APPROACH TO DEPRESSION

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Outline

- Differential diagnosis of the sad state
- Treatment strategies
  - Using medication
  - Management of side effects
  - Drug interactions
  - Augmentation, substitution

DIFFERENTIAL DIAGNOSIS

Sad State

Sad State – Differential Diagnosis

- Rule out organic (DIME VETS)
- Adjustment disorder with depressed mood
- Unipolar depression
- Bereavement (DSM-V slightly changed. I disagree)
- Bipolar disorder, depressed phase
- Postpartum blues/depression
- Dysthymic disorder
- Seasonal affective disorder
- Premenstrual dysphoric disorder

Important to Remember

- r/o past depressive episodes
  - This has treatment implications: **length of time**
- r/o past manic episodes
  - This has treatment implications: **choice of meds**
- r/o medical disorders (i.e., **DIME VETS**)
  - **D**rugs (alcohol, benzodiazepines, steroids, propranolol)
  - **I**nfection
  - **M**etabolic (renal, hepatic)
  - **E**ndocrine (thyroid, parathyroid, Addison's, Cushing's)
  - **V**ascular (stroke, lupus)
  - **E**pilepsy
  - **T**umor
  - **S**yphilis

Seasonal Affective Disorder

Unipolar Depression

- Common in primary care
  - Approximately 5-8% of all outpatients seen by G.P.s have MAD
- 15% lifetime prevalence
  - 10% men
  - 20% women

Diagnosis – SIGECAPS

- Low mood/irritable mood for at least 2 weeks, **but** I would say 3-4 weeks minimum

  - **S**leep
  - **I**nterests (and pleasure)
  - **G**uilt
  - **E**nergy
  - **C**oncentration
  - **A**ppetite
  - **P**sychomotor agitation/retardation
  - **S**ex, **S**uicide

Diagnosis (2)

- NOTE:
  - Bereavement = 2 months (S. Zisook)
  - Breakup of long-term relationship = 2 months
  - Major risk factor: past history of depression

Geriatric Considerations

- Often display more vegetative signs and cognitive disturbance
- Often complain less of subjective dysphoria
- May often focus on physical complaints

Clues Regarding Implication of Organic Factors

1. Old age at first onset of mental illness (older than age 50)
2. Clouded sensorium
3. Non-auditory hallucinations

Depression Screen

“Have you ever had a period of sadness not for a day or two, not for a week or two, but for many weeks and months? You had no energy, no interest in things, and you weren’t eating or sleeping well. Has this ever happened to you?”

Hypomanic Screen

“Have you ever had a period or feeling better than good, not for an hour or an evening, but for days and days where you were unusually full of energy and had a decreased need for sleep? Has this ever happened to you?”

TREATMENT

Education

- Common “illness”
  - Illness model can be helpful
- Epidemiology
- Not crazy
- Very positive treatment results
- Therefore, hope for the future

Counselling

- Stress diathesis model of depression
- Counselling can decrease stress, and increase supports
- Supportive therapy
- Cognitive Behaviour Therapy (CBT)
- Self-help books eg. New Mood Therapy by David Burns
- Mind over Mood by Christine Padesky

Clinical Pearl

- After you see someone one time, even if appears to be clinical depression, bring them back in a few days and see how everything goes. If improving hold off on meds, if not, start
- I think it's okay to start meds if close to depression. Often see more sub-syndromal than I do in psychiatry

