A Randomized, Placebo-Controlled Trial of Citalopram for the Prevention of Major Depression During Treatment for Head and Neck Cancer

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Objective: To determine whether prophylactic treatment with the antidepressant citalopram hydrobromide, compared with placebo, could prevent major depressive disorder in patients undergoing therapy for head and neck cancer (HNC).

Design: Prospective, randomized, placebo-controlled trial.

Setting: Academic medical center.

Patients: Thirty-six subjects were randomized, and 23 completed the study.

Interventions: Subjects were randomized to receive 40 mg of citalopram hydrobromide or matching placebo (hereinafter, citalopram group and placebo group, respectively) for 12 weeks with a final visit at 16 weeks.

Main Outcome Measures: The Hamilton Depression Rating Scale, psychiatric interview, and the University of Washington Quality of Life (UW-QOL) and Clinician Global Impression–Severity (CGI-S) scales.

Results: The numbers of subjects who met predefined cutoff criteria for depression during the 12 weeks of active study were 5 of 10 (50%) taking placebo and 2 of 12 (17%) taking citalopram (Fisher exact test, \( P = .17 \)). No patients in the citalopram group became suicidal, compared with 2 in the placebo group. Global mood state at the conclusion of the study as measured by the CGI-S scale was rated as at least mildly ill in 15% of those receiving citalopram compared with 60% in the placebo group (Fisher exact test, \( P = .04 \)). Quality of life, measured by the UW-QOL, deteriorated in both groups from baseline but less so in the citalopram group.

Conclusions: This study reports data from the first depression prevention trial in HNC and suggests that prophylactic treatment may decrease the incidence of depression during HNC therapy. The clinical significance of the reduction in depression was best demonstrated by the CGI-S scale, which showed a notable difference in global psychiatric and physical well-being.


TREATMENT FOR HEAD AND neck cancer (HNC) can be arduous and debilitating. Psychiatric morbidity in these patients is frequent and underdiagnosed.\(^1,2\) Major depressive disorder (MDD) has been reported in up to 40% of patients with HNC, typically within the first 3 months of diagnosis.\(^3\) Unfortunately, MDD is rarely identified and almost never treated in these patients.\(^1,2\) The reasons are myriad and include a lack of recognition of symptoms by physicians because many treatment-related adverse effects may mimic the symptoms of MDD, lack of comfort in diagnosing and treating psychiatric illness, limited time available in the clinical setting, and therapeutic nihilism regarding the success of MDD therapy.\(^7,13\) Finally, there is a paucity of data on treatment of MDD in patients with cancer in general and those with HNC specifically.

In light of the prevalence of MDD in patients with HNC, alternative strategies for the surveillance and treatment of MDD must be considered. One proactive approach worthy of consideration is prophylactic treatment. The role of pharmacologic prophylactic treatment of medical disease is gaining in popularity and acceptability. The role of \(\beta\)-blockers in prevention of myocardial damage following myocardial infarction and warfarin sodium for thromboembolic prevention in atrial fibrillation has become well established.\(^14,15\) Likewise, ongoing or intermittent use of antidepressants is established as an important means of preventing recurrences of MDD, as is intermittent use in the prevention of premenstrual syndrome.\(^16,18\)

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With this background, the possibility of prophylactic treatment of MDD in patients with HNC was considered.

The hypothesis was that the frequency and/or severity of MDD could be reduced using a prophylactic antidepressant started soon after the cancer diagnosis and just prior to initiation of HNC treatment. The goal was to minimize and prevent MDD by initiating treatment intervention soon after the diagnosis of cancer was made, thus avoiding many of the problems that can result from the development of clinical depression. The additional hope was that quality of life (QOL) might thereby be better preserved. To test this hypothesis, a randomized, prospective, double-blind, placebo-controlled trial of the antidepressant citalopram hydrobromide was conducted to evaluate whether MDD could be prevented in patients undergoing treatment for HNC.

