TREATMENT RESISTANT DEPRESSION:

Theory & Practice

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CPD

Dynamics of Depression

1. Strong fixation on loss
2. Objects are necessary for survival
3. Intolerance of ambivalent feelings
4. Internal attribution style



Major Depressive Disorder

General Statistics

- Prevalence rates vary
  - Point prevalence of 25% worldwide; similar in USA
  - 12-mo prevalence in US is 10%; lifetime prevalence is 27%
- 11th greatest cause of morbidity world wide; 2nd highest cause of morbidity in the United States
- 67% of patients with MDD will begin treatment with PCP
    - 50% of depressed patients are missed in primary care settings
    - Only 20% of patients remained on treatment 1mo after PCP visit

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Major Depressive Disorder

General Statistics

- Response rates of antidepressant (63%) vs placebo (35%)
- 37% of patients in remission following one antidepressant
- 67% of cumulative patients in remission following second strategy
- However, of the non-responders, the data is bleak:
    - 31% response after 2nd treatment,
    - 14% response after 3rd treatment, &
    - 13% response after 4th treatment

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Selective Serotonin Reuptake Inhibitors

Drug	Elimination (hours)	Dose Range (mg/d)	Indications	Details
Citalopram (Celexa) Escitalopram (Lexapro)	36	20-40 10-30	MDD, GAD	Low GI side effects, watch for QTc prolongation (not in elderly)
Fluoxetine (Prozac)	88-384	20-80	MDD, OCD, Panic d/o, Bulimia, PMDD	Activating, 2D6 inhibition, safe in pregnancy, old and effective, very long $t_{1/2}$
Sertraline (Zoloft)	26-32	50-200	MDD, OCD, PTSD, Panic d/o	Variable side effects, GI distress, don't take w/ food, DA-I
Paroxetine (Paxil)	24	20-50	MDD, OCD, panic d/o, GAD, PTSD	Anticholinergic, NE-I, NO in pregnancy, very short $t_{1/2}$
Fluvoxamine (Luvox)	15	50-300	OCD	BID dosing, monitor Clozapine & Coumadin, QTc prolongation

Selective Serotonin Reuptake Inhibitors

Basic details

- Not particularly homogenous: isomers explain side effects
    - Lipophilic
    - Hepatic metabolism and clearance
- Major mechanism of action: *selective reuptake inhibition of serotonin → increased 5-HT output & increased post-synaptic sensitivity*
- Side effects: HA, dizziness, nausea, decreased REM, rare SIADH, tremor, sexual dysfunction, blunting of affect
- **Discontinuation syndrome**: dysphoria (crying spells, irritability), anxiety, restlessness, dizziness, N/V, GI distress, flu-like syndrome (myalgias, chills, fatigue, lethargy)
- Note: black-box warning for increased depression and suicidal ideation in children and adolescents; **consider using higher doses with obsessionality**; **no major monitoring**

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Selective Serotonin & Norepinephrine Reuptake Inhibitors

Drug	Elimination (hours)	Dose Range (mg/d)	Indications	Details
Venlafaxine (Effexor)	5	37.5-225mg/d	MDD, GAD, panic disorder, social anxiety disorder	Increased BP, so monitor in pt's w/ known HTN; use in pain
Desvenlafaxine (Pristiq)	Variable	50-100mg/d	MDD	Metabolite (O-desmethylvenlafaxine) is the active compound, thus variable responses
Duloxetine (Cymbalta)	2-5h	30-120mg/d	Chronic pain, MDD, GAD, fibromyalgia, diabetic neuropathic pain	Increases hepatic transaminases
Milnacipran (Savella)	Variable	Strict titration schedule: Day 1: 12.5mg Day 2-3: 12.5mg PO BID Days 4-7: 25mg PO BID Day 7+: 50mg PO BID	Chronic pain; Off-label for MDD	Preferentially blocks NE-reuptake over 5-HT-reuptake

Other Antidepressants

Drug	Elimination (hours)	Dose Range (mg/d)	Indications	Details
Bupropion (Wellbutrin) IR SR (12h sustained release) XL (24h sustained release)	Variable 21-28h	Max 450mg/d 75mg & 100mg 100mg, 150mg, & 200mg 150mg & 300mg	MDD, SAD, and smoking cessation (SR form); off-label use for (1) sexual-dysfunction with SSRI use and (2) ADHD	Structurally similar to amphetamine
Vilazadone (Viibryd)	24h	10-40mg/d 10mg/d x 7d, then 20mg/d; 40mg/d after an additional ≥7 days based on response and tolerability	MDD	In addition to SSRI, 5-HT_{1A} -R & 5-HT_{1A} -R partial agonist
Vortioxetine (Trintellix)	66h	5-20mg/d Increase dose 5-10mg increments over 7d	MDD	Inhibits reuptake of serotonin (5-HT); also has agonist activity at the 5-HT_{1A} receptor and antagonist activity at the 5-HT_3 receptor.

