TREATMENT OF DEPRESSION

RAMANPREET TOOR, MD
OBJECTIVES

1. Review commonly prescribed antidepressants
2. Understand the basics of treatment selection
3. Discuss duration of treatment
TREATMENT SELECTION

• Mild depression:
  ➢ Psychotherapy alone OR
  ➢ Meds alone  OR
  ➢ Combination

• Moderate-Severe depression:
  ➢ Meds alone OR
  ➢ Meds with psychotherapy

• Psychotic depression
  ➢ Antidepressant + Antipsychotics
  ➢ ECT
ALL ANTIDEPRESSANTS HAVE FAIRLY SIMILAR EFFICACY...

So what factors go into choosing the right antidepressant?

– patient tolerance
– Age, sex, cost
– dosing schedules (once daily, twice daily, three times daily?)
– possible drug interactions, side effects
– past response to med
– family member’s response to med
– Comorbidities (medical/psychiatric)
STEPPED DEPRESSION TREATMENT

SSRI, SNRI, Bupropion

Switch Medication, Switch Class, Augment with Bupropion, Mirtazapine, Trazodone

Antipsychotic, TCA

Other
SSRI

- Block reuptake of serotonin
- Usually well tolerated
- Broad comorbidity coverage
- Comparatively safe (in overdose)
COMMON SIDE EFFECTS

Short term:
- GI upset / nausea
- Jitteriness / restlessness / insomnia
- Sedation / fatigue

Long term:
- Sexual dysfunction (up to 33%)
- Weight gain (5 – 10%)
<table>
<thead>
<tr>
<th>SSRIs</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Citalopram (Celexa) | Less drug interactions  
Possibly slightly lower rate of sexual dysfunction than other SSRIs  
May reduce agitation in demented elderly | QTc prolongation at doses >40mg/day (20 mg for >65 yrs) |
| Escitalopram (Lexapro) | Less drug interactions  
Starting dose usually = maintenance dose | Expensive                                            |
| Fluoxetine (Prozac) | seems to cause least weight gain of SSRIs  
most studied in ESRD pts, no need to change dosing  
long half life so lower risk of discontinuation syndrome | strong 2D6 inhibitor!  
3A4, 2C19 inhibitor                                     |
<table>
<thead>
<tr>
<th>SSRIs</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline (zoloft)</td>
<td>Most studied in post-MI pts Safest in breastfeeding</td>
<td>Most GI sx of SSRIs 2D6 inhibitor (higher doses) Discontinuation syndrome</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>Least prone to cause GI side</td>
<td>Most anticholinergic Most weight gain Teratogenic Discontinuation syndrome</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>Approved for tx of OCD and not for depression</td>
<td>Strong 2D6, 3A4 inhibitor</td>
</tr>
</tbody>
</table>
SNRI

• Dual reuptake inhibitors for serotonin and norepinephrine.
• Little or no effect on muscarinic, histaminic or adrenergic receptors
• Can act as TCAs without the side effects of TCAs
<table>
<thead>
<tr>
<th>SNRIs</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Venlafaxine (Effexor) | No sedation or weight gain  
Weak 2D6 inhibitor and less likely to interact  
Can be used for adult ADD | Increased HR and dose dep increase in BP, 100-225 mg (3-7%) , 300 mg (13%)  
Discontinuation syndrome: More fatal in OD than SSRI |
| Desvenlafaxine (Pristique) | Starting dose therapeutic  
No hepatotoxic side effects  
Less risk of increase in BP | Discontinuation syndrome |
| Duloxetine (Cymbalta) | Also used for pain  
No increase in BP, no weight gain, no effects on cardiac conduction  
Less risk of sexual side effects | 2D6 inhibitor  
Hepatotoxic  
Mydriasis (avoid in glaucoma) |
OTHER IMPORTANT ANTIDEPRESSANTS
<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>augment with SSRI, ADHD, can counteract SSRI induced sexual side effects, no weight gain, safe in depressed cardiac patients, used for smoking cessation</td>
<td>Can worsen anxiety, seizure risk, 2D6 inhibitor</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>anti-nausea, stimulates appetite, sedating (upto 15 mg), less sexual side effects, augment with SSRI, minimal interaction</td>
<td>Weight gain, increase in cholesterol/triglycerides, orthostatic hypotension and HTN, risk of neutropenia (1/1000)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>used more often for sedation, not addictive, off label use for agitation in elderly</td>
<td>Orthostatic hypotension, priapism (1 in 20,000)</td>
</tr>
</tbody>
</table>
DURATION

Adequate Trial
- 4-8 weeks on therapeutic dose
- If partial improvement in 6-12 weeks then increase the dose
- Continue for 6-12 months
- Long term use for second or third episode of depression

Switch:
- First recommend to switch to different antidepressant (SSRI/SNRI)
- After 3 trials can consider augmentation
SEROTONIN SYNDROME