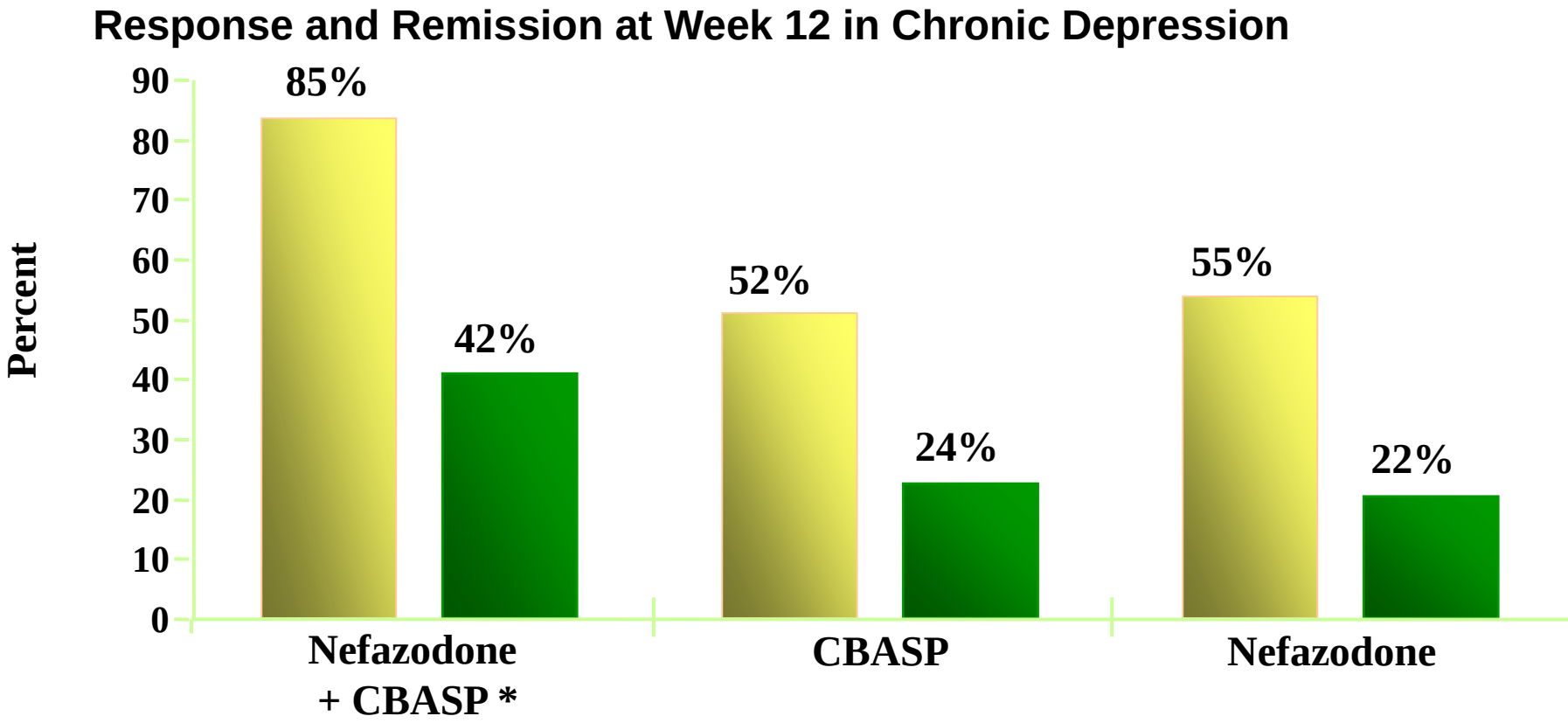
Psychopharmacology

- So you've ruled out organic, it's not bipolar, it's not an adjustment disorder, and they haven't responded to psychotherapy
- You're going to start meds
- How do you do this?

Medications

- 60-80% recover vs. 20-40% placebo
- Efficacy fairly equal in studies
- Therefore, side-effect profile important

Combination Pharmacotherapy and Psychotherapy is More Effective than Either Alone



