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Long-Term Chamomile Therapy of Generalized Anxiety Disorder: A Study Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background—Anxiety symptoms are among the most common reasons for consumers to use Complementary and Alternative Medicine (CAM) therapy. Although many botanicals have been proposed as putative remedies for anxiety symptoms, there has been a paucity of controlled trials of these remedies. A preliminary study of the anxiolytic effect of Chamomile (*Matricaria recutita*) in humans suggests that chamomile may have anxiolytic and antidepressant activity. We now seek to conduct a 5-year randomized, double-blind, placebo-substitution study to examine the short and long-term safety and efficacy of chamomile extract in Generalized Anxiety Disorder (GAD).

Methods/Design—180 subjects with moderate to severe GAD will receive initial open-label pharmaceutical-grade chamomile extract 500–1,500 mg daily for 8 weeks. Responders to treatment who remain well for an additional 4 weeks of consolidation therapy, will be randomized to double-blind continuation therapy with either chamomile extract 500–1,500 mg daily or placebo for an additional 26 weeks.

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Conflicts of Interests

All the authors had no conflict of interest to declare.

Contribution of Each Author to the Study and Manuscript Preparation

All authors participated in study design, writing, and final approval of the manuscript.

The primary outcome will be the time to relapse during study continuation therapy in each treatment condition. Secondary outcomes will include the proportion of subjects in each treatment condition who relapse, as well as the proportion of subjects with treatment-emergent adverse events. Quality of life ratings will also be compared between treatment conditions during short and long-term therapy.

Discussion—Many individuals with mental disorders decline conventional therapy and seek CAM therapies for their symptoms. Thus, the identification of effective CAM therapy is of relevance to reducing the burden of mental illness. This study builds upon our prior findings of significant superiority of chamomile versus placebo in reducing GAD symptoms. We now extend these preliminary findings by conducting a randomized long-term safety and efficacy study of chamomile in GAD.

Keywords

Chamomile; *Matricaria recutita*; Generalized Anxiety Disorder; Anxiety; Herbal Therapy; Botanical Therapy; Alternative Medicine

Background

Anxiety disorders are among the most common psychiatric conditions, ranking just below drug and alcohol dependence and depression in frequency [1, 2]. Approximately one in 4 adults will have some form of anxiety disorder during their lifetime [3]. Less than 30% of individuals with anxiety disorder actually seek medical treatment for it [4].

Generalized Anxiety Disorder (GAD) is characterized by excessive worry about daily matters, and the presence of restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep problems. GAD is generally chronic and recurrent, and usually fluctuates in severity [1]. It has a lifetime prevalence of ~ 5%, with approximately 9 million affected adults in the US [5]. Only 33% of GAD patients will experience spontaneous remission of symptoms. GAD is the second most frequently treated psychiatric disorder in the primary care setting, after depression [2]. It results in substantial distress and disability comparable only to that of major depression [6].

The mainstay therapy for GAD symptoms are benzodiazepine (BZ) tranquilizers and these drugs are still among the most frequently prescribed therapy for GAD in the US [4]. Although effective for short-term treatment, many patients develop tolerance to BZs and experience habituation and distressing discontinuation symptoms that mimic the symptoms of GAD [7, 8]. Some clinicians have questioned whether long-term use of BZs is even effective therapy for GAD, and if its benefits outweigh its risks [9].

Chamomile (*Matricaria recutita*) is one of the most widely used herbal remedies in the world. It is included in the pharmacopoeia of 26 countries [10]. The use of chamomile as an herbal remedy dates back to ancient Greece and Rome. While there are many varieties of chamomile, Roman (A. nobilis) and German (M. recutita) are the most widely used forms. These are members of the Compositae (Asteracae) family. German chamomile is considered the more potent and is most widely used. It has many medicinal uses including carminative

(anti-colic), antiseptic, and anxiolytic [11]. M. recutita use for relief of anxiety symptoms has been previously documented [12–15].

Although chamomile is used extensively throughout the world as a calming agent, few controlled studies have been undertaken in humans. The pathophysiology of anxiety is complex and multi-factorial, and may involve alterations in several neurotransmitter and neuroendocrine systems. A number of animal and human studies suggest that chamomile, and several of its constituent flavonoids, may exert their psychotropic effects via neuromodulation.

