Disclosure: John Zajecka, M.D. (last 12 months)
Relevant Financial Relationships:

Grant/Research Support:
Actavis, Alkermes, Allergan, Axsome, ElMindA, Forest,
Hoffman-LaRoche, Janssen, Neuralstem, Takeda

Consultant/Advisory Boards:
Avanir, ElMindA, Lundbeck, PamLab/Nestle, Takeda

Speakers Bureau:
None

Stockholder:
None

Patent:
None
Disclosure

Off-Label/Investigational Uses

• Product(s)/Device - Medications that are being investigated for possible antidepressant effects (including symptoms of depression) as monotherapy/adjunctive therapy - including the following commercially available products: buprenorphine; ketamine, dextromethorphan, amphetamine (and related compounds); esketamine; methylphenidate, dopamine agonists, atypical antipsychotics not approved for adjunctive treatment of major depression; lithium; anticonvulsants; atomoxetine; modafinal; armodafinal; thyroid hormone; steroid hormones; buspirone; benzodiazepines; vortioxetine. Products/devices commercially available; Brain Network Activation.
Learning Objectives

• Review the importance of treating major depression with the goal to achieve symptomatic and functional remission and recovery early in the course of the illness

• Provide clinical guidelines in the assessment and intervention of major depression at all stages of the illness to optimize acute remission, recovery, and avoid relapse/recurrence

• Present basic guidelines and strategies to optimize outcome to initial treatment and when there is an inadequate response to treatment for major depression.

• Present an overview of the future direction of assessments and treatments for major depression
Unipolar Major Depressive Disorder (MDD)

- Lifetime prevalence: 16.2% (by age 75: 23.3%)
- Among the most “treatable” illnesses in medicine, but continues to have significant morbidity and mortality if not adequately treated
  - Among the most prevalent causes of worldwide disability
  - Contributes to morbidity and mortality of comorbid illness
  - Up to 15% reported death by suicide
Management of MDD should be similar to other treatable illnesses with high morbidity and mortality (e.g. infection, CV disease, cancer)

• Goal is to achieve complete REMISSION and sustain remission to RECOVERY
• REMISSION and RECOVERY is considered the standard of care
• Eradicate all symptoms associated with illness including functional recovery
• Requires ongoing assessment and being prepared with interventions when at risk for relapse/recurrence
• Potentially life-long risk for relapse and recurrence
Response, Remission, Recovery, Relapse, Recurrence & Chronicity

Response, Remission, Recovery, Relapse, Recurrence & Chronicity

Response
Remission
Recovery
Relapse
Recurrence

Time

6-12 mo
12 mo

adapted from Kupfer & Frank 2001
Relapse Risk Factors: Residual Symptoms at Remission are Associated with Subsequent Early Relapse

- Relapse to MDE occurred > 3 times faster in the presence of residual symptoms (p < 0.0001)
- **Best predictor of rapid relapse was the presence of 1 or more residual symptoms**
- History of episode recurrence (1-3 episodes vs. +3 episodes) was not a significant predictor among patients with residual symptoms (p = 0.283)

![Graph showing survival distribution function](image)
Residual Symptoms of Treated Depression

- Majority of patients treated for MDD have residual symptoms
  - 65% of subjects in STAR*D did not achieve remission.
  - 50% of remitters had residual symptoms

- Residual symptoms can persist 2-3 years after response to treatment

- 3-year prospective study (n=267) of patients treated to “remission”
  - 44% residual symptoms: cognitive problems, lack energy, & sleep problems
Treatment of MDD requires ongoing **ASSESSMENT** of the illness at **all stages** and consideration of possible **INTERVENTIONS**

**Assessment**

- Clinical assessment/observation remains the most reliable and informative tool
- Utilize a standardized approach for diagnosis, differential diagnosis, comorbidity, remission, recovery, relapse/recurrence
- Assess/verify adequate treatment trials
- Collateral information
- Consider use of genetic testing or biomarkers as an additional tool to provide information
- Investigational assessments
- When to collaborate, or refer