Response

$p \leq 0.001$ combined vs. treatment nefazodone

$p \leq 0.001$ combined treatment vs. psychotherapy

Remission

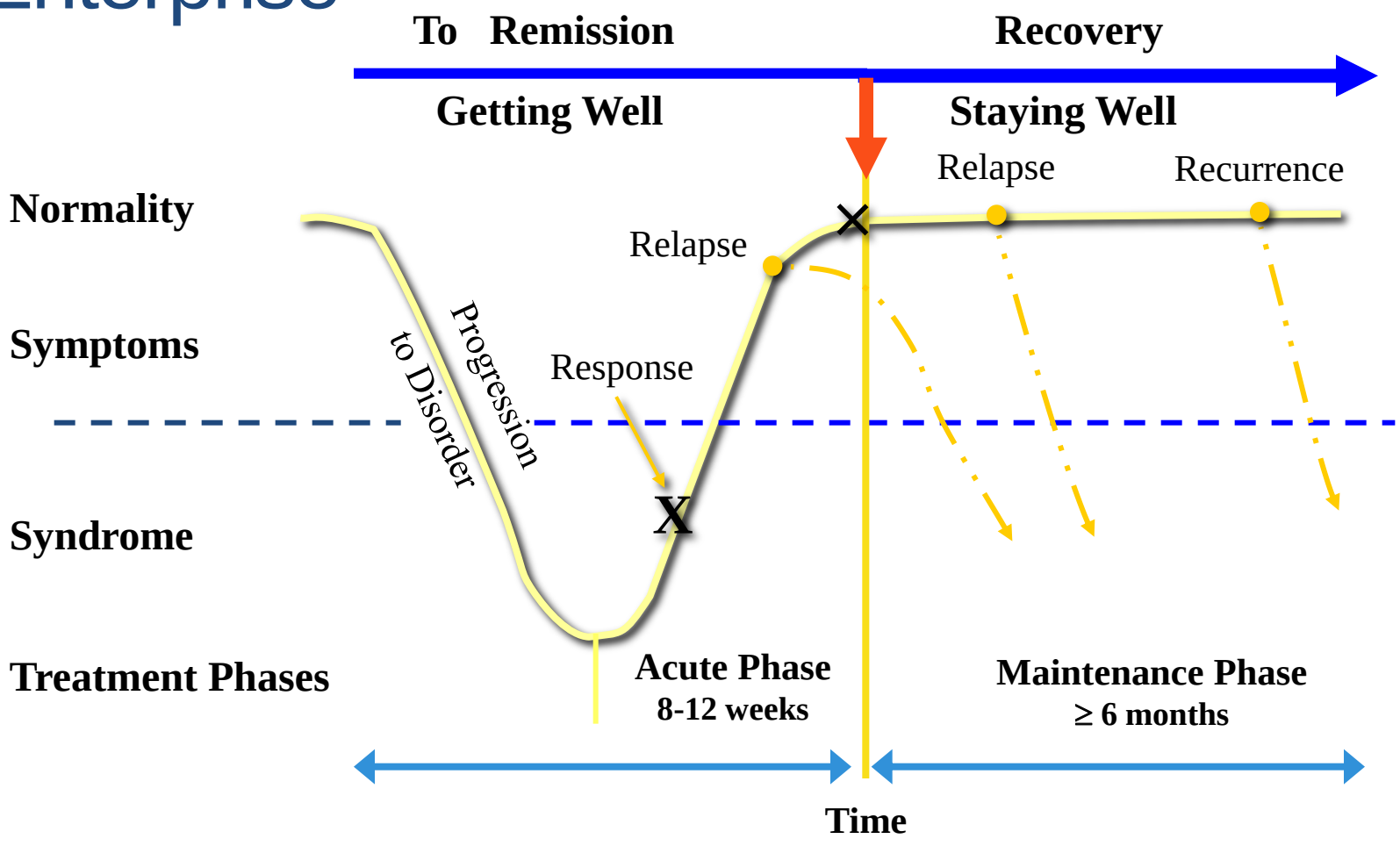
$p \leq 0.001$ combined vs. treatment nefazodone

$p \leq 0.001$ combined treatment vs. psychotherapy

*Cognitive behavior and specific psychotherapy

Keller *et. al.* The New England Journal of Medicine, May, 2000

Treating Depression is a Long-Term Enterprise



Depression is associated with high rates of relapse and recurrence

Adapted from Kupfer. 1991. Adapted from CANMAT Guidelines, June 2001.

SSRIs

Drug (Brand name)	Initial Dose (per day)	Range (per day)
Citalopram (Celexa)	20 mg	20-40 mg
Escitatalopram (Cipralex)	10 mg	10-20 mg
Fluoxetine (Prozac)	20 mg	20-60 mg
Fluvoxamine (Luvox)	50 mg	100-300 mg
Paroxitene (Paxil)	20 mg	20-60 mg
Sertraline (Zoloft)	50 mg	50-200mg

Other Antidepressants

- **SNRI**
  - Venlafaxine (Effexor)
    - Range: 75-225 mg per day
  - Desvenlafaxine (Pristiq)
    - Range: 50 mg per day
  - Duloxetine (Cymbalta)
    - Range 30-60 mg per day
- **NaSSA** (Noradrenergic and Serotonergic Specific Antidepressant)
  - Mirtazapine (Remeron)
    - Range: 15-45 mg per day

Other Antidepressants (2)

- **DNRI**
  - bupropion (Wellbutrin)
    - Range: 150-300 mg per day
- **RIMA**
  - Moclobemide (Mannerix)
    - Range: 150-300 mg **po bid**

Drugs with superior efficacy against comparators:

- **Escitalopram** – level 1 evidence
- **Sertraline** – level 1 evidence
- **Venlafaxine** – level 1 evidence
- **Duloxetine** – level 2 evidence
- **Mirtazapine** – level 2 evidence

  - Suggested to use one of these as 2nd antidepressant if 1st drug not effective

(CANMAT 2009)

Cipriani *et al.*, *Lancet*. 373:764-758, 2009

- Escitalopram and sertraline showed important differences with respect to efficacy and acceptability
- Sertraline also has better cost factor

Optimizing Dose

- Increase dose q3-4 weeks depending on response
- Increment of increase = starting dose
- If doing better, don't adjust
- Once they plateau, increase, unless back to normal
- If comorbid anxiety, reduce starting dose and incremental increases of ½ the amount, increase q2-3 weeks

The issue of non-adherence

- Early non-adherence is high among patients treated for depression
  - **28% stop** taking antidepressants during the first month, mostly during the first two weeks
  - **44% stop** taking antidepressants by the third month

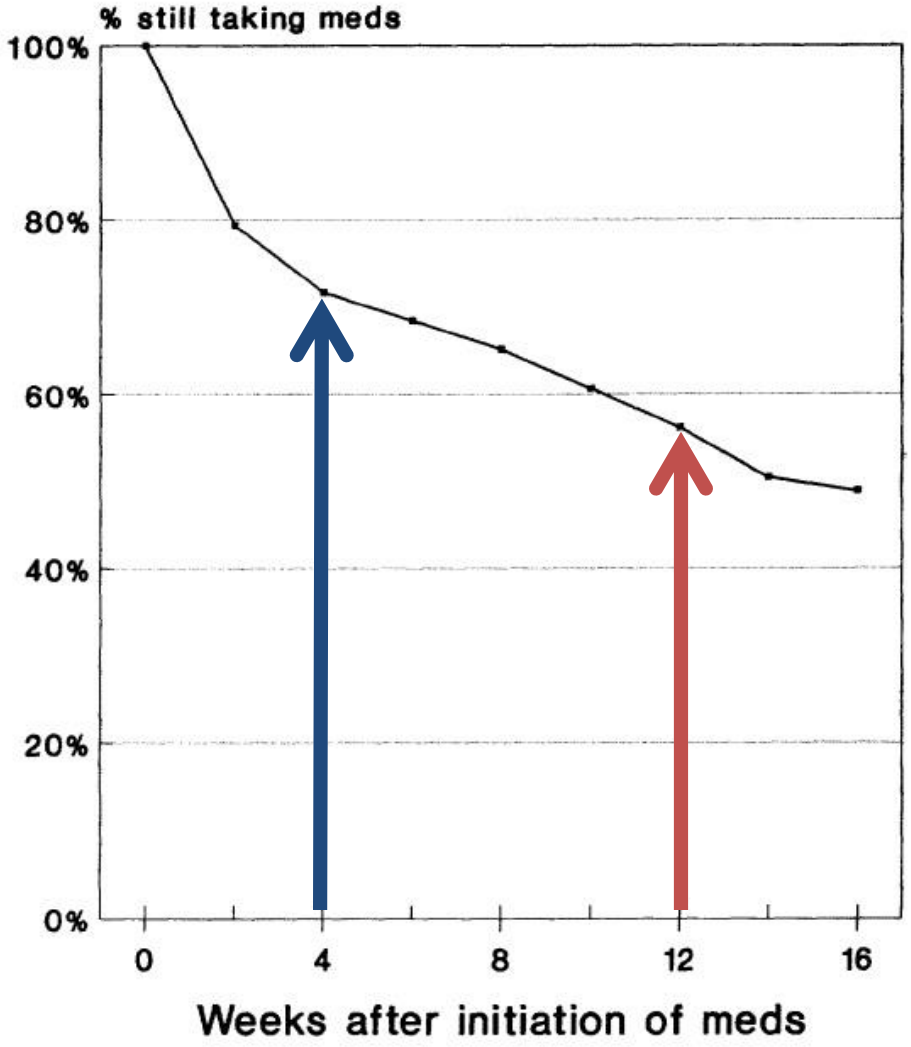


Figure adapted from Keller et al. *Medical Care,* 1995, 33(1):66-74.