To date, there has been only one published controlled clinical trial showing chamomile's anxiolytic effect in humans; however, there is substantial literature suggesting that chamomile (and several of its flavonoid components) may have anxiolytic and antidepressant activity [16, 17]. In that randomized clinical trial, we found a significantly greater reduction in mean total anxiety symptom scores for chamomile versus placebo (60 $\hat{\beta}_3$ =−3.17; 95% confidence interval [CI], −6.29 to −0.45; P=0.047) on our primary outcome measure. We also found a greater, albeit non-significant, reduction in mean anxiety symptom ratings for chamomile versus placebo on our secondary outcome measures. In addition, we observed a clinically meaningful, albeit non-significant, increase in mean total well-being scores for chamomile versus placebo [16].

The recognition that GAD is a recurrent disorder has led to the need for long-term therapy [18]. The *International Consensus Group on Depression & Anxiety* has recommended that initial GAD therapy be continued up to 12 months to establish maximum benefit and prevention of relapse and recurrence [19]. Despite these guidelines, however, long-term therapy for GAD is often hindered by the development of tolerance or unwanted adverse events.

Given the fact that GAD is one of the most common disorders for which individuals seek CAM therapy [20], there is clearly a need to develop alternative, less costly remedies for GAD. Building upon our prior positive results of chamomile therapy of GAD [16, 17], we now seek to extend these results by conducting a 5-year, randomized, double-blind, placebo-substitution, long-term safety and efficacy study of chamomile therapy in GAD.

Specific aims and hypotheses

Primary study aim: To examine if long-term chamomile therapy (versus placebo) prolong the time to relapse of anxiety symptoms following recovery from GAD. We hypothesize that continuation chamomile therapy will result in a prolonged time to relapse (versus. placebo). The primary outcome is the time to relapse during study phase III in each treatment condition.

Secondary study aim: To compare the relative safety and tolerability of long-term chamomile therapy (versus placebo) in subjects who have recovered from GAD. Secondary outcome measures include: (i) the proportion of subjects in each condition who relapse; (ii) frequency, severity, and duration of treatment-emergent adverse events (AEs); (iii) frequency of discontinuation symptoms during double-blind therapy; and, (iv) frequency of early study

discontinuation. We hypothesize that chamomile therapy will result in a lower proportion of anxiety relapses and a lower study discontinuation rate (versus placebo). We further hypothesize that chamomile therapy will result in a similar frequency of treatment-emergent AEs and discontinuation symptoms (versus placebo).

Methods/Design

Study design

180 subjects with moderate to severe GAD will receive open-label chamomile extract 500–1,500 mg daily for 8 weeks. Responders to chamomile who remain well for an additional 4 weeks of consolidation therapy, will then be randomized to double-blind continuation therapy with either chamomile extract 500–1,500 mg daily or placebo for an additional 26 weeks. This study has been approved by the University of Pennsylvania Institutional Review Board.

Study population

Target population will be adult subjects with a *Diagnostic and Statistical Manual of Mental Disorders - Fourth Revision* (DSM IV) diagnosis of GAD as the primary anxiety disorder. Table 1 displays the study inclusion and exclusion criteria, source of study materials, and role of study personnel.

Study Drug

German Chamomile (Matricaria recutita) extract—Pharmaceutical grade chamomile extract 4:1 powder standardized to a content of 1.2% apigenin (Swedish Herbal Institute, Gothenburg, Sweden) will be used. The chamomile extract will be provided with a certificate of analysis (COA) to document its purity and suitability for human use.

The FDA has granted us an IND 107,206 approval for Chamomile (Matricaria recutita) extract use in GAD in a “Safe to Proceed” letter on December 17, 2009.

Placebo—Pharmaceutical-grade lactose monohydrate NF (Spectrum® Quality Products, New Brunswick, NJ), will be used as the placebo and packed in capsule form to give the capsule a ‘feel’ similar to the chamomile capsule. Lactose monohydrate will also be provided with a current COA documenting its purity and suitability for human use.

Drug Preparation & Blinding Procedure—Chamomile and placebo capsules will be prepared and packaged by the Penn Investigational Drug Service (IDS) under *Good Manufacturing Practice Guidelines*, in a HEPA-filtered ISO-8 production room. Pharmaceutical grade chamomile extract 4:1 powder standardized to a content of 1.2% apigenin will be used. A dose of 500 mg (equaling 500 mg of total powder) will be placed into a stock gelatin capsule shell without any additional filler. Identically appearing placebo capsules will contain lactose monohydrate NF. In order to assure blinding due to the very distinct scent of chamomile, a drop of oil of chamomile will be applied to a paper disc placed in the lid of the bulk container in which the placebo capsules are stored. The placebo capsules will remain tightly sealed in this container for at least one week prior to the fill.

