Depressive Disorders and Mood Stabilizers in acute Care Setting

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Medications associated with depression

- Clonidine
- Diuretics
- Hydralazine
- Methyldopa
- Propranolol
- Reserpine
- Oral Contraceptives
- Steroids/adrenocorticotropic hormone
- Isotretinoin
Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.
Treatment options

- All antidepressants equally effective in a population
  - Response varies from person to person
- What to consider when choosing an agent
  - Side effects
  - Drug interactions
  - Past history of pt response or family response
- All antidepressants have black box warning
  - Increased risk of suicidal ideation in children, adolescents, and young adults <24yo
- Failure to respond to 1 class or 1 drug in a class does not predict failed response to another drug class or another drug within the class
N=nearly 100,000 patients, N=372 clinical studies and 11 different antidepressants

Source: Mark Levenson, Ph.D., Chris Holland, M.S., FDA, December 2006
Risk of Suicide

Suicide attempts by depressed health plan members declined after the start of treatment (Simon et al., p. 1029)
Treatment options

- SSRIs
- Tricyclic Antidepressants (TCAs)
- NE/SRIIs
- Triazolopyridines
- Aminoketone
- NE/5HT3 mixed
- MAOIs
- Atypical Antipsychotics
- Vilazodone
Before the 1980s, pharmacologic treatment was limited to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs).
Selective Serotonin Reuptake Inhibitors (SSRI)

- fluoxetine
- citalopram
- sertraline
- paroxetine
- escitalopram
- fluvoxamine
Selective Serotonin Reuptake Inhibitors (SSRI)

- Increase brain serotonin levels
- First line agents
Selective Serotonin Reuptake Inhibitors (SSRI)

- Fewer anticholinergic and cardiovascular adverse effects than TCAs
- Not usually associated with significant weight gain
- Common adverse effects generally mild, short lived
  - Nausea, vomiting, diarrhea
  - Sexual dysfunction
  - Headache
  - Insomnia
Fluoxetine (Prozac)

- **Pros**
  - Long half-life so decreased incidence of discontinuation syndromes. Good for pts with medication noncompliance issues
  - Initially activating so may provide increased energy
  - Secondary to long half life, can give one 20mg tab to taper someone off SSRI when trying to prevent SSRI Discontinuation Syndrome

- **Cons**
  - Long half life and active metabolite may build up (e.g. not a good choice in patients with hepatic illness)
  - Significant P450 interactions so this may not be a good choice in pts already on a number of meds
  - Initial activation may increase anxiety and insomnia
  - More likely to induce mania than some of the other SSRIs
Pros

- Short half life with no active metabolite means no build-up (which is good if hypomania develops)
- Sedating properties (dose at night) offers good initial relief from anxiety and insomnia

Cons

- Significant CYP2D6 inhibition
- Sedating, wt gain, more anticholinergic effects
- Most likely to cause a discontinuation syndrome
Sertraline (Zoloft)

- **Pros**
  - Very weak P450 interactions (only slight CYP2D6)
  - Short half life with lower build-up of metabolites
  - Less sedating when compared to paroxetine

- **Cons**
  - Max absorption requires a full stomach
  - Increased number of GI adverse drug reactions
Citalopram (Celexa)

- **Pros**
  - Low overall inhibition of P450 enzymes so fewest drug-drug interactions of the SSRIs
  - Drug’s intermediate half life leads to low incidence of discontinuation syndrome

- **Cons:**
  - Can be sedating (has mild antagonism at H1 histamine receptor)
  - GI side effects (less than sertraline??)
Norepinephrine/Serotonin reuptake inhibitors

- Venlafaxine/Duloxetine
- Increase levels of norepinephrine/serotonin
- Recent studies show no benefit vs SSRI
- Same side effects as SSRI + hypertension risk
Inhibit both serotonin and noradrenergic reuptake like the TCAS but without the antihistamine, antiadrenergic or anticholinergic side effects
Used for depression, anxiety and possibly neuropathic pain
Venlafaxine (Effexor)

- **Pros**
  - Minimal drug interactions and almost no P450 activity
  - Short half life and fast renal clearance avoids build-up (good for geriatric populations)

- **Cons**
  - Can cause a 10-15 mmHG dose dependent increase in diastolic BP.
  - May cause significant nausea, primarily with immediate-release (IR) tabs
  - Can cause a bad discontinuation syndrome, and taper recommended after 2 weeks of administration
  - Noted to cause QT prolongation
  - **Sexual side effects in >30%**
Duloxetine (Cymbalta)

- **Pros**
  - Some data to suggest efficacy for the physical symptoms of depression
  - Thus far less BP increase as compared to venlafaxine, however this may change in time