Compliance with Antidepressants in General Practice

Reasons for Drop Out & Time of Event			
Proportion of respondents	**Reason**	**Time of drop out**	**Potential MD strategies**
35%	Feel better	6.1 weeks	Reminder to stay on
30%	Side effects	4.5 weeks	Ask/address side effects
17%	Other (e.g., fear of dependence)	8 weeks	Explain antidepressants are non-addictive
15%	Told by doctor	3.2 weeks	Stay on medication, if well
15%	Lack of Efficacy	1-4 weeks	Remind efficacy begins later

"52% stopped taking their medication during a 12 week period. Two-thirds did not inform their GP"

Psychoeducation makes a difference in improving response rates

Recurrence and Treatment Length

- **1 episode: 50% recurrence rate**
  - Treat for 6-9 months of feeling good, overall ~1 year
- **2 episodes: 70% recurrence rate**
  - Treat for 12-18 months of feeling good
  - If 2 difficult episodes, treat indefinitely
- **3 episodes: 90% recurrence rate**
  - Treat indefinitely

Management Approaches to Insomnia

- Wait for tolerance to occur
- Change the timing of antidepressant administration
- Reduce dose (main issue: efficacy could be lost)
- Switch antidepressant
- Pharmacological management:
  - Zopiclone (Imovane)
  - Trazodone
  - TCAs
  - Benzodiazepines
  - Tryptophan

Management Approaches to Hypersomnia / Fatigue / Apathy

- Wait for tolerance to occur
- Bedtime dosing
- Reduce dose (main issue: efficacy could be lost)
- Switch antidepressant

Management Approaches to Nausea

- Lower dose
- Wait for tolerance
- Symptomatic treatment
  - Gravol
  - NOT cisapride
- Switch antidepressant

Dewan & Anand. J Nerv Ment Dis 1999;187: 96-101.

Sexual Side Effects

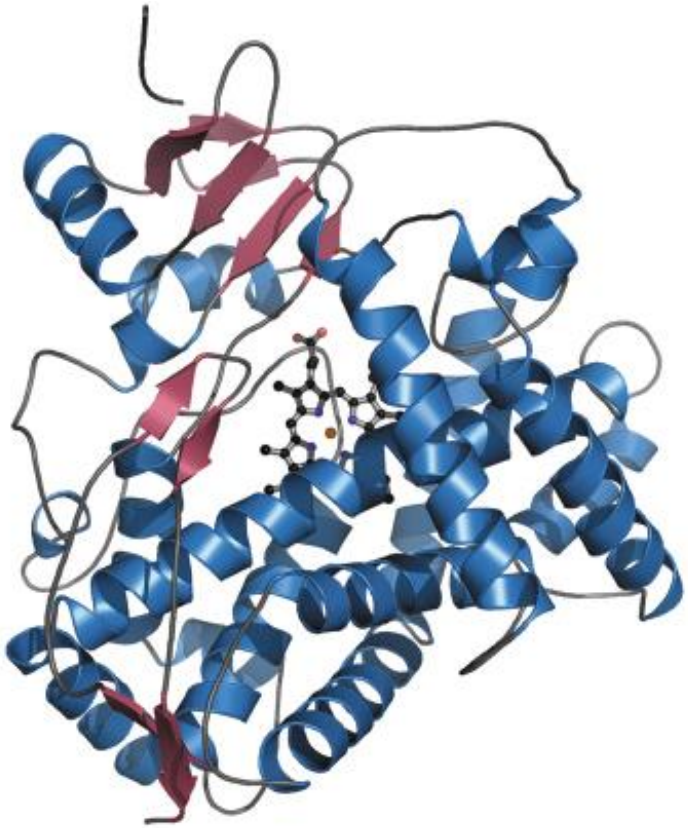
- Affect different phases of sexual response
  - Interest / desire / libido
  - Arousal
  - Orgasm
- Drugs with low sexual side-effects:
  - Bupropion
  - Mirtazapine
  - Mocolbemide

Management Approaches to AD-Induced Sexual Dysfunction

- Possible pharmacological antidotes
  - Bupropion
  - Sildenafil
  - Dose reduction (main issue: potential for relapse)
- Switch antidepressants
  - Bupropion
  - Mirtazapine
  - Moclobemide

Antidepressants and Drug Interactions

- Many drugs, including all antidepressants, are metabolized through the CYP450 enzyme system
- Each agent has an individual profile of inhibitory effects
- Drug plasma levels are affected through inhibition of drug metabolism



