

## DEPRESSION IN THE TERMINALLY ILL

### Rationale

This guideline is adapted for inter-professional primary care providers working in various settings in VIHA and any other clinical practice setting in which a user may see the guidelines as applicable.

### Scope

This guideline provides recommendations for the assessment and symptom management of adult patients (age 19 years and older) living with advanced life threatening illness and experiencing the symptom of depression. This guideline does not address disease specific approaches in the management of depression.<sup>(1-12)</sup>

### Definition of Terms

**Depression** is a primary mood disorder which, according to the DSM-IV-TR includes:

- a depressed mood and/or
- an inability to experience pleasure in normally pleasurable acts (anhedonia).<sup>(13)</sup>

**For major depression**, the DSM-IV-TR states that one of the above symptoms must be present for a period of at least two weeks in combination with four *or more* of the following symptoms:<sup>(13)</sup>

- Feelings of overwhelming sadness and/or fear, or the seeming inability to feel emotion (emptiness).
- A decrease in the amount of interest or pleasure in all, or almost all, daily activities.
- Changing appetite and marked weight gain or loss. Note: ensure not related to disease process.
- Disturbed sleep patterns, such as insomnia, loss of rapid eye movement (REM) sleep, or excessive sleep (hypersomnia).
- Psychomotor agitation or retardation nearly every day.
- Fatigue, mental or physical, also loss of energy.
- Intense feelings of guilt, helplessness, hopelessness, worthlessness, isolation/loneliness and/or anxiety.
- Trouble concentrating, keeping focus or making decisions or a generalized slowing and obtunding (to dull or blunt, especially sensation or pain) of cognition, including memory.
- Recurrent thoughts of death (not just fear of dying), desire to just “lay down and die” or “stop breathing”, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

- Feeling and/or fear of being abandoned by those close to one.

**Minor depression** is a less-used term for a subclinical depression that does not meet criteria for major depression but where there are at least two symptoms present for two weeks.

Note: do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

### Standard of Care

1. Incidence and Risk Factors
2. Assessment
3. Diagnosis
4. Education
5. Treatment: Non-pharmacological
6. Treatment: Pharmacological

#### Recommendation 1

#### Incidence and Risk Factors

### Incidence and Risk Factors

People with advanced illness have a higher incidence of clinical depression than the general population. The prevalence of depression in the general population is 6 to 10%.<sup>(9)</sup> Terminally ill patients have been found to have a higher level of both physical and emotional distress with 24% having depression.<sup>(14)</sup> Clinical depression occurs in 15 to 30 % of cancer patients.

The diagnosis of depression in people with cancer is often under-diagnosed and under-treated.<sup>(9)</sup>

#### Risk factors include:

##### Non-cancer related risk factors:

- History of depression or family history of depression.<sup>(3, 4, 9, 10)</sup>
- Two or more episodes in a lifetime.
- First episode early or late in life.
- Lack of family or social support.<sup>(8, 10)</sup>
- Previous suicide attempts.<sup>(3, 4, 9)</sup>
- Concurrent chronic illnesses such as: stroke or myocardial infarction.<sup>(15)</sup>
- Intercurrent substance abuse

##### Cancer-related risk factors:

- Depression at time of cancer diagnosis.<sup>(3, 4)</sup>
- Advanced stage of cancer.<sup>(4, 9, 10)</sup>
- Additional concurrent life stressors.<sup>(3, 4, 9)</sup>
- Increased physical impairment or discomfort.<sup>(4, 5, 8-10, 12)</sup>
- Being unmarried and having head and neck cancer.<sup>(10)</sup>

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- Pancreatic and primary or metastatic brain cancers.<sup>(4, 8, 10)</sup>
- Medications may contribute to depression (benzodiazepines, corticosteroids, anticonvulsants, methyldopa, propranolol, chemotherapeutic agents).<sup>(4, 7, 8, 10)</sup>
- Chronic pain.<sup>(3,4,8,9,10,12)</sup>