**Interventions**

- Use empirically based treatments
- Tailor treatment to individual patient needs over time
- Remain informed and utilize all treatment modalities (develop resources to collaborate)
- How to chose initial treatment and what to do when a treatment fails
- Guideline for using an adjunct (augmentation) treatment, combining another ADT vs switch ADT
- When to consider investigational treatments
- When to collaborate, or refer
The Constellation of MDD Symptoms

MDD Symptom Domains

1. Depressed mood
2. Loss of interest or pleasure
3. Significant change in weight or appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of worthlessness or excessive guilt
8. Diminished ability to think/concentrate or indecisiveness
9. Suicide ideation

The presence of specific symptoms varies from patient to patient
Assessing Symptoms and Functioning for MDD

- DSM criteria of symptoms and functional impairment provides a framework to establish diagnosis.
  - DSM criteria do not measure remission/recovery.
  - Continue to assess symptoms/functioning when the patient no longer meets full DSM criteria for MDD.
  - Focus on residual symptoms and functional impairment is most critical after an apparent response.

- Follow-up assessments require more precise questioning (e.g., side effects, residual symptoms, new onset symptoms, comorbid illness, possible misdiagnosis).

- Do not assume functional recovery occurs with symptomatic improvement.

- Symptoms and functional status may change over time.

- Initial and follow-up assessment requires questions tailored to the patient.
  - e.g., ask patient to list “Target Symptoms” - document and follow over time.
Think outside the box beyond DSM criteria

• Ask patient for “Target Symptoms” at initial and follow up visits
  • Provides a venue to hear it in the patients words
  • Ask for their “wish list” emphasize return to pre-morbid function
  • Set a gauge that you and patient measure outcome
    “what would it take to feel 100% “
    “on a scale from 1-10, where are you now and what would it take to be a 10?”

• Remain cognizant of possible etiology of baseline and subsequent symptoms
Assessment: Baseline Symptoms and Function

• Establish diagnosis, comorbidity, differential diagnosis, suicide risk
  - Comorbid illness “the rule rather than exception” (SUD, anxiety disorders)
  - Inquire about possible history of mania, hypomania
    (Mood Disorder Questionnaire)
  - Screening tools should not replace a good clinical assessment including current/past medical/psychiatric history, family history

• Establish “Target Symptoms”

• Obtain a historical timeline with the patient
  - Duration of current episode
  - Previous episodes and what occurred between episodes
  - Last time patient “felt like their old self” (symptoms and function)
    THIS ESTABLISHES A REFERENCE POINT FOR EXPECTATIONS!

• Get an accurate history of previous treatments (dose and duration) reference slides
  - Patients and clinicians can be poor historians
  - Get old records or pharmacy records if in doubt
Assessment: Toward Remission and Recovery

• Schedule acute and long-term assessment for impact of treatment (efficacy/safety/tolerability), symptoms/functioning, adherence, comorbidity even after recovery

• Structure your goals for follow-up assessment of symptoms/functioning
  - Revise Target Symptoms
  - Ask about suicidal ideation – even if patient looks better
  - Inquire about adverse events (possible side effects)

• Assessing for remission
  - NO SYMPTOMS and RETURN TO PRE-MORBID FUNCTION
  - Is the patient 100%?
  - Ask questions such as “can you belly laugh”

• Remain vigilant for ANY residual or new onset symptoms – especially when patient looks like they are significantly improved – THIS IS THE CRITICAL STEP TO GET TO REMISSION AND RECOVERY
Persistent Symptoms Among MDD Patients Who Responded but Did Not Remit After Antidepressant Treatment

Patients in STAR*D who responded but did not remit accounted for approximately 15% (N=428/2876) of those completing step 1.

Response was defined as ≥50% reduction in QIDS-SR16. Presence of a symptom was indicated by a QIDS-SR16 score of ≥1.

Percentage of Responders With Residual Symptoms During Long-term (≥3 Months) Antidepressant Treatment

- Prevalence of cognitive and physical impairment* assessed by a study-specific questionnaire
  - The prevalence of physical symptoms ranged from 49% to 52%
  - The prevalence of cognitive impairment symptoms ranged from 32% to 53%

*This study assessed only the cognitive and physical symptoms associated with MDD as defined by the study specific questionnaire.

