Different Strokes for Different Folks: Treating Special Populations with Depression

MDD Treatment Guidelines: Current Recommendations

Monotherapy (6–12 weeks)

- partial response: raise dose or augment
- no response/not tolerated: no response/not tolerated

- no response/not tolerated: Monotherapy (6–12 weeks)
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MDD Treatment Guidelines: Are There Changes in Store?

Monotherapy (6–12 weeks)

- Partial response
  - Raise dose or augment

- No response/not tolerated
  - Monotherapy (6–12 weeks)
    - No response/not tolerated
      - Monotherapy (6–12 weeks)

Meta-Analysis: Majority of Improvement Occurs in First Two Weeks of Treatment

Meta-analysis included 47 trials
Under Investigation: 
Early Medication Change

- Early Medication Change (EMC) trial
- Phase IV, multi-center, multi-step, randomized, observer-blinded, actively controlled, parallel-group clinical trial
- First prospective investigation of whether non-improvers at 14 days of AD treatment with early medication change are more likely to achieve remission by 56 days than treatment as usual


Evidence for the Increased Efficacy of Two Antidepressant Mechanisms Over One: SSRI + NRI

SSRI Treatment
- Remission: 7%
- Response: 36%
- Partial response: 7%
- Non-response: 50%

NRI Treatment
- Remission: 0%
- Response: 17%
- Partial response: 50%
- Non-response: 33%

Combined Treatment
- Remission: 54%
- Response: 8%
- Partial response: 0%
- Non-response: 38%

Review: Enhanced Remission With Early Combination

<table>
<thead>
<tr>
<th>Randomized trial</th>
<th>Drug combination superior to monotherapy from initiation of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al., 2004</td>
<td>SSRI (fluoxetine) + NRI (desipramine)</td>
</tr>
<tr>
<td>Godfrey et al., 1990; Coppen and Bailey, 2000; Resler et al., 2008</td>
<td>SSRI (fluoxetine) + L-methylfolate</td>
</tr>
<tr>
<td>Fava et al., 2006</td>
<td>SSRI (fluoxetine) + eszopiclone</td>
</tr>
<tr>
<td>Blier et al., 2009</td>
<td>SSRI (paroxetine) + mirtazapine</td>
</tr>
</tbody>
</table>
| Blier et al., 2010 | SSRI (fluoxetine) + mirtazapine  
SNRI (venlafaxine) + mirtazapine  
NDRI (bupropion) + mirtazapine |

Stahl SM. J Clin Psychiatry 2009;70.

Antidepressant Combinations at Treatment Initiation

- fluoxetine (N=28)  
- fluoxetine + mirtazapine (N=25)  
- venlafaxine + mirtazapine (N=26)  
- bupropion + mirtazapine (N=26)

Statistically significant difference for fluoxetine monotherapy vs all combination treatment groups (F=3.87; df=3, 101, p=0.011)


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Combination Therapy from the Start: L-methylfolate Plus Antidepressants

• Three randomized controlled trials (fourth in progress)
• Godfrey et al 1990
  – 24 depressed patients with low RBC folate
  – 15 mg of d,l racemic methylfolate or placebo added to antidepressant treatment as usual
  – Mood improved as did folate levels more than antidepressants alone

Combination Therapy from the Start: Folic Acid and Fluoxetine

127 patients

62 patients: 500 μg folic acid and 20 mg fluoxetine

Greater improvement on Hamilton Rating Scale
  • 93.9% of women were good responders
  • results mainly confined to women

65 patients: placebo and 20 mg fluoxetine

• only 61.1% of women were good responders

This increase in plasma folate following treatment lead to a decrease in plasma homocysteine, and also a lower depression score.

Combination Therapy from the Start: 
Folic Acid and Fluoxetine

- Three randomized controlled trials
- Resler et al. 2008
  - 27 depressed patients on fluoxetine 20 mg
  - 10 mg of folic acid or placebo added
  - Mood improved and homocysteine levels decreased on folic acid


Combination Therapy From the Start:
Eszopiclone and Fluoxetine

- 42% remission
- Fluoxetine alone 33% remission

Fava M et al. Biol Psychiatry 2006;59:1052-60;
Under Investigation:
Early Combination

- Combining Oral Medications to End Depression (COMED) on the Depression Trials Network
- Funded by NIMH
- Comparing potential benefits of combining any two antidepressants at initiation (bupropion, escitalopram, mirtazapine, venlafaxine)

Guidelines for Treatment

**Mild depression**

Active support and monitoring (6–8 weeks every 1–2 weeks)

**Moderate depression**

Medication  
Cognitive behavioral therapy  
Interpersonal therapy

**Severe depression**

Medication  
Medication + CBT

Zuckerman RA et al. Pediatrics 2007;120:e1299-1312;  
Medication

- Evidence-based treatments for adolescents include SSRIs
  - Pooled AD trials: NNT=10, NNH=112
  - Fluoxetine and escitalopram are approved
- Warn patient and family about adverse effects
  - Signs of switch to mania (excessive spending, risk taking, needing little sleep, promiscuous behavior, racing thoughts, pressured speech)
  - Signs of behavioral activation (agitation, hostility, restlessness, suicidal ideation or behavior)
- Therapeutic dose is typically lower for adolescents than for adults
- Develop regular, frequent monitoring schedule