CYP450 Interactions

Drug	CYP 1A2	CYP 2C9	CYP 2C19	CYP 2D6	CYP 3A4
Citalopram	Mild	None	Mild	Mild	None
Fluoxetine	Mild	Mild	Mild	Significant	Mild
Fluvoxamine	Significant	Mild	Moderate	Mild	Moderate
Paroxetine	Mild	Mild	Mild	Significant	Mild
Sertraline	Mild	Mild	Mild	Mild	Mild
bupropion	None	None	None	Moderate	None
Moclobemide	Mild	None	Mild	Mild	None
Nefazodone	Mild	None	None	Mild	Significant
Reboxetine	None	None	None	Mild	Mild
Venlafaxine	None	None	None	Mild	None
Mirtazapine	None	None	None	Mild	None

Common Drugs Affected by Inhibition of the CYP450 System

1A2	2C19	2D6	3A4
• Theophylline • Warfarin • Clozapine • Benzodiazepines • Fluvoxamine	• Phenytoin • Warfarin • Amitriptyline • Clomipramine • Omeprazole	• Codeine • Venlafaxine • Trazodone • Resperidone • Haloperidol • Beta-Blockers • Amitryptyline • Nortriptyline • Imipramine • Desipramine	• Ca-Channel Blockers • Olanzapine • Carbamazepine • Cisapride • Corticosteroids • Biaxin • Protease Inhibitors • Statins • Quetiapine • Sildenafil • Citalopram

Common Drug Interactions

- Codeine
  - Inhibition of CYP 2D6 by paroxetine and fluoxetine prevents metabolism of codeine to morphine, making codeine less effective as an analgesic
- Warfarin
  - Inhibition of CYP 1A2 by fluvoxamine will result in higher levels of warfarin
  - INRs need to be monitored more closely
- TCAs
  - Inhibitors of CYP 2D6, such as paroxetine and fluoxetine, prevent the metabolism of tertiary amines, like amitriptyline and imipramine, increasing their blood levels
  - The common practice of using amitriptyline to treat insomnia problems could lead to interactions

Augmentation – Increasing Dose

- For partial response
  - Defined as 25% of the usual range or greater
- Go above the usual range
  - Often take meds one to two increments higher, as long as side effects are not a problem

Augmentation – Adding a different agent

- **First-Line Options:**
  - Lithium – Level 1
  - Aripiprazole – Level 1
  - Risperidone – Level 1
  - Olanzapine (added to fluoxetine) – Level 1
- **Second-line:**
  - Quetiapine
  - T3
  - Combination with bupropion or mirtazapine

Augmentation Strategies – Lithium

- Level 1 evidence for use
- Recommendation:
  - 600-900 mg per day
  - Continue for duration of treatment
- Approximately 60% response rate

Augmentation Strategies – T3 (Cytomel)

- ?Second line
- Recommendation:
  - 25 micrograms per day for 2 weeks
  - If no response increase to 50 micrograms per day
- Approximately 60% response rate

Augmentation Strategies – Atypicals

- Options
  - Olanzapine (Zyprexa) 2.5 – 5 – 7.5 – 10 mg po daily (Level 1 evidence with fluoxetine (Prozac))
  - Risperidone (risperdal) 0.5 – 1.0 – 1.5 – 2.0 mg po daily (Level 1 evidence)
  - Quetiapine (Seroquel) 50-150 mg po daily (?second-line)
- Keep them on as long as antidepressant
- If 3rd episode, for 1 year?

Combination Strategies

- ?Second-line
- Wellbutrin SR (bupropion)
  - 150-300 mg per day
- Mirtazapine
  - 20-60 mg per day

X-Crossover

- For use when switching to a different antidepressant
- Lower first drug by typical increment q5days
- Start 2nd drug at half dose along with starting dose of first drug for 5 days
- Increase second drug to full starting dose while discontinuing the 1st drug

