TREATMENT OPTIONS FOR MAJOR DEPRESSIVE DISORDER

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WHAT KEEPS ME BUSY?

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Disclosures

Relationships with commercial interests:

- **Grants/Research Support:** None
- **Speakers Bureau/Advisory Boards Honoraria:** Lilly, AA Pharma, HLS, Lundbeck, Allergan, Astra Zeneca, Mylan, BMO-Otsuka, Shire/Takeda, Janssen, Sunovion, Pfizer, and Purdue.
- **Consulting Fees:** None

Potential Conflict(s) of Interest

- This program has not received financial support from any pharmaceutical organizations.
OBJECTIVES

1. Overview of Major Depressive Disorder and factors affecting risk of suicide.
3. Discussion of the most recent Meta-Analysis in the Lancet.
4. Options when treating concurrent addiction and depression.
IS DEPRESSION A NEW ILLNESS OF THE PAST CENTURY?

- Old Testament Story of King Saul describes a depressive syndrome.
- The Suicide of Ajax in Homer’s Iliad.
- Hippocrates described melancholia as a medical condition as the condition was thought to be caused by melan ‘black’ and chole ‘bile’ in Greek.
WHAT'S THE BIG DEAL ABOUT DEPRESSION?

Social burden

11.3% of Canadians will experience a major depressive episode in their lifetime^1^

All Canadians are indirectly affected through family, friends, or colleagues^2^

Economic burden

$51 billion: estimated annual burden of mental illness on the Canadian economy^3^

Patient burden

Up to 50% of patients with Major Depressive Disorders (MDD) are untreated^4,5^

Problems linked to MDD such as social dysfunction can result in decreased income due to workplace absenteeism, underperformance or unemployment^6^

STRUCTURAL AND FUNCTIONAL **EFFECTS** OF MDD AND ANTIDEPRESSANT **TREATMENT** ON DIFFERENT BRAIN REGIONS

A comprehensive visual comparison

## GRAND CHALLENGES IN GLOBAL MENTAL HEALTH: THE BURDEN OF DEPRESSION

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause – Worldwide</th>
<th>DALYs (millions)</th>
<th>Cause – High-income Countries</th>
<th>DALYs (millions)</th>
<th>Cause – Low- and Middle-income Countries</th>
<th>DALYs (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unipolar depressive disorders</td>
<td>65.5</td>
<td>Unipolar depressive disorders</td>
<td>10.0</td>
<td>Unipolar depressive disorders</td>
<td>55.5</td>
</tr>
<tr>
<td>2</td>
<td>Alcohol-use disorders</td>
<td>23.7</td>
<td>Alzheimer's and other dementias</td>
<td>4.4</td>
<td>Alcohol-use disorders</td>
<td>19.5</td>
</tr>
<tr>
<td>3</td>
<td>Schizophrenia</td>
<td>16.8</td>
<td>Alcohol-use disorders</td>
<td>4.2</td>
<td>Schizophrenia</td>
<td>15.2</td>
</tr>
<tr>
<td>4</td>
<td>Bipolar affective disorder</td>
<td>14.4</td>
<td>Drug-use disorders</td>
<td>1.9</td>
<td>Bipolar affective disorder</td>
<td>12.9</td>
</tr>
<tr>
<td>5</td>
<td>Alzheimer's and other dementias</td>
<td>11.2</td>
<td>Schizophrenia</td>
<td>1.6</td>
<td>Epilepsy</td>
<td>7.3</td>
</tr>
<tr>
<td>6</td>
<td>Drug-use disorders</td>
<td>8.4</td>
<td>Bipolar affective disorder</td>
<td>1.5</td>
<td>Alzheimer's and other dementias</td>
<td>6.8</td>
</tr>
<tr>
<td>7</td>
<td>Epilepsy</td>
<td>7.9</td>
<td>Migraine</td>
<td>1.4</td>
<td>Drug-use disorders</td>
<td>6.5</td>
</tr>
<tr>
<td>8</td>
<td>Migraine</td>
<td>7.8</td>
<td>Panic disorder</td>
<td>0.8</td>
<td>Migraine</td>
<td>6.3</td>
</tr>
<tr>
<td>9</td>
<td>Panic disorder</td>
<td>7.0</td>
<td>Insomnia (primary)</td>
<td>0.8</td>
<td>Panic disorder</td>
<td>6.2</td>
</tr>
<tr>
<td>10</td>
<td>Obsessive-compulsive disorder</td>
<td>5.1</td>
<td>Parkinson's disease</td>
<td>0.7</td>
<td>Obsessive-compulsive disorder</td>
<td>4.5</td>
</tr>
<tr>
<td>11</td>
<td>Insomnia (primary)</td>
<td>3.6</td>
<td>Obsessive-compulsive disorder</td>
<td>0.6</td>
<td>Post-traumatic stress disorder</td>
<td>3.0</td>
</tr>
<tr>
<td>12</td>
<td>Post-traumatic stress disorder</td>
<td>3.5</td>
<td>Epilepsy</td>
<td>0.5</td>
<td>Insomnia (primary)</td>
<td>2.9</td>
</tr>
<tr>
<td>13</td>
<td>Parkinson's disease</td>
<td>1.7</td>
<td>Post-traumatic stress disorder</td>
<td>0.5</td>
<td>Multiple sclerosis</td>
<td>1.2</td>
</tr>
<tr>
<td>14</td>
<td>Multiple sclerosis</td>
<td>1.5</td>
<td>Multiple sclerosis</td>
<td>0.3</td>
<td>Parkinson's disease</td>
<td>1.0</td>
</tr>
</tbody>
</table>

