Treatment-Resistant Depression in the Primary Care Setting

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Background

- In the US, 14 million adults (6.7%) will suffer from a major depressive episode.
- Recent estimates calculate a cost of at least $44 billion dollars in related direct expenses and productivity loss associated with depression in the US.
- After an initial treatment course,
  - 1/2 of patients do not respond
  - 2/3 of patients do not achieve remission

Defining the Goals of Treatment

- **Response** = a clinically significant degree of depressive symptom reduction following treatment initiation.
  - When used clinically, response implies that the treatment has caused the response
  - Response criteria be met for 3 consecutive weeks
- **Remission** = the virtual absence of depressive symptoms.
  - 3 consecutive weeks must pass, during which each week is characterized by the virtual absence of depressive symptoms, before remission can be ascribed.
  - Remission may end with either relapse or recovery.

Criteria for MDE (DSM-IV)

5 or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

(1) Depressed mood most of the day, nearly every day
(2) Markedly diminished interest or pleasure in all, or almost all, activities
(3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
(4) Insomnia or hypersomnia
(5) Psychomotor agitation or retardation
(6) Fatigue or loss of energy
(7) Feelings of worthlessness or excessive or inappropriate guilt
(8) Diminished ability to think or concentrate, or indecisiveness
(9) Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Defining the Goals of Treatment

- **Recovery (*clinical*)** = ascribed when the period of remission has been sufficiently sustained (typically at least 4 months) that continued well being may be expected (with or without continuing treatment).
- **Recovery (*consumer*)** = successful integration of a mental disorder into the consumer's life and involves rebuilding meaningful lives, hope and optimism, self-empowerment, effective collaboration and direction in clinical care decisions, and decreasing dependence on the mental health system.

Trial and Error

- How long does it take to decide if an antidepressant is not going to work?

Minimum trial duration = 6 weeks
Average trial duration = 8 weeks
Newly recommended trial duration = 12-14 weeks

Summary of the Evidence

- Efficacy and Effectiveness Studies for Newer Antidepressants in Treatment-Resistant Depression
  - Efficacy (1 study)
    - Study 1
      - Quality = Fair
      - Findings: venlafaxine is modestly more effective than paroxetine
  - Effectiveness (2 studies)
    - Study 1
      - Quality = Good
      - Findings: no substantial differences between bupropion SR, sertraline and venlafaxine XR
    - Study 2
      - Quality = Fair
      - Findings: venlafaxine is modestly more effective than citalopram, fluoxetine, mirtazapine, paroxetine and sertraline

Gartlehner G, et al. Comparative Effectiveness Review: Agency for Healthcare Research and Quality. January 2007. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Treatment Level Progression

Treatment Level Progression

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study findings:

Level 1	Select Monotherapy
Chose from:	SSRIs

Treatment Level Progression

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study findings:

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

Treatment Level Progression

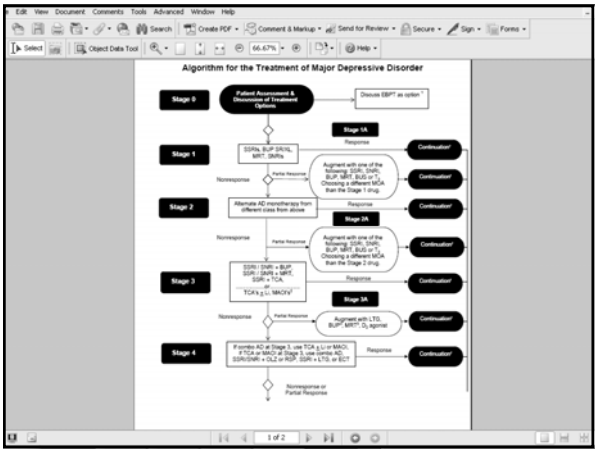
Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study findings:

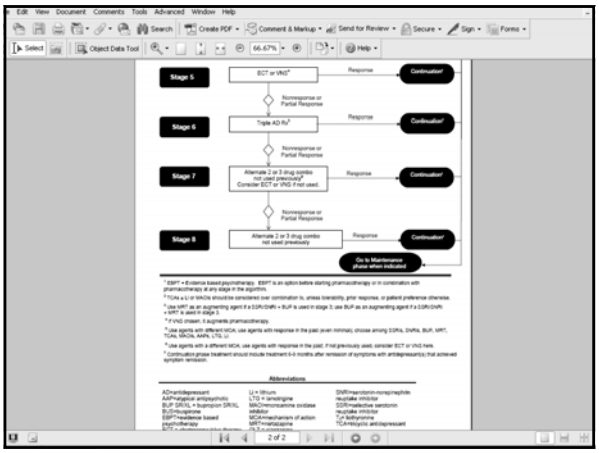
Level 3	Switch or Augment
Switch to:	Mirtazapine or nortriptyline
Augment L2 ATD with:	Lithium or thyroid (T3)

Treatment Level Progression

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study findings:

Level 4	Switch
Switch to:	MAOI or Venlafaxine XR + mirtazapine





Switching

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.

