Physiology of GERD and Treatment Response

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Summary of Revisions Made: Blood draw added

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Summary of Revisions Made: Added Study Pages & Epic lists as recruitment options
Added Physician Satisfaction Questionnaire
Added option to conduct visit 2 remotely

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Summary of Revisions Made: Added the additional option of using a video telehealth platform to conduct study visits.
Added Appendix B.3 COVID-19 symptom screening.
Added Appendix D.14 Impressions of the Study Physician Questions
Modified Appendix E: Standard and Expanded Visits Scripts6
Modified B.1 Telephone Pre-Screening Script
Added another option for Provider Study Flyer

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Summary of Revisions Made: Added the option of reviewing patients' pH study results in EPIC in order to identify potentially eligible study subjects as part of the recruitment approach.

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Summary of Revisions Made: Adjusted eligibility age to include any adults from ages 24 to 70.

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PRÉCIS

Study Title: Physiology of GERD and Treatment Response

Objectives

Primary Aim: To determine in a randomized controlled trial (n=60) whether an expanded, compared to a standard, provider visit can augment the effects of a medication targeting traditional or functional GERD symptoms.

Secondary Aims:

1. To identify physiologic markers of enhanced therapeutic relationships.
2. To identify patient and physician behaviors associated with GERD symptom improvement.

Design and Outcomes

This is a randomized controlled trial to assess the physiologic and behavioral mechanisms associated with augmented medication effects in adult patients with functional GERD-related symptoms.

Subjects will be randomized to receive one of two different semi-scripted visit types – either a "standard visit" modeled after an empathic, conventional primary care evaluation or an "expanded visit" modeled after an integrative medicine consultation. During the visit, we will measure heart rate variability (HRV) and galvanic skin response (GSR) in the patient-provider dyads; in addition, we will video record the interactions for later

analysis of behavioral responses. Subjects will receive a two-month supply of amitriptyline (10 mg/day) or omeprazole (20 mg/day, depending upon the nature of their GERD symptoms), along with instructions for taking it. Following the visit, subjects will complete questions assessing their relationship/rapport with the study provider. Subjects will complete a daily GERD symptom diary during the first and eighth weeks of the study. At the end of the 8-week observation period, they will complete follow-up measures of GERD symptom severity and quality of life.

Interventions and Duration

Subjects will have a single visit with a "study provider," a physician or nurse practitioner who they have never previously met. Subjects will complete a daily symptom diary for the 1st and 8th weeks following this visit and return for a second study visit in which they will complete questionnaires and be debriefed by a member of the study team.

Sample Size and Population

We plan to enroll 60 subjects with functional GERD, age 24-70 with heartburn symptoms 3 or more days per week. Thirty subjects will be randomized to the expanded visit intervention and 30 subjects will be randomized to the standard visit intervention (1:1 expanded vs. standard randomization). We will also enroll approximately 5-6 physicians or nurse practitioners and stratify randomization by study provider such that each provider will see 10-12 subjects (5-6 expanded visits and 5-6 standard visits).

1. STUDY OBJECTIVES

The patient-provider relationship is central to the art of medicine and affects a range of health outcomes. However, the specific benefits, and exact mechanisms, by which this relationship supports the healing process is poorly understood. Emerging data suggests that physiologic biomarkers such as galvanic skin response (GSR) and heart rate variability (HRV) are associated with empathy and correlated with the complex verbal and non-verbal behaviors of patients and providers during an encounter. Physiologic synchrony in patient-provider dyads and supportive non-verbal behaviors may be associated with subsequent health outcomes. This study will test these hypotheses using GERD as a model condition.

1.1 Primary Objective

To determine in a randomized controlled trial whether an expanded, compared to a standard, provider visit can augment the effects of a medication targeting functional GERD symptoms.

1.2 Secondary Objectives

1. To identify the physiologic responses/markers associated with improvement in GERD symptom severity in response to an enhanced vs. standard provider visit and amitriptyline or omeprazole.
2. To determine whether an expanded patient-provider visit modeled after an integrative medicine consultation leads to more supportive provider behaviors, an enhanced patient-provider interaction, and greater improvements in GERD symptom severity compared to a standard provider visit.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

The patient-physician relationship is central to the art of medicine[1,2]. The quality of this relationship affects a range of health outcomes, from irritable bowel[3] and cold symptoms[4] to blood pressure, pain levels, and diabetes outcomes[5–8]. However, the specific benefits, and exact mechanisms, by which this relationship supports healing remain poorly understood. Previous work has demonstrated that when providers maintain eye contact, actively listen, and express empathy, their patients improve more after receiving a placebo than patients receiving care from apparently more detached providers[3,4]. Though studies have suggested a role for communication skills and both cognitive and emotional components of empathy, the variety of measures used and lack of clarity in definitions have limited the interpretation of this work[5,6,9,10].

In most conventional medical settings, practice demands have resulted in reduced time to focus on relational aspects of care. Concomitantly, medical educators and professional societies have called for greater emphasis on humanism, patient-centered care, and improved patient-provider communication[11,12]. Indeed, patients are frequently stressed/in distress when they visit a physician[13]. Perceived lack of time and anxiety about the visit likely contributes to this stress, one manifestation of which is white coat hypertension[14].

The public has become increasingly interested in complementary and integrative medicine (IM) healing approaches in which patient-provider dynamics often differ substantially from most conventional medical visits[15–19]. IM providers frequently spend more time with patients and ask questions that are quite different from those asked during conventional visits. The IM consultation process may produce enhanced placebo effects[19]. It is unclear whether these effects represent a form of interpersonal healing[20], an enhanced patient-provider relationship (e.g., increased perceived empathy or trust), or simply provide patients with the opportunity to reflect on their symptoms in a safe and non-judgmental space (a form of therapeutic narrative medicine[21]) creating an openness to perceiving symptoms differently and enhancing coping[22]. Some patients feel "more heard" by IM providers[23]. IM providers may make patients feel more "at ease" and relaxed, promoting a physiologic response (e.g., reduced heart rate and blood pressure) similar to that elicited by meditation and other mind body techniques[24]. Feeling less stressed during a medical visit may create an openness to change and improved memory of, and follow-through with, the provider's recommendations[25]. Yet there are few studies of these interactions and they largely rely upon patient interviews or responses to surveys[15–18].

Gastroesophageal reflux disease (GERD) is one of the most prevalent health-related conditions in the Western world with prevalence estimates ranging from 20-40%[26,27]. GERD is primarily a clinical diagnosis, characterized by symptoms of heartburn and acid reflux. It is associated with decreased health-related quality of life and significant healthcare costs and lost productivity[28,29]. Standard treatment includes antacids, H2 receptor blockers, and proton pump inhibitors (PPIs), with the latter

generally regarded as the most effective of these therapies and is generally used as an initial treatment for patients who first present with GERD symptoms. Nonetheless, many patients experience continued symptoms despite taking PPIs[30]. Many patients who do not find relief with PPIs have functional heartburn symptoms and/or co-occurring dyspepsia symptoms (e.g., upper abdominal discomfort, bloating, and gas) that do not respond well to this class of medication[31,32]. Moreover, awareness of the interconnections between the central nervous and gastrointestinal systems has led to the recognition that stress can profoundly affect gastrointestinal (GI) symptoms, such as GERD[33], suggesting that interventions targeting these pathways may improve symptoms[34]. Notably, the placebo response rate in trials of GERD medications can be as high as 40%[35].

Many individuals with GERD symptoms who do not respond to PPIs have functional heartburn which is defined as less than 4% acid exposure on pH manometry and esophageal hypersensitivity[36,37]. These patients respond better to neuromodulators such as tricyclic antidepressants, serotonin reuptake inhibitors, gabapentin, and other agents.

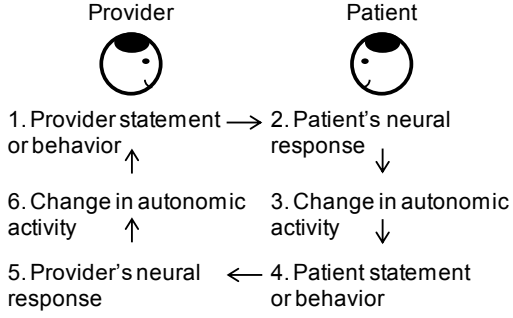
Amitriptyline is a tricyclic antidepressant originally used to treat depression but now frequently prescribed in low doses to treat functional GERD-related symptoms as well as functional dyspepsia, irritable bowel, fibromyalgia, and interstitial cystitis as well as other pain-related conditions[36,38].