- **Cons**
  - CYP₂D6 and CYP₁A₂ inhibitor
  - Cannot break capsule, as active ingredient not stable within the stomach
# Novel antidepressants

**Mirtazapine (Remeron)**

**Pros**

- Different mechanism of action may provide a good augmentation strategy to SSRIs. Is a 5HT₂ and 5HT₃ receptor antagonist
- Can be utilized as a hypnotic at lower doses secondary to antihistaminic effects

**Cons**

- Increases serum cholesterol by 20% in 15% of patients and triglycerides in 6% of patients
- Very sedating at lower doses. At doses 30mg and above it can become activating and require change of administration time to the morning.
- Associated with weight gain (particularly at doses below 45mg)
Bupropion (Wellbutrin)

- **Pros**
  - Good for use as an augmenting agent
  - Mechanism of action likely reuptake inhibition of dopamine and norepinephrine
  - No weight gain, sexual side effects, sedation or cardiac interactions
  - Low induction of mania
  - Is a second line ADHD agent so consider if patient has a co-occurring diagnosis

- **Cons**
  - May increase seizure risk at high doses (450mg+) and should avoid in patients with Traumatic Brain Injury, bulimia and anorexia.
  - Does not treat anxiety unlike many other antidepressants and can actually cause anxiety, agitation and insomnia
  - Has abuse potential because can induce psychotic sx at high doses
Case 1

- Susie Q has a nonpsychotic unipolar depression with no history of hypomania or mania. She has depressed mood, hyperphagia, psychomotor retardation and hypersomnolence. What agent would you like to use for her?
- Establish dx: Major depressive disorder
- Target symptoms: depression, hyperphagia, psychomotor retardation and hypersomnolence
Case 1 continued

- For a treatment naive patient start with an SSRI.
- Using the side effect profile as a guide select an SSRI that is less sedating. Good choices would be Citalopram, Fluoxetine or Sertraline. Buproprion would also have been a reasonable choice given her hypersomnolence, psychomotor retardation and hyperphagia.
Less desirable choices include Paxil and Mirtazapine because of sedation and wt gain.
Not a duel reuptake inhibitors because she is treatment naïve and may not need a “big gun”.
Not a TCA because of side effects
Case 2

Billy bob is a 55 year old diabetic man with mild HTN and painful diabetic neuropathy who has had previous depressive episodes and one suicide attempt. He meets criteria currently for a major depressive episode with some anxiety. He has been treated with paroxetine, setraline and buproprion. His depression was improved slightly with each of these meds but never remitted. What would you like to treat him with?
Case 2 continued

- Establish dx: Major depressive disorder with anxious features
- Target symptoms: depressive sx, anxiety and possibly his neuropathic pain
- Assuming he received adequate trials previously would move on to a duel reuptake inhibitor as he had not achieved remission with two SSRIS or a novel agent.
Case 2 continued

- Given his mild HTN would not choose Venlafaxine. TCA’s can help with neuropathic pain and depression however not a good choice given the SE profile and lethality in overdose. Duloxetine is a good choice since it has an indication for neuropathic pain, depression and anxiety. Three birds with one stone!!

- Keep in mind Duloxetine is a CYP2D6 and CPY1A2 inhibitor and has potential drug-drug interactions.
SSRI—Key Differences

- Least likely to cause GI upset, headache, and insomnia → **escitalopram**
- Least likely to cause drug interactions → **citalopram, escitalopram**
- Least likely to cause withdrawal symptoms → **fluoxetine**
- Most likely to cause withdrawal symptoms → **paroxetine**
Tricyclic antidepressants

- Tertiary Amines
  - Amitriptyline
  - Clomipramine
  - Doxepin
  - Imipramine
- Secondary Amines
  - Desipramine
  - **Nortriptyline**
- Potentiate NE and 5-HT activity by blocking reuptake
  - Potency and selectivity vary greatly
- Other antidepressants are as effective as TCAs but are safer in overdose and better tolerated than TCAs
Tertiary/secondary amines adverse effects

- **Tertiary Amines**
  - ↑ anticholinergic AEs
  - ↑ serotonin reuptake antagonism
  - ↑ orthostatic hypotension
  - ↑ sedation
  - ↑ risk of seizures

- **Secondary Amines**
  - ↑ NE reuptake antagonism
Triazolopyridines

- Trazodone/Nefazodone
- Anticholinergic actions / serotonin reuptake inhibitor
- Nefazodone has BBW for hepatic injury
Trazodone/Nefazodone adverse effects

- Orthostatic hypotension
- Sedation
- Cognitive slowing
- Dizziness
- Priapism
MAOIs