This procedure was used successfully in our prior chamomile study [16]. All chamomile and placebo capsules will be packed, sealed and assigned an internal IDS lot number for each batch. Product in the capsule shell will be given a use-by date of 12 months from the date of compounding, (unless the manufacturer expiration date is less than 12 months). All study drugs will be blister packed using pharmaceutical grade foil-backed paperboard and matching amber blisters (Rx Systems, Inc., St. Charles, MO).

Study Drug Administration Procedure—We will use a 'fixed-flexible' dosing strategy with chamomile therapy initiated at 1,500 mg (3 capsules) daily. We propose this strategy, rather than a dose-escalation design; based upon our preliminary observation that chamomile is well tolerated at higher daily doses [16]. In addition, starting chamomile therapy at a fixed dose of 1,500 mg daily affords each subject the opportunity of receiving maximum chamomile therapy with an enhanced likelihood of response. During the double-blind continuation therapy phase of the study (i.e., study phase III), blinded study drug will be dispensed at each study visit. A drug accountability log will be maintained and pill count will be performed at each study visit throughout the entire study.

Subject Recruitment

Subjects included in the study will be suffering from moderate to severe GAD and recruitment will be made without regard to gender, race or ethnic background, provided the subject meets all protocol inclusion criteria. Subjects will be recruited from media and print advertisements targeting ethnic and racially diverse populations. Additionally, subject will be recruited from collaboration with primary care practices in the community. Subjects will be provided informed consent at the intake evaluation.

Initial subject contact will be made via telephone triage performed by a trained study coordinator who will elicit general information. After the initial phone contact, subjects will be given an appointment for an intake evaluation. If the subject meets criteria for GAD and does not meet other medical or psychiatric exclusion criteria, a study consent visit will be scheduled. All study-related procedures will be performed at the Depression Research Unit of the University Of Pennsylvania School Of Medicine.

Randomization & Stratification Procedure

We will perform a blocked randomization with randomly varying block sizes. This will be accomplished in two stages, within strata defined by gender. First, we will randomly select a block size from among a small set of possible block sizes. The group numbers will then be randomly permuted within that block. We will continue this procedure until we have randomized 45 subjects within each treatment condition. We will generate random numbers and permute the numbers within each block using the random number generator and use written code in STATA statistical software. The randomization is done independently of the researchers.

Study Procedures

Diagnostic & Clinical Outcome Measures

(a) *Structured Clinical Interview (SCID I/P) for DSM IV Axis I Disorders* [21]: will serve as the primary instrument for diagnostic case ascertainment.

(b) *GAD-7* [22]: is a 7-item, subject-rated measure of GAD that is linked to DSM IV-TR criteria (and validated via the SCID). It has excellent internal consistency, test-retest reliability, and convergent construct criterion and factorial validity for the diagnosis of GAD in primary care and general population settings, with a sensitivity of 89% and specificity of 82% [23–25]. A GAD-7 score ≥ 10 will serve as the minimum study entry criterion (i.e., moderately ill), and will be used to stage GAD severity levels with 'cut points' of 5–9 (mild), 10–14 (moderate), and 15–21 (severe). It will also serve to identify relapse of GAD (vs. other anxiety disorders) during study phase III. It will serve as a primary outcome measure of response during study phase I and II, and as a secondary outcome measure in study phase III.

(c) *Clinical Global Impressions/Severity (CGI/S)* [26]: is a clinician–rated global measure of severity that correlates with other symptom severity outcome ratings. It will serve as a dichotomous primary outcome measure of response (along with the GAD-7) in study phase I and II, and as a dichotomous primary outcome measure of relapse (along with DSM IV-TR criteria for GAD) in study phase III.

(d) *Clinical Global Impressions/Change (CGI/C)* [26]: is a clinician-rated global measure of change in symptom severity (i.e., improvement or worsening) during treatment. It has been shown to correlate with other symptom outcome ratings (e.g., HAM-A). It will be completed at the conclusion of each study visit. It will serve as a secondary outcome measure of response in study phase I and II, and of relapse during study phase III.

