Prevention of Depression With Escitalopram in Patients Undergoing Treatment for Head and Neck Cancer: Randomized, Double-blind, Placebo-Controlled Clinical Trial

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IMPORTANCE Major depressive disorder develops in up to half the patients undergoing treatment for head and neck cancer, resulting in significant morbidity; therefore, preventing depression during cancer treatment may be of great benefit.

OBJECTIVE To determine whether prophylactic use of the antidepressant escitalopram oxalate would decrease the incidence of depression in patients receiving primary therapy for head and neck cancer.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled trial of escitalopram vs placebo was conducted in a group of nondepressed patients diagnosed as having head and neck cancer who were about to enter cancer treatment. Patients were stratified by sex, site, stage (early vs advanced), and primary modality of treatment (radiation vs surgery).

MAIN OUTCOME AND MEASURE The primary outcome measure was the number of participants who developed moderate or greater depression (scores on the Quick Inventory of Depressive Symptomology–Self Rated of ≥11).

RESULTS From January 6, 2008, to December 28, 2011, 148 patients were randomized. Significantly fewer patients receiving escitalopram developed depression (24.6% in the placebo group vs 10.0% in the escitalopram group; stratified log-rank test, \( P = .04 \)). A Cox proportional hazards regression model compared the 2 treatment groups after controlling for age, baseline smoking status, and stratification variables. The hazard ratio of 0.37 (95% CI, 0.14-0.96) demonstrated an advantage of escitalopram (\( P = .04 \)). Patients undergoing radiotherapy as the initial modality were significantly more likely to develop depression than those undergoing surgery (radiotherapy vs surgery group; hazard ratio, 3.6; 95% CI, 1.38-9.40; \( P = .009 \)). Patients in the escitalopram group who completed the study and were not depressed rated their overall quality of life as significantly better for 3 consecutive months after cessation of drug use.

CONCLUSIONS AND RELEVANCE In nondepressed patients undergoing treatment for head and neck cancer, prophylactic escitalopram reduced the risk of developing depression by more than 50%. In nondepressed patients who completed the trial, quality of life was also significantly better for 3 consecutive months after cessation of drug use in the escitalopram group. These findings have important implications for the treatment of patients with head and neck cancer.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00536172
ead and neck cancer (HNC) accounts for 4% of all cancers in the United States and is the fifth most common type of cancer worldwide. The term HNC is the collective name for cancers that affect the oral cavity, paranasal sinuses, pharynx, larynx, skin, and salivary glands, 95% of which are epidermoid carcinomas. The incidence of HNC of the oropharynx is increasing worldwide because of the epidemic of human papillomavirus-associated cancer and is increasing the global burden and importance of this disease. Curative treatment consists of either surgery or radiation as the primary modality for early-stage disease. For more advanced disease, combination therapies using surgery, radiation, and chemotherapy are used. The burden of treatment is extensive and frequently includes dysphagia, disfigurement, voice alterations, mucositis, need for tracheostomy and feeding tubes, fatigue, and depression. Mitigation of these adverse effects and enhancement of survivorship are important goals of caregivers and researchers alike.

Psychiatric complications associated with HNC and its treatment are frequent, underdiagnosed, and often untreated. Major depressive disorder (MDD) occurs in 11% to 52% of patients with HNC, typically in the first 2 to 3 months after diagnosis of cancer. Major depressive disorder substantially affects patients with HNC by adversely affecting length of hospital stay, adherence to treatment, self-care abilities, and quality of life. Suicide is of particular concern in patients with HNC, with rates among the highest of all medically ill patients. Compounding this problem, many oncologists are not adept at diagnosing and treating depression or identifying the overlap of signs and symptoms of depression with cancer treatment–related adverse effects. In addition, there is often limited time in the clinical setting to delve into psychiatric symptoms. Patients with depression during HNC treatment have a lower survival rate, yet there remains a scarcity of data about treatment of depression in patients with cancer.