Titration Schedules

- Discontinuing antidepressant medications:
  - If <3w treatment, significant adverse reactions, or not extreme doses: can cold turkey or titrate off in 5-7d by decreasing by 50%
  - If >3w treatment, high doses: titrate off over 2-4w; note: increase titration schedule q4w if using a drug with short $t_{1/2}$ (eg, paroxetine, venlafaxine), prior history of antidepressant withdrawal symptoms, or high doses of antidepressants.
- Switching antidepressant medications:
  - Cross-titration is preferred: over course of 1-4 weeks, lower original medication at 50% increments while gradually increasing the newer medication per guidelines
  - Direct switch is useful in three scenarios:
    1. When switching to another agent in the same or similar class
    2. When original antidepressant has been used for <1 week
    3. When the discontinuation is due to adverse effects

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Treatment Resistant Depression

- Recurrence rate >40% after one MDE; 75% recurrence rate after two MDE

- No consensus definition, but generally defined as:

Failure of two or more novel antidepressants at adequate dose and duration



Treatment Resistant Depression (TRD)

STAR*D Trials

- Level 1 — citalopram utilized (37% response rate)
- Level 2 — two strategies:
    1. Switch to another antidepressant — SSRI vs Bupropion vs SNRI
    2. Augment with alternative — Bupropion vs Buspirone
- Level 3 — two strategies:
    3. Switch to another antidepressant — mirtazapine vs TCA
    4. Augment with Lithium or T3
- Level 4 — switch to MAO-I or combination venlafaxine + mirtazapine
- Level 5 — consider ECT

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Treatment Resistant Depression

STAR*D Trial

- At any level, reconsider diagnosis
    - Borderline or other personality pathology
    - Bipolar disorder
    - Persistent Depressive disorder
- At all levels, utilize adjunctive psychotherapy
- With switch and augmentation, goal is to target alternative monoamine system (5-HT, DA, NE, NMDA)



Treatment Resistant Depression

Other options — Specifiers of Depression

1. *With anxious distress* (obsessional sxs, trauma-related sxs)
    - Consider SSRI use
2. *With mixed features* (questionable manic/hypomanic sxs or those with marked mood instability)
    - Short $t_{1/2}$ SSRI medications, avoid duloxetine (Cymbalta), consider adjunctive strategies w/ antipsychotics, lithium or lamotrigine
3. *With melancholic features* (unresolved grief, note if there is poor concentration/focus)
    - Use Bupropion (Wellbutrin)
4. *With atypical features* (increased sleep, overeating, social anxiety/rejection, etc.).
    - Consider use of SSRIs, SNRIs
5. *With mood-congruent or incongruent psychotic features*
    - Will clearly require use of adjunctive antipsychotic use
6. *With pain*
    - SNRI, TCA
7. *With anorexia*
    - Consider mirtazapine (Remeron)

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Treatment Resistant Depression

R-TMS

- ECT consistently shown to be superior over rTMS; on c
- Electric current passed through coil, generating magnetic fields to depolarize neurons; 1.5-3T
- Indications: MDD, OCD, bipolar depression, smoking cessation
- Side effects: headache, dizziness, seizure, increased auditory threshold
- Contraindications:
    - Increased risks for seizures
    - Implanted metallic hardware
    - Metal fragments (eg, bullets)
    - Cochlear implants
    - Implanted electrical devices (cardiac pacemakers, intracardiac lines, and medication pumps)
    - Tattoos in the head or neck made with ferromagnetic-containing ink
    - Unstable general medical disorders



Treatment Resistant Depression

Ketamine and Esketamine

- Ketamine: non-FDA approved; often refers to the racemic mixture R-/S-ketamine which has IV, IM, PO, SL, and IN formulations; acts as a strong antagonist for NMDA-R
- Esketamine: Spravato®, FDA-approved intranasal treatment, refers to S-ketamine enantiomer; 2x more potent than racemic ketamine and 3x more potent than R-ketamine
- Treatment Resistant Depression (TRD): a diagnosis of Major Depressive Disorder with failure of two or more antidepressants of adequate dose and duration utilized in the current depressive episode
- MDD with Suicidal Thoughts or Actions (MDSI): depressive symptoms in adults with Major Depressive Disorder with acute suicidal ideation and behaviors

Treatment Resistant Depression

Ketamine and Esketamine

- Common Side Effects: Increased Blood Pressure, Dissociation, brain fog, Dizziness, Nausea/Vomiting, Sedation, Vertigo, Hypoesthesia, Anxiety, Lethargy

- Warnings & Precautions: Sedation and Dissociation: monitor patients for at least two hours post administration, Abuse and Misuse of ketamine, Elevated Blood Pressure, Cognitive Impairment, Impaired ability to drive or operate machinery, Ulcerative or Interstitial Cystitis with long-term use

- Mechanism of action: NMDA-R antagonism amongst other actions



Ketamine Dose Comparison Routes of Administration Antidepressant Use		
Route	**Bioavailability**	**Dose Range**
Intravenous	100%	0.5-1.0mg/kg over 40min
Intramuscular	90-95%	0.35-0.5mg/kg
Subcutaneous	90-95%	0.35-0.5mg/kg
Intranasal	30-50%	s-ketamine: 56-84mg
		r-/s-ketamine: 50-150mg
Oral	10-20%	0.5-7.0mg/kg

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Treatment Resistant Depression

Esketamine (Spravato®)

- Patient needs to be on concomitant antidepressant & meets criteria for TRD or MDSI
- Protocol for TRD:
  - Induction Phase (weeks 1-4):
    - Day 1 starting dose: 56mg
    - Subsequent dosing: 56mg or 84mg twice weekly
  - Maintenance Phase
    - Weeks 5-8: 56 or 84mg weekly
    - Weeks 9 and after: 56mg or 84mg every two weeks
- Protocol for MDSI:
  - Weeks 1-4: 84mg twice weekly for 4w
  - Weeks 5 or after: no established guidelines established, must systematically evaluate patient for continued treatment

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