(e) *Hamilton Anxiety Rating Scale (HAM-A)* [27]: is a clinician-rated outcome measure of treatment efficacy. It is the most widely used instrument for ascertaining change in symptom severity of GAD (Shear et al., 2001). It will serve as a secondary outcome measure.

(f) *Beck Anxiety Inventory (BAI)* [28]: The BAI is a well validated subject-rated instrument for ascertaining change in symptom severity of GAD. It will serve as a secondary outcome measure.

(g) *Hamilton Depression Rating Scale (HAM-D)* [29]: is an established and validated clinician-rated measure of depressive symptoms which performs consistently across racial groups [30]. It will serve as a secondary outcome measure.

(h) *Beck Depression Inventory (BDI)* [31]: is an established subject-rated measure of symptom severity of depression in the medical setting. It will serve as a secondary outcome measure.

(i) *Longitudinal Interval Follow-up Evaluation (LIFE)* [32]: will be used in study phase III as one means of ascertaining GAD relapse vs. new onset co-morbid disorder (substituting appropriate DSM IV-TR criteria for RDC criteria). The LIFE is based upon a semi-structured interview, and will be completed at every study visit to provide a continuous assessment of anxiety symptoms vs. other disorders.

(j) *Psychological General Well Being Index (PGWB)* [33, 34]: is a subject-rated measure of 6 health-related QOL domains: anxiety, depressed mood, positive well-being, self-control, general health and vitality. The PGWB index provides an overall measure of well-being in addition to the other domains. It will serve as a secondary outcome measure.

(k) *Modified RUSH Sexual Inventory (RUSH)* [35]: is a subject completed rating of sexual function and satisfaction. It will be used to assess current sexual health and changes in sexual health over time. It will serve as a secondary outcome measure.

(l) *Discontinuation Emergent Signs and Symptoms (DESS)* checklist [36, 37]: is a subject-rated measure of the presence and severity of discontinuation symptoms occurring after medication discontinuation. The DESS is a validated instrument that has been the most widely used measure of drug abstinence. It will serve as a secondary outcome measure.

(m) *Treatment Emergent Symptom Scale (TESS)* [38]: is a clinician-rated profile of adverse events. The TESS includes the date of AE onset and cessation, severity of AE (i.e., mild, moderate, severe), relationship of the AE to treatment or study procedure (i.e., none, possible, probable, definite), and outcome. AE information is obtained via spontaneous subject report, doctor query, and changes in physical and laboratory findings. It will serve as a secondary outcome measure.

(n) *Columbia Suicide History Form (CSHF) & Columbia Suicide Severity Rating Scale (CSSRS)* [39]: are validated, clinician-rated instruments that ascertain past and current suicide risk, ideation, and behavior. They will serve as secondary outcome measures.

(o) *Expectations for Therapy Inventory (ETI):* is a 5-item, subject-rated measure of expectations of outcome modified from the Acupuncture Expectancy Scale [40, 41], a validated instrument to measure outcome expectancy related to treatment.

(p) *Credibility Rating of Blinding Index (CRBI)*: is a single item rating by which the subject and investigator guess the treatment condition (i.e., chamomile, placebo, uncertain) at the completion of study phase III. The proportion of responses will then be compared to assess the adequacy of blinding.

(q) *Expectation of Side Effects of Therapies and (r) Expectation of Therapeutic Effects* [40, 41]: are subject-rated measures of expectations of side-effects and therapeutic effects of the study drug. Both assessments will serve as additional measures to test if early expectancies affect therapeutic effects.

(s) *Insomnia Severity Index (ISI)* [42, 43]: is a 7-item validated self-reported instrument to measure insomnia. It will serve as a secondary outcome measure.

(t) *Brief Fatigue Inventory (BFI)* [44]: is a 9-item validated self-reported instrument to measure fatigue. It will serve as a secondary outcome measure.

Study Visits

Visit 1(Week 0) - Intake Evaluation (to determine eligibility): Initial subject contact will be made via telephone triage. General information about referral source, subject demographics, clinical variables (e.g., duration of current episode, current treatment, medical disorders), and the presence of suicidal ideation will be obtained. A brief description of the procedures will be provided, and the subject will be provided with an appointment for an intake visit. At this appointment, informed consent and initial clinical data will be obtained.

