Part 2: Pain and Symptom Management

Depression

Effective Date: February 22, 2017

Key Recommendations

- Before diagnosing and treating major depressive disorder, first effectively treat pain and other symptoms, then differentiate the symptoms of depression from normal grieving.
- When prescribing antidepressants for this group of patients, select antidepressants with the least drug interactions.

Assessment

1. Depression occurs in 13–26% of patients with terminal illness,\(^1,2\) can amplify pain and other symptoms, and is often recognized too late in a patient’s life.
2. Patients are at high risk of suicide and have an increased desire for hastened death.\(^3\)
3. A useful depression screening question is, “Have you been depressed most of the time for the past two weeks?”\(^4\)
4. A diagnosis of depression in the terminally ill may be made when at least two weeks of depressed mood is accompanied by symptoms of hopelessness, helplessness, worthlessness, guilt, lack of reactivity, or suicidal ideation.
5. DSM-IV criteria for depression are not very helpful because vegetative symptoms like anorexia, weight loss, fatigue, insomnia, and impaired concentration may accompany end stage progressive illness.
6. Risk factors for depression include:
   - personal or family history of depression;
   - social isolation, concurrent illnesses (e.g., COPD, CHF);
   - alcohol or substance abuse;
   - poorly controlled pain;
   - advanced stage of illness;
   - certain cancers (head and neck, pancreas, primary or metastatic brain cancers);
   - chemotherapy agents (vincristine, vinblastine, asparagines, intrathecal methotrexate, interferon, interleukin);
   - corticosteroids (especially after withdrawal); and
   - abrupt onset of menopause (e.g., withdrawal of hormone replacement therapy, use of tamoxifen).

Management

1. Non-pharmacological treatments are the mainstay of treatment for the symptom of depression without a diagnosis of primary affective disorder.
2. Treatment of pain and other reversible physical symptoms should occur before initiating antidepressant medication.
3. If a diagnosis of primary affective disorder is uncertain in a depressed patient, consider psychiatric referral and a trial of antidepressant medication (refer to Appendix A: Medications Used in Palliative Care for Depression). Consider drug interactions, adverse side effect profiles, and beneficial side effects when choosing an antidepressant.
4. In the terminally ill, start with half the usual recommended starting dose of antidepressant.\(^5\)
5. First line therapy is with a selective serotonin reuptake inhibitor (SSRI),\(^2\) selective serotonin norepinephrine reuptake inhibitor (SSNRI), or noradrenergic and specific serotonergic antidepressant (NaSSA).
6. Tricyclic antidepressants (especially nortryptiline and desipramine) can be considered due to their co-analgesic benefit for neuropathic pain (refer to Appendix A – Medications Used in Palliative Care for Depression). Avoid with constipation, urinary retention, dry mouth, orthostatic hypotension, or cardiac conduction delays.

7. When anticipated survival time is short, consider psychostimulants due to their more immediate onset of effect, but avoid them in the presence of agitation, confusion, insomnia, anxiety, paranoia, or cardiac comorbidity.

8. If life expectancy is 1–3 months, start a psychostimulant and an antidepressant together and then withdraw the stimulant while titrating the antidepressant upwards.
Depression screening question
“Have you been depressed most of the time for the past two weeks?”

Assess if depression (A1)
- Hopelessness
- Worthlessness
- Guilt
- Lack of reactivity
- Suicidal ideation (A2)

Review risk factors for depression (A6)

Vegetative symptoms
Due to progressive life-limiting illness (A5)
- Insomnia
- Anorexia
- Weight loss
- Fatigue
- Impaired concentration

Depression (A4)
- Unsure of diagnosis (M3) OR
- Suicidal (A2) OR
- Delusional (vs. depression)

Assess for and manage pain and other symptoms
Palliative Care Consult for refractory symptoms

Normal Grief (vs. depression)

Non-Pharmacological Treatment for Depression (M1)
- Exercise, rest, nutrition, social and spiritual support
- Psychotherapy
- Cognitive Behavioural Therapy

Pharmacological Treatment for Depression (M2)

< 1 month

Life expectancy

Yes
Modafanil
No

Methylenidate OR Dextroamphetamine OR Modafanil

Psychostimulant (M7)
- For rapid onset
- Not if agitation, confusion, insomnia, anxiety, paranoia, cardiac comorbidity

Combination Treatment (M8)
Psychostimulant + Antidepressant

Antidepressant (M4)

First line (M5):
- SSRI or
- SSNRI or
- NaSSA

Second line:
- TCA (M6)

See also the associated BC Guidelines.ca – Major Depressive Disorder in Adults – Diagnosis and Management

Hyperlinks indicate additional information available in guideline sections above:
A = Assessment
M = Management

BCGuidelines.ca: Palliative Care for the Patient with Incurable Cancer or Advanced Disease
Resources

