Complete Summary

GUIDELINE TITLE

The management of depression in cancer patients: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Rodin G, Katz M, Lloyd N, Green E, Mackay JA, Wong R, Supportive Care Guidelines Group. The management of depression in cancer patients: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Oct 17. 39 p. (Evidence-based series; no. 13-6). [78 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- May 2, 2007, Antidepressant drugs: Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Major depression and other depressive disorders in cancer patients

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Psychiatry

INTENDED USERS

Advanced Practice Nurses
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the efficacy of pharmacological and nonpharmacological treatments for major depression and other depressive disorders in cancer populations

TARGET POPULATION

Adult cancer patients with a diagnosis of major depression or other non-bipolar depressive disorders

Note: The recommendations 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 original guideline document for diagnostic criteria for these depressive disorders).

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

Pharmacological

1. Mianserin
2. Fluoxetine
3. Desipramine
4. Alprazolam
5. Paroxetine
6. Amitriptyline

Nonpharmacological

1. Progressive muscle relaxation
2. Multi-component nurse delivered intervention
3. Adjuvant psychotherapy
4. Group psychotherapy plus relaxation
5. Orientation program

MAJOR OUTCOMES CONSIDERED

- Symptomatic response to treatment
- Discontinuation rate of treatment
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

MEDLINE (1985 to June Week 2 2005), EMBASE (1980 to 2005 Week 25), CINAHL (1982 to June Week 3 2005), PsycInfo (1985 to June Week 2 2005), and the

Cochrane Library (Issue 2, 2005) databases were searched using terms for depressive disorders, pharmacological and nonpharmacological treatments, and publication types and study designs (See Appendix 3 in the original guideline document). In addition, conference proceedings from the World Congress of Psycho-Oncology, the American Psychiatric Association (http://www.psych.org/MainMenu/EducationCareerDevelopment/Library/AbstractsAnnualMeetingInstitute_1.aspx), the Academy of Psychosomatic Medicine (http://psy.psychiatryonline.org/contents-by-date.0.shtml), and the American Psychosomatic Society (http://www.psychosomatic.org/events/events_past_meetings.htm) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov/) were also searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials, as were the reference lists from relevant review articles.

An updated search for practice guidelines, systematic reviews, and meta-analyses was conducted in July 2006. Relevant articles were selected and reviewed by one reviewer.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met all the following criteria:

1. The article was a systematic review, meta-analysis, evidence-based practice guideline, or a fully published or abstract report of a randomized or non-randomized controlled trial of an antidepressant treatment compared to observation, placebo, or other active treatment (including pharmacologic and nonpharmacologic) in adult patients. Comparative studies, including prospective cohort, case control, and cross-sectional studies were also eligible for inclusion.
2. The study populations included either:

   Category A: Patients diagnosed with major depression (MD), dysthymic disorder (DD), adjustment disorder, or minor depression, through a structured diagnostic interview, or

   Category B: Patients with depressive symptoms scoring greater than 14 on the first 17 items of the Hamilton Depression Rating Scale (HDRS) or equivalent on another validated assessment scale for depression.

   The latter criterion was added after the initial search and selection due to the relative paucity of studies that met criterion A.

3. The study population included patients with cancer of any histological type.

4. The trial included a standardized outcome measure of depressive symptoms or disorders.

Exclusion Criteria

Letters, comments, editorials, and review papers were excluded. Trials published in a language other than English were also excluded.

NUMBER OF SOURCE DOCUMENTS

One systematic review, ten randomized trials, and one comparative cohort study were included in the systematic review of the evidence.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Due to the heterogeneity of treatments used and variability of reported outcomes, meta-analysis was not used to synthesize the results.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Supportive Care Guidelines Group (SCGG) members raised three questions during the initial discussions about developing a guideline for the treatment of depressive disorders in cancer patients. First, they wanted to know, "How valid and reliable is the diagnosis of depressive disorder in cancer patients, and what is the prevalence and course of this condition in the cancer population?" Members also asked, "To what extent do systematic reviews, meta-analyses, and randomized controlled trials confirm the efficacy of antidepressant treatments in the cancer population?" Finally, members inquired about existing guidelines for the treatment of depressive disorders in cancer patients and in other populations. The evidence suggests that a valid and reliable diagnosis of major depression (MD) can be made in this population despite the overlap of symptoms of

depression with those of cancer and its treatment. Depressive symptoms have been shown to persist and to be associated with significant morbidity in medically ill populations. Because milder depressive symptoms are a common non-specific manifestation of distress in cancer patients, a group decision was made to focus on the syndrome of MD, for which specific interventions have been developed. The gold standard for the diagnosis of MD is a structured diagnostic interview. It was decided that a guideline that focused on the screening and diagnosis of depression in cancer patients would be a topic for future consideration. The version of the guideline circulated for external review incorporated feedback from SCGG members on a draft version that was first circulated in January 2005 and again in May 2005. The most notable change resulting from SCGG members' feedback was the division of the guideline into two categories of evidence: pharmacological trials versus non-pharmacological trials. Further, the guideline was revised to clearly indicate which recommendations are based on the evidence reviewed and which are based on consensus recommendations.