- Phenelzine/ tranylcypromine
- Inhibit monoamine oxidase = increased serotonin
Hypertensive Crisis

- Can occur when MAOIs taken with certain foods
  - 10 mg of tyramine can cause marked pressor effect
  - 25 mg can result in serious hypertensive crisis
- Hypertensive crisis symptoms
  - Occipital headache
  - Stiff neck
  - Nausea
  - Vomiting
  - Sweating
  - Sharply elevated blood pressure
Aripiprazole
- partial agonist at the dopaminergic D₂ and at the serotonergic 5-HT₁A receptors and is an antagonist at the serotonergic 5-HT₂A

Adverse Effects
- Weight gain/lipid + glucose abnormalities
- Sedation
- QTC interval changes
- Extrapyramidal symptoms
- GI AEs
- Dizziness
Vilazodone (Viibryd)

- SSRI + 5-HT1A partial agonist
- Adverse Effects
  - drowsiness
  - dizziness, paresthesias
  - tremor
  - insomnia
  - abnormal dreams
  - GI adverse effects
  - Palpitations
  - Sexual side effects
Adverse Effects—ATD Withdrawal

- Occurs with most antidepressants if the dose is not tapered.
- Mechanism—not true dependence
  - Reduction in intra-synaptic serotonin levels following receptor down-regulation.
  - Noradrenaline, acetylcholine and patient disposition also play a role.
ATD Withdrawal

- Symptoms
  - Typically start 24 to 72 hours after the last antidepressant dose (peaking at 1 week).
  - Typically resolve within 1 to 3 weeks.
  - Severe and disabling withdrawal syndrome seen 5% of patients.
Serotonin discontinuation syndrome

- F = flu-like symptoms
- I = insomnia
- N = nausea
- I = imbalance
- S = sensory disturbances
- H = hyperarousal
# ATD Withdrawal

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<tr>
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<th>Less likely</th>
<th>Likely</th>
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<tr>
<td>Fluoxetine</td>
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Herbal Treatment

- St. John’s Wort
  - Rated A
  - Same AE profile as SSRIs
  - High number of drug-drug interactions

- Tryptophan
  - Rated C
  - GI Upset
  - Interactions with many antidepressants/triptans
  - Renal excretion
  - Caution in epilepsy

- S-adenosyl-L-methionine (SAM-e)
  - Rated C
  - GI Upset
  - Possibly Lowers Blood Glucose
Alternative Treatments

- Electroconvulsive Therapy (ECT)
  - Recommended for:
    - No response to medications
    - Psychotic or catatonic features
    - Previous response to ECT

- Light Therapy
  - UV light
Uncomplicated, physically healthy outpatient without any contraindication to a specific class of antidepressants

SSRI (choice depends on multiple factors)

Failed trial due to nonresponse or limiting adverse effect

Ensure medication adherence

Switch to alternative agent (different SSRI, non-SSRI antidepressant)

Failed trial

Partial response

Fully remits

Consider augmentation (non-SSRI antidepressant, lithium, thyroid hormone, atypical antipsychotic)

-or-

Switch to alternative agent (different SSRI or non-SSRI antidepressant)

Maintain for at least 4 to 9 months for continuation, and if necessary, 12 to 36 months for maintenance

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Clinical Application: Dosing

- Elderly patients: start with ½ usual starting dose, increase slowly
- Use caution when switching from one antidepressant to another
  - 3 to 4 weeks usually required before mood-elevating response is seen
  - Adequate trial: 6-weeks at maximum dosage
- Pay attention to max doses of medications

Therapeutic Outcome Evaluation

- Monitoring parameters
  - Adverse effects
  - Target symptom remission
  - Changes in social/occupational functioning
  - Blood pressure for patients receiving venlafaxine
  - ECG for patients >40 years before starting TCA therapy with periodic follow-up
  - Suicidal ideation after initiation
Therapeutic Outcome Evaluation

- Psychometric rating instruments
  - Patient- and clinician-rated scales
  - Rapid, reliable measurement of symptom nature and severity
  - Administer prior to treatment, 6 to 8 weeks after initiation of therapy, then periodically

- Interview family member/friend (with patient's permission) regarding symptoms and daily functioning
Psychometric scale definitions

- **Nonresponse**: <25% decrease in baseline symptoms
- **Partial response**: 26% to 49% decrease in baseline symptoms
- **Partial remission/response**: >50% decrease in baseline symptoms
- **Remission**: return to baseline functioning; no symptoms


Depression is an underreported treatable disease state

Pharmacologic treatment should be chosen based on adverse effects and patient response

Pharmacologic treatment offers an excellent opportunity for pharmacists to utilize their drug knowledge to select the most appropriate medications for the patient