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The Management of Depression in Cancer Patients: A Clinical Practice Guideline

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Question

What is the efficacy of pharmacological and nonpharmacological treatments for major depression and other depressive disorders in cancer populations? Outcomes of interest include symptomatic response to treatment, discontinuation rate of treatment, adverse effects, and quality of life.

Target Patient Population

These recommendations apply to adult cancer patients with a diagnosis of major depression or other non-bipolar depressive disorders. They do not address the treatment of non-syndromal depressive symptoms, for which specific antidepressant treatment is not usually indicated. Such symptoms are frequent as a non-specific manifestation of distress and/or in association with pain or other suffering. For the purposes of this report, the conclusions were based on evidence from studies of two categories of patients:

- A. Patients diagnosed with major depression by a structured diagnostic interview. This is the gold standard for the diagnosis of a depressive disorder.
- B. Patients with depressive symptoms scoring greater than 14 on the first 17 items of the Hamilton Depression Rating Scale, greater than or equal to eight on the Hospital Anxiety and Depression Scale, or above the equivalent cut-off on another validated assessment scale. These measures were developed to assess symptoms and are used for screening but are less stringent methods to diagnose depressive disorders, because they may be associated with false positives and false negatives. Some but not all of these patients may have been suffering from major depression, dysthymic disorder, adjustment disorder with depressed mood, or minor depression (see Appendices 1 and 2 of the *Systematic Review* for diagnostic criteria for these depressive disorders).

Target Provider Population

The guidelines are intended for both oncology health professionals as well as mental health professionals engaged in the treatment of cancer patients. Referral to a mental health specialist may be valuable for cancer patients diagnosed with major depression but this may not

always be feasible. The rate of detection of depressive disorders in this and other populations is increased by the use of screening measures but there is no evidence that the nature of the disorders or their response to treatment varies by the method of detection or presentation.

Recommendations

There is an absence of clear evidence derived from randomized controlled trials in cancer patients on which to inform the conclusions; therefore, the following recommendations reflect the expert consensus of the guideline panel members (which comprises nurses, palliative care physicians, medical, surgical, and radiation oncologists, an anesthetist, radiation therapists, methodologists, administrators, two psychiatrists and one psychologist) informed by the evidence reviewed and feedback from Ontario health care providers.

- Treatment of pain and other reversible physical symptoms should be instituted prior to the initiation of specific antidepressant treatment.
- Antidepressant medications should be considered to treat moderate to severe major depression in cancer patients. Current evidence, however, does not support the relative superiority of one pharmacological modality of treatment over another nor the superiority of pharmacological versus psychosocial interventions. The choice of an antidepressant should be informed by the side effect profiles of medication, tolerability of treatment including the potential for interaction with other current medications, response to prior treatment, and patient preference.
- Cancer patients diagnosed with major depression may benefit from a combined modality approach that includes both psychosocial and pharmacological interventions. Psychosocial treatment approaches that may be of value include those that provide information and support and which address emotional, cognitive, and/or behavioural factors.

Qualifying Statements

- Referral to a mental health specialist is appropriate where the diagnosis of depression is unclear, the syndrome is severe, the patient is not responding to treatment, or there are other complicating factors that may affect the choice of treatment.

Key Evidence

- One systematic review, ten randomized trials, and one comparative cohort study were included in this systematic review of the evidence. Six of the trials compared pharmacologic treatments, four trials compared various non-pharmacological therapies, and one trial compared pharmacologic therapy to relaxation. The treatment period and follow-up was short in the trials of pharmacological treatments (10 days – 12 weeks), which limits the conclusions that can be reached regarding long-term treatment.
- The systematic review of 24 studies in cancer patients, six focused on antidepressant agents and 18 on psychosocial interventions, found limited evidence in favour of both treatments. However, few studies in the review focused on patients diagnosed with a depressive disorder; most were preventive studies or included patients with mild depressive symptoms.
- Two drug trials, which compared mianserin to placebo, detected a significant benefit with treatment. In another trial, alprazolam was found to be superior to progressive muscle relaxation in reducing depressive symptoms.
- Four of the drug trials found no significant difference between groups on a measure of depression. Two of those trials compared low-dose fluoxetine to placebo, one compared fluoxetine to desipramine, and one compared paroxetine to amitriptyline. In these latter two studies, there were significant pre-post treatment effects for both active comparators; but the significance of these findings in the absence of placebo comparators is limited. Only one of

the pharmacologic trials assessed outcome based on remission of depressive symptoms to within the normal range as opposed to response, which is a less stringent outcome.

- Two of the four trials that assessed non-pharmacological therapies for the management of depression found a significant difference between treatment groups. One trial found a benefit in using a multi-component nurse delivered intervention, with a reduction in the number of patients diagnosed with major depression, and the other positive trial found the use of an orientation program to be beneficial in reduction of depressive symptoms. In both trials, the control group received usual care. Neither group psychotherapy nor adjuvant psychological therapy (cognitive behavioural therapy) was found to significantly reduce depressive symptoms in the other two non-pharmacological trials.
- Four of the eleven trials included only patients diagnosed with major depression through structured diagnostic interview. The remaining seven trials included patients with depressive symptoms above a predefined cut-off score using a validated assessment tool. Significant benefit on depression measures were found in two of the former studies and in three of the latter studies.

Future Research

- Large multicentre studies of patients with histologically similar cancers are required to evaluate the efficacy of antidepressant interventions including the relative benefit of psychological versus pharmacological interventions in specific cancers (in which there may be different medication side effect profiles, physical symptoms and psychosocial problems) and the efficacy of specific antidepressant medications with respect to broader health care outcomes. Indications that may be of interest include the potential value of mirtazapine in the treatment of mood disorders accompanied by nausea, weight loss, insomnia, or anxiety; the use of dual action antidepressants such as mirtazapine, venlafaxine, and duloxetine in the treatment of comorbid pain and depression; and the use of sustained release bupropion for cancer patients with significant symptoms of depression and fatigue.
- Further studies are needed to evaluate the relative effectiveness and tolerability of newer antidepressant treatments and the use of combination strategies for treatment-resistant depressive disorders. The latter potentially include the use of two antidepressant medications used in combination, and antidepressants combined with either lithium or atypical antipsychotics.
- Research is needed to identify strategies to improve the rates of detection and treatment completion of cancer patients with depressive disorders.

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