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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.

Switching Strategies

		3	1	2	3	1	3
	1	1	1	2	3	2	3
	1	1	1	2	2	2	3
	2	2	2		2	2	3
	3	3	2	2		2	3
	1	1	1	2	2		3
	3	3	3	3	3	3	

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 tranylcypromine): AVOID dextromethorphan, phenylephrine, pseudoephedrine; CAUTION with sulfonylureas and metformin

Monoamine Oxidase Inhibitors

- *Parnate* (tranylcypromine)
  - Available in 10mg tablets
  - Most well studied of the MAOIs
  - 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 struction is more amphetamine-like than any other MAOI

Monoamine Oxidase Inhibitors

- *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

Monoamine Oxidase Inhibitors

- *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

Monoamine Oxidase Inhibitors

- *Eldepryl* (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

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

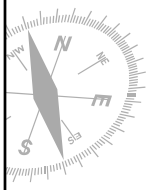
Foods to AVOID
- Aged cheeses
- Tap beer
- Fava beans
- Sauerkraut
- Some aged, cured or smoked meats

Foods that are RISKY
- Tofu
- Soy sauce
- Miso soup

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

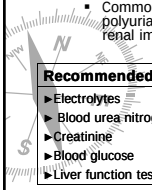
Foods that are SAFE
- Fresh cheeses
- All other dairy products
- Alcohol
- Chocolate
- Coffee

Augmentation



Antidepressant Augmentation

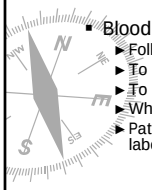
- Lithium
  - Particularly effective when added to a TCA, less effective with an SSRI
  - Postulated mechanism: net enhancing effect on serotonergic neurotransmission where the TCA increases postsynaptic serotonin receptor sensitivity
  - Use is supported by multiple randomized, controlled trials
  - 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 hypothroidism (<5% of tx pts)



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

Antidepressant Augmentation

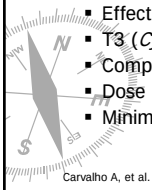
- Lithium
  - Dosing:
    - ►Long half-life allows once daily dosing if tolerated. Otherwise BID is adequate.
    - ►600-900mg daily, which translates in a lithium serum level of at lest 0.4mEq/l.
  - Blood Level Monitoring Frequency:
    - ►Following dosage changes
    - ►To confirm compliance
    - ►To determine adequacy of dose
    - ►Whenever lithium toxicity is suspected
    - ►Patients on stable maintenance doses of lithium should have laboratory monitoring 1-2X per year



Carvalho A, et al. *Curr Opin Psychiatry.* 22:7-12

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



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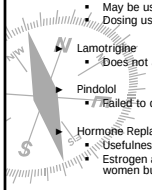
T3 is effective, has a favorable side effect profile, and is only $35/month

Antidepressant Augmentation

Limited or No Efficacy

- Psychostimulants
  - 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 SSRIs but data is limited
  - Dosing usually 15-30 mg/day
- Lamotrigine
  - Does not appear to be better than placebo as an augmenting agent
- Pindolol
  - Failed to demonstrate efficacy
- Hormone Replacement Therapy
  - Usefulness 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 perimenopausal women who are depressed



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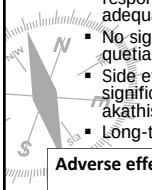
Antidepressant Augmentation

- Atypical Antipsychotics
  - Aripiprazole (*Abilify)* is FDA indicated as an adjunctive or augmenting agent in major depressive disorder
    - ► Dose range 5-20mg/d (15mg/d max 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



Adverse effects and higher cost make atypical antipsychotics less favorable

Antidepressant Augmentation

►Cost

Agent	Cost/30 days*
buspirone	$16
lithium	$17
Cytomel (T3)	$35
risperidone	$90
Symbyax (olanz/fluox)	$375
Abilify	$550

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

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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.