In the final SCGG review of the report in October 2006, the only revision required was an increased emphasis in the *Introduction* section of the *Systematic Review* (section 2 in the original guideline document) on the mixed evidence regarding the impact of screening on patient outcomes.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Development and Internal Review

This evidence-based series was developed by the Supportive Care Guidelines Group (SCGG) of Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC). The SCGG comprises medical, radiation, and surgical oncologists; psychiatrists; palliative care physicians; nurses; radiation therapists; methodologists; administrators; a psychologist; and an anesthetist.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the SCGG circulated the clinical practice guideline and systematic review to health care providers in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 236 health care providers in Ontario including 101 psychiatrists, 40 medical oncologists, 41 pharmacists, 39 nurses, and 15 palliative care physicians. The survey consisted of items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out over a period of four months (September through December 2005) as contact information for additional provider groups became available. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The SCGG reviewed the results of the survey.

Report Approval Panel

The final Evidence-based Series report was reviewed and approved by the PEBC Report Approval Panel (RAP) in October 2006. The Panel consists of two members including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included: a need for clarification on the intended provider audience for the report and consideration of the presentation of the information for the specific audience; a suggestion to separate the practitioner feedback results by clinician types; and, given the limited evidence for treatment options in cancer patients, a request for further discussion of evidence for treatment effectiveness in non-cancer populations.

RECOMMENDATIONS

MAJOR 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials, a systematic review, and a comparative cohort study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- 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.

POTENTIAL HARMS

Pharmacological Trials

- Adverse effects were reported in all of the pharmacological trials. In three of the four trials in which an antidepressant was compared to placebo, adverse effects were more frequent in the antidepressant arm, while they were more common in the placebo arm in the fourth trial. The most frequent adverse effect of mianserin in one trial was drowsiness, which was reported in six patients in the first week. Although there was a significant difference between groups in the overall number of withdrawals from two of the trials, there was no significant difference in withdrawals due to adverse effects (p=0.704). Initial effects related to mianserin (that disappeared later in the study) included sedation, tiredness, drowsiness, and slowed thinking.
- The two studies that compared fluoxetine to placebo reported similar adverse effects. Digestive and neuropsychiatric toxicities were more common in the fluoxetine group (24% and 49%, respectively) compared to placebo (13% and 35%, respectively), but these differences were not statistically significant (p=0.16 and p=0.17, respectively). One study reported a significantly higher frequency of emesis in fluoxetine-treated patients compared to placebo. No other toxicities were reported.
- There was no significant difference in withdrawals due to adverse events in the trial comparing fluoxetine vs. desipramine. Six patients withdrew in the fluoxetine group because of adverse effects which included somnolence, tachycardia, abnormal thinking, symptoms of depersonalization, and pain. Four desipramine-treated patients withdrew because of symptoms which included dyspepsia, abnormal thinking, pain, and somnolence. The only significant difference was in the incidence of dry mouth, which was more frequent in fluoxetine-treated patients (p=0.008).
- In the trial comparing alprazolam with progressive muscle relaxation, five of the 70 patients in the alprazolam arm required a dose reduction to 0.25mg due to drowsiness and sedation. Additional drug-related adverse effects included light-headedness (eight patients), sleepiness/grogginess (two patients), nightmares (one patient), facial edema (one patient), and nausea and vomiting (one patient), although none of these patients required a dose reduction.
- There was a high incidence of adverse effects in the paroxetine vs. amitriptyline trial but no statistically significant difference between drug treatment groups was reported. Nine of the 88 patients in the paroxetine group were withdrawn from the trial because of adverse effects. For six of these nine patients, the adverse effects included abdominal pain, tremor, dry mouth, insomnia, agitation, confusion, dizziness, headache, and abnormal thinking. Between ten and twelve patients in the amitriptyline group were

also withdrawn due to adverse effects and in six of these patients effects included abdominal pain, tremor, dry mouth, insomnia, anxiety, asthenia, depersonalization, nervousness, somnolence, and vertigo. The most frequent adverse effects overall were nausea (13.6%) and leukopenia (10.2%) in the paroxetine group, and dry mouth (14.6%) and constipation (11.2%) in the amitriptyline group.

Non-pharmacological Trials

Adverse effects were not evaluated in the four trials assessing nonpharmacologic interventions.

QUALIFYING STATEMENTS

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.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Rodin G, Katz M, Lloyd N, Green E, Mackay JA, Wong R, Supportive Care Guidelines Group. The management of depression in cancer patients: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Oct 17. 39 p. (Evidence-based series; no. 13-6). [78 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Oct

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Supportive Care Guidelines Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Katz has acted as a consultant or received honoraria from Wyeth, a manufacturer of venlafaxine; Lundbeck, a manufacturer of escitalopram and citalopram; and Organon, a maker of mirtazapine. No other potential conflicts of interest were declared by the authors of this Evidence-Based Series report.

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on March 27, 2008.

COPYRIGHT STATEMENT

This NGC summary is based on the original guideline, which is subject to the guideline developer's copyright restrictions. Please refer to the Copyright and Disclaimer Statements posted at the Program in Evidence-Based Care section of the Cancer Care Ontario Web site.

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and

related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

© 1998-2008 National Guideline Clearinghouse

Date Modified: 9/15/2008