Optimizing treatment of depressive disorders: What our patients can teach us

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Faculty/Presenter Disclosure

• **Faculty**: Mimi Israel

• **Relationships with commercial interests**: Not applicable

• Disclosure of Commercial Support: No commercial support

• Mitigating Potential Bias: Not applicable
Harry

- 42 year-old manager in a hospital
- Lack of energy and concentration, loss of enthusiasm for 4 months
- Worried about impending reorganization of his department, his family, and recently undertaken home renovations
- Poor sleep and tension with colleagues at work
PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(Use “✓” to indicate your answer)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total Score: \(0 + 1 + 2 + 3 = 20\)

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

<table>
<thead>
<tr>
<th>Total score</th>
<th>Depression severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Minimal</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderately severe</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe depression</td>
</tr>
<tr>
<td></td>
<td>Over the last 2 weeks, how often have you been bothered by the following problems?</td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Feeling nervous, anxious or on edge</td>
</tr>
<tr>
<td>2</td>
<td>Not being able to stop or control worrying</td>
</tr>
<tr>
<td>3</td>
<td>Worrying too much about different things</td>
</tr>
<tr>
<td>4</td>
<td>Trouble relaxing</td>
</tr>
<tr>
<td>5</td>
<td>Being so restless that it is hard to sit still</td>
</tr>
<tr>
<td>6</td>
<td>Becoming easily annoyed or irritable</td>
</tr>
<tr>
<td>7</td>
<td>Feeling afraid as if something awful might happen</td>
</tr>
</tbody>
</table>

(For office coding: Total Score \( T_{14} = \_ + \_ + \_ )

Cutoff 13
Antidepressants are a first-line treatment for:
- moderate and severe major depression in adults irrespective of environmental factors & depression symptom profile
- depression of any severity that has persisted for 2 years or more

(Clear et al. Journal of Psychopharmacology 2015)

What would be your first choice of antidepressant for Harry?
Options (in Canada)

### 9 classes

- **SSRI:** Serotonin reuptake inhibitor
- **SARI:** Serotonin reuptake inhibitor & 5-HT2 antagonist
- **NaSSA:** Noradrenergic and specific serotonin reuptake inhibitor
- **NRI:** Norepinephrine reuptake inhibitor
- **SNRI:** Serotonin-norepinephrine reuptake inhibitor
- **NDRI:** Norepinephrine-Dopamine reuptake inhibitor
- **TCA:** Tricyclics
- **MAOI:** Monoamine Oxidase Inhibitors
- **Multimodal:**
  - 5-HT3, 5-HT7, 5-HT1D antagonist; 5-HT1A agonist; 5-HT1B partial agonist; 5-HT transporter inhibitor

> 25 antidepressants
Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis

Andrea Cipriani, Yoshiaki A Furukawa, Georgia Salanti, John R Geddes, Julian P T Higgins, Rachel Churchill, Norio Watanabe, Atsuo Nakagawa, Ichiro Omori, Hugh McGuire, Michele Tansella, Corrado Barbui

Summary

Background Conventional meta-analyses have shown inconsistent results for efficacy of second-generation antidepressants. We therefore did a multiple-treatments meta-analysis, which accounts for both direct and indirect comparisons, to assess the effects of 12 new-generation antidepressants on major depression.

Method We systematically reviewed 117 randomised controlled trials (25 928 participants) from 1991 up to Nov 30, 2007, which compared any of the following antidepressants at therapeutic dose range for the acute treatment of unipolar major depression in adults: bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine. The main outcomes were the proportion of patients who responded to or dropped out of the allocated treatment. Analysis was done on an intention-to-treat basis.

Findings Mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more efficacious than duloxetine (odds ratios [OR] 1.39, 1.33, 1.30 and 1.27, respectively), fluoxetine (1.37, 1.32, 1.28, and 1.25, respectively), fluvoxamine (1.41, 1.35, 1.30, and 1.27, respectively), paroxetine (1.35, 1.30, 1.27, and 1.22, respectively), and reboxetine (2.03, 1.95, 1.89, and 1.83, respectively). Reboxetine was significantly less efficacious than all the other antidepressants tested. Escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than did duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine.