Omeprazole is a PPI that is used as a first line treatment for patients who initially present with GERD symptoms.

2.2 Study Rationale

Studies are beginning to reveal the neural correlates of empathy, both in general[39] and in patient-provider relationships[40,41]. Activation of specific neural pathways drives changes in autonomic nervous system regulation[42], resulting in downstream changes in physiologic biomarkers such as galvanic skin response (GSR) and heart rate variability (HRV)[43,44]. A growing body of research has identified concordance in physiologic biomarkers between individuals. An excellent review of this topic, also known as "interpersonal autonomic physiology" or "physiologic synchrony," has been published[45]. The authors reviewed 61 studies covering relationships between therapist and client, couples, mother and child, teammates, and other relationships. There were 8 studies of the therapist-client relationship which examined either heart rate (HR) or skin conductance/galvanic skin response (GSR). Multiple studies found positive correlations between empathy ratings and physiologic synchrony. The study I have proposed would be the first to examine physiologic biomarkers in the context of physician-patient interactions in a medical setting.

Figure 1: Proposed model for mechanisms underlying the patient-provider relationship



As illustrated in Figure 1 above, we hypothesize that moment-to-moment autonomic changes in patients and providers over the course of a visit collectively influence perceptions of the encounter (part of the "neural response") and response to treatment and that improved treatment response is associated with increased concordance in these autonomic changes.

GSR and HRV can also be used to assess relative physiologic stress vs. relaxation[46]. Typically GSR and HR decrease and high frequency HRV increases in the relaxed state[24,47,48]. While empathic visits may theoretically reduce patients' allostatic load and distress[49], this hypothesis has not been studied rigorously. Newer computational approaches incorporating complexity theory to the analysis of physiologic data[50] have yielded valuable insights to the study of human disease (e.g., decreased HRV is associated with increased cardiovascular mortality[51,52]) and the effects of integrative modalities such as tai chi[53,54]. There is limited data using these approaches to study client-therapist interactions[55–57].

Social psychologists have developed and validated a variety of coding schemes to analyze providers' verbal and non-verbal behaviors and to link these behaviors with patient satisfaction, understanding, trust, rapport, empathy, and a variety of related factors[9,58–63]. This rich literature has yielded many insights and a variety of tools used in studies of physician-patient communication, but rarely have these tools been linked with physiology or health outcomes[7].

Dr. Dossett recently observed that an "expanded" provider visit modeled after a visit to an IM provider was more effective in decreasing heartburn and dyspepsia symptoms in patients with GERD than a "standard" provider visit modeled after an empathic conventional medical visit[64]. This study used a script of pre-determined questions for each visit type. The standard visit script included questions about GERD history, symptoms, prior evaluation and treatments, and past medical history. The expanded visit script included the same questions plus additional questions that inquired about their GI symptoms, non-GI symptoms, and overall temperament. Thus, the main differences between the visits were the length of time spent with the subject and the additional questions that were asked. Many of the subjects in this study were already taking pharmaceutical medications for GERD, suggesting that symptom improvement resulting from the expanded provider visit may enhance the efficacy of some medications in providing adequate symptom relief. We intend to formally test this hypothesis, that augmented patient-provider visits can enhance medication-related benefits, in this current study.

While some may argue that increasing visit length is impractical in conventional healthcare settings, one reason why payers will not adequately reimburse for increased visit lengths is the lack of data linking visit length with health outcomes. Increased visit length has been associated in clinical practice with reduced number of prescriptions and increased patient satisfaction, engagement, and quality of care[65–67]. Other studies suggest mechanisms by which provider communication (verbal & non-verbal) may affect health outcomes[68]. Yet we really do not know what makes longer visits more effective. By better understanding the mechanisms that make the expanded visit intervention effective, we will be able to make informed decisions

regarding future changes to this intervention and adaptations that may make it more feasible in today's healthcare environment.

3. STUDY DESIGN

Study design: Single-center, single-blind, randomized controlled trial

Primary outcome:

1. Change in the average daily GERD symptom severity score from baseline to the last week of the study in the expanded vs. standard group. GERD symptom severity is based on the sum of scores assessing the severity of daytime heartburn, nighttime heartburn, and acid reflux each on a 0-4 point scale (none, mild, moderate, severe, very severe; higher scores signify worse symptoms).

Secondary outcomes:

1. Ratio of the sum of positive correlations over the sum of negative correlations in GSR (or HRV) across patient-provider encounters for standard vs. expanded visit types and for responders vs. non-responders (those with a 50% or greater improvement in their GERD symptom severity).
2. Absolute change in GSR (or high frequency HRV signal) in patient recordings from the beginning of the study visit to the end of the study visit and correlation with subsequent change in GERD symptom severity.
3. Differences in blinded ratings of 2 minute thin slices of study visit videos from the beginning to the end of the study in supportive global impressions (e.g., engagement, relaxed, patient seems pleased/satisfied) and non-verbal behaviors (e.g., smiling) between standard and expanded visit types and correlation with subsequent change in GERD symptom severity.

Study population:

Men and women age 24-70 with heartburn symptoms 3 or more days per week not responsive to proton pump inhibitors or with known functional heartburn. We will enroll until we reach 60 completing subjects.

Study location:

University of California Davis Medical Center

Length of subject participation: 8 weeks

Length of study enrollment: 2 years

Groups:

1) Standard visit (n=30), modeled after an empathic, high quality conventional primary care visit.

2) Expanded visit (n=30), modeled after a visit with an integrative medicine provider

Randomization:

The randomization code will be generated by the study statistician as described below (sections 4.3 and 9.2). The study will be single-blinded (study providers and the research team will know what the subject is receiving but the subject will not). Randomization will be stratified based on study provider. We anticipate 5 or 6 providers each seeing 10-12 subjects (5-6 standard visits, 5-6 expanded visits).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Research subjects eligible to receive amitriptyline must meet all of the following inclusion criteria to participate in the study:

- Adults ages 24-70 years old (rationale: population of interest, GERD frequency increases with age; amitriptyline is not recommended in older adults and may have increased risk of suicidality in adults younger than 24)
- Functional heartburn (defined as <4% of time with reflux on 24 hour pH manometry) symptoms 3 or more days per week with an average daily symptom severity of 3 or more on a 7-day baseline symptom diary (see section 6.2.2 for description of instrument; rationale: subjects must be symptomatic enough that improvement in symptoms is detectable. This threshold is similar to that seen in my pilot study[64]).
- English language proficiency (rationale: feasibility)
- Willingness to be videotaped and connected to physiologic monitoring devices during the visit (rationale: feasibility/study procedures)
- Willingness to take amitriptyline daily for 8 weeks following study visit 1 (rationale: feasibility/study procedures)

Research subjects eligible to receive omeprazole must meet all of the following inclusion criteria to participate in the study:

- Adults age 24 and older
- Heartburn symptoms 3 or more days per week with an average daily symptom severity of 3 or more on a 7-day baseline symptom diary
- English language proficiency
- Willingness to be videotaped and connected to physiologic monitoring devices during the visit
- Willingness to take omeprazole daily for 8 weeks following study visit 1

4.2 Exclusion Criteria

Any candidates eligible to receive an 8-week supply of amitriptyline meeting any of the following exclusion criteria at baseline will be excluded from study participation.

