Findings: venlafaxine is modestly more effective than paroxetine.
Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study findings:

**Level 1**
- **Select Monotherapy**
- **Chose from:** SSRIs

**Level 2**
- **Switch or Augment**
- **Switch to:** A different SSRI, bupropion SR or venlafaxine XR
- **Augment L1 ATD with:** Bupropion SR

**Level 3**
- **Switch or Augment**
- **Switch to:** Mirtazapine or nortriptyline
- **Augment L2 ATD with:** Lithium or thyroid (T3)

**Level 4**
- **Switch**
- **Switch to:** MAOI or Venlafaxine XR + mirtazapine
Switching Strategies

► There are 2 options for switching medications:
  • Immediate substitution or cross-taper
  • In most cases, especially when changing from one SSRI to another, one drug can immediately be substituted for another.
    ▶ The risk of serotonin syndrome is relatively small, since the half-lives of SSRIs are relatively short.
    ▶ The only exception is fluoxetine, which has a half-life of up to 4 days and an active metabolite with a half-life of 7 to 15 days. Theoretically, when switching from fluoxetine to another SSRI, especially in patients who have been on higher dosages of fluoxetine for any significant length of time, it may be safest to consider stopping the fluoxetine for a few days before beginning the new drug.

Switching Strategies

► A direct switch between SSRIs and venlafaxine is acceptable.
► Mirtazapine, however, has a different mechanism of action from the SSRIs, so a cross-taper is usually recommended when switching mirtazapine either to or from an SSRI.
► There are case reports of serotonin syndrome in patients taking an SSRI with nefazodone.
  ▶ The safest approach to changing either to or from nefazodone to an SSRI would include tapering the first medication (usually by 50% every 5 days or by 1 dosage level each week) and then allowing for a few days’ washout before starting the new medication.
Monoamine Oxidase Inhibitors

**General Facts**
- Prior to starting an MAOI—wait 5 half-lives after discontinuing the current SSRI, TCA or SNRI (this is typically about 1 week)
- Prior to starting an SSRI, TCA or SNRI on current MAOI users—wait 14 days prior to new drug initiation
- Drug-drug interactions (more frequently seen with tramadol: AVOID dextromethorphan, phenylephrine, pseudoephedrine; CAUTION with sulfonylureas and metformin

**Target antidepressant dose is 45mg/day**

**Dietary restrictions are still imposed at all doses**

- Very expensive ($14/patch—1 patch used each day)
- Patients with Parkinson’s Disease who are already taking L-Dopa—may use in patients who are particularly agitated and for those who may not follow the MAOI diet to the letter

**Maximump dose is typically 60mg/day**

**Maximum dose is 60mg/day**

**Why does the hypertensive effect occur?**
- MAOIs prevent the breakdown of tyramine in the gut
- Tyramine in the bloodstream leads to the displacement of NE from nerve terminals
- MAOIs inhibit the breakdown of NE inside the neurons

**Foods that are RISKY**
- Chocolate
- Alcohol
- All other dairy products
- Aged, cured or smoked meats
- Fava beans
- Aged cheeses
- Miso soup

**Foods that are SAFE**
- Tofu
- Cheese pizzas made with mozzarella
- Some aged, cured or smoked meats

**Foods that are a little RISKY but probably safe**
- Cheese pizzas made with mozzarella

**Foods that are normal foods with restricted amounts**
- Pasta
- White rice

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**Parnate (tranylcypromine)**
- Available in 10mg tablets
- Maximum dose is typically 60mg/day
  - Start 30mg/day and increase q2weeks by 10mg as needed
  - Tends to cause less sedation, but more insomnia than Nardil
  - More likely to cause hypertension than Nardil when given in combination with tyramine or adrenergic medication
  - May be due to the fact that Parnate’s chemical structure is more amphetamine-like than any other MAOI

**Marplan (isocarboxazid)**
- Available in 10mg tablets
- Maximum dose is 60mg/day.
  - Start at 10mg BID and increase by 10mg q2-4 days with a maximum of 40mg in the 1st week
  - Better tolerated than Nardil
  - Outperforms Nardil or Parnate compared to placebo

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**Nardil (phenelzine)**
- Available in 15mg tablets
- Target dose is 1mg/kg or 75mg (split TID) for most patients
- Considered the “high side effect” MAOI
  - Causes sedation, weight gain and sexual dysfunction
  - Patient selection
  - Might use in patients who are particularly agitated and for those who may not follow the MAOI diet to the letter

**Available in 5mg tablets**

**Target antidepressant dose is 45mg/day**

**At doses no higher than 20mg/d it is MAO-B selective, meaning**

**EMSAM (selegiline patch)**
- Very expensive ($14/patch—1 patch used each day)
- Dietary restriction are still imposed at all doses
  - >6mg/day

