

# Buspirone for Functional Dysphagia - Protocol

## Introduction

Functional Dysphagia has been defined by the Rome Criteria as a syndrome in which patients report symptoms of dysphagia without evidence of GERD and without any histopathology-based esophageal motility disorder. (Rome Criteria) Ineffective Esophageal Motility is a manometric diagnosis (based on the Chicago Classification) without a histopathology correlate which has been shown to cause dysphagia. (Kahrilas, PJ) Data related to treatment of this disorder are limited. Buspirone is a serotonin modulating anxiolytic and antidepressant medication with a reliable safety profile, which has been shown to improve esophageal motility. (Blonski W) We plan to perform a prospective randomized double-blind crossover style placebo controlled trial of the effect of buspirone on patients with functional dysphagia and ineffective esophageal motility.

## Background and Significance

Functional Dysphagia has been defined by the Rome Criteria as a syndrome in which patients report symptoms of dysphagia without evidence of GERD and without any histopathology-based esophageal motility disorder. (Rome Criteria) Ineffective Esophageal Motility (IEM) is a manometric diagnosis (based on the Chicago Classification) without a histopathology correlate which has been shown to cause dysphagia. (Kahrilas, PJ)

While the etiology of functional dysphagia is widely debated, there are data that argue that ineffective esophageal motility is the manometric correlate of functional dysphagia. In a study of about 200 patients, Roman, et al. showed that patients with history of dysphagia without any other structural abnormalities were 3-6 times more likely to have ineffective esophageal motility. (Roman S 2011). Furthermore, the prevalence of IEM in functional dysphagia increases with age and has been found to be up to seven times as high in patients above the age of 70 compared to patients below 70. (Ratuapli, SK)

IEM may also be partially responsible for the pathogenesis of Gastro-esophageal Reflux Disease (GERD) because of poor acid clearance from the esophagus. (Martinucci I et al, Ribolsi M et al, Savarino E et al, and Fouad YM et al).

Data about treatment of IEM are limited. Bethanechol has been tested in this patient population. Agrawal, et al studied seven patients diagnosed with IEM were treated with 50 mg of bethanechol before repeat manometry was performed by providers who were blinded to the experiment. Bethanechol in this population caused an increase in the contractility of the esophagus as well as complete bolus clearing. (Agrawal A) In addition, one study showed that buspirone, pyridostigmine, or bethanechol administration in healthy volunteers causes enhances contractility in the distal esophagus. (Blonski W)

While there are no data which have studied medical management of functional dysphagia, functional gastrointestinal disorders of the upper gastrointestinal tract have been treated extensively with antidepressants and anxiolytics, especially buspirone. Functional dyspepsia, for example, is a disorder of gastric motility without histopathologic abnormality on endoscopy. A double-blind randomized controlled crossover style trial of buspirone in this disorder showed increased gastric accommodation, which was correlated with symptom improvement in patients with functional dyspepsia. (Tack J) There are no consensus guidelines for the treatment of functional dysphagia or ineffective esophageal motility. However, various experts argue for the utility of antidepressants and anxiolytic medications for treatment of these disorders. Dr. Ronnie Fass, Chairman of the Functional Esophageal Disorders Committee for Rome Criteria IV, says, "...antidepressants are likely to remain the mainstay of treatment of functional esophageal disorders..." (Weijenborg RA et al and Maradey-Romero C)

Based on the above observations, we suspect that patients with IEM treated with buspirone will experience improvement in esophageal motility, dysphagia, and GERD.

## Study Design

### Methods

Randomized Double-Blind Crossover Placebo controlled prospective trial

### Sample

Inclusion Criteria: >18 years old, diagnosis of IEM, negative EGD or barium swallow, biopsies negative for EOE

Exclusion Criteria: Have not had any changes to serotonin modulating medications over the last 6 weeks

This is a cross-over style study and all participants will be both studied in the treatment and control arms.

Previous studies have shown up to a 100% improvement in baseline manometric findings in patients treated with buspirone. We hope to show at least a 25% difference with a  $p < 0.05$  and power 0.8. To show this effect, we will need 15-20 patients (depending on the standard deviation of the specific marker being tested).

### Research Procedures – Define the data to be collected to answer the hypothesis/research question(s)

Nurses at the Swallowing Center facilitate the final read by a licensed physician of all manometries performed here. For every patient diagnosed with functional dysphagia and IEM who meets the inclusion and exclusion criteria, the nurses will notify the investigators. Review of electronic charts for all patients undergoing manometry is part of the routine medical practice and responsibility of the nurses. The nurses will also seek the patient's permission to be contacted to hear about the details of an ongoing study related to their diagnosis.

Once the investigators are notified of this diagnosis, one of the investigators will contact the patient to discuss the logistics of the study as well as obtain informed consent. After informed consent is obtained, patients will be randomized to either group A or group B. Both patients and investigators will be blinded to the assignment.

All patients will be administered a Mayo Dysphagia Questionnaire as well as a validated GERD questionnaire. Subsequently, all patients in Group A will receive placebo and Group B will receive buspirone administered by pharmacy.

After two week of treatment, all patients will undergo repeat administration of questionnaires as well as assessment of side effects. They will also undergo repeat manometry. All participants will be reimbursed with \$100 for travel expenses.

Subsequently, all patients will be treatment free for a washout period of two weeks.

Patients in Group A will then be treated with buspirone and Group B will be treated with placebo for two weeks followed by repeat questionnaires and manometry. All participants will be reimbursed with another \$100 for travel expenses.

All participants will be contacted by phone one week after they start their treatments to assess for tolerability and side effects related to the medication.

The two interventions that are part of the study are buspirone as well as the two subsequent manometries. Both costs will be incurred by the investigators.

### Data Analysis

Descriptive statistics will be computed for all variables. This includes means, standard deviation and percentiles for continuous variables and frequencies and percentages for categorical factors the t test and odds ratio will be calculated for comparison. All analyses will be performed using SAS (version 9.2, The SAS Institute, Cary, NC).

The analysis will be completed by one of the investigators.

### Adverse Events and Data Monitoring Committee(DMC)

This project does not require an independent DMC or DSMB because this is an open-label intervention looking solely at symptom/sign changes related to buspirone.

After two weeks of being on the medication, each patient will be questioned about his/her baseline symptoms, new symptoms, and any side effects related to the medications (specifically the common side effects of buspirone).

All Adverse Events will be reported to the IRB using the Adverse Event Form.

### Consent

The consent interview will take place in private patient rooms at the Swallowing Center.

The consent interview will take place after patients are diagnosed with functional dysphagia or IEM. One of the investigators will discuss the study in detail and answer all questions. The patients will then be provided the opportunity to sign the consent or take time to think about the study before signing or rejecting the study.

The consent will be documented on the informed consent form attached with the application.