DALY: Disability-Adjusted Life-Year

Subjects that recovered \textit{asymptomatically} remained relapse/recurrence-free \textbf{4.2 times longer} than those with residual subsyndromal symptoms of depression (SSD)

SSD was associated with significantly:

- longer and more severe episodes
- more symptoms of illness
- increased long-term psychosocial dysfunction
- greater depressive illness burden during the following 10–20 years

\textbf{Asymptomatic resolution was the strongest predictor of remaining relapse/recurrence-free}
(e.g., vs. age of onset, number of prior episodes, etc.)
SUICIDE RISK FACTORS

• Previous suicide attempt
• Mental illness, such as depression
• Social isolation
• Criminal problems
• Financial problems
• Impulsive or aggressive tendencies
• Job problems or loss
• Legal problems
• Serious illness
• Substance use disorder
SUICIDE RISK FACTORS

- **Relationship:**
  - Adverse Childhood Events as child abuse and neglect
  - Bullying
  - Family history of suicide
  - Relationship problems such as a break-up, violence, or loss
  - Sexual violence
- **Community:**
  - Barriers to health care
  - Cultural and religious beliefs such as a belief that suicide is noble resolution of a personal problem
  - Suicide cluster in the community
- **Societal:**
  - Stigma associated with mental illness or help-seeking
  - Easy access to lethal means among people at risk (e.g. firearms, medications)
  - Unsafe media portrayals of suicide

SUICIDE PROTECTIVE FACTORS

- Coping and problem-solving skills
- Cultural and religious beliefs that discourage suicide
- Connections to friends, family, and community support
- Supportive relationships with care providers
- Availability of physical and mental health care
- Limited access to lethal means among people at risk

# CANMAT Clinical Guidelines: Recommended Non-Pharmacologic First-Line Treatments

<table>
<thead>
<tr>
<th>Modality</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complementary and alternative medicine treatments</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>Monotherapy for mild to moderate MDD</td>
</tr>
<tr>
<td>Light therapy</td>
<td>Monotherapy for seasonal (winter) MDD</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Monotherapy for mild to moderate MDD</td>
</tr>
<tr>
<td><strong>Psychological treatments</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cognitive-behavioural therapy (CBT)</td>
<td>Acute and maintenance (relapse prevention) phases</td>
</tr>
<tr>
<td>Interpersonal therapy (IPT)</td>
<td>of treatment</td>
</tr>
<tr>
<td>Behavioural activation (BA)</td>
<td>Acute phase of treatment</td>
</tr>
<tr>
<td>Mindfulness-based cognitive therapy (MBCT)</td>
<td>Maintenance (relapse prevention) phases of treatment</td>
</tr>
</tbody>
</table>

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CANMAT, Canadian Network for Mood and Anxiety Treatments; MDD, major depressive disorder.
Healthy diet and regular physical activity can regulate energy metabolism, reduce inflammation and ROS, and increase BDNF.

- Healthy diet
- Exercise
  - Energy metabolism
    - ADP+Pi ⇌ ATP
- Poor diet
- Sedentary
  - ROS
  - Declining brain function?