Prevention of illness is a major focus of modern health care (eg, aspirin use to prevent stroke). Antidepressants can prevent recurrent depressive episodes in persons with major depression, depression after stroke, and depression associated with interferon alfa treatment. A small pilot trial by our group suggested that citalopram hydrobromide might have a role in preventing depression in patients with HNC who were about to undergo treatment for cancer. However, no adequately powered randomized trial has demonstrated depression prevention in a cancer population.

The hypothesis for the Prevention of Depression in Patients Being Treated for Head and Neck Cancer Trial (PROTECT) was that prophylactic escitalopram would decrease the incidence of depression in patients receiving primary therapy for HNC. To test the hypothesis, this randomized, double-blind, placebo-controlled trial was conducted. To maximize safety, patients were removed from the trial if they reached a predefined score on a self-rated depression measure (the primary outcome) or 1 of 3 other clinician-rated measures. A secondary aim was to assess quality of life in the patients before, during, and after cancer treatment and study drug therapy.

Methods

Patients

The study was conducted at 2 sites: the University of Nebraska Medical Center (UNMC) and the Nebraska Methodist Cancer Center (NMCC), a community hospital. Institutional approval was obtained from both sites. Patients were approached by one of the head and neck surgeons and given an overview of the study, including the risks, benefits, and alternatives to participation. A delayed study consent process was used, allowing the patients ample opportunity to review the study plan and consent form, ask questions, or decline to participate with no influence on their subsequent care.

Patients were eligible if they were older than 18 years with newly diagnosed or recurrent stage II to IV epidermoid cancer of the head and neck. Patients were excluded if they were cognitively impaired; had advanced cancer or other conditions that limited life expectancy to less than 6 months; met diagnostic criteria for psychosis, schizophrenia, or MDD; were receiving treatment for depression or anxiety; had a persistent inability to verbally communicate; had uncontrolled pain; were currently participating in another research study involving a therapeutic intervention; or were females of childbearing age who were pregnant, nursing, or not practicing a reliable method of birth control.

Choice of Prevention Method

Pharmacotherapy was selected as the modality for prevention based on its effectiveness in the treatment of depression, comfort level of the clinicians, ease of administration, ability to be compared with placebo control, and ease of use in this population of patients in which many are quite ill and have significant impairments in speech.

Data about antidepressant use in patients with HNC are limited, and cancer patients are typically excluded from depression trials. The selective serotonin reuptake inhibitor escitalopram 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, safety in older adults and in medically fragile patients, few dosage adjustment steps, ability to be given through a nasogastric or percutaneous endoscopic gastrostomy, and minimal drug interaction potential. In our pilot study, citalopram was well tolerated. The S-stereoisomer of citalopram, escitalopram, was used in this trial because of the availability of a matching placebo tablet from the manufacturer.

Study Design and Intervention

This randomized, double-blind, placebo-controlled trial of escitalopram vs placebo was conducted in a group of nondepressed patients diagnosed as having stage II to IV epidermoid HNC. Patients were stratified by site (UNMC or NMCC), sex, stage (early [stage II] vs advanced [stage III/IV]), and primary modality of treatment (radiation with or without chemotherapy vs surgery [not biopsy] with or without radiation). The trial design was developed to maximize safety; therefore, patients were removed from the study if they met...
the primary end point of depression to avoid risk of untreated depression in this population at high risk of suicide and morbidity from MDD. Patients would also be withdrawn from the study if they exhibited other depression indicators, including significant suicidal ideation or intent or a diagnosis of depression on the Mini-International Neuropsychiatric Interview (MINI) depression module, a brief, structured, diagnostic interview.27

After giving informed consent, patients were randomized by a pharmacist with no involvement in the evaluation in a 1:1 ratio to either escitalopram or matching placebo according to a randomization table prepared by the study statistician. Study medication was dosed at 1 tablet for the first week (either placebo or escitalopram, 10 mg/d) and then increased to 2 tablets per day (2 placebo pills or 2 escitalopram pills, 10 mg/d) until week 16 (the acute phase). The dosage of the study medication was decreased to 1 tablet per day for an adverse event. Tablet counts were performed at the end of weeks 4, 8, 12, and 16. At 16 weeks, all patients taking 2 tablets daily had their dose reduced to 1 tablet daily for 1 week and then stopped. Those who were taking only 1 tablet had their medication use stopped at the end of 16 weeks.

