Pharmacotherapy: Risks and Benefits

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Disclosure Statement 2007-2008

Dr. Raymond Lam, MD, FRCPC

Speaker/Advisory Boards
- AstraZeneca
- Biovail
- CANMAT
- Eli Lilly
- GlaxoSmithKline
- Janssen
- Litetool Company, Inc.
- Lundbeck
- Servier
- Wyeth

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- None

Clinical Trials/Grants
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- CANMAT
- H. Lundbeck
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- Mathematics of Information and Advanced Technology Systems
- VGH-UBC Hospital Foundation

Outline

- Antidepressant efficacy, effectiveness and tolerability
- Antidepressant safety
  - Suicidality
  - Drug interactions
- Measurement-based care
- Maintenance treatment
- Managing limited or partial response
  - Sequencing
  - Combination treatment
Profile of the ideal antidepressant

- Safe
- Well tolerated
- No drug interactions
- Simple to use
- Rapid onset of action
- Excellent efficacy to remission
- Broad spectrum (depression & anxiety)
- Good relapse/recurrence prevention
- Inexpensive

**Antidepressants**

<table>
<thead>
<tr>
<th>TCA</th>
<th>SSRI</th>
<th>SNRI</th>
<th>NDRI</th>
<th>RIMA/B</th>
<th>NaSSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Citalopram (Celexa)</td>
<td>Duloxetine (Cymbalta)</td>
<td>Buproprion-SR/XL (Wellbutrin)</td>
<td>Moclobemide (Manerix)</td>
<td>Mirtazapine (Remeron)</td>
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<tr>
<td>Imipramine</td>
<td>Escitalopram</td>
<td>Venlafaxine-XR (Effexor)</td>
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<tr>
<td>Clomipramine</td>
<td>Fluoxetine (Prozac)</td>
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<tr>
<td>Trimipramine</td>
<td>Fluvoxamine (Luvox)</td>
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<tr>
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<td>Sertraline (Zoloft)</td>
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<tr>
<td>Anoxapine</td>
<td>Paroxetine (Paxil)</td>
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<tr>
<td>Nortrimpyline</td>
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<td>Desipramine</td>
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<tr>
<td>Phenelzine</td>
<td>Trazodone (Nefazodone)</td>
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<tr>
<td>Tranylcypromine</td>
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</tbody>
</table>

**CANMAT Depression Guidelines Revision, 2009**

- Evidence-based update of 2001 CPA/CANMAT Guidelines
- Psychotherapy, pharmacotherapy, complimentary therapies, neurostimulation treatments
- Question-Answer format
- International commentary
- Published as a supplement in the Journal of Affective Disorders

www.canmat.org
There’s been a lot of research lately on your condition. Now I’m sorry I didn’t read any of it.”

CANMAT Depression Guidelines Revision, 2009

Evidence for antidepressant efficacy and effectiveness, since 2000:

- 224 randomized controlled trials.
- 30 systematic reviews and meta-analyses.
- 3 major reports.
  - National Institute for Clinical Excellence (UK). Management of depression in primary and secondary care, 2004

<table>
<thead>
<tr>
<th>Product</th>
<th>Tactile</th>
<th>Cramp</th>
<th>Fatigue</th>
<th>Headache</th>
<th>Sedation</th>
<th>Sleep</th>
<th>GI Distress</th>
<th>Tremor</th>
<th>GI Distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td></td>
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<td>Duloxetine</td>
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<td>Venlafaxine</td>
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<tr>
<td>Sertraline</td>
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<td>Paroxetine</td>
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<td>Mirtazapine</td>
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<td>Bupropion</td>
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</table>

Antidepressant Medications: General Conclusions

- Antidepressants demonstrate clear efficacy versus placebo, although effect sizes are mild to moderate
  - Placebo rates are high (and increasing)
  - Greater efficacy when clinical outcomes are measured
  - More evidence for efficacy when severity is moderate to severe
- SSRIs and third-generation agents are as effective but better tolerated and safer than older medications
- Not all antidepressants are alike, even within the same class
- There are no clear predictive factors for choice of agent

Profile of the ideal antidepressant

- Safe
- Well tolerated
- No drug interactions
- Simple to use
- Rapid onset of action
- Excellent efficacy to remission
- Broad spectrum (depression & anxiety)
- Good relapse/recurrence prevention
- Inexpensive
Suicidality associated with antidepressants in children and adolescents?