Enhanced brain function
↑ Synaptic plasticity

Cognition
Mood

ADP, adenosine diphosphate; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; Pi, orthophosphate; ROS, reactive oxygen species.

**WHAT ARE CANMAT RECOMMENDATIONS FOR FIRST-LINE ANTIDEPRESSANTS?**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine</td>
<td>MT&lt;sub&gt;1&lt;/sub&gt; and MT&lt;sub&gt;2&lt;/sub&gt; agonist; 5HT&lt;sub&gt;2&lt;/sub&gt; antagonist</td>
<td>25–50 mg</td>
</tr>
<tr>
<td>Bupropion</td>
<td>NDRI</td>
<td>150–300 mg</td>
</tr>
<tr>
<td>Citalopram</td>
<td>SSRI</td>
<td>20–40 mg</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>SNRI</td>
<td>50–100 mg</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>SNRI</td>
<td>60 mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>SSRI</td>
<td>10–20 mg</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>20–60 mg</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>SSRI</td>
<td>100–300 mg</td>
</tr>
<tr>
<td>Mianserin</td>
<td>α&lt;sub&gt;2&lt;/sub&gt; antagonist; 5HT&lt;sub&gt;2&lt;/sub&gt; antagonist</td>
<td>60–120 mg</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>SSRI</td>
<td>100 mg</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>α&lt;sub&gt;2&lt;/sub&gt; antagonist; 5HT&lt;sub&gt;2&lt;/sub&gt; antagonist</td>
<td>15–45 mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>SSRI</td>
<td>20–50 mg*</td>
</tr>
<tr>
<td>Sertraline</td>
<td>SSRI</td>
<td>50–200 mg</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>SNRI</td>
<td>75–225 mg</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>SSRI; 5HT&lt;sub&gt;1A&lt;/sub&gt; agonist; 5HT&lt;sub&gt;1B&lt;/sub&gt; partial agonist; 5HT&lt;sub&gt;1D&lt;/sub&gt;, 5HT&lt;sub&gt;3A&lt;/sub&gt;, and 5HT&lt;sub&gt;7&lt;/sub&gt; antagonist</td>
<td>10–20 mg</td>
</tr>
</tbody>
</table>

* 25–62.5 mg for CR version

# CANMAT-RECOMMENDED ADJUNCTIVE MEDICATIONS

## First-line Recommendations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Level of Evidence</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Level 1</td>
<td>2–15 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Level 1</td>
<td>150–300 mg</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Level 1</td>
<td>1–3 mg</td>
</tr>
</tbody>
</table>

## Second-line Recommendations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Level of Evidence</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brexpiprazole</td>
<td>Level 1</td>
<td>1–3 mg</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Level 2</td>
<td>150–300 mg</td>
</tr>
<tr>
<td>Lithium</td>
<td>Level 2</td>
<td>600–1200 mg*</td>
</tr>
<tr>
<td>Mirtazapine/mianserin</td>
<td>Level 2</td>
<td>30–60 mg</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Level 2</td>
<td>100–400 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Level 1</td>
<td>2.5–10 mg</td>
</tr>
<tr>
<td>Triiodothyronine</td>
<td>Level 2</td>
<td>20–50 mcg</td>
</tr>
</tbody>
</table>

*Therapeutic serum levels*
HOW DO WE CURRENTLY DECIDE ON WHICH ANTIDEPRESSANT TO USE?

Consider clinical factors in selecting an antidepressant

Is the patient on concomitant medications?

- NO
  - Consider potential for drug-drug interactions
  - Avoid particular side effects?
    - NO
    - Consider tolerability differences
    - YES
    - Select and initiate a first-line antidepressant
  - YES

- YES
  - Select and initiate a first-line antidepressant
## CANMAT ANTIDEPRESSANT RECOMMENDATION: SPECIFIERS AND DIMENSIONS

<table>
<thead>
<tr>
<th>Specifiers/Dimensions</th>
<th>Recommendations and level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With psychotic features</strong></td>
<td>Use antipsychotic and antidepressant cotreatment</td>
</tr>
<tr>
<td><strong>With melancholic features</strong></td>
<td>No specific antidepressants have demonstrated superiority</td>
</tr>
<tr>
<td><strong>With atypical features</strong></td>
<td>No specific antidepressants have demonstrated superiority</td>
</tr>
<tr>
<td><strong>With cognitive dysfunction</strong></td>
<td>- Vortioxetine</td>
</tr>
<tr>
<td></td>
<td>- Bupropion, Duloxetine, SSRIs, Moclobemide</td>
</tr>
<tr>
<td><strong>With catatonic features</strong></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td><strong>With seasonal pattern</strong></td>
<td>No specific antidepressants have demonstrated superiority</td>
</tr>
<tr>
<td><strong>With anxious distress</strong></td>
<td>Use an antidepressant with efficacy in generalized anxiety disorder</td>
</tr>
</tbody>
</table>