**Tablet is only approved as adjunctive treatment for patients with Parkinson’s Disease who are already taking L-Dopa**

**Has been used in depression with reasonable success.**

**Available in 5mg tablets**

**Target antidepressant dose is 45mg/day**

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**Edepryl (selegiline)**
- Tablet is only approved as adjunctive treatment for patients with Parkinson’s Disease who are already taking L-Dopa
- Has been used in depression with reasonable success.
- Available in 5mg tablets
- Target antidepressant dose is 45mg/day
  - At doses no higher than 20mg/d it is MAO-B selective, meaning that it does not require dietary restrictions
- EMSAM (selegiline patch)
  - Very expensive ($14/patch—1 patch used each day)
  - Dietary restriction are still imposed at all doses
    - >6mg/day

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**Monoamine Oxidase Inhibitors**

**Dietary Restrictions**
- Why does the hypertensive effect occur?
  - MAOIs prevent the breakdown of tyramine in the gut
  - Tyramine in the bloodstream leads to the displacement of NE from nerve terminals
  - MAOIs inhibit the breakdown of NE inside the neurons

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Antidepressant Augmentation

► Lithium
  • Particularly effective when added to a TCA, less effective with an SSRI
  • Postulated mechanism: net enhancing effect on serotonergic neurotransmission where the TCA increases postsynaptic serotonin receptor sensitivity
  • Use is supported by multiple randomized, controlled trials
  • Reported to have an anti-suicide effect
  • Common treatment emergent side effects: gastrointestinal distress, polyuria, and tremor. Potential long-term adverse effects: may cause renal impairment, may cause hypothyroidism (<5% of tx pts)

Recommended Pretreatment Assessments:
- Electrolytes
- Blood urea nitrogen
- Creatinine
- Blood glucose
- Liver function tests
- Thyroid function, including thyroid-stimulating hormone
- Complete blood count with differential
- Urinalysis
- Electrocardiogram (optional)

Antidepressant Augmentation

► Lithium
  • Dosing:
    - Long half-life allows once daily dosing if tolerated. Otherwise BID is adequate.
    - 600-900mg daily, which translates in a lithium serum level of at least 0.4mEq/L.
  • Blood Level Monitoring Frequency:
    - Following dosage changes
    - To confirm compliance
    - To determine adequacy of dose
    - Whenever lithium toxicity is suspected
    - Patients on stable maintenance doses of lithium should have laboratory monitoring 3-2X per year

Electrolytes
Electrolytes
Electrolytes
Electrolytes

Antidepressant Augmentation

► Thyroid
  • Can be used as enhancement (speeds antidepressant response) at the start of therapy or as augmentation
  • Considerable evidence supports its combined use with TCAs; newer evidence emerging with SSRIs
  • Effective even in euthyroid patients
  • T3 (Cytomel/triiodothyronine) superior to T4
  • Comparable in efficacy compared to lithium
  • Dose range = 25-50 mcg/day
  • Minimal adverse effects


T3 is effective, has a favorable side effect profile, and is only $35/month

Antidepressant Augmentation

Limited or No Efficacy

► Psychoestimulants
  • Limited evidence to support improvement in depression
  • Reserve use for patients with significant fatigue
  • Need to weigh risk of abuse potential, particularly in patients with comorbid substance abuse disorders

► Buspirone
  • May be useful, particularly with SSRI but data is limited
  • Dosing usually 15-30 mg/day

► Lamotrigine
  • Appears to be better than placebo as an augmenting agent

► Pindolol
  • Failed to demonstrate efficacy

► Hormone Replacement Therapy
  • Place of testosterone in depressed men is unclear
  • Estrogen augmentation does not seem to be effective in depressed postmenopausal women but may be useful in symptomatic premenopausal women who are depressed

Adverse effects and higher cost make atypical antipsychotics less favorable


Antidepressant Augmentation

► Atypical Antipsychotics
  • Aripiprazole (Abilify) is FDA indicated as an adjunctive or augmenting agent in major depressive disorder
  • Dose range 5-20mg (15mg/day with 2D6 inhibitors)
  • Olanzapine/fluoxetine (Symbyax) is indicated for treatment-resistant depression in people who do not respond to 2 separate trials of different antidepressants of adequate dose and duration
  • No significant differences among olanzapine, risperidone, quetiapine, or aripiprazole
  • Side effects associated with atypical antipsychotics are significant and can include metabolic abnormalities, akathisia, tardive dyskinesia, and hyperprolactinemia
  • Long-term efficacy and safety studies are not available

Antidepressant Augmentation

**Cost**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost/30 days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>buspirone</td>
<td>$16</td>
</tr>
<tr>
<td>lithium</td>
<td>$17</td>
</tr>
<tr>
<td>Cytomel (T3)</td>
<td>$35</td>
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<tr>
<td>risperidone</td>
<td>$90</td>
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<tr>
<td>Symbyax (olanz/fluox)</td>
<td>$375</td>
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<tr>
<td>Abilify</td>
<td>$550</td>
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</tbody>
</table>

*Average retail cost for 30-days to OHP. Exclude rebate

**Summary Points**

- **Key to treating treatment-resistant depression is formulating a treatment plan at the start of therapy.**
- **Prior to switching or augmenting an antidepressant consider a longer trial (12-14 weeks) at a therapeutic dose.**
- **T3 is a first-line choice for antidepressant augmentation.**