In the follow-up phase, patients who completed the acute phase were assessed at 20, 24, and 28 weeks to gauge potential longer-term outcomes of the acute phase intervention. All patients received standard clinical psychosocial interventions throughout the study, primarily education and counseling performed by the physicians and nurses as needed. Per the standard practice of our clinic, patients were offered the opportunity to join a monthly support group but did not receive formal psychotherapy.

Measurement Tools
The assessment measures chosen for this study reflected the needs of the unique population of patients with HNC. These tools were (1) not burdensome to the patient (primary treatment of cancer is arduous), (2) could be self-rated (given the difficulties with verbal communication some of these patients experience), and (3) allowed for remote assessment (given the distance many of the patients live from the research clinic). The Quick Inventory of Depressive Symptomatology (QIDS) scales were initially developed to improve on available clinician and patient ratings by providing equivalent weightings for each depressive symptom and to provide clear anchors for each item. The self-rated version of the QIDS (QIDS-SR) was chosen as the primary outcome measure.28 The QIDS-SR was administered at baseline and at weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28. This trial used a score of 11 or higher as indicative of moderate or greater depression.

At baseline, patients were screened for psychiatric illness using the MINI.27 At subsequent visits, the MINI depression and suicide modules were administered as an additional way to monitor patient safety. Likewise, the clinician version of the QIDS (QIDS-C) was conducted at each rating period.

Quality of life was assessed throughout the study using the University of Washington Quality of Life Scale (UW-QOL).29 The UW-QOL is a self-administered scale designed specifically for patients with HNC. It consists of 9 categories, including pain, disfigurement, activity, recreation/entertainment, employment, eating/chewing, eating/swallowing, speech, and shoulder disability. Because it is concise and specific to the illness, the UW-QOL has been reported to have excellent psychometric properties and acceptability to patients in the midst of treatment for HNC.29

Adverse effects were monitored closely. The Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) is a self-report measure that focuses on the last 7 days and is composed of 3 global ratings that encompass all adverse effects to study treatment.30

Study Oversight
An independent data and safety monitoring committee was composed of UNMC faculty with knowledge and experience relevant to the conduct of this study but not involved in the study as either an investigator or participating clinician. Formal interim analyses conducted by the data and safety monitoring committee reviewed the data at the 25% and 50% study completion time points.

The study was designed to have 80% power (testing at the .05 level of statistical significance [2-sided]) to detect a difference in depression rates at week 16 of 20%. Thus, assuming a 20% loss to follow-up rate, we planned to randomize 188 patients to achieve 150 patients not lost to follow-up. In this context, patients lost to follow-up were patients for whom no post-randomization follow-up observations were available. Because of slower than expected accrual, the study closed to enrollment on December 31, 2011, with 148 patients randomized and 125 evaluable.

Statistical Analysis
The stratified log-rank test was used to compare the groups on the primary end point (moderate or greater depression) defined as a QIDS-SR score of 11 or higher. A Cox proportional hazard regression model was used to compare the 2 treatment groups after adjusting for age, baseline smoking status, and stratification factors. Health-related quality of life was descriptively summarized, by treatment group at each time point, as the percentage reporting good, very good, or outstanding during the past 7 days. Patients rated their adverse effects using the FIBSER, which includes 3 questions, each with a 7-point scale. The FIBSER responses were dichotomized because of small cell counts (frequency: 0%-25% vs >25%; intensity: none, trivial, mild vs moderate, or greater; burden: none to mild impairment vs moderate or greater impairment), and differences between treatment groups were assessed using the Fisher exact test.