1. From DSM-5 (e.g., MDD with anxious distress, etc.); *Comparisons only with placebo*
SHOULD WE EVEN BE CONSIDERING ANTIDEPRESSANTS?

CULTURE

WHY ANTIDEPRESSANTS ARE NO BETTER THAN PLACEBOS

BY SHARON BEGLEY ON 1/28/10 AT 7:00 PM
Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

ARTICLE SELECTION PROCESS

24,200 Records identified through database searching

421 Eligible full-text articles

86 Unpublished records

15 Records identified from hand-searched reviews

116,447 Patients

522 Total studies included in meta-analysis

58% Placebo-controlled

77% Outpatients only

1979-2016

Multiple treatments (network) meta-analysis

A newer technique that allows multiple treatments (placebo-controlled and head-to-head) to be compared within a single meta-analysis.

Technique is used in other areas of medicine (e.g., statins to prevent cardiovascular mortality; smoking cessation therapies in COPD).

Example of indirect comparison:
2 treatments can be compared if both have been compared to a 3rd treatment, and all 3 have been compared to placebo.

If $A > B$ and $B > C$, then $A > C$.

Antidepressants are closely clustered

All are better than placebo (22)

Data are reported as ORs in comparison with reboxetine, which is the reference drug. Error bars are 95% Crls. Individual drugs are represented by different coloured nodes. Desvenlafaxine, levomilnacipran, and vilazodone were not included in the head-to-head analysis because these three antidepressants had only placebo-controlled trials. ORs=odds ratios. 1=agomelatine. 2=amitriptyline. 3=buproprion. 4=citalopram. 5=clomipramine. 6=desvenlafaxine. 7=duloxetine. 8=escitalopram. 9=fluoxetine. 10=fluvoxamine. 11=levomilnacipran. 12= milnacipran. 13=mirtazapine. 14=nefazodone. 15=paroxetine. 16=reboxetine. 17=sertraline. 18=trazodone. 19=venlafaxine. 20=vilazodone. 21=vortioxetine. 22=placebo.

ALL ANTIDEPRESSANTS ARE EFFECTIVE IN MDD

- Summary effect sizes were mostly modest
- Differences between antidepressants were small when all studies were included
- When only head-to-head studies were considered, there was more variability between antidepressants
- Novel antidepressants tended to show a better efficacy profile than older agents
- Industry sponsorship did not influence results

• 3 antidepressants had the most favourable profile for efficacy and acceptability:

1. Vortioxetine (21) had the greatest net clinical benefit
   - Highest OR for efficacy
   - Lowest OR for all-cause discontinuation

2. Escitalopram (8)

3. Agomelatine (1)

Data are reported as ORs in comparison with reboxetine, which is the reference drug. Error bars are 95% Crls. Individual drugs are represented by different coloured nodes. Desvenlafaxine, levomilnacipran, and vilazodone were not included in the head-to-head analysis because these three antidepressants had only placebo-controlled trials. ORs=odds ratios. 1=agomelatine (not available in Canada). 2=amitriptyline. 3=buproprion. 4=citalopram. 5=clomipramine. 6=desvenlafaxine. 7=duloxetine. 8=escitalopram. 9=fluoxetine. 10=fluvoxamine. 11=levomilnacipran. 12=milnacipran. 13=mirtazapine. 14=nefazodone. 15=paroxetine. 16=reboxetine. 17=sertraline. 18=trazodone. 19=venlafaxine. 20=vilazodone. 21=vortioxetine. 22=placebo.

MORE DATA, MORE ANSWERS: PICKING THE OPTIMAL ANTIDEPRESSANT

- This work represents a major contribution to the field
  - Addresses key clinical questions:
    - Do some antidepressants work better than others for depression?
    - Are some more tolerable than others?
  - Reassures patients and clinicians of the efficacy of antidepressants despite high placebo response rates
  - Identifies significant differences between antidepressants that are relevant to all stakeholders, notably: agomelatine, escitalopram, and vortioxetine offered the best net clinical benefit

“In everyday clinical practice, medications with the highest net efficacy and acceptability ratings merit discussion with patients for use as the first treatment.”