- Diagnosis of Crohn's disease, systemic sclerosis, known active ulcer disease, gastric cancer, or untreated/active Barrett's esophagitis based on subject self-report and/or medical record review (rationale: heartburn symptoms may be due to another, more serious medical illness)

- Heavy alcohol use (> 6 drinks/week for women and > 13 drinks/week for men) based on subject self-report (rationale: can exacerbate heartburn symptoms)
- Pregnant, attempting to become pregnant, or breast-feeding (rationale: feasibility/medical safety - amitriptyline is not recommended in pregnancy or breast-feeding and the physiology of heartburn is different in pregnant women).
- Dementia or significant memory difficulties as determined by the study team and medical record review (rationale: feasibility and human subjects concerns)
- Severe, unstable psychiatric disease based on subject self-report, study team determination, and/or medical record review (rationale: feasibility and human subjects concerns)
- Bipolar disorder, concurrent treatment with a SSRI or another antidepressant that interacts with tricyclic antidepressants (rationale: medical safety)
- Prolonged QTc or severe heart disease (rationale: medical safety – amitriptyline can prolong cardiac conduction).
- History of seizure disorder (rationale: medical safety – amitriptyline can lower the seizure threshold).
- Severe liver impairment – e.g., cirrhosis, hepatocellular carcinoma, hepatitis (rationale: medical safety, not recommended in patients with hepatic impairment).
- Currently taking a tricyclic antidepressant, allergy to tricyclic antidepressants, or another medical contraindication to taking amitriptyline or related medications (rationale: safety and feasibility).
- Greater than 15 doses of nonsteroidal anti-inflammatory drugs (NSAIDS) within the prior 30 days (aspirin ≤ 325 mg daily permitted) or ongoing NSAID use at a level deemed likely to interfere with the study (rationale: NSAIDS can exacerbate GERD and cause peptic ulcers)
- Failure to complete the baseline symptom diary for at least 6 of 7 days (rationale: feasibility)
- Change in GERD treatment regimen within the last 2 weeks (subjects may use antacids, H2 receptor blockers, and/or proton pump inhibitors as long as they are symptomatic on a stable regimen; rationale: feasibility, need a stable symptom baseline)
- Allergy to adhesives (rationale: feasibility/study procedures)
- Inability to provide informed consent (rationale: human subjects concerns)
- In the opinion of the investigator, unable to comply with the study protocol or has a condition that would likely interfere with the study (rationale: feasibility)

Any candidates eligible to receive an 8-week supply of omeprazole meeting any of the following exclusion criteria at baseline will be excluded from study participation.

- Diagnosis of Crohn's disease, systemic sclerosis, known active ulcer disease, gastric cancer, or untreated/active Barrett's esophagitis based on subject self-report and/or medical record review (rationale: heartburn symptoms may be due to another, more serious medical illness)
- Concurrent treatment for H. pylori infection (rationale: treatment for H. pylori may resolve heartburn symptoms)
- Heavy alcohol use (> 6 drinks/week for women and > 13 drinks/week for men) based on subject self-report (rationale: can exacerbate heartburn symptoms)
- Pregnant, attempting to become pregnant, or breast-feeding (rationale: feasibility/medical safety - the physiology of heartburn is different in pregnant women and omeprazole may not be safe during breast-feeding).
- Dementia or significant memory difficulties as determined by the study team and medical record review (rationale: feasibility and human subjects concerns)
- Severe, unstable psychiatric disease based on subject self-report, study team determination, and/or medical record review (rationale: feasibility and human subjects concerns)
- Greater than 15 doses of nonsteroidal anti-inflammatory drugs (NSAIDS) within the prior 30 days (aspirin ≤ 325 mg daily permitted) or ongoing NSAID use at a level deemed likely to interfere with the study (rationale: NSAIDS can exacerbate GERD and cause peptic ulcers)
- Currently taking a medication that is contraindicated with omeprazole treatment (e.g., acalabrutinib, cefuroxime, dacomitinib, dasatinib, delavirdine, erlotinib, infigratinib, pazopanib, pexidartinib, rilpivirine, sotorasib, and strong CYP2C19 inducers)
- Allergy to a proton pump inhibitor
- Failure to complete the baseline symptom diary for at least 6 of 7 days (rationale: feasibility)
- Change in GERD treatment regimen within the last 2 weeks (subjects may use antacids, H2 receptor blockers, and/or proton pump inhibitors as long as they are symptomatic on a stable regimen; rationale: feasibility, need a stable symptom baseline)
- Allergy to adhesives (rationale: feasibility/study procedures)
- Inability to provide informed consent (rationale: human subjects concerns)
- In the opinion of the investigator, unable to comply with the study protocol or has a condition that would likely interfere with the study (rationale: feasibility)

4.3 Study Enrollment Procedures

Patient Recruitment*:*

Initial recruitment efforts will start with the UC Davis Gastroenterology Clinic, and in particular, the motility disorders group. We will review scheduled patient visits and results from pH studies performed at the Midtown GI Clinic in EPIC. Patients identified as having typical GERD symptoms who have not yet tried a PPI or esophageal hypersensitivity will be contacted by Dr. Garcia or their UCD gastroenterologist regarding their results and this study. The research team will contact the patient about the study only if the patient expresses interest and gives permission to the gastroenterologist to be contacted by the research team. If Dr. Garcia is unable to reach the patient by phone, we will send the patient a letter in the mail or a MyChart message to inform them of the study.

Clinicians will also have copies of flyers they can hand to patients and the study research coordinator may also meet with some patients directly in the clinic. Study flyers may also be posted within the clinic. We may also recruit from primary care clinics. If a patient is interested in learning more about the study, they may request additional information during their appointment or may call the phone number on the flyer. Providers may also obtain verbal permission to give their prospective subjects' contact information to a study staff member who can provide further details about the study. This information may be shared with study staff in the form of an Epic patient list. We will also recruit using Study Pages and may use similar electronic recruiting platforms.

We will also recruit patients from the UCD Otolaryngology Reflux Clinic using procedures similar to those described above.

Patient Screening*:*

Potential subjects will undergo a telephone or in person prescreen by study staff and have the opportunity to ask questions about the study (see telephone script). Potential subjects will be informed that the study involves taking amitriptyline or omeprazole (depending upon their diagnosis and treatment plan with their physician) daily for 8 weeks. Assuming the potential subject receives care at UC Davis, their medical record will be reviewed as part of the eligibility assessment. A standardized form (see attached) will be used to ascertain potential eligibility and an electronic screening log will be kept to keep track of reasons for ineligibility. Those who are deemed potentially eligible and are interested in participating will be sent a 7 day baseline symptom diary (by email or via the post office) and scheduled for a baseline visit and 8 week follow-up visit. Potential subjects will be mailed a copy of their medication list and asked to update it or bring a complete list of medications, vitamins, herbs, and supplements that they are taking to the baseline visit. Potential subjects will be called several days after the diary is mailed to ensure that they received it and that the instructions for completing the diary are clear. One day prior to the scheduled study visit, potential subjects will also be called and screened for COVID-19 symptoms/exposure to ensure the safety of the study staff and other employees of UD Davis Health.

Baseline Visit and Consent*:*

At the first study visit, the baseline symptom diary will be reviewed by a study team physician (one of the study investigators) and potential subjects will be rescreened. If

they are deemed eligible, they will have an opportunity to review the written informed consent document, ask any questions, and will be consented by a study team physician. The consent process will include a discussion of the risks and benefits of taking amitriptyline or omeprazole (whichever medication is most appropriate to their condition).

To avoid alerting subjects to the fact that we are directly studying the effect of the patient-provider relationship on health outcomes (which could influence study results[69,70]), subjects will be told during the consent process that 1) we are studying the relationship between their symptoms, their physiology, and their response to amitriptyline or omeprazole and 2) we are studying whether physicians mirror patients' physiology as has been suggested by some neuroimaging studies[40,71] (to explain why providers are being similarly monitored). While it is challenging to study patient-provider interactions without subjects' direct knowledge, particularly since both are being monitored in this study, we believe that framing the study in this way is the most sensible way to proceed and the least likely to substantively affect the study's results. As the standard vs. expanded visit intervention is minimal risk, we believe it meets the federal criteria for modification of informed consent[72], which allows us to conceal from participants that we are studying the patient-provider interaction.

Individuals who sign the informed consent document and elect to participate in the study will be considered enrolled. Only individuals who can provide informed consent will be eligible to participate.

Provider Recruitment and Screening*:*

We will advertise the study to primary care internal medicine and family medicine physicians and nurse practitioners via email. We may also recruit providers from the division of gastroenterology. We may also present the study at practice group meetings. Providers must be willing to adhere to the study protocol and not provide specific treatment recommendations (pharmacologic or non-pharmacologic) as this is outside the scope of the study. Providers must also be willing to receive a brief training to understand how to deliver the standard and expanded visit interventions.