**METHODS**

**PATIENTS**

University of Nebraska Medical Center (Omaha) institutional review board approval was sought and secured. Inclusion criteria included an age of 19 years or older and newly diagnosed or recurrent cancers of the oral cavity, larynx, pharynx, neck, and paranasal sinuses requiring more than limited excision. Subjects were excluded if they had a Mini-Mental State Examination (MMSE) score of less than 24; if they were suicidal; met diagnostic criteria for MDD, psychosis, or schizophrenia; were currently taking antidepressant medication; or had a contraindication to taking citalopram. Subjects were approached by 1 of the participating surgeons (W.M.L.) and given a detailed explanation of the study. A delayed consent process was used, which allowed subjects time to review the study plan and consent form and then return to the research clinic at a later date to complete the consent process and for the baseline interview.

**ANTIDEPRESSANT CHOICE**

There are almost no data on the use of antidepressants in patients with HNC. Citalopram was selected as the study medication based on evidence of its efficacy; safety; favorable adverse effect profile; ease of discontinuing treatment; ease of administration as a single daily dose as a pill, liquid, or via nasogastric tube; safety in older adults and in medically fragile patients; ease of titration; and minimal drug interaction potential. It is a member of the class of selective serotonin reuptake inhibitors (SSRIs).

**TREATMENT AND FOLLOW-UP**

A physical examination and mental status examination were performed to verify that subjects were eligible to participate. Subjects were randomized in the University of Nebraska pharmacy by coin toss in a 1:1 fashion to receive placebo or citalopram (hereinafter, placebo group and citalopram group, respectively). Subjects were randomized to receive active drug or placebo for 12 weeks. Each subject received identical capsules either containing citalopram hydrobromide, 20 mg, or a matching placebo and were asked to begin with 1 pill per day for 1 week and increase the dosage to 2 pills per day until the 12th week when they were asked to take 1 pill per day for 1 week and stop. Subject visits were performed every 4 weeks throughout the intervention period. A follow-up visit off study medication was then performed at 16 weeks. Pill counts were performed at each visit to verify at least 80% compliance. At baseline, each subject underwent thyroid function studies to verify the euthyroid state.

Tumor- and treatment-specific information was given as per the usual standard in the head and neck clinic. For additional background information about HNC and its treatment, subjects also received the book Cancers of the Mouth and Throat: A Patient’s Guide to Treatment. Each subject received supportive care in the usual fashion as needed by clinical staff, and each was invited to join the HNC support group. Subjects were asked not to enter into formal psychotherapy or to take other antidepressants during the active portion of this trial.

Cancer therapy was delivered in the usual manner and consisted of surgery and radiation therapy with or without chemotherapy as per the standard care of our head and neck clinic and generally according to the National Comprehensive Cancer Network guidelines. Subjects began their cancer therapy and baseline study visit concurrently.

A medical history was taken and physical examination performed by a head and neck surgeon or physician’s assistant at each visit, noting abnormal findings related to either cancer therapy or study treatment.

**POWER ANALYSIS**

A baseline power analysis was conducted. The study was designed to have 80% power (testing at the 5% level of statistical significance) to detect a difference of 0.5 standard deviation (SD) in the time-averaged differences in the mean scores between the 2 treatment groups. Given the expected mean value of the various scales in this population, a difference of 0.5 SD translates into a difference of about 15%. Assuming a correction of 0.3 between observations from the same individuals, a sample size of 68 (34 per treatment) would provide the necessary power. Because up to 15% to 20% of subjects could be lost to follow-up, the total sample size was set at 80 to assure the sufficient power. The study was stopped early because of personnel changes, making adequate accrual unlikely.

**ASSESSMENT TOOLS**

Baseline evaluations performed to evaluate psychiatric and cognitive status included the Mini-International Neuropsychiatric Interview (MINI) and MMSE. The MINI is a brief, structured psychiatric diagnostic interview for use in clinical and research settings. The MINI provides broad coverage of psychiatric diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), and has been used very widely in psychiatric research. The MINI covers a variety of psychiatric disorders of particular interest to this study, including major depressive episode (current and past), suicidality (in past month), and alcohol abuse or dependence (past 12 months). The MINI was used at baseline to identify any exclusionary psychiatric diagnoses, and the depression and suicide modules of the MINI were repeated at each subsequent visit.