Interpretation Clinically important differences exist between commonly prescribed antidepressants for both efficacy and acceptability in favour of escitalopram and sertraline. Sertraline might be the best choice when starting treatment for moderate to severe major depression in adults because it has the most favourable balance between benefits, acceptability, and acquisition cost.

Funding None.

Introduction In the past 20 years, several new drugs have been added to antidepressant treatment options...
Comorbidities

What to prescribe what to avoid
• A 25 year-old woman with depression, hypersomnia and increased appetite
  Prescribe? __________  Avoid? ______________

• A 55 year-old man with severe anhedonia, diurnal variation, weight loss, significant agitation, and hypertension
  Prescribe? __________  Avoid? ______________

• A 40 year-old woman with depression, anxiety and panic attacks
  Prescribe? __________  Avoid? ______________
• A 20 year-old woman with depression, and comorbid bulimia (daily bingeing and purging)
  Prescribe?__________  Avoid?__________________

• A 35 year-old man with depression, and longstanding never treated GAD
  Prescribe?__________  Avoid?__________________

• A 70 year-old woman with depression, mood-congruent auditory hallucinations and nihilistic delusions
  Prescribe?__________  Avoid?__________________
• A 32 year-old unsuccessful businessman with depression and never treated ADHD
  Prescribe?__________ Avoid?______________
• A 52-year-old woman with depression, new onset of painful diabetic neuropathy in her legs, and perimenopausal vasomotor hot flashes.
  Prescribe?__________ Avoid?______________
• A 16 year-old girl with depression and social phobia
  Prescribe?__________ Avoid?______________
- Modest benefit of antidepressants in moderate to severe MDD, with NNT of 10 for clinical response.
- Small risk for increased suicidality (suicidal ideation/behaviours): 4/100 (AD) vs 2/100 (placebo).
- Balance risk of antidepressants versus risk of untreated MDD.

FDA approved: Fluoxetine (age 8 or older), and escitalopram (age 12 or older).
FDA approved to treat obsessive-compulsive disorder (OCD) in children: Fluoxetine, sertraline, fluvoxamine, and clomipramine.

Avoid Paroxetine
# Psychiatric Comorbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>First line</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder</td>
<td>SSRI: All</td>
<td>Bupropion</td>
</tr>
<tr>
<td></td>
<td>SNRI: Venlafaxine</td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>SSRI: Escitalopram, Paroxetine; Sertraline SNRI: Venlafaxine; Duloxetine</td>
<td></td>
</tr>
<tr>
<td>Social Phobia</td>
<td>SSRI: All</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SNRI: Venlafaxine</td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>SSRI: Fluoxetine, Paroxetine, Sertraline SNRI: Venlafaxine</td>
<td></td>
</tr>
<tr>
<td>Eating Disorder</td>
<td>SSRI: All except Paroxetine SNRI: Venlafaxine; Duloxetine</td>
<td>Bupropion: Avoid Mirtazapine: Not recommended Paroxetine: Not recommended as first line</td>
</tr>
<tr>
<td>OCD</td>
<td>SSRI: Escitalopram, Paroxetine; Sertraline Fluoxetine, Fluvoxamine</td>
<td></td>
</tr>
</tbody>
</table>

SSRI: Fluoxetine, Citalopram, Escitalopram, Sertraline, Fluvoxamine, Paroxetine
Sally

- 32 year-old teacher
- Taking Sertraline 100mg QD for 5 months
- Returned to work but finds she lacks energy and derives less pleasure than before
- Has not had an orgasm since starting meds
Neurotransmitter Specificity

Norepinephrine
- Attention
- Concentration
- Motivation
- Energy

Anxiety
Pain
Mood
Anhedonia
Sleep

Serotonin
- Impulsivity
- Suicidality

Appetite

Dopamine

Norepinephrine: TCA (Nortriptyline; Desipramine); SNRI; Bupropion
Serotonin: SSRI, SNRI, clomipramine
Dopamine: MAOI; Bupropion; high dose SNRIs; second-generation antipsychotics; stimulants
Integrated neural pathways of MDD*

5-HT2c interneuron → DA

Sexual dysfunction
Apathy/indifference
Cognitive dulling
Fatigue, loss of energy

5-HT → DA

D2 excitatory

5-HT2A interneuron → NA

Decreased anxiety
Decreased agitation

Blue inhibitory
Red excitatory

If you want to block inhibitory effect of 5-HT on NE and DA; block 5-HT2A (atypical antipsychotics) or 5-HT2c (Mirtazapine)

*Adapted from Blier, 2011
How:
Sexual dysfunction occurs through several brain pathways involving increases in 5-HT, decreases in DA and inhibition of nitric oxide synthase.