- 2003 – of 15 MDD studies done in children/adolescents, only 6 were published.
- In 3 studies of paroxetine, an excess risk of suicidal behaviours was detected (3.4% vs. 1.2% for placebo).
- 2004 – FDA commissioned a re-analysis of all paediatric clinical trials using Columbia University suicide research group criteria.
- June 2004 – black box warning for antidepressants in Canada and later in US; warning letter and contraindication in UK.

Possible reasons for suicidality associated with antidepressants

- Worsening of underlying depression before benefit of medication.
- Unexpected psychosocial stressor (e.g., relationship breakup).
- Improvement of physical symptoms (e.g., energy) before mood symptoms.
- Non-specific side effect of medication (e.g., headaches, anxiety).
- Specific side effect of medication (e.g., activation syndrome).

Suicidality and antidepressants Summary of evidence

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Adults</th>
<th>Youth</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs and meta-analyses</td>
<td>Safe ✓</td>
<td>Caution indicated</td>
</tr>
<tr>
<td>Prescription databases</td>
<td>Safe ✓</td>
<td>Caution indicated</td>
</tr>
<tr>
<td>Forensic databases</td>
<td>Safe ✓</td>
<td>Safe ✓</td>
</tr>
<tr>
<td>Phamaco-epidemiology</td>
<td>Safe ✓</td>
<td>Safe ✓</td>
</tr>
</tbody>
</table>

Lam RW, Kennedy SH, 2005
## Clinical Recommendations

### ALL AGES

- Patients treated for MDD must be monitored closely for worsening, especially at the start of treatment.
- When medications are used, patients should be educated about side effects including anxiety, agitation, hypomania or suicidality.

Lam RW, Kennedy SH, 2005

### CHILDREN & ADOLESCENTS

- Only fluoxetine has an acceptable benefit-risk ratio to recommend as first-line treatment of MDD.
- Other SSRIs are considered second-line treatments, to be used for MDD that is severe, chronic, comorbid with other conditions, or not responding to psychosocial treatments.
- Paroxetine and other novel antidepressants (e.g., SNRIs) are considered third-line treatments because of higher adverse events profile.
- Tricyclic antidepressants are not recommended.

Lam RW, Kennedy SH, 2005

## Negative Effects of the Black Box Warnings?

[Graphs showing SSRI prescription rates and suicide rates among youth]

Psychnat News, Oct 2007; 42: 3-34
Safety profile of first-line antidepressants

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Safety</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
<td>Marked inhibition of CYP 2D6</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td>Marked inhibition of CYP 2D6</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion-SR/XL</td>
<td>Caution in overdose</td>
<td>Moderate inhibition of CYP 2D6</td>
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<tr>
<td>Duloxetine</td>
<td></td>
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<tr>
<td>Mirtazapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine-XR</td>
<td>Caution in overdose</td>
<td></td>
</tr>
</tbody>
</table>

 Benefit-Risk Assessment for Antidepressants in Major Depressive Disorder

<table>
<thead>
<tr>
<th>Group</th>
<th>Medication</th>
<th>Benefit (Efficacy)</th>
<th>Risk (Suicidality, etc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (18-65 yrs)</td>
<td>All antidepressants</td>
<td>Level 1</td>
<td>Level 2</td>
</tr>
<tr>
<td>Elderly (&gt;65 yrs)</td>
<td>All antidepressants</td>
<td>Level 1</td>
<td>Level 2</td>
</tr>
<tr>
<td>Children &amp; Adolescents (&lt;18 yrs)</td>
<td>Fluoxetine</td>
<td>Level 1</td>
<td>Level 2</td>
</tr>
<tr>
<td></td>
<td>Other antidepressants</td>
<td>Level 2</td>
<td>Level 2</td>
</tr>
</tbody>
</table>