Results
Patient Characteristics
From January 6, 2008, to December 28, 2011, 298 patients were screened, with 160 (53.7%) agreeing to participate (Figure 1). Although patients were not specifically asked why they did not participate, 42.0% volunteered a reason. The 2 most common reasons for nonparticipation were unwillingness in tak-
ing a study medicine and lack of time. Demographics did not differ between the screened population and the randomized population.

Twelve patients (7.5%) did not meet eligibility criteria. Nine had a QIDS-SR or QIDS-C score of 11 or higher. One patient was not willing or able to return to the clinic for follow-up visits at 16 and 28 weeks. One patient was not diagnosed as having epidermoid cancer and also met criteria for MDD at baseline. The remaining patient had received another antidepressant in the prior week (Figure 1).

The demographics and stratification for the 148 patients randomized are listed in Table 1. Per protocol, patients were not evaluable if they went off study for reasons other than the study endpoint or only completed the baseline visit. Patients were considered evaluable if they had at least one visit after baseline. Sixty-five of 74 patients (87.8%) were evaluable in the placebo arm and 60 of 74 (81.1%) in the treatment arm. Reasons for dropouts other than study end point are depicted in Figure 1. Adverse effects as reported by the patients were the primary reason for dropout in 5 patients in the placebo group and 14 in the treatment group. The proportion of evaluable patients was not significantly different between the placebo and treatment arms ($\chi^2 = 1.29, P = .26$) or for the proportion who dropped out because of adverse effects ($\chi^2 = 3.39, P = .07$). Although not statistically different, there were more patients in the treatment group listing adverse effects as a reason for dropping out. Table 2 lists the responses to the FIBSER questionnaire by treatment assignment. No significant difference was found in the proportion reporting frequency of adverse effects more than 25% of the time (3.3% in the placebo group vs 8.8% in the escitalopram group; $P = .26$), the proportion reporting moderate or greater intensity of adverse effects (4.8% in the placebo group vs 14.0% in the escitalopram group; $P = .12$), or the proportion reporting moderate or greater impairment because of adverse effects (3.2% in the placebo group vs 5.3% in the escitalopram group; $P = .67$) between treatment and placebo groups. Furthermore, Table 2 indicates that 91.2% of the escitalopram groups and 96.7% of the placebo group reported adverse effects 25% of the time or less, and 95.2% and 86.0% of placebo and escitalopram groups, respectively, reported adverse effects to be of mild or less impairment. Together, adverse effects were not statistically signifi-
cantly different between the groups, although more patients dropped out of the treatment group than the placebo group. The stratified log-rank test used to compare the 2 treatment groups revealed a significant difference in depression rates (QIDS-SR score ≥11) for patients taking escitalopram compared with placebo (10.0% vs 24.6%, \(P = .04\)). The difference in depression rates between treatment assignments is 14.6% (95% CI, 1.1%-27.5%), and the relative risk reduction is 59.4% (95% CI, 3.0%-83.0%). Figure 2A compares the product limit estimates.

Table 3 lists the results of a Cox proportional hazard regression model comparing the 2 treatment groups after controlling for age, sex, baseline smoking status, study site, stage of disease, and initial treatment. The hazard ratio of 0.37 (95% CI, 0.14-0.96, \(P = .04\)) demonstrates that escitalopram was superior to placebo even after controlling for possible confounders. The only stratification variable significantly related to depression was the initial treatment for HNC. Those receiving radiation as primary treatment were more likely to reach the primary end point than those undergoing surgery (hazard ratio, 3.6; 95% CI, 1.38-9.40; \(P = .009\)). On subgroup analysis, 38.7% of placebo patients vs 13.8% of escitalopram patients who developed depression in the surgery group (Figure 2B). The number needed to treat for treatment vs placebo is 6.8. Suicidality was not reported by any participant after baseline on the suicidality module of the MINI.