With the exception of bupropion, agomelatine (not available in Canada), mirtazapine, and moclobemide, all antidepressants cause sexual side-effects.

Vortioxetine may cause sexual dysfunction in a dose-dependent manner.

Options:
1) Choose an antidepressant that doesn’t cause sexual dysfunction.
2) Add:
   Mirtazapine: antagonizes 5-HT2 (sex) and 5-HT3 receptors (satiation)
   Bupropion: increases DA
   Buspirone (15-60 mg daily): Partial 5-HT_{1A} agonist (↓ 5-HT tone)
   Sildenafil/Tadalafil: phosphodiesterase inhibitors: increases nitric oxide, which in turn, increases blood flow to genitalia
Cathy

26 year-old kindergarten teacher treated for MDD with Fluoxetine 60mg and Trazodone 50mg
Calls you in a panic: 6 weeks pregnant!!!
What do you advise?

Marie

25 and married. Strong family hx of MAD (several suicides).
Had first depressive episode (severe; non-psychotic) 1 year ago.
Responded well to Sertraline.
Couple wants children and your advice?
To stop or not to stop?

- Risk of depressive relapse (Cohen et al., 2006):
  - Stop medication in anticipation of pregnancy = 68%
  - Maintain medication in anticipation of pregnancy = 26%

- Unplanned pregnancy risk factor for discontinuation of SSRI (Roca et al., 2013):
  - Prospective study n=132; 54% discontinued meds; 57% reintroduced them
Risk-benefit analysis prior to conception

- Choose the right moment (stable vs in crisis)
- Address impact of stopping and restarting meds
- Reflect on best moment for conception (season; stress)
- Minimise the “off meds” pre-conception period
- Examine maternal risks of taking meds (side effects, complications) versus risk of relapse
- Involve the partner as much as possible
Mother-risk (Sick kids--Anglophone):
http://www.motherisk.org/women/index.jsp
IMAGe (Sainte-Justine--Francophone):
Lactmed site web:
Mr. D

- 71-year-old man, whose wife died 6 months previously, presents with foot pain from diabetic neuropathy, poor sleep, lack of energy. On examination, he also notes lack of interest in usual activities, decreased appetite, weight loss of 4.5 kg over the past 3 months, and intermittent thoughts that he would be better off dead.

What’s your approach?
- ↑ sensitivity to therapeutic and toxic effects
- ↑ likelihood of medical comorbidity, and concomitant meds
- ↑ risk orthostatic hypotension, sedation, delirium, parkinsonism
- ↑ risk of falls and fracture
**SSRIs: Generally well-tolerated**
- ↑ risk mild parkinsonism, loss of balance
- ↑ risk SIADH (check lytes a few weeks into treatment)

**Fluoxetine:** long half-life + drug-drug interactions (avoid)
**Paroxetine:** anticholinergic, drug-drug interactions, withdrawal
**Citalopram/Escitalopram:** lower the dose (risk prolonged QT)

**Venlafaxine:** Start at 37.5 mg. Try not to exceed 150. Monitor BP
**Mirtazapine:** May be good choice if insomnia, weight loss. Age may affect clearance. Start at 7.5 mg, aim for 30 mg. Watch for sedation, hypotension, weak anticholinergic effects (constipations etc.)