Concurrent use of anti-anxiety tranquilizer, antidepressant or mood stabilizer therapy; over-the-counter (OTC) anti-anxiety and/or antidepressant preparations; established antidepressant, mood stabilizer, or tranquilizer therapy for pre-existing affective disorder will not be permitted during the trial. Subjects will be informed about the risks and benefits of discontinuing their established anxiolytic and/or antidepressant medication. If the subject meets all study inclusion criteria, a baseline study appointment will be scheduled (see Table 2).

Study Phase I (Visit 2/Week 1 to Visit 5/Week 8)

Visit 2/Week1 – Baseline Visit: At the baseline visit, the study informed consent will be reviewed and signed, and all questions will be answered. A complete psychiatric evaluation and medical history will be obtained, along with a physical examination and laboratory evaluation (including drug screen and ECG). Any subject with abnormal laboratory results that may constitute a meaningful co-morbid medical illness will be excluded from the trial. Subjects will also have clinical and QOL outcome ratings performed. Subjects will then start Chamomile therapy 1,500 mg daily (500 mg three times daily). The dose of chamomile may be reduced to 500 mg BID (or 500 mg daily) due to side effects. Subjects who cannot tolerate a minimum chamomile dose of 500 mg daily will be discontinued from the study, and treated as clinically warranted.

Visit 3/Week 2 to Visit 5/Week 8: Subjects will return for follow up study visits at weeks 2, 4 and 8. Subjects will be provided with the self-rating instruments designated for that study visit. Subjects will be evaluated by a study clinician to assess the presence and severity of anxiety symptoms. The study clinician will assess the presence and severity of suicidal ideation, and the presence of treatment-emergent AEs (i.e., dates of occurrence, severity, relationship to study drug). A list of concomitant medication will be obtained. Response in study phase I is dichotomously defined as a ≥ 50% reduction in baseline GAD-7 score *plus* a final CGI/S score ≤ 3 at study visit 5. Non-response is defined as a < 50% reduction in total GAD-7 score or a CGI/S score ≥ 4 at study visit 5. Subjects meeting criteria for non-response will be discontinued from the trial and treated as clinically warranted.

Study Phase II (Visit 6/Week 12)—This is a 4-week, open-label, treatment consolidation phase during which subjects continue on their established chamomile dose. Subjects return for study visit 6 at week 12. The study clinician will assess the presence and severity of suicidal ideation, and the presence of treatment-emergent AEs (i.e., dates of occurrence, severity, relationship to study drug). A list of concomitant medication will be obtained. Response in study phase II is defined the same as in study phase II which is a continued ≥ 50% reduction in baseline GAD-7 score *plus* a final CGI/S score ≤ 3 at study visit 6 (week 12). *Non-response* is defined the same as in study phase I which is a < 50% reduction in total GAD-7 score or a final CGI/S score ≥ 4 at study visit 6. Subjects meeting criteria for non-response will be discontinued from the trial and treated as clinically warranted. Laboratory testing will be done at this visit (or at early study termination in visit 5/week 8).

At the end of visit 6/week12, subjects who continue to be responders will be randomized to double-blind continuation therapy with either chamomile extract 500–1,500 mg daily or placebo for an additional 26 weeks.

Study Phase III (Visit 7/Week 14 to Visit 11/Week 38)—This is a 26-week, double-blind, placebo-substitution phase comparing chamomile (at the established phase II dose) vs. placebo in subjects who have responded to initial chamomile therapy. Subjects in study phase III will return for follow up study visits at weeks 14, 16, 20, 28, and 38. Capsule counts will be maintained at each study visit to enhance compliance. The study clinician will assess the presence and severity of suicidal ideation, and the presence of treatment-emergent AEs (i.e., dates of occurrence, severity, relationship to study drug). A list of concomitant medication will be obtained. Repeat laboratory tests will be obtained at week 38 (or at early study discontinuation) (Table 3).

In study phase III, relapse will be dichotomously defined as: (i) an increase CGI/S score from ≤ 3 (at study visit 6) to ≥ 4 (on two consecutive scheduled or unscheduled study visits ≥ 2 weeks apart) *plus* meeting DSM IV-TR criteria for GAD (minus the 6-month time criterion). To differentiate between GAD relapse vs. new onset co-morbid anxiety or mood disorder, we will perform the LIFE. Subjects with an increase in anxiety or mood symptoms on the LIFE, or who demonstrate a clinically meaningful increase in their GAD-7, HAM-A, or HAM-D score during 2 consecutive scheduled or unscheduled study visits will be evaluated using the appropriate MINI-SCID anxiety and/or mood disorder module to differentiate GAD relapse vs. new onset co-morbid disorder. Subjects meeting criteria for relapse or for a new onset disorder will be discontinued from the trial and treated as clinically warranted.