Provider Consent*:*

Participating providers will be consented by the study PI. As study providers will deliver both visit interventions, they will be trained in both visit type formats. Providers will be notified of which intervention they are delivering immediately before walking into the room to conduct the study visit.

Randomization:

Once enrolled, subjects will be randomized to receive either the standard visit intervention (n=30) or the expanded visit intervention (n=30). They will not know that there are two possible visit choices. This aspect will be revealed to subjects during a debriefing at the follow-up visit at the end of their participation in the study. We will stratify by provider and create permuted block sizes of 2 and 4 with the intent to enroll 5-6 providers who will each see 10-12 subjects. If a provider cannot commit to this many

visits, the study biostatistician may need to adjust the randomization scheme and we will consent additional providers.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Subjects will be randomized to receive either a "standard visit" or an "expanded visit" with a study provider. The standard visit is based on a high quality, empathic, conventional primary care encounter. The expanded visit is based on an integrative medicine consultation. Both visits are based on a script of questions and statements to the patient/subject (see Appendix E). The standard visit script includes questions about GERD history, symptoms, prior evaluation and treatments, and past medical history as well as a brief physical exam. The expanded visit script includes the same questions as the standard visit script plus additional questions that inquire about the modalities of their GI symptoms (e.g., nature of the reflux taste, sensation of heartburn pain and/or abdominal fullness, time of day better/worse), details about non-GI symptoms, quality of sleep, the effect of the weather on symptoms, food cravings and aversions, menstrual flow, fears/phobias, and overall temperament. In this way, the expanded visit tries to understand the patient's/subject's constitution in a way that many systems of integrative medicine attempt to do. To reduce the potential for introducing bias by using the words "standard" and "expanded", the visit templates that the study providers will follow will simply refer to the number of questions to be asked on the template (e.g., 6 Question Template).

At the end of both the standard and expanded visits, the provider will recommend the subject take the study medication and describe how to take it and what to expect. Subjects will receive the same scripted advice in both groups. Each subject will receive an 8-week supply of amitriptyline or omeprazole with instructions for how to take it (10 mg daily at bedtime or 20 mg daily when waking up, respectively).

In our pilot study[64] we did not limit the amount of time spent with the study subject. On average, the standard visit lasted 18 minutes (range 11-32 minutes) and the expanded visit lasted 42 minutes (range 23-74 minutes). The study providers will be instructed to maintain equal empathy in both groups (e.g., kind and friendly manner, maintain eye contact, active listening and repeating back the patient's words, expressions of empathy). Thus, the main differences between the visits will be the length of time spent with the subject and the additional questions that are asked.

Each study provider will participate in an orientation session to learn how to deliver the standard and expanded visit interventions. Providers will be explicitly instructed not to offer lifestyle treatment advice for GERD to maintain uniformity of the intervention across providers. The study PI will review video recordings of the interactions to offer feedback to study providers and ensure protocol fidelity. As each study provider finishes his/her portion of the study, the PI will interview them to understand their experiences of the study, the two visit types, and their views on the doctor-patient relationship.

5.2 Handling of Study Interventions

To minimize potential bias that could affect study staff interactions with subjects, the subject will be randomized immediately before the study visit and the study provider will receive the appropriate study visit script. At the time of consent, study subjects will not be informed about the two different interview types or that part of the study involves testing the effect of the doctor-patient interaction on response to treatment. Concealment of these aspects of the study protocol is essential to maintaining the validity of the study as data suggests that patients' responses change when they know that the doctor-patient interaction is being studied[69,70]. The study PI, or another study team member, will notify subjects at their follow-up study visit, after the exit interview, that there were two possible types of physician visits, that this aspect of the study was concealed from them initially, and of the rationale for doing so. A script outlining this planned debriefing is present in Appendix F. We believe that this intervention is minimal risk and that our plan meets the federal criteria for permitting alteration of some elements of informed consent[72].

Subjects will be informed about taking amitriptyline or omeprazole as part of the study during the consent process and the study physician will discuss this with them during the study visit. Subjects will receive a container with an 8 week supply of the medication from a study team member at the end of the study visit.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Subjects are permitted to remain on all baseline medications, over-the-counter products, and dietary supplements, including those used to treat GERD symptoms during the study. We will request that they not change doses of medications used to treat GERD symptoms during the 8 weeks that they are enrolled in the study.

5.3.2 Required Interventions

Amitriptyline 10 mg or omeprazole 20 mg daily for 8 weeks.

5.3.3 Prohibited Interventions

We will ask subjects not to increase their dose of GERD medications, add additional GERD medications, or change their GERD treatment regimen (with the exception of introducing amitriptyline or omeprazole) during the study. This will be monitored via the daily symptom diary and a follow-up visit medication review.

5.4 Adherence Assessment

Subject adherence is defined by subjects completing at least 6 out of 7 days of their daily symptom diary during the last week of the study period and taking amitriptyline

or omeprazole at least 6 out of 7 days during that week. Adherence will be assessed when subjects return their symptom diaries at their follow-up visit. For subjects who return incomplete symptom diaries, average daily symptom severity for the days completed will be calculated. If there is insufficient data to make this calculation, we will assume that symptoms are unchanged from baseline.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations for Subjects/Patients

Assessment	Telephone Screening: (Day -30 to -7)	Baseline, Enrollment, Randomization: Visit 1 (Day 0)	Post Intervention: Visit 1 (Day 0)	Follow-up: Visit 2 (Day 53 - 60)
Screening Form	X	X		
GERD Daily Symptom Diary Reviewed		X		X
Informed Consent Form		X		
Current Medication List		X		X
Height and weight		X		
Demographics & Health Behaviors		X		
Blood Draw (optional)		X		X
GERD-Health Related Quality of Life Questionnaire (GERD-HRQL)		X		X
Patient Reported Outcomes Measurement Information System (PROMIS) GERD		X		X
Gastrointestinal Symptom Rating Scale (GSRS)		X		X
Perceived Stress Scale-10 (PSS-10)		X		X
Current Stress Question		X	X	X
NEO Five Factor Inventory (NEO-FFI)		X		
Randomization		X		
HRV, respiratory rate, skin temperature, and GSR		X		
Video recording		X		
Study visit		X		
Impressions of the Study Physician			X	
Consultation And Relational Empathy questionnaire (CARE)			X	
HEAL Patient-Provider Connection			X	
Adverse Events				X
Debriefing				X

Schedules of Evaluations for Providers

Assessment	Enrollment	Prior to each subject/patient encounter	After each subject/patient encounter	After the last study visit
Informed Consent Form	X			
Interpersonal Reactivity Index (IRI)	X			
NEO-FFI	X			
Demographics	X			
Intervention Training	X			
PSS-10		X		
Current Stress Question		X		
Fatigue Scale		X		
Physician Satisfaction Questionnaire			X	
Interview at completion of study				X

6.2 Description of Evaluations

6.2.1 Telephone Screening (Day -30 to -7)

A standardized pre-screening form will be used to assess the potential subject's eligibility for the study. See Appendix B.

6.2.2 COVID-19 Screening (Day -1)

A standardized COVID-19 screening form will be used to assess whether the potential subject has symptoms consistent with COVID-19 or exposure to someone recently diagnosed with COVID-19, prior to the scheduled study visit. If the potential subject is experiencing any symptoms or has had a recent exposure, the potential subject will be rescheduled for another time at least 2 weeks later in order to ensure everyone's safety. See Appendix B.3.

6.2.3 Enrollment, Baseline, and Randomization (Visit 1, Day 0)

Potential subjects will be rescreened using the pre-screen form by a study physician. The study physician will also review the baseline symptom dairy to ensure that the individual is symptomatic enough to enroll. If the individual is eligible to participate in the study, they will be given a copy of the consent form to review.