There may be some symptoms of MDD that are less responsive to conventional ADT and require additional inquiry and intervention

- Cognitive symptoms and “physical symptoms” are common residual symptoms in patients who respond and remit to treatment
- Can result in significant functional impairment and risk of relapse if not addressed
- The expression of these symptoms may have a different pathophysiological etiology than other core depressive symptoms
- Do not avoid inquiring because of a perception the symptoms may be more difficult to treat
- Increased attention being focused on assessment and interventions (e.g. vortioxetine)
Patient Self-Report Cognitive Symptoms Mapped to Cognitive Domains

ATTENTION
- Lose train of thought
- Not listening
- Concentration
- Brain is cloudy
- Lack of focus
- Slow motion

MEMORY
- No short-term memory
- Attention
- Forgetful
- Can’t calculate

EXECUTIVE FUNCTION
- Procrastinate
- Lack confidence
- Indecisive
- Can’t multi-task

PSYCHOMOTOR SPEED
- Tired / lethargic
Differential Diagnosis of Residual/New Onset Symptoms

- Persistent or new MDD symptoms
- Side effect of treatment (e.g. apathy)
- Poor adherence
- New onset illness (e.g. thyroid, inflammatory illness)
- Drug interactions
- Folic acid depletion
- Comorbid illness (medical, iatrogenic, psychiatric e.g. anxiety, bipolar, Axis II, SUD)
Assessment: How you know you achieved remission and recovery?

- The absence of all symptoms associated with the illness (including acute or late-onset side effects to treatment)
  - Sustained remission is recovery
  - “Asymptomatic” as defined in clinical research
- Return to pre-morbid function
- Stable comorbid illness – medical or psychiatric
- Patient educated about:
  - Adherence
  - Sleep hygiene
  - Avoiding other risk factors for relapse or recurrence
**Strategies for Achieving and Sustaining Remission/Recovery**

- Accurate diagnosis of depression
- Adequate medication doses and duration
- Encourage patient adherence
- Measure symptomatic/functional outcome
- Educate patients that remission/recovery is the goal
- Define treatment resistant depression (TRD) vs refractory depression
- Consider augmentation or combination therapy
  - pharmacotherapy
  - pharmacotherapy + psychotherapy
  - ECT, rTMS, VNS, and investigational treatments
The Art and Science of Achieving and Sustaining Remission

• Adequate dose and duration of treatment
  • Medication, psychotherapy, ECT, VNS, rTMS, adjunctive and combination treatments
• Consider impact of acute and long-term adverse events
• Do not delay attempt to achieve remission
  • ‘if I had only one chance at this…’
• Factors involved in choosing the next step
  • Switching ADT
  • Adjunctive treatment to current ADT
  • Combination by adding another ADT
There is a paucity of evidence-based data comparing treatment strategies in patients failing to remit to monotherapy

- Until the last decade, very few controlled trials on the use of adjunctive therapy or combining ADTs in failure to respond to monotherapy
- Growing acceptance of using multiple medications (similar to the treatment of hypertension, cancer, and other medical illness where remission is the acute outcome)
- Clinicians need to continue to tailor the treatment to individual patients and to still consider the use of all classes of ADTs
- Clinicians need to remain familiar and have access to utilize all ADTs (including TCAs, MAOIs, novel treatments, ECT) and evidence-based adjunctive treatments
- Large community based samples provide a guide for clinicians to utilize in clinical practice (STAR-D, CPT3, and ongoing studies)
STAR*D Results Demonstrate Diminishing Effectiveness of TRD Treatments

*Remission rates are after 12 weeks of treatment and are based on the HRSD$_{17}$

Remission Rate Decreases With Each Treatment Level

The overall cumulative remission rate (QIDS-SR16) after 4 treatment steps was 67%*

*This estimate assumes no dropouts, and assumes that those who exited the study would have had the same remission rates as those who stayed in the protocol.