Statistical Analysis

Overview—The primary aim of this study will test the hypothesis that long-term chamomile (vs. placebo) therapy will prolong the time to relapse in subjects who have recovered from GAD. The primary outcome measure is the difference in time to relapse. A secondary aim of the study is to test the hypothesis that subjects who have recovered from GAD will have a lower proportion of relapses and fewer study discontinuations during long-term chamomile vs. placebo therapy. Chamomile and placebo will also be compared with

respect to the proportion of subjects who survive in each condition (i.e., no relapse) in study phase III. Other secondary outcome measures will include the frequency, severity, and duration of AEs, and the frequency of discontinuation symptoms at the start of double-blind therapy occurring in each treatment condition.

Sample Size Justification—NqQuery Advisor sample size calculation software was used to conduct the power calculations for this study. The sample sizes required in study phase III will depend on the response and drop-out rates in study phase I and II. We will enroll a total of 180 subjects. We estimate a screen failure rate of 10% and a non-response rate of 40% in study phase I and II, resulting in a total of 90 subjects randomized in study phase III (or 45 subejcts per condition). This sample size has sufficient power to test our primary hypothesis of equality of relapse rates between treatment conditions. With 45 subjects per group, we will have 80% power to detect a difference between conditions at the 0.05 level using a log-rank test, assuming the proportion of subjects who have no relapse by week 38 is 45% on placebo vs. 74% on chamomile. Table 4 displays the power available to detect significant differences between conditions at the end of study phase III, assuming several relapse rates.

Support for these relapse rates derive from the analysis of our prior relapse-prevention study of gepirone vs. placebo in GAD subjects with co-morbid depression [45]. In this study, we found relapse rates of: (i) 55% on placebo vs. 26% on gepirone (p=0.030), based on an increase in HAM-D score criterion; and (ii) 61% on placebo vs. 31% on gepirone (p=0.023), based on an increase in the CGI/C criterion. These observed differences were not only statistically significant, but were also clinically meaningful. Smaller differences may not necessarily be clinically meaningful. Thus, the current project is designed to detect clinically meaningful superiority of chamomile vs. placebo that is similar to the superiority of gepirone vs. placebo. Moreover, these rates comport with results of other multi-site studies of a similar design using SSRI and other anxiolytic agents [46–48]. Analyses will be conducted according to the Intention to treat principle, so that subjects will be analyzed according to their initial randomization group.

We will also have sufficient power to detect clinically meaningful differences in the secondary outcomes. For example, a two group χ^2 test with a 0.050 two-sided significance level will have 81% power to detect the difference between a dropout rate of 20% in one group vs. 48% in the other group (odds ratio = 3.692 with 45 subjects per group). Other dropout rates (odds ratios) detectable with 80% power in the two groups include 30% vs. 60% (odds ratio = 3.5), 10% vs. 35% (odds ratio = 4.85) and 15% vs. 42% (odds ratio = 4.2). These detectable differences can also be applied to proportions of subjects in each treatment condition with AEs, so that we have sufficient power to detect meaningful differences in the proportion of subjects with AEs.

Statistical Procedures—Analyses will be conducted using the latest version of STATA (STATA Corporation, College Station, TX). The primary outcome is time to relapse of GAD symptoms during study phase III. Graphical displays of Kaplan-Meier product-limit estimates of survivor functions (probability of survival from relapse over time) for each treatment condition will be generated. These curves will allow for visual comparison of the

time to relapse, drop-out, or completion of the study. The median time to relapse will also be estimated for each treatment condition. The log rank test will then be used to test the primary hypothesis that there is no difference between groups in the probability of relapse at any time point. Survival analyses are appropriate for a comparison of time to relapse between groups because they adjust for censoring in the data, which occurs when a subject is lost to follow up before he/she has a relapse. We will use Cox proportional hazards modeling to compare the hazard (instantaneous relapse rate) between treatment conditions. The Cox proportional hazard analyses will allow for estimation of the relative risk of relapse for the treatment conditions, while also adjusting for other potential correlates of relapse including various demographic and clinical factors (e.g., Axis II disorder). For example, we will include an indicator variable for Axis II disorder (yes/no) and a treatment group x Axis II disorder interaction term in the Cox regression model. This will allow us to test whether the difference in hazard between treatment groups depends on the presence (or absence) of an Axis II disorder. Indicator variables for particular sub-types of Axis II disorders (e.g., OCPD) and treatment group x disorder interaction terms may also be included, to allow for examination of sub-types of Axis II disorders. Cox regression will also allow for stratification on the basis of prior mood disorder, if this is appropriate. We will use graphical checks in STATA to assess the critical assumption of proportionality of the hazard ratios for these models. However, we note that the primary analyses will be unadjusted and will be based on a survival analysis of the time to relapse between the two treatment conditions.