The primary outcome measure was the number of subjects who developed depression according to the Hamilton Rating Scale for Depression (HRSD) (the predefined cutoff for depression was ≥15). The HRSD is a standard, physician-administered, assessment tool used to measure depression severity in efficacy evaluations of antidepressants. The HRSD, which consists of 21 items that quantify depressive symptoms, was administered at each of the 5 visits. Higher scores on the HRSD indicate higher levels of depression.

The physician-administered MINI depression module served as a secondary measure of depression. A global assessment of depression severity, the Clinical Global Impression–Severity (CGI-S) scale, was also obtained at each visit. The CGI-S provides an overall rating of the severity of depression on a simple 7-point scale.
Health-related QOL was assessed with the University of Washington Disease-Specific Quality of Life Questionnaire (UW-QOL), which was developed to assess QOL in patients with HNC. It is self-administered and includes 9 categories emphasizing important areas of daily living frequently affected by HNC or its treatment.26 A score of 100 represents the highest level of function, and zero indicates the lowest level of function. The tested domains include pain, disfigurement, activity, recreation/entertainment, employment, eating/chewing, eating/swallowing, speech, and shoulder disability.

All assessments were performed in a blinded fashion. Neither the investigators nor the subjects knew whether they were receiving active drug or placebo. Unblinding did not occur until the last subject had completed the final assessments.

STATISTICAL ANALYSIS

Analyses used a modified intent-to-treat sample that included all subjects who provided informed consent, were not depressed (HRSD <15 at baseline), and were available for evaluation at the first postrandomization visit (4 weeks). Subjects with HDRS scores of at least 15 at baseline were continued in the study because data on the treatment vs the natural history of untreated MDD have also not been studied in HNC. They were excluded from the primary analysis of MDD prevention because, by definition, MDD was already present. The Fisher exact test was used to compare the frequency of MDD in the 2 treatment groups at weeks 12 and 16 as well as at any time during the study. Fisher exact tests were also used to compare the frequency of a diagnosis of MDD on the MINI and the frequency of having a global illness rating of “mildly ill” or greater on the CGI-S. The Wilcoxon rank-sum test compared change in QOL from baseline with week 12 and week 16 between the treatment groups. All analyses were conducted using SAS statistical software for Windows (version 9.1; SAS Inc, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS

From July 2002 through April 2005, 36 subjects were randomized (see Figure 1 for details). Five were ineligible owing to baseline depression (HRSD scores were ≥15 [base rate of MDD preintervention = 14%]), and 1 was ineligible owing to a low MMSE score. The ineligible subject should have not been randomized and was done so through an error. Those with baseline depression were randomized, but in retrospect our eligibility criteria should have excluded these subjects. Two subjects failed to make baseline visits after randomization but prior to allocation of the drug.

Twenty-eight subjects began medication; 2 in the citalopram group quit because of adverse events (1 each, owing to diarrhea and nausea), and 1 in the placebo group failed to return for visit 1. Twenty-five subjects completed the first visit. Two subjects in the placebo group dropped out after the first visit; 1 did so after week 4 owing to hospitalization for severe MDD, the other because she was placed in a care facility for the duration of her cancer treatment. Twenty-two subjects were evaluated at week 12 of the study, and 23 completed the study (13 in the citalopram group, and 10 in the placebo group). One subject in the citalopram group was not available for the week 12 visit because of travel difficulties but did return for the follow-up visit at week 16.

Twelve men and 11 women, with a mean (SD) age of 61.0 (10.6), completed the study. Subjects did not significantly differ according to age, sex, tumor grade, type, or location (Table 1). However, there was a trend toward more women in the placebo group (60% vs 38%). There were no notable differences in the number of HNC treatment modalities received (ie, surgery, chemotherapy, radiation, either individually or in combination).

MDD MEASURE

The primary outcome measure was the number of subjects who met the predefined cutoff (≥15) on the HRSD (Figure 2). The numbers who met this criteria for clinically significant MDD at any time during the 12 weeks of active study were 5 of 10 (50%) in the placebo group and 2 of 12 (17%) in the citalopram group (Fisher exact test, P=.17; Figure 2). The percentage whose HRSD was at least 15 stayed roughly at 15% in the citalopram group throughout the study but increased to 30% in the placebo group at weeks 12 and 16.

