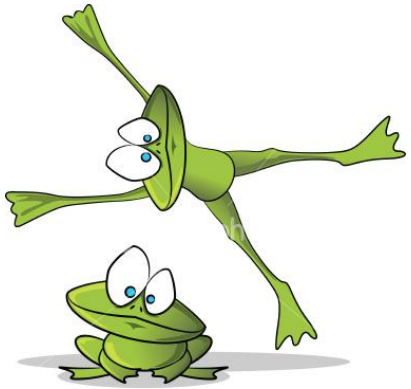
Antidepressant Therapy
Discontinuing Therapy

- Gradual reduction of therapy over weeks recommended
  - Allows for early detection of relapse & facilitates return to full treatment
  - Avoids discontinuation syndrome
- If treatment involved polytherapy, reduce one agent at a time
- Keep close follow-up

Antidepressant Therapy Discontinuation Syndrome

- More common with antidepressants with shorter half lives
- Gradually cross-tapering to new agent or tapering to discontinuation will minimize or avoid this syndrome
- Onset within 1-3 days
- Unpleasant experience!
  - Flu-like experiences: headache, chills & body aches
  - Insomnia
  - Nausea
  - Instability: light-headedness
  - Sensory disturbances : paresthesias, electric shock-like phenomena
  - Hyperarousal: irritability & anxiety
- Typically self-limited course resolving in 2 weeks

Lisa



- 29yo married Caucasian female presents complaining of 6 weeks of anhedonia with associated insomnia, low energy, weight loss, and concentration problems without an identified stressor. She denies any desire for death and endorses hope for recovery. These symptoms have caused her to withdraw from family and friends as well as miss days of work. She admits to similar mood episodes in the past as well as "really good" mood states with high energy despite little sleep, talkativeness, and productivity.

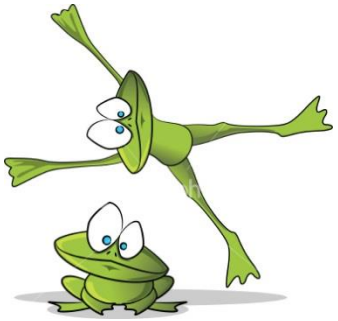
BIPOLAR DISORDER

- Lifetime prevalence at most 3%
- Approximately 8 million (2.7%) US adults symptomatic annually
- More common in women than men yet men with earlier age of onset
- Average age of onset 25yo
- Associated with increased rates of divorce and incarceration
- Accounts for significant cause of disability

Bipolar Disorder
DSM 5 Criteria For Hypomania

- SYMPTOMS
  - Elevated, expansive, or irritable mood*
  - Increased energy*
  - Grandiosity
  - Decreased need for sleep
  - Talkativeness
  - Racing thoughts
  - Distractibility
  - Increased goal-directed activity
  - Excessive involvement in activities with high potential for negative consequence
- Mood disturbance noticeable yet does not cause significant impairment or result in hospitalization

Lisa



- Lisa admits that she was previously hospitalized for depression after a suicide attempt by overdose. She reports a good support system currently and denies need for psychiatric hospitalization. Her alcohol use is reported 2-3 times a month with episodes qualifying as binge drinking; no illicit drug use. She has no chronic medical conditions other than mild obesity. She is not pregnant but is sexually active with birth control "most of the time". Lisa is interested in medication treatment for her depression.

Treating Depression in Bipolar disorder

- Guidelines on medication strategies for still developing
- Antidepressant monotherapy not recommended
  - Likely to induce hypomania/mania
  - May cause acceleration of mood cycles
- Recommended medications include lithium, anticonvulsants and atypical antipsychotics

Medication treatment options for bipolar Depression during acute & maintenance stages

	Starting Dosage	Target/Max Dosage
Carbamazepine Tegretol®	200mg BID	800-1200mg daily *Trough level 4-12mcg/mL*
Lithium Eskalith® Lithobid®	300-600mg daily	900-1800mgdaily *Trough level 0.6-1.2mEq/L*
Lurasidone Latuda®	20mg daily	120mg daily
Olanzapine/Fluoxetine Symbyax®	6/25mg daily	12/50mg daily
Quetiapine Seroquel®	IR: 50mg daily XR: 50mg daily	IR: 600mg daily XR: 300mg daily
Valproic acid Depakote®	IR: 250mg TID ER: 20mg/kg	1000-2500mg Max 60mg/kg/day *Trough level 50-125mcg/mL*