### Recommendation 2

### Assessment of Depression

Ongoing comprehensive assessment is the foundation of effective management of depression, including interview, physical assessment, medication review, medical and surgical review, psychosocial review, review of physical environment and appropriate diagnostics. Assessment must determine the cause, effectiveness and impact on quality of life for the patient and their family.<sup>(1, 2, 5, 16)</sup>

Recognition and diagnosis of depression is variable depending on the clinical setting and the diagnostic acumen of those delivering end of life care.<sup>(9)</sup>

*Table 1: Suggested Questions for the Assessment of Depressive Symptoms in Adults with Terminal Illness*<sup>(15, 17).</sup>

How well are you coping with your illness. Well? Poor?	Well being
How are your spirits since diagnosis? During treatment? Down? Blue?	Mood
Do you cry sometimes? How often? Only alone?	Mood
Are there things your still enjoy doing, or have you lost pleasure in things you used to do before you became ill?	Anhedonia
How does the future look to you? Bright? Black?	Hopelessness
Do you feel you can influence your care, or is your care totally under others' control?	Helplessness
Do you worry about being a burden to family and friends during the treatment?	Worthlessness
<b>Physical symptoms (Evaluate in the context of disease related symptoms)</b>	
Do you have pain that is not controlled?	Pain
How much time do you spend in bed?	Fatigue
Do you feel weak? Fatigue easily? Rested after sleep? Any relationship between how you feel and a change in treatment or how you otherwise feel physically?	Fatigue
How is your sleeping? Trouble going to sleep? Awake early? Often?	Insomnia
How is your appetite? Food tastes good? Weight loss or gain?	Appetite
How is your interest in sex? Extent of sexual activity?	Libido
Do you think or move more slowly than usual?	Psychomotor slowing

## VIHA EOL Symptom Guidelines

Table 1 adapted from Roth, AJ, Holland JC: Psychiatric complications in cancer patient. In: Brain MC, Carbone PP, eds.: Current Therapy in Hematology-Oncology. 5th ed. St Louis, Mo: Mosby-Year Book, Inc., 1995, pp 609-618.

**Mnemonics** commonly used to remember the DSM-IV criteria are:

- **SIGECAPS** (sleep, interest (anhedonia), **g**uilt, **e**nergy, **c**oncentration, **a**ppetite, **p**sychomotor, **s**uicidality)<sup>(17)</sup> and
- **DEAD SWAMP** (**d**epressed mood, **e**nergy, **a**nhedonia, **d**eath (thoughts of), **s**leep, **w**orthlessness/guilt, **a**ppetite, **m**entation, **p**sychomotor).<sup>(17)</sup>

### Recommendation 3

#### Diagnosis

Identifying the underlying etiology of depression is helpful in determining the interventions required.

The usual somatic symptoms of depressed patients (fatigue, loss of appetite, sleep disturbance, poor concentration, etc.) are often present in advanced cancer and terminal illness and cannot always be relied upon for diagnosis.<sup>(4, 10)</sup>

Psychological symptoms of depression that are persistent, out of character and severe are of greater diagnostic value in patients with advanced illness.<sup>(5, 18)</sup> In particular, watch for pervasive dysphoria, feelings of helplessness, hopelessness and worthlessness, guilt, loss of self-esteem, loss of interest and wishes to die. Even very mild or passive suicidal ideation is indicative of significant depression in terminally ill patients.<sup>(1, 4-6)</sup>

If the diagnosis of depression is uncertain, consider psychiatric referral and a trial of antidepressant medication or therapy. When in doubt, treat.<sup>(1, 6)</sup>

### Recommendation 4

#### Education

Depression is a distressing symptom to experience and witness. It is commonly under reported as many of the signs and symptoms are a feature of terminal illness.<sup>(1, 5)</sup>

Reinforce to patient and family the importance of reporting symptoms that are causing distress, physical or psychological, as both may influence psychological well being.<sup>(1, 5, 9)</sup>

Reinforce that if depression is diagnosed it can be managed. Treatment can be effective even when life expectancy is short.<sup>(1, 5, 9)</sup>