The secondary measure of MDD was the number of subjects who met the criteria for MDD on the depression module of the MINI (Figure 3). The number of subjects who met criteria at any visit was 5 of 10 (50%) in the placebo group and 4 of 13 (31%) in the citalopram group.
After 12 weeks of participation in the study, 40% of the placebo group vs 17% of the citalopram group had MDD. On the follow-up visit, 1 subject from the citalopram group developed MDD after stopping the drug. No patients in the citalopram group exhibited suicidal ideation (suicide module of the MINI) during the 16 weeks of study, compared with 2 in the placebo group. No subjects in either group attempted suicide.

Overall severity of depression, as estimated by CGI-S rating, was “mildly ill” or worse in 25% of citalopram-treated participants at week 12 and 15% at week 16 compared with 50% and 60% of the placebo-treated patients, respectively (Figure 4) (Fisher exact test: at week 12, \( P = .38 \); at week 16, \( P = .40 \)). No patient in the citalopram group had a CGI-S rating worse than “mildly ill” at any point during the study compared with 30% in the placebo group. The treatment group showed improvement at 16 weeks compared with worsening scores in the placebo group. Table 2 reports the summary of results for primary and secondary outcomes. Table 3 demonstrates confidence intervals for 1 primary and 2 secondary outcomes.

**QUALITY OF LIFE**

The UW-QOL deteriorated in both groups from baseline but less so in the citalopram group (Figure 5). The median UW-QOL change from baseline to week 12 was 18 points in the citalopram group and 30 points in the placebo group (\( P = .60 \)). At week 16, the decline was 7 points in the citalopram group and 32 points in the placebo group (Wilcoxon rank-sum test, \( P = .14 \)). The placebo group continued to decline at follow-up, whereas the citalopram group improved.

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**Table 1. Demographics of Subjects Completing Visit 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (N = 12)</th>
<th>Citalopram Hydrobromide Group (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (median)</td>
<td>61.4 (62.5) (48.0-76.0)</td>
<td>60.9 (64.0) (43.0-81.0)</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>Squamous cell tumor type</td>
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<td>11</td>
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<td>II</td>
<td>1</td>
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<td>Tumor location</td>
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<td>4</td>
</tr>
<tr>
<td>Larynx</td>
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<td>4</td>
</tr>
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<td>0</td>
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<td>Unknown primary</td>
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<tr>
<td>Ear</td>
<td>1</td>
<td>0</td>
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</table>

*Data are given as numbers, except where indicated.*
COMMENT

KEY FINDINGS

This study suggests that the use of a prophylactic antidepressant (citalopram) may prevent some cases of MDD during the first 16 weeks following initiation of cancer therapy in patients with HNC. It further suggests that some mitigation in the expected decline in QOL typically seen during HNC therapy may be achieved. Finally, overall psychological health as measured by the CGI may be better retained.

MDD DIAGNOSIS

Diagnosis and treatment of MDD is critical to the overall treatment of patients with HNC. It is likely that MDD is the end result of a complicated interplay between genetic predisposition and environmental influences. Concurrent life events (such as the diagnosis and treatment of cancer with a subsequent change in lifestyle) can substantially elevate an individual's risk for MDD, particularly when magnified by a lack of interpersonal support and deficient social skills. Finally, the symbolic meaning of loss (e.g., the loss of voice) can be profound.

Untreated MDD in patients with other types of cancer has been shown to adversely affect length of hospital stay, self-care abilities, compliance with medical treatment, QOL, and survival. The full effect of untreated MDD in patients with HNC has not been studied; however, it is likely to play an important role for these reasons. It is known that timely completion of radiation therapy is also an important predictor of successful disease control. Major depressive disorder may be 1 factor that adversely affects adherence to therapy timelines.

One of the most important reasons that prevention, recognition, and treatment of MDD is so vital in patients with HNC is the known increased risk of suicide.