HOW LONG DO YOU LEAVE PATIENTS ON ANTIDEPRESSANTS?

CANMAT 2016 Guidelines for the Management of Adults with MDD

“...maintain treatment with antidepressants for 6 to 9 months after achieving symptomatic remission, while those with risk factors for recurrence extend antidepressant treatment to 2 years or more.”

Risk factors for recurrence include:
- Frequent, recurrent episodes
- Severe episodes (psychosis, severe impairment, suicidality)
- Chronic episodes
- Presence of comorbid psychiatric or other medical conditions
- Presence of residual symptoms
- Difficult-to-treat episodes

CANMAT: Canadian Network for Mood and Anxiety Treatments

**HOW DO I TAPER PATIENTS OFF ANTIDEPRESSANTS?**

- Discontinuation symptoms include flu-like experiences such as nausea, headache, light-headedness, chills, and myalgias.
- Neurological symptoms include parasthesias, insomnia, and ‘electric-shock’ phenomena (similar to L’Hermittes sign in MS).
- These symptoms spontaneously resolve in about 1-2 weeks for most patients.
- Paroxetine causes the most protracted discontinuation.
- There are some patients that may present with a persistent post-withdrawal disorder for months or years. This however generally is regarded as potential somatic symptoms secondary to an untreated mental illness.

- Slow taper is the first recommendation but is primarily based on case report data.
- Switch from medications with a short half life (such as Paroxetine and Venlafaxine) and switch to Fluoxetine.
- Clonazepam
- CBT
- Review interactions with other medications. For instance Fluvoxamine is a potent Cytochrome p450 1A2, 2D6 and 3A4 inhibitor. Removing an inhibitor would then decrease plasma levels of other medications including other antidepressants, PPIs, and anti-epileptics.

MAJOR DEPRESSIVE DISORDER WITH CONCURRENT ALCOHOL USE DISORDER

Integrated Treatment recommended.
Cognitive Behavioral Therapy.
Close monitoring in consultation (at least weekly)
The electrocardiogram before treatment administration,
The prescription of antidepressant treatment after reassessment of mood, once appropriate care for physical withdrawal syndrome is over.

Mirtazapine monotherapy
Naltrexone monotherapy
Add-on naltrexone to sertraline
Add-on acamprosate to escitalopram
Escitalopram and Aripiprazole
Majority of SSRIs and SNRIs can be considered.

Imipramine may differentiate for impact on mood, but not on SRE.

Orexin Antagonist therapy
OREXIN RECEPTOR ANTAGONISM

- Orexin receptor antagonists reduce wakefulness and hence assist in prolonging sleep.
- Sleep disruption is common with acute and prolonged alcohol use due to changes in sleep architecture and continuity, increasing proportion of NREM sleep.
- Sleep deprivation is a potent factor predicting relapse to alcohol use.
- Treating insomnia improves sleep quality and ameliorates depressive symptoms in AUD patients with comorbid insomnia.
- Orexin-1 antagonism prevents alcohol seeking behavior in lab studies, while Orexin-2 antagonism has reduced motivation for cocaine.
- Orexin receptor antagonism ameliorates alcohol withdrawal-induced negative affective state.
- May benefit for abstinence if combined with Baclofen or Gabapentin.

Campbell E. et. al. Suvorexant for the treatment of AUD. Brain Research. 2020. Vol 1731
CONCLUSIONS

- There a number of risk factors and protective factors involved in suicide assessment.
- There are non-pharmacologic options with good evidence for treatment of mild to moderate depression.
- All 21 antidepressants were more efficacious than placebo with a modest effect size. Some have better evidence in different clinical scenarios.
- In head-to-head comparisons, agomelatine, escitalopram, and vortioxetine offered the best net clinical benefit.
- There are some specific options for treatment of concurrent Alcohol Use Disorder.

QUESTIONS, COMMENTS?
TAYAS@EHNCANADA.COM

LOOK FOR SOMETHING POSITIVE IN EACH DAY, EVEN IF SOME DAYS YOU HAVE TO LOOK A LITTLE HARDER.
RECOVERYEXPERTS.COM