Consenting Procedure and Enrollment

Written informed consent will be obtained by a study team physician (see also section 4.3). The subject will be given adequate time to read the consent form, and any questions the subject has will be answered. The study team physician will confirm that the subject understands that he/she will be connected to physiologic monitors during the visit and that the visit will be video recorded. The physician will also discuss the risks and benefits of taking amitriptyline or omeprazole. The subject will also have the opportunity to choose whether or not to consent to blood draws as part of the study which will involve one blood draw at the first visit and one blood draw at the second visit. The subject will receive a copy of the consent form and the original signed copy will be kept in a study binder. If the subject agrees to participate and signs the informed consent form, they will be considered "enrolled".

Study providers will be consented by the study PI, following a similar process, using a different written informed consent form.

Baseline Assessments

Evaluations for study participants/patients (self-administered questionnaires take about 15-25 minutes to complete):

- Current medication List – will be pulled from Epic and verified with the patient by a study team physician
- Height and weight – will be obtained by a study team member.
- Demographics and health behaviors – will access things such as age, gender, race/ethnicity, smoking status, alcohol & caffeine use (see Appendix D)
- Blood draw (optional) – 10 mL of blood will be obtained by a trained study staff member or phlebotomist. Blood will be processed to obtain RNA, DNA, and plasma then frozen at -80^{o}C for later omics analyses.
- Baseline Symptom Diary – 7-day diary indicating the frequency and severity of 9 different GERD and dyspepsia-related symptoms on a 5-point scale as well as any medications, supplements, or other products used to help manage symptoms. The first 3 symptoms (daytime heartburn, nighttime heartburn, and acid reflux) will be used to assess severity of GERD symptoms.
- GERD-HRQL – a validated 11 item scale for assessing the impact of GERD symptoms on health-related quality of life[73].
- NIH PROMIS GERD scale – a validated 13 item instrument assessing frequency and severity of GERD symptoms over a 7-day recall period[26].
- GSRS: The Gastrointestinal Symptom Rating Scale is a validated 15 item instrument for measuring the severity of gastrointestinal symptoms[74]. It contains 5 subscales: abdominal pain, reflux syndrome, diarrhea syndrome, indigestion syndrome, and constipation syndrome.
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress)
- Perceived Stress Scale (PSS) – a widely used 10 item measure of perceived stress that has been shown to correlate with a variety of different health outcomes[75]. We have adapted the originally validated measure to ask about stress over the past week (7 days), rather than the past month, to better fit the timeframe of the study. We have used this timeframe in other studies.
- NEO Five Factor Inventory (NEO-FFI) – a validated 60 item instrument that measured five major dimensions of personality: extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience[76]. Some dimensions have been associated with response to enhanced patient-provider interactions in others' studies[77].
- Physiologic Measures and Video Recording: During the intervention we will measure HRV, respiratory rate, skin temperature, and GSR in both study patients and study providers. The study visit will also be video recorded. During the COVID-19 pandemic, in order to allow us to collect physiologic and nonverbal behavior data (e.g., smiles) with the patient and physician unmasked, while also complying with institutional and state public health guidelines, the patient and doctor will sit in separate but adjacent, exam rooms with the door closed and use a video telehealth platform (e.g., Zoom, Cisco Meeting) to communicate. We will use the recording function to capture video data.

Evaluations for study providers:

- Interpersonal Reactivity Index (IRI) – a validated 28 item self-assessment of cognitive and affective components of empathy[78].
- NEO Five Factor Inventory (NEO-FFI) – a validated 60 item instrument that measures five major dimensions of personality: extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience [73]. Some dimensions have been associated with response to enhanced patient-provider interactions in others' studies[77].
- Demographics and practice – will assess things such as age, gender, race/ethnicity, and clinical experience (see Appendix D).
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress). Study providers will complete this question immediately prior to each study subject visit.
- Perceived Stress Scale (PSS) – a widely used 10 item measure of perceived stress that has been shown to correlate with a variety of different health outcomes[75]. Study providers will complete this questionnaire immediately prior to each study subject visit.
- Fatigue Scale – 1 item self-report measure of the current fatigue level on a scale of 0 (no fatigue) to 10 (extreme fatigue). Study providers will complete this question immediately prior to each study subject visit.
- Physician Satisfaction Questionnaire (PSQ) – 20 item self-report measure assessing physician satisfaction with the patient visit. This measure includes a global satisfaction question and 19 items assessing 4 other domains: satisfaction with the patient-physician relationship, with the data collection process, with the appropriateness of the use of time, and with the absence of excessive demands on the part of the patient. Study providers will complete this questionnaire immediately after each study visit[79].

Randomization

Subjects will be randomized on the day of their baseline visit (Visit 1) to receive either the standard or expanded visit with the specific provider that they are scheduled to see that day. We will stratify randomization by provider so that each provider does the same proportion of standard and expanded visits. Randomization will occur during or immediately after subjects have completed their baseline questionnaires, immediately prior to the study visit.

6.2.4 Blinding

This is a single-blinded study. Subjects will be unaware of the possibility for two different types of study visits. Study providers and staff will be aware of the study intervention delivered, but only immediately prior to the study visit to decrease the potential for introducing bias in how study staff interact with subjects during recruitment and consent. Subjects will be debriefed at the end of the Visit 2 regarding the nature of the study and the intervention that they

received. Data will be analyzed in a blinded fashion, also to avoid introducing bias. Given the low-risk nature of the study, we do not anticipate a need to break the blind while a subject is enrolled.

6.2.5 Post-Intervention Measures (Day 0)

Immediately following the study physician visit, subjects will be asked to complete the following questionnaires:

- Impressions of the Study Physician questionnaire – a 4 item measure assessing the patient's impression of the study physician including overall rating of the physician, satisfaction with the physician, willingness to recommend the physician to others, and desire to see the physician again.
- Consultation and Relational Empathy questionnaire (CARE) – a validated and commonly used 10 item measure for assessing the quality of the patient encounter and perceptions of empathy from the treatment provider[80]. I used it in my pilot study.
- HEAL Patient-Provider Connection – a subset of the Healing Encounters and Attitudes, a recently validated 7-item measure of the patient-provider connection. This is a patient-reported outcome developed as part of a set of tools to measure non-specific factors in treatment using the NIH PROMIS methodology[81].
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress)

6.2.6 Telephone Check-in

Study coordinators will call enrolled subjects who have completed study visit 1 twice to check in. The first time will be approximately 1 week after the first study visit and the second time 1 week before the second study visit. These telephone check-ins will 1) serve as a reminder to participants to complete their daily symptom diary, 2) remind participants to take the medication as prescribed 3) address any participant questions or concerns, and 4) remind/confirm participants' second study visit appointment.

Participants who wish to discontinue the study medication and unenroll from the study will be directed to speak with the study PI to receive instructions for tapering off of the medication if they have not done so already.

6.27 Completion/Final Evaluation

We will attempt to schedule subjects' Visit 2 appointments as close to the 8-week window as possible but will allow a window of several days (53-60 days). Visit 2 will be scheduled simultaneously with Visit 1 to help promote adherence to this timeline. If it is not safe for the subject to come to the lab for study Visit 2 (due to the COVID-19 pandemic), we will have the subject complete questionnaires online and schedule a video or telephone call to obtain adverse

event data, determine whether the subject benefited from the medication, and conduct the debriefing.

- Blood draw (optional) – 7.5 mL of blood will be obtained by a trained study staff member or phlebotomist. Blood will be processed to obtain RNA and plasma then frozen at -80^{o}C for later omics analyses.
- Current medication List – will be pulled from Epic or the prior visit and verified with the subject by a study team physician.
- GERD-HRQL - a validated 11 item scale for assessing the impact of GERD symptoms on health-related quality of life[73].
- NIH PROMIS GERD scale – a validated 13 item instrument assessing frequency and severity of GERD symptoms over a 7 day recall period[26].
- GSRS: The Gastrointestinal Symptom Rating Scale is a validated 15 item instrument for measuring the severity of gastrointestinal symptoms[74]. It contains 5 subscales: abdominal pain, reflux syndrome, diarrhea syndrome, indigestion syndrome, and constipation syndrome.
- Current Stress Question – 1 item self-report measure of current stress level on a scale of 0 (no stress) to 10 (extreme stress).
- Perceived Stress Scale (PSS) – a widely used 10 item measure of perceived stress that has been shown to correlate with a variety of different health outcomes[75].
- Adverse events – study staff will ask subjects if they experienced any adverse events and ask about any hospital or emergency room visits since enrollment.
- Daily symptom diary – Identical in content to the baseline symptom diary, this diary allows subjects to track the frequency and severity of 9 different GERD and dyspepsia-related symptoms on a 5 point scale as well as any medications, supplements, or other products used to help manage symptoms.
- Debriefing – a study team member will debrief with each subject regarding the two different visit types and the patient-provider interaction being studied. See Appendix F for a debriefing script.