Table 2. Summary of Results and the Estimated Effect Size

<table>
<thead>
<tr>
<th>End Point</th>
<th>Citalopram Hydrobromide Group (n = 13)</th>
<th>Placebo Group (n = 10)</th>
<th>Difference, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end points</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Depressed (HDRS &gt; 15) at any visit</td>
<td>2/12 (17)</td>
<td>5/10 (50)</td>
<td>-33 (-71 to 4)</td>
<td>.17</td>
</tr>
<tr>
<td>Diagnosis of MDD at any visit</td>
<td>4/13 (31)</td>
<td>5/10 (50)</td>
<td>-19 (-59 to 21)</td>
<td>.42</td>
</tr>
<tr>
<td>CGI-S rating of at least mildly ill at any visit</td>
<td>4/13 (31)</td>
<td>7/10 (70)</td>
<td>-39 (-77 to -1)</td>
<td>.10</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed (HDRS &gt; 15) at 12 wk</td>
<td>2/12 (17)</td>
<td>5/10 (50)</td>
<td>-33 (-71 to 4)</td>
<td>.17</td>
</tr>
<tr>
<td>Diagnosis of MDD at 12 wk</td>
<td>2/12 (17)</td>
<td>4/10 (40)</td>
<td>-23 (-60 to 14)</td>
<td>.35</td>
</tr>
<tr>
<td>CGI-S rating of at least mildly ill at 12 wk</td>
<td>3/12 (25)</td>
<td>5/10 (50)</td>
<td>-25 (-65 to 15)</td>
<td>.38</td>
</tr>
<tr>
<td>Depressed (HDRS &gt; 15) at follow-up</td>
<td>2/13 (15)</td>
<td>5/10 (50)</td>
<td>-35 (-71 to 2)</td>
<td>.17</td>
</tr>
<tr>
<td>Diagnosis of MDD at follow-up</td>
<td>3/13 (23)</td>
<td>4/10 (40)</td>
<td>-17 (-55 to 21)</td>
<td>.65</td>
</tr>
<tr>
<td>CGI-S rating of at least mildly ill at follow-up</td>
<td>2/13 (15)</td>
<td>6/10 (60)</td>
<td>-45 (-81 to -8)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CGIS, Clinical Global Impression–Severity; CI, confidence interval; HDRS, Hamilton Rating Scale for Depression; MDD, major depressive disorder.

a Data are given as number/total number (percentage). The table contains the results summarized for each group for the primary and secondary end points. It contains the number out of the total and percentage for the citalopram and placebo groups, along with the difference in percentages and the asymptotic 95% CI for the difference. The P value is computed using Fisher exact test. If a subject was depressed at any of the 4 visits they were said to be depressed at any visit, for the primary end point for HDRS. The other primary end points were computed similarly.

b One subject in the citalopram group did not have week 12 data.

c Asymptotic CIs.

d According to the Mini-International Neuropsychiatric Interview I.

Table 3. Confidence Intervals (CIs) for the Citalopram Hydrobromide and Placebo Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Who Were Depressed (HDRS &gt; 15) at Any Visit</th>
<th>Patients With Diagnosis of MDD (MINI) at Any Visit</th>
<th>Patients With a CGI-S Score of Mildly Ill or Greater at Any Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram group, n/N (%)</td>
<td>2/12 (17)</td>
<td>4/13 (31)</td>
<td>4/13 (31)</td>
</tr>
<tr>
<td>Placebo group, n/N (%)</td>
<td>5/10 (50)</td>
<td>7/10 (70)</td>
<td></td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>-33 (-71 to 4)</td>
<td>-19 (-59 to 21)</td>
<td>-39 (-77 to -1)</td>
</tr>
<tr>
<td>P value</td>
<td>.17</td>
<td>.42</td>
<td>.10</td>
</tr>
<tr>
<td>Relative risk reduction (95% CI)</td>
<td>0.67 (−0.36 to 0.92)</td>
<td>0.39 (−0.71 to 0.78)</td>
<td>0.36 (−0.093 to 0.82)</td>
</tr>
<tr>
<td>Absolute risk reduction (95% CI)</td>
<td>0.33 (−0.04 to 0.71)</td>
<td>0.19 (−0.21 to 0.59)</td>
<td>0.39 (0.013 to 0.77)</td>
</tr>
<tr>
<td>NNT</td>
<td>3.0</td>
<td>5.2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Abbreviations: CGI-S, Clinical Global Impression–Severity; HDRS, Hamilton Rating Scale for Depression; MDD, major depressive disorder; MINI, Mini-International Neuropsychiatric Interview I; NNT, number needed to treat.

a The CIs for these 3 outcomes expand on the data shown in Table 2 and demonstrate the potential effect size that might be shown with adequate numbers.
larynx and tongue accounted for 2 of the 3 highest suicide rates among patients with cancer. Cancers of the larynx and tongue accounted for 19% of the cases in this series of in-hospital suicides. Suicidal rates also seem highest in the first 3 months following diagnosis, suggesting a critical window of opportunity for treatment strategies.