Management of Depression

Antidepressants (ADT)
- Tricyclics (TCA)
- Heterocyclics (HCA)
- Monoamine Oxidase Inhibitors (MAOI)
- Selective Serotonin Reuptake Inhibitors (SSRI)
- Serotonin Norepinephrine Reuptake Inhibitors
- Bupropion
- Mirtazapine
- Nefazodone
- Vortioxetine

Augmentation agents

Psychotherapy
- Evidence-based (CBT, DBT, ITP)
- Intensive Outpatient Programs
- Tailored therapy for comorbid illness

Neuromodulation
- Transcranial Magnetic Stimulation (TMS)
- Electroconvulsive Therapy (ECT)
- Vagus Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS)*

Phototherapy

* investigational for MDD
Evidence-Based Psychotherapy for Major Depression

• Cognitive Behavioral Therapy (CBT, CBASP)

• Interpersonal Therapy (ITP)

• Other investigational time-limited therapies

• Acute phase (monotherapy or as adjunctive)
  • initial intervention
  • inadequate response to medication

• Special populations
  • medical illness
  • adherence issue
  • childhood trauma
  • acute life stressor
  • medication taper
  • pregnancy
Empirically-Based Adjunctive Treatments ADT(Augmentation)

- Vagus Nerve Stimulation*
- L-methylfolate*
- Aripiprazole*
- Brexpiprazole*
- Olanzapine*
- Quetiapine*
- Other atypical antipsychotic agents
- Lithium
- Thyroid hormone (T3)
- Stimulants
- Modafinil/Armodafinil
- Buspirone

- Electroconvulsive therapy*
- TMS*
- Anticonvulsants (DVPX, LTG, CBZ)
- Dopamine agonists (e.g. pramipexole)
- Estrogen (as replacement)
- Buprenorphine
- SAMe
- Phototherapy
- CBT and IPT Psychotherapy

* Approved - Adjunctive treatment MDD ** Approved - monotherapy MDD
Choosing an ADT or Adjunctive Treatment: General Guidelines

- Past response, comorbidity, family history
- Safety and tolerability – consider acute and late onset adverse effects
- What will the patient tolerate for the long-term
- Cost and formulary concerns – use what you believe is the best treatment even if it requires prior authorization, patient assistance programs etc
- Put time and energy into the early intervention to achieve remission to avoid potential treatment resistance
- Attempt to assure adequate dose and duration of each trial, maximize dose, and acute side effects
- If switching ADTs, consider switch/bridging to an ADT with a different MOA
- Have access to clinicians to collaborate for collaboration or referral
- Use empirically-based treatments and tailor treatments to individual patient needs
- Always have “Plan B” in place to avoid delay in achieving or sustaining remission
Genotyping & Direction of Future Diagnostics & Treatment Intervention

• **Good clinical assessment/observation - MOST IMPORTANT TOOL!**
  • Identify Target Symptom over time
  • Prior history, family history, collateral history
  • Always assess risk for suicide

• **Genotyping**
  • Cytochrome P450 - rapid or slow metabolism – pharmacokinetic
  • Serotonin Transporter SLC6A5 (treatment response, side effect burden, AIM+)
  • MTHF polymorphism – reduced ability to metabolize folic acid/folate to L-methylfolate
    • rate-limiting step in synthesis of 5-HT, NE, DA
  • COMT activity resulting in low DA activity
  • Increased recognition by Medicare and insurance providers for reimbursement
Definitions

• **MONOTHERAPY ANTIDEPRESSANT TREATMENT**
  • The use of one antidepressant with adequate dose and duration, AND
  • The absence of an adequate dose/duration of another antidepressant or augmentation treatment.

• **COMBINATION ANTIDEPRESSANT TREATMENT**
  • The use of > 2 antidepressants with adequate dose and duration of each antidepressant
Definitions

- AUGMENTATION TREATMENT
  - The use of an adequate dose of one antidepressant, AND
  - ≥ 1 somatic treatment(s) (with empirical evidence of augmentation effects) with adequate dose and duration, NOT categorized as an antidepressant (Augment Non-ADM), OR
  - Sub-therapeutic dose of an antidepressant
    - Serum levels not expected to be in a therapeutic antidepressant dose range with concurrent medications
    - Augment ADM
Definitions

• COMBINATION AND AUGMENTATION TREATMENT
  • The use of adequate dose and duration of > 1 antidepressant AND ≥ 1 augmentation used concomitantly.