If a subject experienced benefit taking amitriptyline or omeprazole, they will be offered a 30 day prescription so that they may continue taking the medication until they have a chance to follow-up with their PCP or gastroenterologist who can continue prescribing and monitoring the medication. If a subject did not experience any benefit and/or wishes to stop the medication, they will be instructed in how to taper off of it.

7. SAFETY ASSESSMENTS

Expected risks to subjects are as follows:

- Study questionnaires: Symptom and behavioral data collection involves virtually no risk; however, psychosocial tests or questions about symptom intensity may cause minor emotional distress. Because participants are free to stop at any time and will be reminded of this throughout the assessment process, the risk of distress is low. In our experience, such questionnaires are well-tolerated and complications are extremely rare.

- Discomfort from ECG/GSR leads and physiologic monitoring: Some participants may experience minor skin irritation due to the adhesive used to apply leads for physiologic monitoring. Subjects with known adhesive allergies will not be eligible to participate in the study. Some participants may experience psychological distress knowing that their physiology is being monitored. The physiologic monitoring will be described in the consent document and care will be taken to minimize such distress. Participants will be free to stop at any time. In general, such monitoring is well-tolerated.

- Discomfort from blood draws: some participants may have an aversion to needles, blood, and/or the drawing of blood. Blood will be drawn by trained study staff or phlebotomists and care will be taken to minimize discomfort to participants. Blood draws are generally well-tolerated, although occasionally there may be bruising or discomfort at the site. Rarely an infection can occur. The blood draw will be an optional component of the study, and if an enrolled subject consents to the blood draw and is particularly challenging to draw blood from, we cancel the blood draw and will not require a successful blood draw to be a condition of continued enrollment in the study.

- Videotaping: Some participants may experience psychological distress knowing that they are being videotaped. Participants will be free to stop at any time. In general, videotaping is generally well-tolerated.

- Amitriptyline: The most common side effects are dry mouth, sleepiness, and constipation. Less common side effects include dizziness, fatigue, headache, agitation, tremor, blurred vision, nausea, insomnia, and sexual dysfunction. Rare side effects include an allergic reaction, changes in heart conduction causing slowing or speeding up of the heart rate, serotonin syndrome, and suicidal ideation. We are prescribing low doses of this medication and have excluded those most vulnerable to adverse effects and so do not anticipate any serious adverse events. If a study subject calls with concerns about side effects, they will be directed to speak with a physician on the study team to assess their symptoms and determine whether any dose modification or further evaluation is needed. If it is deemed that the subject should stop the medication, they will be instructed in how to do so. If it is determined that they need further medical evaluation, they will be instructed what to do.

- Omeprazole: The most common side effects are headaches, abdominal pain, diarrhea, and nausea. Less common side effects include skin rash, constipation, dizziness, and back pain. Rarely someone may develop a hypersensitivity reaction, acute interstitial nephritis, lupus, or an enteric infection. Long-term use may increase the risk of

fractures, vitamin B12 deficiency, or low magnesium levels. Despite these risks, omeprazole is generally well-tolerated and available over-the-counter. If a study subject calls with concerns about side effects, they will be directed to speak with a physician on the study team to assess their symptoms and determine whether any dose modification or further evaluation is needed. If it is deemed that the subject should stop the medication, they will be instructed in how to do so. If it is determined that they need further medical evaluation, they will be instructed what to do.

- Severe GERD symptoms: It is possible that subjects may experience a flare in their GERD symptoms during the study. If a subject calls with severe GERD symptoms, he or she will be directed to speak with a study physician to discuss their symptoms and determine the best course of action. In some cases as needed antacids may be recommended for refractory symptoms. If this recommendation does not suffice, the subject may need to initiate additional medication and possibly be removed from the study.
- Deception: Subjects may experience minor psychological distress at study visit 2 when they learn that some information was withheld from them at enrollment. Based upon our experience with our prior studies, we feel this is unlikely to happen or to be problematic as we have experience conducting such debriefings and subjects generally understand why such information was withheld initially.

7.1 Specification of Safety Parameters

As amitriptyline is known to cause cardiac conduction delays and lower the seizure threshold in some individuals, we will not enroll anyone with known cardiac disease or seizure history that would be allocated amitriptyline during the study. We will also not enroll anyone with bipolar disorder (to avoid causing mania) or medications that could interact with amitriptyline and cause serotonin syndrome that would be allocated amitriptyline during the study.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Subjects will be instructed to call the research team if they have any questions or concerns during the study period. A research team member will call subjects approximately 1 week into the study period to confirm that they are taking their study medication as prescribed and to see if they have any questions or concerns. If so, a physician on the study team will reach out to them.

When subjects return for their follow-up visit, a study team member will inquire about any changes to their health or medical visits (including emergency room visits or hospitalizations) since their initial study visit. We will ask specifically if they experienced any adverse effects from the amitriptyline or omeprazole. If a subject reports a new or worsening symptom that is medically concerning (e.g., bright red blood per rectum), they will be referred for further evaluation.

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is any unfavorable or unintended diagnosis, symptom, sign, syndrome or disease which either occurs during the study (having been absent at baseline), or if present at baseline, appears to worsen.

A **serious adverse event (SAE)** is any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

During the follow-up visit, the study team member will specifically ask about any new or worsening symptoms in the last 8 weeks, unanticipated medical appointments, emergency room, or hospital visits.

In addition, during telephone check-ins, the study research coordinator will record any health concerns reported by subjects (not specifically solicited) and report these to the study PI. If there are any signs or symptoms of concern or that require further clarification, the study PI will contact the subject.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the National Center for Complementary and Integrative Health (NCCIH) Program Officer within 3 business days of the investigator becoming aware of the event and to the study's Independent Safety Monitor(s) and UC Davis IRB within 5 business days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 5 business days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH and the UC Davis IRB on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed (see Data Safety and Monitoring Plan).

7.4 Reporting Procedures

Study staff and visit intervention providers will be instructed to report all adverse events (or potential AEs) to the study PI (Dr. Dossett). Determination of relatedness will be made in conjunction with Dr. Henry and/or Dr. Garcia. An electronic log of various types of AEs will be kept and updated by study staff.

7.5 Follow-up for Adverse Events

AEs will be followed-up by the study PI by phone calls to the subject and/or

monitoring of the medical record until they are resolved or considered stable. Formal AE follow-up will end with subjects' follow-up visit unless they have an ongoing issue or call to report an event after completing the study.

7.6 Safety Monitoring

Please see the separate data safety and monitoring plan for this study, found in Appendix G.

8. INTERVENTION DISCONTINUATION

Subjects who decline to participate in study procedures (e.g., completion of study questionnaires, physiologic monitoring, and/or video recording) will be terminated from the study without further follow-up. Any subjects who are disruptive or felt to pose a threat to study staff will also be terminated without follow-up. If a subject experiences an adverse reaction to amitriptyline or omeprazole and decides to stop taking the medication, or if a study physician deems it in the subject's best interest to stop the medication, the subject will continue to be followed for the duration of their initially planned participation (out to 8 weeks), unless the subject declines to participate further.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Design: This is a single-blinded randomized controlled trial in which subjects will be randomized in a 1:1 fashion to receive either an expanded or standard visit with a healthcare provider about their GERD symptoms and then treated with amitriptyline or omeprazole for 8 weeks to determine whether an expanded visit can augment the effects of a medication compared to a standard visit.

Primary hypotheses:

1. Subjects who receive an expanded visit will have a greater improvement in their GERD symptoms after 8 weeks of treatment with amitriptyline or omeprazole compared to subjects who receive a standard visit.