Teach the purpose of Non-pharmacological and pharmacological measures and the goal of each.<sup>(5)</sup>

Teach that many antidepressant medications take time to become effective.<sup>(5)</sup>

Recommendation 5

Treatment: Non-pharmacological

Depression in patients with advanced disease is optimally managed by utilizing a combination of supportive psychotherapy, cognitive-behavioural techniques, and antidepressant medications.<sup>(8, 12)</sup>

Always ensure that pain is well treated or alleviated. Uncontrolled pain is a major risk factor for depression and suicide among patients with cancer.<sup>(1, 2, 4)</sup>

For patient and family consider psychosocial therapies, relaxation techniques, massage therapy and therapeutic touch.<sup>(1, 4-6, 8, 12, 15)</sup>

Recommendation 6

Treatment: Pharmacological

**“Medication without ongoing contact is often seen as abandonment and never acceptable.”<sup>(19)</sup>**

- Start with low doses and increase slowly.<sup>(1, 5, 6, 8, 15)</sup>
- When anticipated survival time is short, consider psychostimulants due to their more immediate onset of effect.<sup>(1, 5, 6, 8, 15)</sup>
- Consider side effects and additional therapeutic benefit (tricyclic antidepressants may benefit neuropathic pain but worsen constipation; avoid tricyclics in patients with cardiac conduction delays, etc.).<sup>(1, 2, 5, 6, 8, 15)</sup>
- Withdrawal symptoms may be of significant importance in palliative patients who are unable to continue with oral medications.
- There are similar response rates when comparing antidepressant medications.<sup>(20)</sup>

**Selective Serotonin Re-uptake Inhibitors (SSRIs):**<sup>(1, 2, 5, 8, 10, 15)</sup>

Example: **Citalopram**,<sup>(6)</sup> **Paroxetine**, **Fluoxetine**, **Sertraline**<sup>(15)</sup>

Initial and maintenance doses are specific for each of the SSRI's.

Initial dose for Citalopram: 10 to 20 mg per day to start, increasing at intervals of no less than one week. Maximum daily dose is 60 mg, although doses above 40 mg are not ordinarily recommended.<sup>(20)</sup> Usual maintenance dose is 20 to 30 mg per day.

- Have fewer side effects than tricyclic antidepressants (TCAs).
- Start SSRI at half the usual dose for the general population.
- Paroxetine and fluoxetine are active inhibitors of the enzyme responsible for metabolizing oxycodone and codeine to its active analgesic form. Concurrent use of these opioids and SSRIs can therefore result in decreased pain control.

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- The sudden cessation of SSRI therapy when a patient is unable to swallow can produce a withdrawal syndrome. Withdrawal risk is greater with short-half life drugs such as paroxetine, lowest with long-half life drugs such as fluoxetine, and are of intermediate risk for other SSRI's.<sup>(20)</sup>

**Fluoxetine has less selective receptor sites and a much longer half-life than the other SSRIs and should not be the drug of choice. Switching to other antidepressants after having been on fluoxetine can be complicated due to the extended half life.**<sup>(5)</sup>

### **Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs):**

Example: **Venlafaxine**<sup>(10)</sup>

Initial dose: Venlafaxine XR – 37.5-75 mg per day then maintenance dose: 150 to 375 mg per day.

### **Atypical Antidepressants:**

Example: **Bupropion**<sup>(1, 2, 8, 15)</sup>

- Initial activating dose-related seizure-inducing potential. Contraindicated in patients with a history of seizure, in those with concomitant conditions predisposing to seizure, and in patients taking other drugs that lower seizure threshold.
- Low incidence of sedative, hypotension and anticholinergic side effects.
- Can cause over stimulation.
- Generally considered third line treatment.
- Initial: 100 mg per day then maintenance: 200-300 mg per day.