Treating Depression in Bipolar Disorder *Keep in Mind . . .*

- Atypical antipsychotics
  - c/o sedation & weight gain
  - EPS
  - Metabolic syndrome
  - QT prolongation
  - Most pregnancy category C
  - Expensive
- Carbamazepine (Tegretol®)
  - c/o dizziness, headache, weight gain, & sedation
  - Bloodwork monitoring for impact on bone marrow & Na
  - Potent CYP450 3A4 inducer
  - Teratogenic: cranial facial deformities and neural tube defects
  - Generic & cheap
- Lithium (Eskalith®, Lithobid®)
  - c/o nausea, polyuria, polydipsia, weight gain, tremor, hair loss
  - Narrow therapeutic window
  - Blood work monitoring for impact on kidneys and thyroid
  - Teratogenic: cardiac abnormalities
  - Generic & cheap
- Valproic acid (Depakote®)
  - c/o nausea, sedation, weight gain, hair loss
  - Blood work monitoring for impact on liver and bone marrow
  - Teratogenic: Neural tube defects
  - Generics available

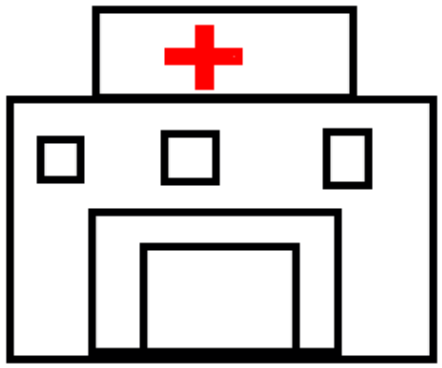
Mark

- Mark is a 26yo single Caucasian male presenting requesting evaluation to facilitate his return to work. While he states the requested evaluation is "ridiculous", his employer reports finding him irritable and inappropriate over the past week. He was put on leave after interrupting a board meeting claiming he had been appointed. He has been unproductive at work and sexually inappropriate towards support staff. His employer states Mark's recent behaviors are totally out of character and have never been previously witnessed. Mark states his boss feels threatened by his "inspirational ideas". He reports little need for sleep in recent days with his speech being difficult to interrupt.

Bipolar Disorder
DSM 5 Criteria for Mania

- SYMPTOMS
  - Elevated, expansive, or irritable mood*
  - Increased energy*
  - Grandiosity
  - Decreased need for sleep
  - Talkativeness
  - Racing thoughts
  - Distractibility
  - Increased goal-directed activity
  - Excessive involvement in activities with high potential for negative consequence
- Mood disturbance noticeable and severe with marked impairment or need for hospitalization

Treatment for Bipolar Mania



- Facilitate emergency room evaluation directly from office
- Attempts to help patient gain insight into mania during acute episode minimally effective
- Patient should be under care of mental health professional following discharge

Medication treatment options for bipolar I Mania during acute & maintenance stages

	Acute Mania Monotherapy	Acute Mania Adjunct	Maintenance Mania Monotherapy	Maintenance Mania Adjunct
Aripiprazole Abilify®	YES	YES	YES	YES
Asenapine Saphris®	YES	YES	NO	NO
Carbamazepine Tegretol® Equetro®	YES	YES	YES	YES
Lamotrigine Lamictal®	NO	NO	YES	YES
Lithium Eskalith® Lithobid®	YES	YES	YES	YES
Lurasidone Latuda®	NO	NO	NO	NO
Olanzapine Zyprexa®	YES	YES	YES	NO
Risperidone Risperdal®	YES	YES	NO	NO
Quetiapine Seroquel®	YES	YES	NO	YES
Valproic Acid Depakote®	YES	YES	YES	YES
Ziprasidone Geodon®	YES	NO	NO	YES

References

- Centers for Disease Control & Prevention
- National Institute of Mental Health
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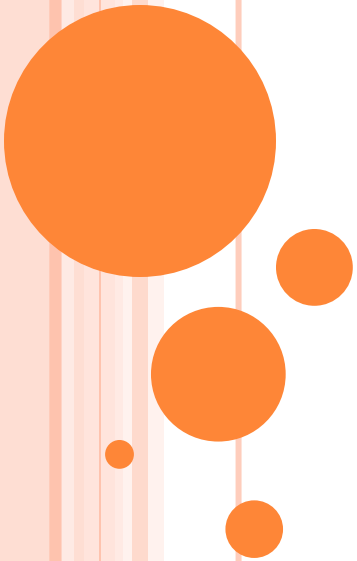

Questions