Secondary hypothesis:

1. Patient-provider dyads in expanded visits will have a greater percentage of the total visit time spent in physiologic concordance (measured by either GSR or HRV) compared patient-provider dyads in standard visits.
2. Percentage of visit time with physiologic concordance (in GSR or HRV) will be correlated with GERD symptom improvement.
3. Subjects who experience physiologic changes similar to those elicited by mind-body techniques (i.e., decreased GSR and increased high frequency HRV) over the course of their visit (first several minutes compared to the last several minutes of the visit) will demonstrate greater improvements in GERD symptom severity than subjects who do not.

4. Healthcare providers in expanded visits will demonstrate more patient-centered non-verbal behaviors (e.g., smiles and gazes) and global impression (e.g., engaged, friendly, relaxed) compared to providers in standard visits as rated by blinded reviews of thin slices of video excerpts.
5. Patient and provider smiling at the end of study visits will be significantly associated with GERD symptom improvement 8 weeks later.

Primary outcome:

1. Change in the average daily GERD symptom severity score from baseline to the last week of the study in the expanded vs. standard group. GERD symptom severity is based on the sum of scores assessing the severity of daytime heartburn, nighttime heartburn, and acid reflux each on a 0-4 point scale (none, mild, moderate, severe, very severe; higher scores signify worse symptoms).

Secondary outcomes:

1. Ratio of the sum of positive correlations over the sum of negative correlations in GSR (or HRV) across patient-provider encounters for standard vs. expanded visit types and for responders vs. non-responders (those with a 50% or greater improvement in their GERD symptom severity).
2. Absolute change in GSR (or high frequency HRV signal) in patient recordings from the beginning of the study visit to the end of the study visit and correlation with subsequent change in GERD symptom severity.
3. Differences in blinded ratings of 2 minute thin slices of study visit videos from the beginning to the end of the study in supportive global impressions (e.g., engagement, relaxed, patient seems pleased/satisfied) and non-verbal behaviors (e.g., smiling) between standard and expanded visit types and correlation with subsequent change in GERD symptom severity.

Validity and reliability of outcome measures:

1. Assessment of physiologic concordance has been described by a number of groups and we will be using similar methodology[45,82].
2. GERD symptom severity will be assessed by a daily symptom diary used by a number of other groups in medication trials and in our previous study[64,83,84]. The average daily GERD symptom severity is based on the daily sum of scores from the first three questions assessing severity of daytime heartburn, nighttime heartburn, and acid reflux averaged over a 7 day period. The change in GERD symptom severity is calculated by subtracting the average daily GERD symptom severity score during the last 7 days of the study from the average daily GERD symptom severity score at study enrollment. The other GERD symptom questionnaires we are using have also been validated[26,73,74].
3. Social psychologists have developed and validated a variety of coding schemes to analyze providers' verbal and non-verbal behaviors and to link these behaviors with patient satisfaction, understanding, trust, rapport, empathy, and a variety of related factors[9,58–63]. We will use a subset of these validated coding

schemes. Thin slices have shown high reliability and validity for behaviors such as gaze, nods, and smiles[85].

9.2 Sample Size and Randomization

The combined standard deviation (root mean square error) in my pilot fellowship study was 1.5[64]. We are conservatively assuming that this number will likely be larger in this study given the greater number of providers involved. Given 30 subjects in each group (n=60 total), 80% power, a two-sided significance test with alpha = 0.05, the minimal detectable difference (MDD) in GERD symptom severity scores between the standard and expanded groups given the estimated standard deviations (SD) is shown in the adjacent table. These MDD values are similar to those found in my fellowship study[64] and are clinically meaningful[86,87].

Minimal Detectable Difference Between Groups	
SD	MDD
1.5	1.10
2.0	1.47
2.5	1.84

Treatment Assignment Procedures

A randomization scheme will be devised before the start of the study by the study biostatistician who will retain the code and will be responsible for breaking the blind at the end of the study. We do not anticipate a need to break the blind during the study because we are not expecting serious adverse events to occur more frequently in one visit group than another. Randomization will be stratified by provider, with permuted block sizes of 2 and 4 with a goal to have 5-6 providers each see 10-12 subjects. If a provider cannot commit to this many visits, the study biostatistician may need to adjust the randomization scheme and we will consent additional providers.

The study biostatistician will enter the randomization scheme into REDCap and subjects will be randomized immediately prior to the study visit intervention.

If a subject drops out or is unable to complete the study, the statistician may need to rebalance the randomization scheme.

Subjects will be informed of their visit group assignment during the debriefing at the end of the second study visit.

9.3 Definition of Populations

For analyses including the intervention group type, we will analyze our data according to which visit intervention subjects received (standard or expanded). We do not anticipate any discrepancies between what subjects were assigned to receive by randomization and what they actually received. Study visit type will be guided by a written script that the providers will follow during the visit. The actual intervention received will also be verified by reviewing study video recordings.

The intent to treat analysis will include all randomized subjects who received a study visit intervention. The per protocol analysis will include all individuals who received a study visit intervention and completed the follow-up questionnaires at 8

weeks.

9.4 Interim Analyses and Stopping Rules

No interim analyses are planned. The study PI will periodically review video recordings of visit interventions as the study progresses to offer feedback to the study intervention providers and ensure adherence to the protocol.

If at any point 20% or more of participants have dropped from the study due to adverse effects from amitriptyline or omeprazole and/or there is a serious adverse event likely due to amitriptyline or omeprazole, the study team will meet with the study safety monitor to determine whether any protocol modifications are necessary.

9.5 Outcomes

A combination of description statistics, pearson correlations, and general linear models (GLM) such as ANCOVA, will be used for analyzing the data.

Assessment	Time Points Collected	Analysis Plan	Section
Demographics, health behaviors, height & weight	Visit 1	Descriptive statistics	9.6
Daily GERD Symptom Diary	Visit 1 & Visit 2	Primary Outcome – ANCOVA analysis adjusting for baseline GERD symptom severity and visit type using follow-up GERD symptoms as the outcome.	9.5.1
GERD-HRQL	Visit 1 & Visit 2	Descriptive statistics and secondary measures of GERD symptom severity in ANCOVA analyses.	9.6
NIH PROMIS GERD			
GSRS			
Current Stress	Visit 1 (both before & after provider visit) &Visit 2	Descriptive statistics and covariate in GLM analyses.	9.6
PSS-10	Visit 1 (before provider visit) &Visit 2	GLM to determine whether perceived stress is a modifying factor for change in GSR and HRV in the context of the visit intervention	9.6
FFI	Visit 1	GLM to determine whether personality is a modifying factor for change in GERD symptoms in the context of the visit intervention	9.6
GSR & HRV	Visit 1	Secondary Outcome – GLM assessing change in GERD symptom severity and physiologic concordance in patient-provider dyads	9.5.1
Video Recording	Visit 1	Secondary Outcomes - GLM to compare the frequency of supportive provider behaviors between the standard and expanded visit groups and responders vs. non-responders (those with a 50% or greater improvement in GERD symptoms).	9.5.2
Impressions of the Study Physician	Visit 1, post-intervention	GLM to determine whether empathy and the patient-provider connection modify change in GERD symptoms in the context of the visit intervention	9.6
CARE			
HEAL Patient-Provider Connection			

9.5.1 Primary Outcome

1. Change in the average daily GERD symptom severity score from baseline to the last week of the study in the expanded vs. standard group. GERD symptom severity is based on the sum of scores assessing the severity of daytime heartburn, nighttime heartburn, and acid reflux each on a 0-4 point scale (none, mild, moderate, severe, very severe; higher scores signify worse symptoms). We will use ANCOVA for the primary analysis, adjusting for baseline GERD symptom severity and visit type assignment using the 8 week follow-up GERD symptom severity as the outcome. Potential moderators that will be assessed in exploratory analyses will include gender (both patient and provider), race, visit length, patient stress, personality type, and perceived connection with/empathy of the provider.