Investigations of differences between treatment groups in quality of life over time revealed that patients taking escitalopram report better health-related quality of life compared with those taking placebo at each time point throughout the study (Table 4).

**Discussion**

This study has 3 important findings. First, prophylactic escitalopram reduced the rate of depression in patients with HNC undergoing treatment. Second, the rate of developing depression was significantly higher in patients receiving radiation as their primary therapy compared with those undergoing surgery. Third, those who received escitalopram reported better overall and health-related quality of life throughout the trial than the placebo group and during the 3 consecutive months after drug cessation.

Table 1. Baseline Characteristics of Randomized Study Participants by Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Participants (a)</th>
<th>Escitalopram (n = 74)</th>
<th>Placebo (n = 74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td></td>
<td>63.2 (11.3)</td>
<td>62.8 (12.5)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>59 (79.7)</td>
<td>59 (79.7)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>72 (97.3)</td>
<td>71 (96.0)</td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td>2 (2.7)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td>2 (2.7)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Smoker at baseline</td>
<td></td>
<td>16 (21.9)</td>
<td>18 (24.7)</td>
</tr>
<tr>
<td>Study site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMCC</td>
<td></td>
<td>41 (55.4)</td>
<td>39 (52.7)</td>
</tr>
<tr>
<td>UNMC</td>
<td></td>
<td>33 (44.6)</td>
<td>35 (47.3)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>17 (23.0)</td>
<td>18 (24.3)</td>
</tr>
<tr>
<td>III/IV</td>
<td></td>
<td>57 (77.0)</td>
<td>56 (75.7)</td>
</tr>
<tr>
<td>Initial treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery, not biopsy</td>
<td></td>
<td>42 (56.8)</td>
<td>39 (52.7)</td>
</tr>
<tr>
<td>Radiation with/without chemotherapy</td>
<td></td>
<td>32 (43.2)</td>
<td>35 (47.3)</td>
</tr>
<tr>
<td>Cancer site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td>29 (39.2)</td>
<td>36 (48.7)</td>
</tr>
<tr>
<td>Pharynx</td>
<td></td>
<td>25 (33.8)</td>
<td>24 (32.4)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>9 (12.2)</td>
<td>8 (10.8)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td></td>
<td>6 (8.1)</td>
<td>5 (6.8)</td>
</tr>
<tr>
<td>Sinus</td>
<td></td>
<td>5 (6.8)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Cancer type (b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td></td>
<td>65 (87.8)</td>
<td>67 (93.1)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td></td>
<td>5 (6.8)</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td>4 (5.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Abbreviations: NMCC, Nebraska Methodist Cancer Center; UNMC, University of Nebraska Medical Center.

\(a\) Data are presented as number (percentage) of study participants unless otherwise indicated.

\(b\) There are 2 missing values in the placebo group.

Table 2. Maximum Reported Frequency, Intensity, and Adverse Effect Burden as Rated by the FIBSER by Treatment Assignment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 62^{a})</th>
<th>Escitalopram (n = 57)</th>
<th>Total No.</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25% of time</td>
<td>60 (96.7)</td>
<td>52 (91.2)</td>
<td>112</td>
<td>.26</td>
</tr>
<tr>
<td>&gt;25% of time</td>
<td>2 (3.3)</td>
<td>5 (8.8)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild or less</td>
<td>59 (95.2)</td>
<td>49 (86.0)</td>
<td>108</td>
<td>.12</td>
</tr>
<tr>
<td>Moderate or greater</td>
<td>3 (4.8)</td>
<td>8 (14.0)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild or less</td>
<td>60 (96.8)</td>
<td>54 (94.7)</td>
<td>114</td>
<td>.67</td>
</tr>
<tr>
<td>Moderate or greater</td>
<td>2 (3.2)</td>
<td>3 (5.3)</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: FIBSER, Frequency, Intensity, and Burden of Side Effects Rating.