Investigations into the psychological aspects of HNC have primarily focused on establishing the prevalence of, and predictive factors for, psychiatric morbidity. There are very few studies applying interventions aimed at improving psychiatric and psychological outcomes to prevent or reduce suffering and improve health-related QOL. Remarkably, to our knowledge there are no published studies evaluating the effects of antidepressants on clinical MDD and their impact on health-related QOL in patients with HNC.

Interesting work in the field of laboratory research in MDD suggests a potential model for depression surrounding HNC and perhaps other cancer treatments. Exposure to severe, inescapable stress results in subsequent behavioral depression, termed “learned helplessness.” Learned helplessness has been extensively studied in the rat but also can be demonstrated in a range of other species, including humans. Learned helplessness is considered to be an animal model for MDD. In the rat, learned helplessness can be prevented by treatment with antidepressant drugs, including SSRIs, if these agents are administered in repeated doses prior to inescapable stress exposure. Antidepressants given prior to stress maintain levels of cortical serotonin and prevent stress-induced depletion of serotonin in proportion to prevention of stress-induced depressive behavior. If learned helplessness models are relevant to clinical MDD induced by the stress of the diagnosis and treatment of cancer, prior treatment with antidepressants should prevent subsequent depression in humans. This hypothesis may best explain the findings in this study. It may be hypothesized that repeated stress from cancer therapy lowers cortical serotonin, and an antidepressant given prophylactically may serve to lesson this decrement. Additional study is clearly needed to support or refute this hypothesis.

To consider prophylactic therapy for a disorder, several conditions must first be met. The agent must be safe and effective in preventing the disease. The disease must exist with a high enough frequency and result in sufficient morbidity to warrant the risk of the intervention to the entire group. The agent must be cost-effective.

First, consider the types of therapies for MDD. Treatment options for clinical MDD include psychotherapy, pharmacological therapy, and electroconvulsive therapy. Medication and/or psychotherapy are effective in most medically ill patients experiencing mild to moderate depression. However, patients with HNC frequently have marked impairment in communication, making psychotherapy difficult and possibly limiting its effectiveness, particularly in the first 3 months following diagnosis of cancer. Antidepressant medications may be particularly advantageous for these patients because they require less interaction on the part of the patient and, furthermore, are readily available to nonpsychiatric physicians.

Antidepressants are considered to be safe for the treatment of MDD in patients with cancer. The use of antidepressants as prophylactic agents in medically ill patients is an emerging field. Musselman et al reported that the risk of depression in patients with malignant melanoma treated with interferon could be reduced by prophylactic use of the SSRI paroxetine hydrochloride. Treatment also significantly reduced the likelihood that therapy for the melanoma would be discontinued. Thus, early intervention in a high-risk population resulted in marked diminution of depressive symptoms plus improved delivery of treatment.

Roscoe et al studied fatigue in women undergoing chemotherapy for breast cancer and, as a secondary focus, also measured depression. Patients who reported fatigue by day 7 following the second of at least 4 cycles of chemotherapy were randomly assigned to receive either paroxetine, 20 mg, or a placebo. Patients then completed questionnaires at home to measure fatigue and depression. A total of 244 patients treated with paroxetine and 235 patients treated with placebo had assessable data. Although the authors did not see any improvement in fatigue in the treatment group, paroxetine significantly reduced depression as measured by the CES-D during chemotherapy. Taken together, these studies support the role of prevention of depression in high-risk patients. None of these studies address the specific and unique nature of HNC. The present data reinforce these studies’ findings in other malignant neoplasms and support the concept of MDD prevention in patients with cancer.