References

Abbreviations
- CHF: congestive heart failure
- COPD: chronic obstructive pulmonary disease
- DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition
- NaSSA: noradrenergic & specific serotonergic antidepressant
- SSRI: selective serotonin reuptake inhibitor
- SSNRI: selective serotonin norepinephrine reuptake inhibitor
- TCA: tricyclic antidepressant

Appendices
- Appendix A – Medications Used in Palliative Care for Depression
Appendix A: Medications Used in Palliative Care for Depression

Tailor dose to each patient; those who are elderly, cachectic, debilitated or with renal or hepatic dysfunction may require reduced dosages; consult most current product monograph for this information: [http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php)

### ANTIDEPRESSANTS

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name/Available Dosage Forms</th>
<th>Standard Adult Dose (palliative)</th>
<th>Drug Plan Coverage</th>
<th>Approx. cost per 30 days</th>
<th>Therapeutic Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NaSSA: Noradrenergic and Specific Serotonergic Antidepressant</strong></td>
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<tr>
<td>mirtazapine</td>
<td>Remeron®, G Tabs: 15, 30, 45 mg</td>
<td>Start: 7.5 to 15 mg PO at bedtime Goal: 15 to 45 mg PO at bedtime Max: 60 mg² PO at bedtime</td>
<td>Yes, LCA Yes, LCA</td>
<td>$3–9 (G) $27–80</td>
<td>• Useful for night-time sedation • Rapid dissolve formulation</td>
</tr>
<tr>
<td></td>
<td>Remeron RD® ODT: 15, 30, 45 mg</td>
<td>Yes, LCA Yes, LCA</td>
<td>$3–9 (G) $16–47</td>
<td></td>
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<tr>
<td><strong>SSNRI: Selective Serotonin Norepinephrine Reuptake Inhibitors</strong></td>
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<tr>
<td>venlafaxine XR</td>
<td>Effexor XR®, G XR caps: 37.5, 75, 150 mg</td>
<td>Start: 37.5 mg PO qAM Goal: 75 to 225 mg PO qAM Max: 375 mg PO daily</td>
<td>Yes, LCA Yes, LCA</td>
<td>$11–32 (G) $64–191</td>
<td>• May cause nausea</td>
</tr>
<tr>
<td>duloxetine</td>
<td>Cymbalta® Caps: 30 mg, 60 mg</td>
<td>Start: 30 mg PO qAM Goal: 30 to 60 mg PO qAM Max: 120 mg² PO qAM</td>
<td>No No</td>
<td>$62–127</td>
<td>• Effective for diabetic neuropathy • Should not be given to individuals with chronic hepatic disease or excessive alcohol consumption</td>
</tr>
<tr>
<td>desvenlafaxine</td>
<td>Pristiq® XR tabs: 50, 100 mg</td>
<td>Start: 50 mg PO once daily Goal: 50 to 100 mg PO once daily Max: 100 mg PO daily</td>
<td>No No</td>
<td>$89</td>
<td>• Should not be discontinued abruptly</td>
</tr>
<tr>
<td><strong>SSRI: Selective Serotonin Reuptake Inhibitors</strong></td>
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<td></td>
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</tr>
<tr>
<td>citalopram</td>
<td>Celexa®, G Tabs: 10, 20, 40 mg</td>
<td>Start: 10 mg PO qAM Goal: 10 to 40 mg PO qAM Max: 60 mg PO qAM</td>
<td>Yes, LCA Yes, LCA</td>
<td>$5–58 (G) $22–45</td>
<td>• Least pharmacokinetic drug interactions</td>
</tr>
<tr>
<td>escitalopram</td>
<td>Cipralex®, G Tabs: 10, 20 mg</td>
<td>Start: 5 mg PO qAM Goal: 5 to 20 mg PO qAM Max: 30 mg² PO qAM</td>
<td>Yes Yes</td>
<td>$6–12 (G) $29–62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ODT: 10, 20 mg</td>
<td>No No</td>
<td>$29–62</td>
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</tbody>
</table>
## ANTIDEPRESSANTS A, B

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name/ Available Dosage Forms</th>
<th>Standard Adult Dose C (palliative)</th>
<th>Drug Plan Coverage D</th>
<th>Approx. cost per 30 days E</th>
<th>Therapeutic Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCA: Tricyclic Antidepressants</strong></td>
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<tr>
<td>desipramine</td>
<td>G Tabs: 10, 25, 50, 75, 100 mg</td>
<td>Start: 10 to 25 mg PO qAM G</td>
<td>Yes, LCA</td>
<td>Yes, LCA</td>
<td>$22–29 (G) • increase dose every 3 to 7 days until goal reached • may help neuropathic pain • useful for night-time sedation • anticholinergic side effects • desipramine and nortriptyline least anticholinergic of TCAs • monitor for postural hypotension</td>
</tr>
<tr>
<td>nortriptyline</td>
<td>Aventyl, G Caps: 10, 25 mg</td>
<td>Start: 10 to 25 mg PO at bedtime Goal: 50 to 75 mg PO at bedtime Max: 150 mg PO at bedtime</td>
<td>Yes, LCA</td>
<td>Yes, LCA</td>
<td>$33–49 (G) $33–49</td>
</tr>
</tbody>
</table>