\(a\) Three participants each in the placebo and escitalopram group did not answer the adverse effects question and are not included in the denominator.
Prevention of depression in a large oncology trial has not been demonstrated previously. Only 10.0% of the patients who received escitalopram reached our depression threshold compared with 24.6% in the placebo group. This represents a number needed to treat of 6.8, similar to the number needed to treat of 7.2 that Robinson et al²³ reported for depression prevention with escitalopram in patients with acute stroke.

These findings have important implications for treatment recommendations in HNC and potentially other cancers. Determining which cancer patients will become depressed is nebulous. Social support, sex, and history of depression are all potential predictors of MDD; however, they are not consistent and are not exclusive. Because of the lack of a clear method to predict who will become depressed, the use of a prevention paradigm seems to offer considerable benefit at an acceptable risk.

Failing to identify depressed patients until they have blatant manifestations could be perilous given that patients with HNC have a risk of suicide 3 times greater than the general population and 1.5 times the risk of the average patient with...
cancer. In this study no patient exhibited suicidality. This surprising result is likely attributable to the study design whereby patients were carefully assessed every 2 weeks for the development of suicidality and depression. If either developed, the patient was removed from the study and referred to psychiatric care. This type of overview does not happen in clinical practice and suggests that prevention strategies might help reduce suicidality.

There are downsides to treating all patients with HNC with escitalopram, including the potential for adverse effects and additional costs. Adverse effects sufficient to cause withdrawal from the study were substantially more common in the treatment group. This is an important consideration for the clinician because patients in both groups cited adverse effects as the reason for dropping out, which may somewhat limit the use of this approach. Patients did not detail the specific adverse effects but merely reported the general category as the reason for study cessation. This difference likely reflects, in part, our decision to use the maximum recommended daily dose of escitalopram in this proof-of-concept trial. The common clinical use of a 10-mg dose may have been better tolerated because adverse effects are dose related. We also used a rapid ramp-up of 1 week as opposed to the common practice of 1 month. However, the burden of adverse effects was generally minor. In addition, stopping use of the drug will result in cessation of the adverse effects. Future trials or clinical use should allow more flexibility in dosing. Depression is considered to have the greatest associated disability of any medical illness and has an array of costs associated with it. Although there are many costs associated with adopting a prevention strategy for patients with HNC, the availability of low-cost generic antidepressants (including escitalopram) reduces cost as a potential barrier. The 16-week cost of escitalopram should not be a barrier because the drug is now available as a generic. A 90-day prescription of generic escitalopram ranges from $100 to $150.

This study was not designed to look at quality of life. Because quality of life was only measured in those patients continuing in the study and not in those who dropped out, it is impossible to get a full appreciation of the magnitude of difference between the 2 groups. However, overall quality of life was rated as better in the escitalopram-treated group throughout the study and achieved statistical significance during the 3 consecutive months after cessation of drug therapy. Osborn et al also observed improved long-term quality of life in a meta-analysis of psychosocial interventions in patients with cancer. Quality of life has been demonstrated as a predictor of survival in patients with HNC and thus represents an important end point. Depression has been demonstrated to lower self-care abilities, decrease quality of life, and potentially lead to increased treatment delay. The importance of maintaining and recovering quality of life is essential for healthy survivorship. The fact that improved quality of life was observed in nondepressed patients in this trial suggests a benefit to therapy that may extend beyond prevention of depression.

The mechanism by which escitalopram prevents depression is unknown. In an animal model, exposure to inescapable stress results in subsequent behavioral depression termed learned helplessness. Prophylactic administrations of selective serotonin reuptake inhibitors can prevent or decrease learned helplessness in animals. In these experiments, cortical serotonin levels and stress-induced depletion of serotonin in proportion to prevention of stress-induced depressive behavior has been seen. Thus, this may be one mechanism in humans that mitigates the onset of depression. Recent research in rodents suggests that neuritin, also known as the CPG15 gene, and the protein it encodes may be factors in chronic, unpredictable, stress-associated depression. Anti-depressant use has been reported to increase neuritin expression in the rat brain. The evidence for better overall quality of life seen after use of the study drug was stopped may reflect these long-term changes.