• Interaction between multiple meds that increase net serotonergic neurotransmission
• It can also occur after starting or increasing a single serotonergic medication
• Other non psychiatric meds which increase serotonin:
  ➢ antiemetic (ondansetron, metoclopramide)
  ➢ antimigraine (sumatriptans)
  ➢ antibiotics (linezolid, ritonavir)
  ➢ OTC (dextromethorphan)
SEROTONIN SYNDROME

• Mental status changes
  confusion → agitation → delirium

• Neuromuscular changes
  hyperreflexia, clonus, myoclonus, shivering, tremor

• Autonomic instability
  tachycardia, diaphoresis, fever, diarrhea
DEPRESSION IN PREGNANCY

Untreated depression

For mother
- gain less weight, more likely to use drugs
- higher rates of miscarriage, premature delivery, pre-eclampsia

For newborn:
- smaller head circumference
- lower weight
- lower APGAR scores

Treated mothers

First trimester
- No increase risk of miscarriage
- No overall risk of birth defects (except paroxetine)

Later Pregnancy
- Increase risk of premature delivery (<37 wks)
- PPHN
- Neonatal distress syndrome

No long-term effects on development with SSRI/SNRI
ALL ANTIDEPRESSANTS HAVE FAIRLY SIMILAR EFFICACY...

So what factors go into choosing the right antidepressant?

– patient tolerance
– Age, sex, cost
– dosing schedules (once daily, twice daily, three times daily?)
– possible drug interactions, side effects
– past response to med
– family member’s response to med
– Comorbidities (medical/psychiatric)
<table>
<thead>
<tr>
<th>NAME/Generic (Trade)</th>
<th>Dosage</th>
<th>Key Clinical Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressant Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>Start: 100 mg bid or tid; Max: 450 mg/day</td>
<td>Combaitned increased seizure disorder because it increases seizure threshold; stimulating; not good for treating anxiety disorders; second line TX for ADHD; abuse potential.</td>
</tr>
<tr>
<td>Clomipramine (Cellax)</td>
<td>Start: 25-50 mg qd; Range: 50-200 mg/day</td>
<td>Best tolerated of SSRIs; few and limited CYP 450 interactions; good choice for anxiety pts.</td>
</tr>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>Start: 30 mg qd; X 1 wk; then to 60 mg qd; Range: 60-120 mg/day</td>
<td>More GI side effects than SSRIs; tx neuropathic pain; need to monitor BP, 2nd line TX for ADHD.</td>
</tr>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>Start: 5 mg qd; X 2; then to 10 mg qd; Range: 10-20 mg (see clinical trials).</td>
<td>More side effects than other SSRIs; long half-life reduces withdrawal symptoms.</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>Start: 10 mg qd; X 2; then to 20 mg qd; Range: 20-40 mg/day.</td>
<td>More activating than other SSRIs; long half-life reduces withdrawal symptoms.</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>Start: 15 mg qd; X 2; then to 30 mg qd; Range: 30-60 mg/day.</td>
<td>Sedating and appetite promoting; Neuropenia risk (1 in 1000) so avoid in immunocompromised pts.</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>Start: 10 mg qd; X 2; then to 20 mg qd; Range: 20-60 mg/day.</td>
<td>Anticholinergic; sedating; substantial withdrawal syndrome.</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>Start: 25 mg qd; X 2; then to 50 mg qd; Range: 50-200 mg/day.</td>
<td>Few and limited CYP 450 interactions; mildly activating.</td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>Start: 37.5 mg qd; X 2; then to 75 mg bid; Max: 150 mg qd; X 2; then to 150 mg qd; Range: 75-225 mg/day.</td>
<td>More agitation &amp; GI side effects than SSRIs; tx neuropathic pain above 150 mg qd; need to monitor BP; 2nd line TX for ADHD.</td>
</tr>
</tbody>
</table>