9.5.2 Secondary Outcomes

1. To analyze physiologic synchrony in GSR, first, an average slope of the GSR will be calculated in the patient and provider recordings in moving 5 second windows, offset by 1 second. Next, Pearson correlations with lag zero will be calculated over successive 15 second windows between time-locked patient and provider GSR slope values. Then, a single session index will be calculated from the ratio of the sum of the positive correlations across the entire visit divided by the sum of the absolute value of the negative correlations across the entire visit. To reduce skew, the natural logarithm of the index will be calculated. Thus, an index value of zero reflects equal positive and negative correlations, a value greater than zero reflects more concordance in GSR than not, while a value less than zero reflects less concordance in the dyad (less than 50%)[82]. These index values will be used in GLM analyses with GERD symptom severity and/or correlated with visit type.

   We will also perform similar analyses on the HRV data – comparing variation in the beat-to-beat intervals over short segments of time and calculating Pearson correlation coefficients for time-locked patient and provider data for these intervals.

2. We will calculate absolute changes in both GSR and also high frequency HRV within study subjects from the beginning to the end of the study visit. We will assess the Pearson correlation between these changes and reported changes in GERD symptom severity. We will also look at absolute levels of GSR and HRV at the end of the study visit and compare those values with changes in GERD symptom severity in GLM models. As an exploratory analysis, I will test whether changes in GSR and HRV are a function of baseline perceived stress and if that relationship differs between the standard and expanded visit interventions.

3. To analyze study visit videos, 2 minute thin slices of each video at three time points (beginning, middle, and end of study visits) will be analyzed by trained and blinded coders, for the presence of 1) micro-level non-verbal supportive behaviors (e.g., gazes, smiles, nods, gestures – measured as absolute number or

length of time) as well as 2) macro-level impression ratings of the interaction (e.g., engagement, friendliness, relaxed, empathic, reciprocity – measured on a 1-9 scale). The PI will meet weekly with the coders to review findings and resolve areas of disagreement until greater than 70% concordance is achieved between coders using Cronbach's alpha. Each of these variables will be assessed in a GLM examining time, visit type, and time x visit type effects. We will also calculate the Pearson correlation coefficient for each variable relative to improvement in GERD symptoms and construct a GLM examining patient and provider smiling as a predictor of improvement in GERD symptoms. Other models may also be constructed based on the results of the initial video analyses.

9.6 Data Analyses

We will perform descriptive statistics on the sample demographics similar to our prior paper[64] including age, gender, race, ethnicity, body mass index (BMI), smoking status, and current medication use for GERD symptoms. We will also assess whether perceived stress, perceived empathy (both patient and provider), personality type (five factor inventory), or demographic factors modify improvement in GERD symptoms using generalized linear models. We will use the GERD-HRQL, NIH PROMIS GERD, and GSRS as adjunct/corroborating measures of GERD symptom severity. Blood samples will be processed and stored at - 80ºC for later omics-based analyses that will be the subject of a future grant/study.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Most questionnaire data will be collected on iPads at the study site using Research Electronic Data Capture (REDCap; http://project-redcap.org/) forms. In the event that a subject cannot physically return for the second study visit, a link to the follow-up questionnaires will be emailed to the subject. Subjects will complete GERD symptom dairies either online (REDCap) or in paper format daily. Paper data will be doubled entered into a REDCap database by study personal and checked for consistency. REDCap is a secure, web-based application developed at Vanderbilt University for electronic collection and management of clinical research study data and is hosted locally by UC Davis.

Study staff will maintain an electronic screening file and enrollment log file and paper files of consent forms.

Study participant confidentiality will be maintained by a unique identifier. An electronic file linking participants' personally identifying information and study ID will be password protected. All paper data will be stored in a locked filing cabinet. Only study affiliated personnel will have access to the study database and associated files. Electronic communication with collaborators will only involve deidentified information. All published data will be presented in aggregate format and deidentified.

10.2 Data Management

All paper symptom diaries will be reviewed in real time with subjects to ensure that data can be transferred completely and accurately to electronic form. Such data will be double entered and cross checked as described above. All data (questionnaire, physiologic, video) will be cleaned by study staff and reviewed every 1-2 months by the study PI to ensure accuracy, completeness, and timeliness of subsequent analyses.

10.3 Quality Assurance

10.3.1 Training

The study PI will personally train and supervise all research coordinators and interns working on the study in collaboration with relevant consultants to ensure that study measures are collected appropriately. All research coordinators/interns will have completed the appropriate human subjects training programs and may complete additional training depending upon the capacity in which they will serve in the study.

10.3.2 Protocol Deviations

Protocol deviations will be documented and reported to the UC Davis IRB. Unapproved major protocol deviations will be reported to the IRB and NCCIH within 5 business days of discovery.

Unapproved minor protocol deviations will be reported to the IRB at the time of the annual continuing review and to NCCIH annually as well. Should a protocol deviation become repetitive and/or problematic, the investigational team may consider submitting a protocol amendment to adjust study procedures.

10.3.3 Monitoring

The study PI will regularly review study questionnaires, HRV and GSR data, video recordings, and logs for completeness and quality. Such review will follow each subject initially but will occur at least every 1-2 months for the duration of the study.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent documents and any subsequent modifications will be reviewed and approved by the UC Davis IRB.

11.2 Informed Consent Forms

Written informed consent will be obtained by a study team physician at the initial study visit after reviewing inclusion and exclusion criteria, the participant's symptom diary, and the electronic medical record if the participant is a patient at UC Davis. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Participants will have the opportunity to ask questions. A copy will be given to each participant and this fact will be documented in the participant's record. Participants who cannot consent for themselves or who are not fluent in English will not be eligible to participate due to the nature of the study.

11.3 Participant Confidentiality

Study visits will be conducted in a private setting. Whenever possible, questionnaire data will be collected electronically using REDCap. REDCap is a secure, web-based application developed by Vanderbilt University for electronic collection and management of clinical research study data. All electronic data not gathered using REDCap (symptoms diaries, physiologic data, video recordings) will be stored on a UC Davis shared drive which is backed up regularly to protect against data loss and is behind the UC Davis firewall. Any data that cannot be collected directly onto a shared drive (i.e., must be saved on a local hard disk during data collection) will be collected on an encrypted laptop and transferred to a UC Davis-affiliated server shortly after collection. Any paper questionnaire data will be stored in a locked filing cabinet.

Only those researchers involved in the study will have access to electronic and paper data. The file linking participants' personally identifiable information with their participant identification number (PID) will be password protected and access will be restricted to the fewest number of staff required but will include at least the PI and a research coordinator. Electronic access to videos will also be password protected. All paper records will be kept in a locked file cabinet. All computer entry and analysis will be done using PIDs only. Any data, forms, reports, video recordings, and other records that leave the site will be identified only by a PID to maintain confidentiality. Digital video files may be stored for up to 12 years but may be destroyed sooner.

Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the NCCIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the Office of Human Research Protections (OHRP), or other government agencies as part of their duties to ensure that research participants are protected.

12. POTENTIAL BENEFITS

12.1 Potential Benefits to Participating Individuals

Study subjects ("patients") may experience improvement in their GERD symptoms by participating in this study. The placebo response in GERD-related trials may be as high as 40% [35] and our prior data suggests that a therapeutic encounter such as the expanded visit can result in at least temporary symptom improvement for some individuals [61]. In addition, subjects may also experience improvement in their GERD symptoms from taking amitriptyline or omeprazole. It is also possible that subjects may not experience any direct benefit from participating in this study. Subjects will receive $30 and a 2 month supply of amitriptyline or omeprazole for participating in the first study visit and $50 for attending the second study visit.

Participating study providers will also be remunerated for their time ($80.00 per visit) and may benefit by learning skills for relating to patients more effectively.

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16. LIST OF SUPPLEMENTS/APPENDICES

Appendix A: Recruitment Materials
- A.1 Study flyer for patient subjects
- A.2 Study Flyer/email for healthcare providers
- A.3 Modified Provider Study Flyer

Appendix B: Screening Documents
- B.1 Telephone script for pre-screening (amitriptyline substudy
- B.1.1 Telephone script for pre-screening (omeprazole substudy)
- B.2 Screening form
- B.3 COVID-19 Screening

Appendix C: GERD Daily Symptom Diary

Appendix D: Study Questionnaires

Appendix E: Standard and Expanded Visit scripts
- E.1 Standard Visit Script
- E.2 Expanded Visit Script

Appendix F: Debriefing Script

Appendix G: Data Safety and Monitoring Plan

Appendix H: Provider semi-structured exit interview