**Bupropion:** well-tolerated. Good for apathy, psychomotor slowing. May exacerbate anxiety, insomnia. Avoid if risk of convulsions. Possible decreased clearance.
**Tricyclics:** If necessary; opt for Nortriptyline or Desipramine

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Drug-Drug Interactions

**Minimal or low potential** *
- Citalopram
- Desvenlafaxine
- Escitalopram
- Mirtazapine
- Venlafaxine

**Moderate potential**
- Agomelatine (1A2 substrate)
- Bupropion (2D6)
- Duloxetine (2D6; 1A2 substrate)

**Higher potential**
- Fluoxetine (2D6, 2C19)
- Fluvoxamine (1A2, 2C19, 3A4)
- Moclobemide (MAO inhibitor precautions)
- Paroxetine (2D6; p-glycoprotein)
- Sertraline (2D6; p-glycoprotein)

Caution: Amphetamines and Aripiprazole are substrates of CYP2D6 (may need to reduce doses with 2D6 inhibitors)
Jane

- Jane (31), first depressive episode, starts Venlafaxine-XR 75 mg after failed attempt with Sertraline?
- Within 10 days calls to thank you profusely. She is cured! New drug is her best friend.
- Sleeping 4-5 hrs./night wakes up energetic.

What’s your approach?
Melissa

- Melissa (32), second depressive episode (moderate to severe).
- First episode (age 16) treated with Sertraline responded well but gained 40 lbs.
- Also suffers from bulimia; is currently improving but still purges a few times per month
- Very phobic about gaining weight!

What’s your approach?
Weight gain compared to Citalopram chosen:

- **Bupropion, Nortriptyline and Amitriptyline** significantly less.
- **SSRIs** (escitalopram, fluoxetine, sertraline paroxetine) similar.
- **Venlafaxine** similar.
- **Duloxetine** somewhat less (not statistically significant).
- **Mirtazapine** greater.

1-year prospective study n=22,610 (Blumenthal et al., 2014)
Control: 3366 on anti-obesity medication or albuterol

Vortioxetine was not associated with treatment-emergent weight gain (but the data are relatively short term).
Harry

At 6 weeks
- Not doing so well
- Has had a trial of Sertraline up to 150 mg which had no effect
- What next?

At 12 weeks
- On Venlafaxine-XR 225 mg feels a bit better (less sad); tired; gets headaches; low motivation; tends to stay home
Augmentation

**Aripiprazole:**
1-2mg am, ↑ to 5mg PRN, may need 7mg.
Long half-life (3 days); titrate Q 2weeks

**Quetiapine XR:**
50 mg x 2-4 d, 100-150 mg, at supper, ↑ PRN till 300 mg

**Olanzapine:**
2.5-5mg HS, up to 7.5-10 mg

**Risperidone:**
0.25 HS, up to 1.5 mg hs

**Lithium:**
Start at 600 mg hs; ↑ to 900 (levels 0.5-1.0); anti-suicidal effects
**Augmentation**

**Thyroxine (T3)** 25-50μg per day

**Buspirone**: 15-60 mg  
**Folate**: 15 mg/day  
**Modafinil**:  
**Pramipexole**: .25 BID to 1 BID  
**Stimulants**

**Asenapine**  
5 mg S/L) hs  
(sedating; weight gain possible; no sexual side effects)

**Lurasidone**  
40 mg HS or 20 mg at supper with food (350 cal)  
(sedating; weight gain possible; can have sexual side effects)
Combination

Bupropion:
Positive effect on weight libido

Mirtazapine:
Sedation and weight gain
Prescribe?_________ Avoid?_________

Caution: Drug-Drug interactions, serotonin syndrome
Karen

- 29 year-old mother of 3. Panic attacks since age 16 (not treated but disappeared).
- Depressive symptoms after birth of second child. Tried on Citalopram (up to 40 mg; no effect), then on Effexor up to 150 mg. Switched to Duloxetine; now on 60 mg.
- Complains of ups and downs lasting a few days each. When down; demotivated, irritable, impatient, sleeps more, unable to function. When up, energetic, irritable, impatient, spends more money, talks a lot. No psychotic symptoms.
- Currently down. had fleeting suicidal thoughts (which scared her with no intent or plan).
How long do you continue treatment?

Distinguish remission from recovery

Assess if in remission (PHQ < 4; HAM-D score of ≤ 7 and CGI-I score of 1)

Assess risk of recurrence: >2 episodes, age, severity, TRD.

Distinguish relapse from recurrence

Continuation treatment: Once in remission continue treatment for 9-12 months.

Maintenance treatment: At least 2 years
Questions?