Treatment of HNC can be an extremely stressful process, likened to the learned helplessness model in animals. The higher incidence of depression in the cohort receiving radiation suggests that radiation represents a greater and longer duration stress event than surgery. Radiation may also generate greater inflammatory cytokines during treatment, which could contribute to the higher rate. Surgery, on the other hand, is a discreet, one-time event in which maximal morbidity occurs in one setting and typically improves from that point forward. The patient is able to begin adjusting to the mental and physical alteration immediately, lessening the stress response. Depression as the result of radiation therapy has been previously observed in patients with oral cavity cancer. The observed relationship between radiation dose and development of depression in this study suggests a direct link between radiation and depression. Even though this study was not powered to detect differences in depression rates for placebo compared with escitalopram within the surgery or radiation group, we observed that fewer patients taking escitalopram developed depression in both groups, and the difference was larger in the radiation group. The mechanism behind these differences in rate will require further investigation.

Although these findings are significant for the treatment of patients with HNC, they must be interpreted in the context of the study design. All patients came from a single group of clinicians practicing in 2 settings: an academic and a community hospital. The population served by these clinicians is essentially ethnically and racially homogenous (ie, primarily white). Replication in a broader population will address this issue.

In conclusion, this study found that prophylactic use of escitalopram is effective in reducing the rate of depression in patients undergoing HNC treatment independent of stage, sex, or primary cancer treatment modality. In addition, the quality of life of patients who continued in the trial and did not develop depression was better in those who received escitalopram for the 3 months after cessation of study drug. Finally, the rate of depression was higher in the group who received radiation as the primary modality, but the intervention reduced rates of depression in both. Adverse effects may limit the use somewhat, but the significant benefit of this approach warrants careful consideration. Prophylactic use of escitalopram should be strongly considered in patients who fit the inclusion criteria for this study. These findings deserve confirmation in a multicenter trial.
Escitalopram for Depression Prevention

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Study concept and design: Lydiatt, Schmid, Burke.

Acquisition of data: Bessette, Burke.

Analysis and interpretation of data: Lydiatt, Schmid, Burke.

Drafting of the manuscript: Lydiatt, Schmid, Burke.

Critical revision of the manuscript for important intellectual content: All authors.

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Study supervision: Lydiatt.

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Additional Contributions: This manuscript is presented on behalf of the PROTECT study team: Mary Morris, BSN, James C. Lynch, PhD, Jonathan D. Beck, PharmD, Daniel L. Lydiatt, MD, Oleg N. Militsakh, MD, Alan T. Richards, MD, Russell B. Smith, MD, Aaron M. Wieland, Katerina Goldman, PA-C, Jenellea R. Montanez, PA-C, Lora L. Dosen, BSN, Nikie Herrera, RN, Jane Hill, LPN, Sheryl Jungbluth, BSN, Danya O’Brien, RN, Nicole R. Strohman, BSN, Matthew Egbert, MD, Christopher J. Kratcchvil, MD, Ashish Sharma, MD, Jane Theobald, MD, Steven P. Wengel, MD, Paula Danekas, PharmD, Randy Rasmussen, PharmD, Barbara L. Bayer, MSN, Michi T. Bethea, BS, Deborah S. Heimes, BS, Delores A. McArthur-Miller, MA, and Rosella Squires, BS. The data safety monitoring committee was chaired by James Anderson, PhD, with Charles A. Enike, MD, Mark H. Fleisher, MD, Donald Leopold, MD, Fredrick Petty, PhD, Toby L. Schonfeld, PhD, and Weiying Zhen, MD.

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