**Antimania & Sleep (Hypnotic) Medications** |
| Alprazolam (Xanax) | Start: 0.25 mg bid; Max: 4 mg/day | Equil: dose: 0.6 mg. Onset: intermediate (1-2 hrs). T1/2: 11 hrs. More addictive than other benzodiazepines and has uniquely problematic withdrawal syndrome. | |
| Chlordiazepoxide (Librium) | Start: 10-30 mg qd; Max: 200 mg/day | Equil: dose: 25 mg. Onset: intermediate (0-5 hrs). T1/2: 10-48 hrs (parent compound); 14-65 hrs (metabolites). Useful for treating outpatient ETOH withdrawal because of long half-life. | |
| Clonazepam (Klonopin) | Start: 0.25 mg bid or tid; Max: 2 mg/day | Equil: dose: 5 mg. Onset: intermediate (0-5 hrs). T1/2: 45-50 hrs. Helpful in b mania. | |
| Diazepam (Valium) | Start: 2-4 mg bid or qid; dose depends on symptoms severity; Max: 30-40 mg/day | Equil: dose: 5 mg. Onset: immediate (highly lipophilic). T1/2: 20-60 hrs. Note: the presence of liver disease will significantly lengthen half-life. | |
| Lorazepam (Ativan) | Start: 0.5-1 mg bid; Max: 6 mg/day | Equil: dose: 1 mg. Onset: intermediate (0.5 hrs). T1/2: 12 hrs. No active metabolites. So safer in liver dz. | |
| Triazolam (Hypnovel) | Start: 0.25-1 mg bid; Max: 3 mg/day | Note: no FDA approved for anxiety. May take 6 weeks to become fully effective. | |
| Hydroxyzine (Vistaril) | Start: 25-100 mg qd; Max: 300 mg/day | Antihistamine/anticholinergic drug FDA approved for anxiety. Consider in pts w/ w's of substance abuse. | |
| Prazepam (Midpress) | Start: 1 mg qd; dose increases q 2-3 d until symptoms abate; Max: 10 mg qd | Old antihypertensive used by night-ohms and night sweats of PTSD. Need to warn about orthostatic hypotension in AM at first dose and after each new dosage change. | |
| Traczone (Desyrel) | Start: 50 mg qd; Max: 200 mg/day | Commonly used as sleep aid. Inform about priapism risk in men. | |
| Temazepam (Restoril) | Start: 15 mg at bedtime; Max: 45 mg qd | T1/2: 8-12 hrs. Older benzodiazepine. No P80 metabolism. More potential for physical dependence than Ambien/Sevutrop. | |
| Zolpidem (Ambien) | Start: 5-10 mg qd; Max: 20 mg qd | T1/2: 2-3 hrs. Potential for sleep-eating and sleep-driving. Available in longer acting form (CR) | |

**Mood Stabilizers** |
| Lithium | Start: 300 mg bid; Max: Target plasma level: acute mania: blood level 0.6-1.2 mmol/L Maintenance: 0.4-1 mmol/L. Available in ER form dosed once daily usually at 11AM. Lithium toxicity: plasma levels related to renal clearance. | Black box warning for toxicity. Teratogenic (cardiac malformations) and will need to inform patients of childbearing age of this risk. Check TSH and T4 before starting and q4-12 months thereafter. Advise about concurrent use of NSAIDs and H1N1 vaccines as can decrease renal clearance. Lithium strongly anti-suicidal. Lithium carbonate, citrate, tartrate (Lithobid, Eskalith) | |
| Divalproex (Depakote) | Start: 750 mg/day (bid or tid; OR: qid, ER: qid) Dose increases as quickly as tolerated to clinical effect. Target plasma level: 75-150 mg/day (ER: 85-129 mg/day) (ER). | Multiple black box warnings including for hepatotoxicity, pancreatitis, and teratogenicity (need to inform women of childbearing age of this risk). Need to monitor LFTs, platelet counts, and coag initially and qid-mo. Significant weight gain common. | |
| Lamotrigine (Lamictal) | Start: 25 mg/day; dose increases q 2 weeks to 150-400 mg/day; Max: 1500 mg/day. | No drug level monitoring typically required. Need to strictly follow published titration schedule. Fewer cognitive and appetite stimulating side effects. | |

**Antipsychotics/Mood Stabilizers** |
| Aripiprazole (Abilify) | Mania: Start: 15 mg qd; Range: 15-30 mg/day. MDD adj bp: Start: 2-5 mg/day; adj dose: q 1 week by 2.5-5 mg/day. | EPS: mild (especially extrapyramidal). Metabolic side effects low. Very long half-life 15 hrs. Limit amount of psychotropic side effects. FDA indication for adjunctive treatment of MDD. Potential increased suicidality in first few months. Need to screen glucose and lipids regularly. | |
| Olanzapine (Zyprea) | Bipolar Dep: Start: 15 mg qd; Init: 300 mg qd; Range: 300-600 mg/day. MDD adj bp: Start: 15 mg qd; Init: 150 mg qd; Range: 150-300 mg/day. | EPS: Low. Metabolic side effects: High weight gain and sedation common. Do not prescribe to diabetics. Need to screen glucose and lipids regularly. | |
| Quetiapine (Seroquel) | Bipolar Dep: Start: 50 mg qd; Init: 200 mg qd; Range: 400-900 mg/day. MDD adj bp: Start: 50 mg qd; Init: 150 mg qd; Range: 150-300 mg/day. | EPS: Higher: Metabolic side effects: moderate. Hyperprolactinemia and sexual side effects common. Need to screen glucose and lipids regularly. | |
| Risperidone (Risperdal) | Start: 0.5-1mg qd; Init: 4-6mg qd. Available as long acting injectable q 2 weeks called Risperdal Consta. | EPS: highest. Metabolic side effects: moderate. Hyperprolactinemia and sexual side effects common. Need to screen glucose and lipids regularly. | |
| Ziprasidone (Seroquel) | Start: 40 mg qd; Init: 40-80 mg qd. Needs to be taken w/eat (doubles absorption). | EPS: moderately high (especially extrapyramidal). Metabolic side effects: low. Need to screen glucose and lipids regularly. Lower dosage can be more tolerable than others. Contraindicated in combination with medications due to QTc prolongation. | |