• BRIDGING
  • The transition of reducing one antidepressant that overlaps with starting another antidepressant
What to do with MDD that fails to remit to monotherapy ADT: Switch? Combine? Augment?

• General guidelines:
  • <25% efficacy: **SWITCH** vs. augment
    (COMBINE during SWITCH \(\rightarrow\) Bridging)
  • 25-50% efficacy: **SWITCH** vs **AUGMENT**
  • >50% efficacy: **AUGMENT** vs switch
  • Consider patient preference, tolerability of monotherapy, and risk:benefit

Zajecka J, Goldstein C (2006)
CPT III Study
Design

1st Randomization

ADM and CT
(N=227)

Response

Relapse

MEDS = medications alone

2nd Randomization

ADM (N=90)

No ADM (N=75)

Response Relapse

Combined = MED + CBT

Maintenance/Follow-up (36 months)

ADM (N=70)

No ADM (N=70)

Remission Recovery

Acute Treatment (up to 18 months)

Continuation (6-18 months)
CPT3 Study: ADT Strategy to Reflect Real-World Clinical Practice

- Initial treatment based on: history of previous ADT efficacy/tolerability, comorbidity, family history, and use of an SSRI or SNRI for treatment naive patients
- Initial treatment in naïve patients also included bupropion, mirtazapine, nefazodone, (would have included vortioxetine available at time of study), or used as 2nd, 3rd, interventions before use of a TCA or MAOI
- Basic ADT treatment guidelines: use adjunctive treatments for partial response; bridge ADTs in switching to next ADT with different mechanism of action; and assure exposure to a TCA and MAOI within the 12 month acute treatment before identifying patient as refractory
- Similar to basic design of STAR-D
Medication Sequence to Model Real-World Clinical Practice

SNRI or SSRI → TCA → MAOI

SNRI or SSRI → Augment/Combine

SNRI or SSRI → Augment/Combine

SNRI or SSRI → Augment/Combine

SNRI or SSRI → Augment/Combine
Example Patient History*

Venlafaxine → Citalopram → Bupropion → Buspirone

75 → 150 → 20 → 100 → 200 → 15

Too Slow → Too Slow → Too Slow → Too Slow → Too Slow → Too Slow

Illogical Too Low → Too Low → Too Low

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

5 months → 5 months → 3 months → 4 months → 2 months → 5 months
Example Patient History*

Citalopram ———> Duloxetine

Bupropion ———> Aripiprazole

Weeks

Example only, not a real patient
Treatment-Resistant Depression

• No universally accepted definition

• Failure to remit to an adequate trial (dose and duration) of an ADT

• Stages based upon number of failed trials of monotherapy and adjunctive therapy

• Majority of TRD have identified modifiable factors associated with lack of adequate response (e.g. misdiagnosis (bipolar); inadequate treatment trials)

• Theories of etiology include repeated exposure to multiple ADTs before achieving remission (similar to antibiotics and resistant infections)

• Management of MDD should include early intervention and adequate trials to achieve remission as quickly as possible to avoid TRD
Future Directions in Pharmacotherapy for MDD

- Monotherapy vs. adjunctive therapy remains an important question, even in the development of novel treatments.
- New is not always better (e.g. MAOIs, TCAs, lithium remain ‘gold standards’)
- Use of imaging to predict outcome to early treatment (e.g. Brain Network Activation – BNA)
- New treatments will need to provide some advantage over conventional treatments (when utilized as intended, including)
  - Rapid action, suicidal patients
  - Target common residual symptoms (e.g. cognition, fatigue)
  - Novel mechanism
  - Risk: Benefit safety and tolerability
Novel Targets in Pharmacotherapy for MDD

- Glutamatergic agents/N-methyl-D-aspartate (NMDA) modulation/anti-inflammatory
  - I.V. ketamine/intranasal esketamine – rapid onset
  - Other rapid-acting I.V. NMDA modulators
  - Riluzole
  - Dextromorphan (adjunctive treatment)

- Compounds that stimulate neurogenesis of hippocampus/optimize neuronal plasticity of neurotrophins (e.g. BDNF)