**Abbreviations:** caps capsules; G generics available; IR immediate release; LCA subject to Low Cost Alternative Program; max maximum dose; ODT oral disintegrating tablet; PO by mouth; qAM every morning; SR sustained release; tabs tablets; XR extended release

A Refer to guideline and/or algorithm for recommended order of use.
B Not a complete list of antidepressants
C Start doses listed are recommended starting doses for geriatric patients (half the recommended doses for adults), except for duloxetine
D PharmaCare coverage as of October 2016 (subject to revision). Obtain current coverage, eligibility, and coverage information from the online BC PharmaCare Formulary Search page at pharmacareformularysearch.gov.bc.ca
E Cost as of October 2016 and does not include retail markups or pharmacy fees. Generic and brand name cost separated as indicated by (G).
F This maximum dose used in palliative care, but not approved for marketing by Health Canada
G Bedtime dosing may be appropriate for patients experiencing sedation with desipramine
## Psychostimulants

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Available Dosage Forms</th>
<th>Standard Adult Dose (note age specific recommendations)</th>
<th>Drug Plan Coverage</th>
<th>Approx. cost per 30 days&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>methylphenidate&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Ritalin®, G</td>
<td>IR tabs: 5, 10, 20 mg</td>
<td><strong>Age over 65 years:</strong> Not recommended</td>
<td>Yes, LCA Yes, LCA</td>
<td>$6–18 (G) $14–41</td>
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<td></td>
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<td></td>
<td><strong>Age 18 to 65 years:</strong> Start: 5 mg PO bid (AM and noon); use 2.5 mg for frail patients Max: 15 mg PO bid (AM and noon)</td>
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<tr>
<td></td>
<td>Biphentin®</td>
<td>SR caps: 10, 15, 20 mg</td>
<td>Once dose stabilized on IR, give equivalent daily dose as SR or XR form once daily in AM</td>
<td>No No</td>
<td>$23–59</td>
</tr>
<tr>
<td></td>
<td>Concerta®</td>
<td>XR tabs: 18, 27, 36, 54 mg</td>
<td></td>
<td>No Special Authority&lt;sup&gt;e&lt;/sup&gt;</td>
<td>$71–93</td>
</tr>
<tr>
<td></td>
<td>Ritalin-SR®, G</td>
<td>SR tabs: 20 mg</td>
<td></td>
<td>No Yes, LCA</td>
<td>$9 (G) $24</td>
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<tr>
<td>dextro-amphetamine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Dexedrine®, G</td>
<td>IR tabs: 5</td>
<td><strong>Age over 65 years:</strong> Not recommended</td>
<td>No Yes</td>
<td>$18–134 (G) $24–188</td>
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<tr>
<td></td>
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<td>SR caps: 10, 15 mg</td>
<td><strong>Age 18 to 65 years:</strong> Start: 2.5 mg PO bid (AM then in 4 to 6 h) Max: 20 mg PO bid (AM then in 4 to 6 h) Once dose stabilized on IR, give equivalent daily dose as SR form once daily in AM</td>
<td>No Yes</td>
<td>$33–135</td>
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<tr>
<td>modafinil&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Alertec®, G</td>
<td>Tabs: 100 mg</td>
<td><strong>Age over 65 years:</strong> Start: 100 mg PO qAM Max: 100 mg PO bid (AM and noon)</td>
<td>No Special Authority&lt;sup&gt;f&lt;/sup&gt;, LCA</td>
<td>$30–60 (G) $45–90</td>
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<td></td>
<td><strong>Age 18 to 65 years:</strong> Start: 100 mg PO bid (AM and noon) Max: 200 mg PO bid (AM and noon)</td>
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<td>$60–120 (G) $90–180</td>
</tr>
</tbody>
</table>

<sup>a</sup> Refer to guideline and/or algorithm for recommended order of use.
<sup>b</sup> PharmaCare coverage as of October 2016 (subject to revision). Obtain current coverage, eligibility, and coverage information from the online BC PharmaCare Formulary Search page at pharmacareformularysearch.gov.bc.ca
<sup>c</sup> Cost as of October 2016 and does not include retail markups or pharmacy fees. Generic and brand name cost separated as indicated by (G).
<sup>d</sup> This indication (i.e. depression) used in practice, but not approved for marketing by Health Canada
<sup>e</sup> Special authority required to obtain coverage for Concerta® for ADHD as second line treatment
<sup>f</sup> Special authority required to obtain coverage for modafinil for patients with narcolepsy

**Abbreviations:** caps capsules; G generics; h hours; IR immediate release; LCA subject to Low Cost Alternative Program; max maximum dose; PO by mouth; qAM every morning; SR sustained release; tabs tablets; XR extended release