The data from this pilot trial suggest that prevention of MDD in patients undergoing treatment for HNC may be an attainable goal. The data show trends toward MDD prevention in this small sample. All measures of psychiatric well-being favored the group taking citalopram. The HRSD, the most widely used measure of depression severity in clinical trials evaluating antidepressants, showed a clear trend toward a reduction in depressive symptoms in the citalopram group compared with placebo. Similarly, the number of patients who met criteria for a diagnosis of MDD showed the same trend. Although cau-
tion is indicated in evaluating these outcomes, additional investigation is warranted, as suggested by the confidence intervals reported in Table 3. Given the range of the confidence intervals, a substantial effect may possibly be attained.

QUALITY OF LIFE

Clinical MDD is one of the few factors consistently found to be an independent predictor of health-related QOL both during treatment for HNC and for years thereafter. Patients who are clinically depressed at diagnosis are more likely to have a poor health-related QOL during and after treatment. Diminished health-related QOL is reflected in increased severity of symptoms and poorer physical, psychological, and social functioning. The nature of the relationship between MDD and health-related QOL in terms of cause and effect is complex and incompletely understood. The data from this study suggest 2 important findings. First, although both groups demonstrated the expected worsening of QOL as measured by the UW-QOL, the placebo group evidenced a steeper slope. Second, at the 16-week visit, the placebo group continued to show a decline in QOL, whereas the citalopram group demonstrated a slight improvement.

GLOBAL ASSESSMENT OF PSYCHOLOGICAL HEALTH

The global assessment of psychological health, the CGI, did demonstrate a statistically significant improvement in the treatment arm compared with placebo at 16 weeks (see Table 2 for P values). At that time, only 15% of the patients treated with citalopram were considered to be mildly ill or worse compared with 60% of the placebo group. As a global measure, the CGI may be the most clinically relevant measure of mood. A patient who is feeling stronger psychologically may be more likely to complete therapy and have an improved QOL.

SUICIDE

Suicide is likely an underreported problem in patients with HNC. Suicide prevention is difficult for the head and neck oncologist to manage owing to lack of training and expertise. It is important to emphasize that this discussion is not dealing with the question of suicide at the end of life but rather the premature termination of life owing to active MDD. The data from this study are very sparse on this issue, but 2 subjects in the placebo group experienced suicidal ideation compared with none in the treated group. This suggests that prophylaxis with citalopram may be an avenue warranting further study, particularly in the first 3 months following diagnosis. This is known to be a high-risk period for suicidal ideation among patients with cancer, particularly male patients.

In summary, this study provides preliminary evidence suggesting that prophylactic use of the SSRI citalopram may lessen the risk of MDD occurring in the first 3 months following diagnosis and initiation of treatment for HNC. Furthermore, this strategy may also preserve QOL compared with a placebo condition. This study, which to our knowledge is the first in HNC, begins to lay the groundwork for a more proactive approach to the global health of the patient with HNC.

This study has a number of limitations. Clearly, the sample size is small, and the study was stopped prior to achieving the predicted power necessary for statistical significance owing to personnel changes. The initial inclusion and randomization of subjects with MDD to include more subjects was likely not ideal, but because these individuals were not included in the analyses, it did not affect the results. Because this was a pilot study, multiple assessments were used. This possibly created a burden that reduced the ability to recruit subjects to this study and ultimately may have led to slow accrual.

Many questions still exist. The study needs to be repeated in a larger, appropriately powered study. There is the possibility that preventing MDD might have additional benefits not detected in short-term clinical trials like the one reported herein. Given that many patients with HNC have been shown to experience MDD for years after diagnosis of their cancer, long-term studies and follow-up studies of patients treated prophylactically also need to be performed. In addition, 1.4% of the patients had MDD at baseline in the current study and were excluded from analysis. There is a clear need to establish whether treatment with an antidepressant might help patients who already have MDD at the time treatment is instituted as well.

In conclusion, this study reports data from the first MDD prevention trial in HNC and suggests that prophylactic treatment may decrease the incidence of MDD during HNC therapy. The clinical significance of the reduction in MDD was best demonstrated by the CGI-S scale, which showed a notable difference in global psychiatric and physical well-being between the treatment arm and the placebo arm. Finally, no subjects in the treatment arm expressed suicidal ideation. This study suggests a tangible means to improve outcome in patients with HNC and supports additional research toward this aim.

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