The secondary analyses that involve comparison of treatment conditions will be conducted using χ^2 test for equality of proportions, or the Fisher's exact test, as appropriate. Change in outcomes (e.g., GAD-7, CGI/S, CGI/C, HAM-A, HAM-D, BAI, BDI, and PGWB) in each phase will be compared between groups via generalized estimating equation (GEE) analysis. GEE is a regression approach that allows for comparison of the change over time in the outcomes while adjusting for potential correlation between the repeated measurements on each subject. GEE requires specification of a regression model for the outcome variable. Each regression model will include the covariates of time, an indicator variable for the chamomile condition, and a time x chamomile group interaction term. If the regression coefficient for the interaction term differs significantly from zero, this will indicate that the change over time differs significantly between treatment conditions. In addition, we will use the GEE model to estimate the overall changes in each outcome variable.

Safety profiles of the treatment conditions will be compared via descriptive analyses and by the Chi-Square test to frequency of AEs among treatment groups.

Data and Safety Monitoring

Data and Safety Monitoring Board (DSMB)—In order to assess possible changes in risk/benefit ratio to study subjects and to obtain independent oversight of the study conduct, an external Data and Safety Monitoring Board (DMSB) will be established to oversee the progress of the study. External DSMB study reviews will be conducted at 6-month intervals. The DSMB members will review and monitor the study procedures, potential risks, changes in risk/benefit ratio, subject enrollment, number and nature of medication side effects, and any study-related serious adverse events (SAEs). All SAEs will be reviewed by the DSMB

members in order to determine whether additional safety measures should be initiated, or whether there is a change in the risk/benefit ratio for study subjects.

Adverse Event Monitoring & Documentation—The principal investigator and his co-investigators will be responsible for maintaining and assessing subject safety in the study, monitoring the presence and severity of adverse events, and monitoring compliance with study drug use. Information on adverse events will be obtained by several methods: (i) spontaneous subject reports; (ii) clinician-elicited reports; and, (iii) changes in laboratory and physical findings (e.g., vital signs, weight). An adverse event will be defined as any untoward medical or non-medical occurrence that arises after the subject has signed the ICF, irrespective of a causal relationship to the treatment or study procedure. Lack of drug efficacy will *not* be defined as an adverse event, whereas symptom worsening may be described as an adverse event. All adverse events will be listed on the TESS profile. All adverse events will be monitored and/or treated until resolved. If clinically significant laboratory changes occur, these changes will be reported as adverse events. They will be evaluated and monitored until they have resolved. All SAEs or life-threatening adverse events will be promptly reported to the IRB, the DSMB and the FDA.

Data Monitoring—A project manager trained in regulatory procedures and experienced in managing clinical and research documentation will be responsible for maintaining the completeness of all source documentation and case report forms (CRF). A study and database manager will verify the accuracy of data recorded on the CRFs in the subject study binder and identify any discrepancies and inconsistencies. Study quality assurance and data checking process will take place in a continuous fashion to maintain the integrity of the data.

Discussion

Anxiety disorders are among the most common psychiatric conditions. Despite recent advances in the pharmacotherapy of anxiety disorders, the high cost of conventional drug therapy for anxiety with its attendant side effect burden, served to reduce subject compliance. Therefore, a large segment of the population remains largely untreated [49]. Many of these individuals decline conventional therapy for medical, financial, cultural, or personal reasons. As a result, many will seek CAM therapies for their symptoms.

Chamomile's anxiolytic mode of action is unknown. However, several lines of evidence suggest that some of its flavonoid constituents may produce anxiolytic activity by affecting γ-amino butyric acid (GABA), noradrenalin (NA), dopamine (DA), and serotonin neurotransmission [50–52] or by modulating hypothalamic-pituitary-adrenocortical axis function [53].