Antidepressants: Proven Efficacy across a Spectrum of Disorders

- Major depressive disorder
- Dysthymic disorder
- Bipolar depression
- Seasonal affective disorder
- Premenstrual depressive disorder
- Panic disorder
- Generalized anxiety disorder
- Obsessive-compulsive disorder
- Social anxiety disorder
- Post traumatic stress disorder
- Bulimia nervosa
- Chronic pain
- Fibromyalgia
- Smoking cessation
Using Validated Outcome Measures

<table>
<thead>
<tr>
<th>CLINICIAN-RATED</th>
<th>PATIENT-RATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Depression Rating Scale (HDRS, Ham-D)</td>
<td>Beck Depression Inventory (BDI)</td>
</tr>
<tr>
<td>Montgomery Asberg Depression Rating Scale (MADRS)</td>
<td>Geriatric Depression Scale (GDS)</td>
</tr>
<tr>
<td>Primary Care Evaluation for Mental Disorders (PRIME-MD)</td>
<td>Personal Health Questionnaire (PHQ-9)</td>
</tr>
</tbody>
</table>

BC Depression Guidelines: Recommendation #7b – Monitoring Outcomes
The PHQ-9 (Personal Health Questionnaire) Self-rated scale is the “HbA1c” of depression. It takes 3-5 minutes to complete. It is highly sensitive and specific for the diagnosis of depression. It can be used to monitor progress (including remission criteria scores).

<table>
<thead>
<tr>
<th>TOTAL SCORE</th>
<th>DEPRESSION SEVERITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>None</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild Depression</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate Depression</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderate-severe Depression</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe MDD</td>
</tr>
</tbody>
</table>

PHQ-9 is adapted from PRIME MD TODAY, developed by Spitzer RL, Kroenke K, & Williams JBW, ©1999 Pfizer Inc.; Yeung A et al, 2008.

There are 2 phases of treatment for depression.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>8-12 wks</td>
<td>- Remission of symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Return to function</td>
</tr>
<tr>
<td>Maintenance</td>
<td>6-24 mos, or longer</td>
<td>- Rehabilitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prevention of recurrence</td>
</tr>
</tbody>
</table>

BC Depression Guidelines: Recommendation #1a – Detection

Recommendations for Maintenance Treatment

- ALL patients should continue on antidepressants for 6 months after remission of symptoms
- Patients who require longer maintenance treatment (> 2 years) include those with:
  - Chronic episodes
  - Severe episodes (suicidality, psychosis)
  - Difficult to treat episodes
  - Recurrent, frequent episodes (2 episodes in 2 years, or 3 in 5 years)
  - Older age
  - Comorbidity

Recommendation #7c – Maintenance Treatment
PREVENT Study for Recurrent Major Depression

- Venlafaxine-XR (N=129)
- Placebos (N=129)

Cumulative Recurrence Rate

- 6 months: 10%
- 12 months: 15%
- 18 months: 20%
- 24 months: 25%

VEN dose: 75-300 mg, median 221 mg
10 wks acute, 6 months continuation
Re-randomized after 12 months
Recurrence: HDRS>12, <50%


Evidence-Based Algorithm for Non-Response

- Assess Response
- Optimize
- Remission
- Partial or Non-Response
- Augment
- Switch
- Combine
- Maintenance

Evidence
- Level I
- Level II
- Level III


Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Question:
- “What do you do if the first antidepressant doesn’t work?”