Example: **Trazodone**<sup>(1, 10)</sup>

- Trazodone may cause hypotension including orthostatic hypotension and syncope; caution is required if it is given to patients receiving antihypertensive drugs and an adjustment in the dose of the antihypertensive medication may be required
- Increased serum digoxin and phenytoin levels have been reported with concurrent trazodone use.<sup>(1,10)</sup>
- Treatment should be started with low initial doses of 25 to 50 mg daily in divided doses or in an evening single dose. The dose may be increased slowly to a maximum of 300-400 mg daily in ambulatory patients and to 600 mg daily in hospitalized patients.

Example: **Mirtazapine**<sup>(10, 21)</sup>

- A tetracyclic antidepressant. Mirtazapine elimination is decreased in elderly persons.
- When used concomitantly with drugs that reduce the seizure threshold (e.g., phenothiazines), mirtazapine may increase the risk of seizure.
- Initial dose: 7.5 to 15 mg daily, maintenance dose: 15 to 45 mg daily.

**Psychostimulants:**<sup>(1, 2, 5, 10, 12)</sup>

Examples: **Methylphenidate and Dextroamphetamine.**

- Consider this class of medication when life expectancy may be short,<sup>(1, 5, 6, 8, 15)</sup> as these drugs work within hours to days.
- They often enhance opioid analgesia, reduce opioid sedation and improve appetite. They can improve attention, concentration and overall performance.
- Side effects include agitation, confusion, insomnia, anxiety and paranoia. Use cautiously in the elderly, avoid in delirious patients<sup>(1)</sup> and underlying medical conditions that may be compromised by increases in blood pressure or heart rate such as pre-existing hypertension, heart failure, recent myocardial infarction, or hyperthyroidism.<sup>(21)</sup>
- A common clinical practice is to start a psychostimulant and a SSRI together and then withdraw the stimulant while titrating the SSRI upward.
- Start methylphenidate at 5 mg PO at 8 AM and noon. Initial doses could be lower at 2.5 mg b.i.d. in very frail patients. Increase 2.5 to 5 mg every 1 or 2 days until desired effect is reached, or to a maximum daily dose of 30 mg per day.<sup>(23)</sup> Afternoon dosing can affect nighttime sleep and is generally not recommended.<sup>(5)</sup>

**Tricyclic Antidepressants (TCA)**<sup>(1, 2, 5, 8, 10, 15)</sup>

Examples: **Nortriptyline, Amitriptyline, Desipramine, Imipramine and Doxepin**

- Requires a careful risk-benefit ratio analysis because the adverse effect profile may be troubling to patients in a palliative/hospice setting.<sup>(1)</sup> Effects include sedation and anticholinergic effects; dry mouth, blurred vision, urinary hesitancy, or retention, constipation.
- Avoid TCA's in patients with cardiac conduction delays,<sup>(1, 2, 5, 6, 8, 15)</sup> coronary artery disease, or history of myocardial infarction in past six months.<sup>(20)</sup>
- Adverse effects usually decrease 3 to 4 days after initiation of a TCA or after increasing the dosage.
- The secondary amines (desipramine and nortriptyline) generally have fewer side effects, such as sedation and anticholinergic effects, than the tertiary amines (imipramine, amitriptyline, and doxepin).<sup>(23)</sup>
- The specific liver enzyme cytochrome P450 metabolism pathway may affect drug levels. From 5 to 10% of Caucasians have a recessive gene that results in deficient 2D6 metabolism which would affect desipramine and nortriptyline.<sup>(20)</sup> Twenty percent of Asians are deficit in the 2C19 enzyme affecting the metabolism of TCA's such as imipramine.<sup>(20)</sup>
- Start at low doses (10 to 25 mg PO at bedtime) and increase by 10 to 25 mg PO every 4 days.
- Onset of antidepressant effect may take 2 to 4 weeks.
- May provide additional neuropathic pain benefits.

### References

Information was compiled using the CINAHL, Medline (1996 to April 2006) and Cochrane, DSR, ACP Journal Club, DARE and CCTR databases, limiting to reviews/systematic reviews, clinical trials, case studies and guidelines/protocols using depression terms in conjunction with palliative/hospice/end of life/dying/terminally ill. Palliative care textbooks mentioned in generated articles were hand searched. Articles not written in English were excluded.

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