Treatment of Resistant Depression in Adolescents (TORDIA)

N=334 adolescents with SSRI-resistant depression randomly assigned to alternate SSRI, venlafaxine, or medication switch + CBT.
Log time: p<0.001; remission: p=0.07; remission-by-log time: p<0.001.
Cognitive Behavioral Therapy (CBT): Goals and Benefits

- Typically weekly sessions for 12–16 weeks
- Identify self-defeating behaviors
- Correct maladaptive thoughts
- Encourage participation in pleasurable activities
- Develop or reactivate social skills
- Develop problem solving strategies

Interpersonal Therapy (IPT)

- Typically 12–16 weeks
- Addresses relationship difficulties arising from
  - Grief (loss of someone significant)
  - Interpersonal disputes (frequent fights with peers or family members)
  - Role transition (change in school, break up)
  - Interpersonal deficits (no significant relationship outside of family)
Risks of Antidepressants vs Depression

- No randomized controlled trials comparing effects of antidepressants vs depression during pregnancy

<table>
<thead>
<tr>
<th>Untreated depression</th>
<th>Antidepressant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First trimester</td>
</tr>
<tr>
<td>Impaired feto-placental function</td>
<td>Minor physical anomaly</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>Low fetal growth</td>
<td></td>
</tr>
<tr>
<td>Premature delivery</td>
<td></td>
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<tr>
<td>Low birth weight</td>
<td></td>
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<tr>
<td>Small gestational age</td>
<td></td>
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<tr>
<td>Perinatal complications</td>
<td></td>
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</tbody>
</table>


Antidepressant Use During Pregnancy and Lactation

<table>
<thead>
<tr>
<th>Generic</th>
<th>Pregnancy Risk Category</th>
<th>American Academy of Pediatrics (AAP) Rating</th>
<th>Lactation Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Bupropion</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L3</td>
</tr>
<tr>
<td>Citalopram</td>
<td>C</td>
<td>Not available</td>
<td>L3/L3 in older infants</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Desipramine</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Doxepin</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L5</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>C</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>C</td>
<td>Not available</td>
<td>L3/L3 in older infants</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L2 in older infants, L3 if used in neonatal time</td>
</tr>
</tbody>
</table>

Antidepressant Use During Pregnancy and Lactation (cont.)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Pregnancy Risk Category</th>
<th>American Academy of Pediatrics (AAP) Rating</th>
<th>Lactation Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvoxamine</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Imipramine</td>
<td>D</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>C</td>
<td>Not available</td>
<td>L3</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>C</td>
<td>Not available</td>
<td>L4</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>D</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>D</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Sertraline</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Trazodone</td>
<td>C</td>
<td>Unknown, of concern</td>
<td>L2</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>C</td>
<td>Not available</td>
<td>L3</td>
</tr>
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</table>


Depression With or Without Dementia: Is it a Mood Disorder, a Cognitive Disorder, or Both?

<table>
<thead>
<tr>
<th>Disorder Symptom</th>
<th>MDD</th>
<th>Geriatric MDD</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cognition</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Apathy, Fatigue, Motivation</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Agitation</td>
<td>+/-</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

+++ Most common
++ Common
+ Average
- None

Treatment Recommendations

- Use of validated screening instrument
- Individual CBT and/or antidepressant treatment
- Patient education
- Insufficient evidence
  - Individual or group psychotherapy
- Not recommended for depression
  - Individual psychotherapy for overall mental health
  - General education and/or skills training
  - Geriatric health evaluation and management
  - Exercise not targeting depression
  - Rehabilitation and occupational therapy


Pharmacokinetics of Antidepressants in the Elderly

- Absorption is generally complete, but slower
  - Some medical conditions may reduce extent of absorption
- Elderly have less fluid, so water-soluble medications can reach toxic levels more quickly
- Elderly have more adipose tissue, so fat-soluble medications (many psychotropics) are absorbed into less well-vascularized fat stores
  - Take longer to reach therapeutic level
  - Take longer to be excreted
- Decreases in liver and kidney functions also cause longer time to clearance and excretion
- Protein malnutrition is common, leaving more freely circulating protein-bound drugs (e.g., warfarin)
  - Some psychotropics displace highly protein-bound drugs, increasing risk

Amella EJ. Am J Nursing 2006;83(2):372-89.
Summary

• New research may soon lead to a revision of established treatment guidelines
• Treatment guidelines and risk/benefit ratios for antidepressants can vary for different subgroups
• For adolescents, don’t be afraid to use medication, but be sure to monitor and educate patients and their families about warning signs for mania and suicidality
• For pregnant women, discuss risks/benefits with the patient, the father, and coordinate with the pediatrician if treatment will occur postpartum
• For elderly, medication is often warranted but be aware of potential drug interactions and pharmacokinetic differences related to age