- Botulinum toxin
  - Paralyze trigeminal nerve -> reduced sensitivity of amygdala

- Broad pharmacotherapy aimed to provide
  - Rapid onset
  - Prevent tachyphalaxis
Novel Directions for Non-Pharmacological Treatments

• Assess genotype, phenotype, brain imaging, and other biomarkers for predicting efficacy (acute and long-term), safety, and tolerability

• Modifiable comorbidities
  • Compounds with multiple mechanisms (e.g. inflammation, methylation)

• Role of empirical psychotherapies (MAYBE NOT TIME-LIMITED!)
  - Ongoing work with CBT
  - DBT
  - Behavior Activation (BA)

• Modifications of rTMS as monotherapy and adjunctive therapy

• Deep Brain Stimulation
Conclusion

• Similar to other illnesses - goal should be complete remission and recovery of symptoms and functional impairment
• Avoid relapse and recurrence
• Avoid development of TRD by treating early and to full remission
• Assessment and interventions need to be standardized yet tailored to individual patient over time – “personalized medicine”
• Consider all treatment options to meet the goals of SYMPTOM and FUNCTIONAL RECOVERY
• Consider the use of all available treatment modalities and collaborate or refer if necessary
• Stay informed about novel assessment and treatments
• Partner with patient and other health providers involved in the management of the MDD or other comorbid illness
Learning Objectives

• Review the importance of treating major depression with the goal to achieve symptomatic and functional remission and recovery early in the course of the illness

• Provide clinical guidelines in the assessment and intervention of major depression at all stages of the illness to optimize acute remission, recovery, and avoid relapse/recurrence

• Present basic guidelines and strategies to optimize outcome to initial treatment and when there is an inadequate response to treatment for major depression.

• Present an overview of the future direction of assessments and treatments for major depression
Mayo Clinic
Locations
Questions & Discussion
Reference Slides

For reference and will not be presented
## Minimal and Optimal Trials (SSRIs)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Name</th>
<th>Minimal dose/duration</th>
<th>Optimal dose/duration</th>
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<tr>
<td>citalopram</td>
<td>Celexa</td>
<td>20 mg / 4 wks</td>
<td>60 mg / ≥ 6 wks</td>
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<td>escitalopram</td>
<td>Lexapro</td>
<td>10 mg / 4 wks</td>
<td>30 mg / ≥ 6wks</td>
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<td>vilazodone</td>
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<td>40 mg / &gt; 6wks</td>
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<td>80 mg / ≥ 6 wks</td>
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<td>Zoloft</td>
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<td>Luvox</td>
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<td>paroxetine</td>
<td>Paxil, Paxil CR</td>
<td>20 mg / 4 wks</td>
<td>50 mg / ≥ 6 wks</td>
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## Minimal and Optimal Trials (SNRIs/Others)

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<td><strong>SNRIs:</strong></td>
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<td>venlafaxine</td>
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<td>bupropion</td>
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<td>bupropion SR</td>
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## Minimal and Optimal Trials (TCAs)

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<td>Surmontil</td>
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<td>proptrityline</td>
<td>Vivactil</td>
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*Lower doses if documented serum levels in therapeutic range
Minimal and Optimal Trials (MAOIs)

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<tbody>
<tr>
<td>tranilcypromine</td>
<td>Parnate</td>
<td>30 mg / 4 wks</td>
<td>&gt; 40 mg / &gt; 6 wks</td>
</tr>
<tr>
<td>isocarboxid</td>
<td>Marplan</td>
<td>30 mg / 4 wks</td>
<td>&gt; 40 mg / &gt; 6 wks</td>
</tr>
<tr>
<td>phenelzine</td>
<td>Nardil</td>
<td>60 mg / 4 wks</td>
<td>&gt; 75 mg / &gt; 6 wks</td>
</tr>
<tr>
<td>selegeline</td>
<td>EMSAM patch, Eldepryl</td>
<td>6 mg / 4 wks</td>
<td>&gt; 12 mg / &gt; 6 wks</td>
</tr>
</tbody>
</table>

** Lower doses if documented side effects (e.g. hypotension) prevent dose escalation