“State-of-the-Art” Features
- Real-world population
- Large sample size
- “Measurement-based” care
- Focus on remission
- Patient preference/clinical equipoise
- Psychotherapy and pharmacotherapy

STAR*D Level 1: Response to Citalopram

- STAR*D effectiveness study of moderate to severe depression
- "Real world" patient sample
- Citalopram 20-60 mg/d x 12 weeks
- Mean dose = 42 mg
- Outcome by QIDS-SR

Response=14%
Non-Response=53%
Remission=33%
N=2,876

Remission=33%
Response=14%
Non-Response=53%


Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Level 1
Open treatment with Citalopram 20-60 mg/d x 12 weeks

Patients not in remission

Level 2
Switch to monotherapy with:
- Sertraline
- Bupropion-SR
- Venlafaxine-XR

Combination therapy with:
- Bupropion-SR
- Buspirone


STAR*D switch and augmentation strategies

- No significant differences between 3 switch treatments
- No significant differences between 2 augmentation treatments

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) – Level 2

Conclusions for 2nd Step

- Switch within class or out-of-class is equivalently effective for SSRI-nonresponders.
- Bupropion combination is more effective and better tolerated than buspirone augmentation.
- May want to use combination before switch in partial responders.

Cumulative Remission Rates in STAR*D

<table>
<thead>
<tr>
<th>Level</th>
<th>Interventions</th>
<th>Remission Rate</th>
<th>Cumulative Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 N=3,671</td>
<td>CITALOPRAM</td>
<td>36.8%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Step 2 N=1,439</td>
<td>Switch: VEN / BUP / SER  Combine: BUP / BUS  Switch / Combine: CT</td>
<td>30.6%</td>
<td>56.1%</td>
</tr>
<tr>
<td>Step 3 N=390</td>
<td>Switch: NOR / MIR  Augment: LI / T3</td>
<td>13.7%</td>
<td>62.1%</td>
</tr>
<tr>
<td>Step 4 N=123</td>
<td>Switch: TCP / MIR+VEN</td>
<td>13.0%</td>
<td>67.0%</td>
</tr>
</tbody>
</table>

* QIDS-SR<sub>16</sub> ≤ 5

<table>
<thead>
<tr>
<th>Residual symptoms</th>
<th>Anxiety, insomnia</th>
<th>Hypersomnia, fatigue</th>
<th>Cyclicity, bipolarity</th>
<th>Seasonality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add-on strategies</td>
<td>Benzodiazepine  Atypical antipsychotic  Mirtazapine</td>
<td>Bupropion  Citalopram  Modafinil  Stimulants  Light therapy</td>
<td>Bupropion  Atomoxetine  Modafinil  Stimulants  Atypical antipsychotic</td>
<td>Light therapy  Bupropion</td>
</tr>
</tbody>
</table>

Note: these recommendations are based only on Level 3-4 evidence currently, but take into account probable efficacy and tolerability.
Antidepressants: Risks and Benefits

- Antidepressants are safe and effective treatments for a spectrum of conditions, but the decision for use must weigh benefits vs. risks for an individual.
- Some people will require more intensive treatment to achieve clinical remission.
- Maintenance treatment is necessary.
- There is no good evidence that suicidality is associated with antidepressants in adults, and only limited evidence for the association in youth.
- ALL patients should be closely monitored for treatment-emergent effects including suicidality.

Antidepressants: What do we need to know?

- What is the comparative effectiveness of agents?
- How effective are medications for real-world outcomes?
- How can we optimize/predict/tailor response?
- When should we combine medications?
- Which medications should we combine?
- How long to maintain on medications or Who can come off medications?
- What are the best medication strategies for comorbid conditions, both psychiatric and medical?
Typical Clinical Trial Depressed Subject

- Single Axis I diagnosis
- Moderately depressed outpatient
- Not actively suicidal
- No medical problems
- No substance abuse/dependence
- No significant personality disorder
- Highly compliant
- Able to spend at least 3 hrs/week in clinic
- Willing to take placebo

Difficulties in Studying Suicidality Associated with Antidepressants

- Suicidality is associated with the underlying disease
- Patients present and start treatment at a time when they are feeling worst
- Suicidality is an uncommon occurrence
- Suicidality can be easily mis-identified
- Other clinical factors may mediate higher risk of suicidality (previous suicidality, comorbid conditions)
- In clinical trials, those at higher risk for suicidality are excluded
- In naturalistic/epidemiologic studies, selection of antidepressants is not random
Negative Effects of the Black Box Warnings?