Substitution

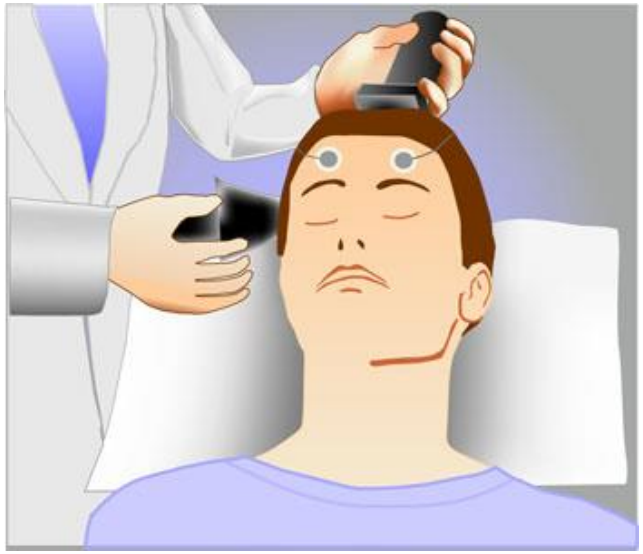
First Drug	Second Drug	Considerations
RIMA	MAOI	48 hour washout period
RIMA	SSRI	48 hour washout period (caution with paroxetine)
SSRI	SSRI	No washout period
SSRI	TCA	No washout period, Start TCA at lower dose
SSRI	MAOI	Two week washout, Five week washout for fluoxetine
SSRI	RIMA	Two week washout, Lilly recommends 5 weeks when switching fluoxetine to RIMA

ECT – Electroconvulsive Therapy

- Highest rate of therapeutic success
- No absolute contraindications
- Chief side effects are cognitive
  - Memory impairment typically resolves in a few weeks after cessation of treatment
  - Rarely, more pervasive and persistent cognitive disruption
- Method
  - Unilateral, non-dominant
  - Fewer side effects (e.g., cognition disruption)

ECT – Indications

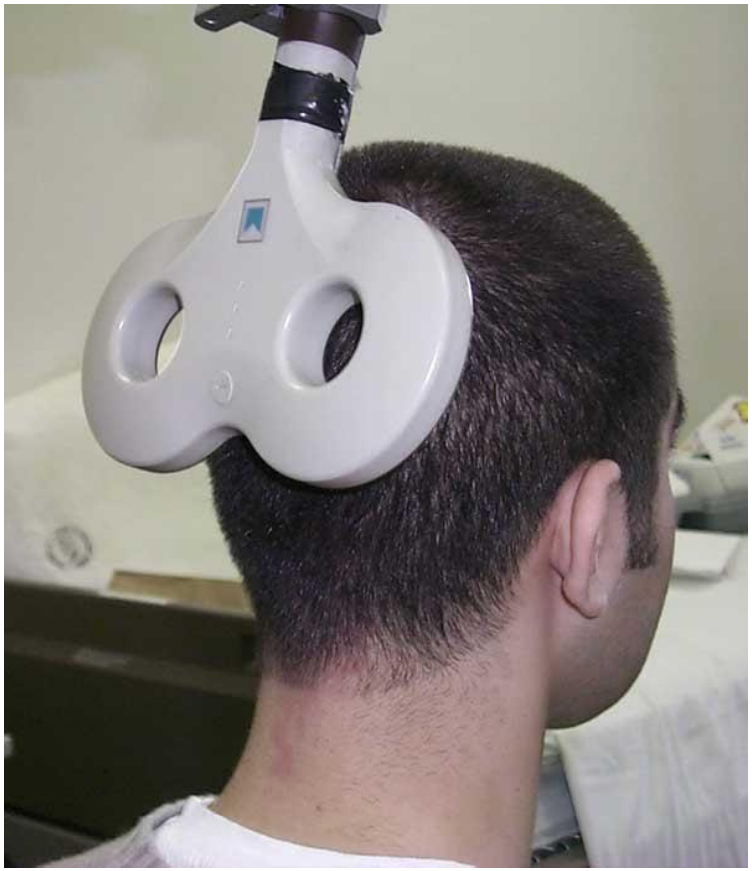
- Non-response to antidepressant medication
- Food refusal leading to nutritional compromise
- Unable to tolerate antidepressant medications
- Past response to ECT
- Medical condition precludes use of antidepressant medications



ECT (in Hollywood)

TMS

- Transcranial Magnetic Stimulation
- Not officially approved, experimental
- Has helped some people



Pediatric Depression

- Depression can present a little differently
- Watch for decreased school performance
- Use Fluoxetine (RCT evidence)
- Increased suicidal ideation and behaviours (not completed suicides)
  - True in kids, not in adults
- NNH-143

Patient Health Questionnaire (PHQ)

- Self report
- Does not replace clinical interview
- Supports diagnosis and can follow treatment effects

End

- Questions?

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