Protocol Title: Serotonin-Neuroepinephrine Reuptake Inhibitors for the Prevention and Treatment of Pain, Depression, and Anxiety in Patients with Head & Neck Cancer
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I. Background and Significance/Preliminary Studies

The incidence of major depressive disorder (MDD) in head and neck cancer (HNC) patients is estimated to be anywhere from 15-50% compared to the 15-25% seen in patients with other types of cancer. Around 25% of HNC patients have depression prior to treatment. It has been suggested that physical disfigurement and loss of the ability to speak or swallow are contributing factors. Around 15-40% of head and neck cancer survivors report chronic pain. Patients with chronic pain are more likely to have depressive symptoms. Depression can also lead to lower quality of life, non-compliance, apathy about treatment, and suicide. A systematic review by Barber et al from Alberta, Canada showed worse overall survival in H&N cancer patients with depressive symptoms although the exact mechanism of this is unclear. Pharmacologic treatment is first-line therapy for depression.

In 2008, Lydiatt et al. conducted the first randomized, placebo-controlled trial for the prevention of depression during treatment for cancer patients. Thirty-six patients with newly diagnosed HNC were enrolled in this pilot study. Patients were initially screened using the Mini-International Neuropsychiatric Interview (MINI) depression module. Patients were randomized to receive either citalopram or placebo for 12 weeks. Patients were evaluated every 4 weeks for a total of 16 weeks. The Hamilton Rating Scale for Depression was used to determine whether or not patients developed depression. The Clinical Global Impression Severity Scale was used to determine severity of depression. The Washington Quality of Life scale was used to determine quality of life. These tests were administered at all 5 visits. By the end of the study, the patients on citalopram had a lower incidence of depression than the placebo group (17% vs 50%). The placebo group also had worse severity of depression and worse quality of life. Additionally, during a retrospective analysis of patients enrolled in this study, the authors found that patients who developed depression at any point during the study had worse overall survival than those patients who did not develop depression.

Lydiatt et al. then conducted a larger randomized, placebo-controlled trial in which non-depressed patients about to begin treatment for HNC were randomized to receive escitalopram or placebo. Patients were again initially screened using the Mini-International Neuropsychiatric Interview (MINI) depression module. The Quick Inventory of Depressive Symptomatology (QIDS) scales was administered at baseline and at weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28. 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). The study concluded that in nondepressed patients undergoing treatment for head and neck cancer, prophylactic escitalopram reduced the risk of developing depression by more than 50%. This is the only RCT that has been performed to evaluate the use of an anti-depressant to reduce rates of depression in HNC patients.

Since incidence of both depression and pain is high in patients with HNC, a medication that stabilizes mood and improves pain could be beneficial. SNRIs have been shown to treat both depression and neuropathic pain. Smith et al used a Randomized, double-blind, placebo-controlled crossover trial at 8 National Cancer Institute (NCI)-funded cooperative research networks to study the effectiveness of duloxetine at reducing chemotherapy-induced neuropathy. Patients were randomized to receive either duloxetine or placebo over a 5-week period then the study groups were crossed over. There was a two-week washout period between. Patients were assessed weekly with the Brief Pain Inventory Short Form. The duloxetine-first group reported greater decreased in pain (59% vs 38%).

There has been no previous study examining the role of SNRIs in the prevention and treatment of

depression, anxiety, and pain control in patients undergoing HNC treatment.

II. Study Aims

The purpose of this research study is to initiate a pharmacotherapy protocol for at-risk patients with newly diagnosed head and neck cancer in order to decrease the incidence of anxiety, depression, and uncontrolled pain during cancer treatment.

III. Administrative Organization

The investigators will screen their clinics for potential patients and pass this information to the study coordinator, who will reach out to the participants about the study and enrolling. Ideally, the study coordinator will be able to call the patient prior to their clinic visit to discuss the study; however, even if they are initially approached in clinic, all participants will be given at least 24 hours to consider whether or not they wish to enroll in the study, and will reminded that they may withdraw at any point, for any reason, if they so choose, without any changes to the care they are receiving for their disorder.

IV. Study Design

Participants will be randomized into either the Treatment Group or the Control Group via a computer-based algorithm. Those who are randomized to the Treatment Group will begin the study drug at that visit. They will have telephone visits with a study coordinator over the next 3 weeks as the dose of the study drug is titrated per its package insert to the desired level of 300 mg/day (taken as 150 mg/day). Those participants with kidney or liver impairment will be dosed accordingly, as per the package insert instructions. Participants will be asked to complete a daily medication diary.

All participants will have study visits at Week 6, Month 6, Month 9, and Month 12. These research visits will be scheduled to coincide with their standard of care visits - we will not ask them to come for research-only visits. They will complete the study procedures as outlined in Section 8.1 of the study protocol. All participants will have adverse events and concomitant medications reviewed, and will complete the study questionnaires, and those in the Treatment Group will have their medication diary reviewed and will have a pill count of the study drug for medication reconciliation.
Study questionnaires will be given to participants via paper forms, which they will complete and give back to the study coordinator.

V. Study Procedures

Participants will be enrolled for 12 months. Baseline visit will take approximately 75 minutes. Visits at Week 6, Month 6, Month 9, Month 12 will take approximately 45 minutes each. Those who are randomized into the Treatment Group will have telephone visits at Weeks 2, 3, and 4, which will take approximately 15 minutes.

VI. Risks and Benefits

Common side effects from previous clinical studies include: nausea (30.0%), somnolence (15.3%), dry mouth (14.8%), sweating (11.4%), abnormal ejaculation (9.9%), anorexia (9.8%), constipation (9.3%), impotence (5.3%) and decreased libido (5.1%).
A major potential benefit of the study is optimizing management of mood disorders in patients who are at-risk for developing moderate or severe depression and anxiety. By initiating medication to

patients who are not yet meeting criteria for moderate or severe depression, our goal is to prevent major depression and anxiety during treatment. Another benefit of this study is the increase in knowledge we will obtain from initiating pharmacotherapy to patients who are already showing signs of moderate to severe depression. Since we will recommend initiation of pharmacotherapy and referral to counseling for all patients who demonstrate moderate or severe depression, we will better understand our ability to intervene and the effects of that intervention. This is the first study, to our knowledge, that will utilize a serotonin-norepinephrine reuptake inhibitor to assess its efficacy in preventing depression and pain in patients undergoing treatment for head and neck cancer. The knowledge we gain from this study will add to the growing understanding of mood disorders in patients with head and neck cancer in order to appropriately and effectively provide quality and effective care.