Apigenin (a constituent of chamomile) has been shown to bind to benzodiazepine receptors and reduce GABA-activated activity in cultured nerve cells. This effect is blocked by the benzodiazepine receptor antagonist Ro 15–1788 [54]. Moreover, another study found that a semi-synthetic derivative of chamomile, 6,3′-dinitro-flavone, was 30-times more potent than diazepam at the benzodiazepine receptor [55].

In summary, while there are no published controlled clinical trials of the anxiolytic effect of chamomile in humans, there is substantial literature suggesting that chamomile (and several of its flavonoid components) may have anxiolytic and antidepressant activity. This may occur via an effect on GABA, 5-HT, NA, and DA neurotransmission, as well as via an indirect action on the HPA axis and vasomotor systems.

Conclusion

Anxiety symptoms are among the most common reasons for consumers choosing to use CAM therapy [20, 56]. Thus, the identification of effective CAM therapy for anxiety is of relevance, particularly among minority populations [57, 58], the uninsured, and individuals who may avoid conventional psychiatric treatment due to social stigma [59]. Moreover, the majority of people visiting a mental health provider for anxiety were also using CAMs [60]. Long-term clinical and observational studies are needed to establish the safety of prolonged use of CAMs, as well as overall efficacy, in the context of anxiety symptom treatment and management [61]. Therefore, we seek to address some of the scientific questions regarding chamomile treatment for GAD by conducting a randomized, double-blind, placebo-substitution, long-term safety and efficacy evaluation of chamomile therapy in preventing GAD relapse.

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Table 1

Inclusion Criteria and Source Document

Inclusion Criteria	Source	Assessor
Age ≥ 18 years	Self-report	Study nurse, Study Coordinator
DSM IV Axis I diagnosis of GAD as the primary anxiety disorder	Structured Clinical Interview for DSM-IV (SCID)	Study nurse, Diagnostician
Baseline GAD-7 ≥ 10	GAD-7 (self-report)	Study nurse, Study Coordinator
Clinical Global Impression rating ≥ 4 (≥ 'moderate')	Clinical Global Impression (CGI)	Study nurse
Not taking anti-anxiety medication (e.g., BZ, buspirone, SSRI, SNRI)	Baseline visit	Study nurse
Not taking antidepressant, mood stabilizer, or tranquilizer therapy for a prior Axis I mood disorder that is in remission	Baseline visit	Study nurse
Able to provide signed informed consent	Baseline visit	Study nurse, Study Coordinator
Able to participate in a 38-week study	Baseline visit	Study nurse, Study Coordinator
Final, overall eligibility		Principal Investigator

Table 2

Study Phase I&II Procedures

	Baseline	V 3, Week 2	V 4, Week 4	V 5, Week 8	V 6, Week 12
GAD-7, HAM-A, BAI	X	X	X	X	X
CGI/S, CGI/C	X	X	X	X	X
HAM-D, BDI, ISI, BFI	X	X	X	X	X
TESS, CSSRS	X	X	X	X	X
PGWB, RUSH	X		X	X	X
ETI, CRBI	X				
Expectations (2)	X	X			
Dosage, Con Meds	X	X	X	X	
Vital Signs, Weight	X	X	X	X	X
Laboratory Tests, ECG, βHCG					X
Saliva collection	X			X	
Biomarker collection and Chamomile Plasma Level	X			X	

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Table 3

Study Phase III Procedures

	V 7, Week 14	V 8, Week 16	V 9, Week 20	V10, Week 28	V 11, Week 38
GAD-7, HAM-A, BAI, ISI, BFI	X	X	X	X	X
CGI/S, CGI/C, HAM-D, BDI	X	X	X	X	X
DESS	X				
TESS, CSSRS	X	X	X	X	X
PGWB, RUSH	X	X	X		X
ETI, CRBI,					X
LIFE, MINI-SCID Modules	X		X	X	X
Dosage, Con Meds	X	X	X	X	X
Vital Signs, Weight	X	X	X	X	X
Laboratory Tests					X
Biomarker collection and Chamomile Plasma Level banking					X

Table 4

Power to detect differences in relapse rates using log-rank test for several relapse rates

Relapse rate on Placebo	Relapse rate on Chamomile	Power
55%	26%	84%
61%	31%	80%
47.5%	20%	80%
65%	35%	81%