- **SSRI Prescription Rates Drop for Youth After 2003**
  - The number of SSRI prescription rates declined for all antidepressants between 2000 and 2003, with the decline being greatest for the younger patient population.

- **Suicide Rate Among Youth Leaps From 2003 to 2004**
  - After a decline of 19.9% in mortality rates among people aged 2-19 in the United States in 2000, the rate of suicide in 2004 increased by 22.0% per 100,000 deaths, with the highest rate of suicide in the United States in 2000.

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Antidepressant Treatment Reduces Sick Days

- **Number of sick days in 3 months**
  - Before escitalopram: 11.0
  - During escitalopram: 5.4
  - Treatment saves 5.5 sick days per patient

- Naturalistic Austrian study
- 505 physicians (GPs & psych)
- Escitalopram mean dose = 12.4 mg

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Remission Rates in Primary Care Studies: A Meta-analysis

- **Remission Rate (%)**
  - Placebo: 32
  - Usual Care: 35
  - Collaborative Care: 50
  - Psychotherapy: 58
  - Meds: 55
  - Meds + Psychotherapy: 67

Collaborative care addresses the efficacy-effectiveness gap.
### Treatment of chronic depression (n=681)

- **Nefazodone**
- **Psychotherapy**
- **Combined**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>HRSD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
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<td>6</td>
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<td>6</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

**Response Rates**

- 55
- 52
- 85

p<0.01

Keller et al, NEJM, 2000

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### Augmentation Strategies c.2004

- **Proven effective**
  - Lithium (TCAs only?)

- **Possibly effective**
  - Amphetamines
  - Buspirone
  - Tryptophan
  - Omega-3 Fatty Acids
  - Lamotrigine
  - Modafinil

- **Probably effective**
  - T3 (Cytomel)
  - Atypical antipsychotics

- **Not effective**
  - Pindolol

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### Biological Treatments for Depression, c.2008

#### Pharmacologic
- Antidepressants
- Lithium
- Anticonvulsants
- Antipsychotics
- Augmenters

#### Somatic
- Electroconvulsive Therapy
- Wake Therapy
- Light Therapy
- Transcranial magnetic stimulation
- Magnetic seizure therapy
- Vagus nerve stimulation
- Deep brain stimulation
- Limbic neurosurgery

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5 Simple Messages to Promote Medication Adherence

- Take medication daily
- It may take 2 to 4 weeks to start noticing improvement
- Do NOT stop taking medication without talking to doctor, even if feeling better
- Mild side effects are common when starting treatment, and usually temporary
- Call with any questions

Recommendation #6g – Acute Treatment
Majority of lost productivity is hidden by reduced performance while at work

<table>
<thead>
<tr>
<th>Response</th>
<th>Intolerant due to GI side effects</th>
<th>Intolerant due to sexual side effects</th>
<th>No response</th>
<th>Partial response* or Residual symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication strategies</td>
<td>Switch to escitalopram</td>
<td>Switch to bupropion</td>
<td>Augment Cytomel or atypical antipsychotic</td>
<td>Augment or combine</td>
</tr>
<tr>
<td></td>
<td>Switch to sertraline</td>
<td>Switch to mirtazapine</td>
<td>Switch to another first-line agent</td>
<td></td>
</tr>
</tbody>
</table>

Note: These recommendations are based on varying levels of evidence currently, but take into account probable efficacy and tolerability.

* Based on symptom rating scales