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Short-term open-label chamomile (*Matricaria chamomilla* L.) therapy of moderate to severe generalized anxiety disorder☆

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ABSTRACT

Background: Conventional drug treatments for Generalized Anxiety Disorder (GAD) are often accompanied by substantial side effects, dependence, and/or withdrawal syndrome. A prior controlled study of oral chamomile (*Matricaria chamomilla* L.) extract showed significant efficacy versus placebo, and suggested that chamomile may have anxiolytic activity for individuals with GAD.
Hypothesis: We hypothesized that treatment with chamomile extract would result in a significant reduction in GAD severity ratings, and would be associated with a favorable adverse event and tolerability profile.
Study design: We report on the open-label phase of a two-phase randomized controlled trial of chamomile versus placebo for relapse-prevention of recurrent GAD.
Methods: Subjects with moderate to severe GAD received open-label treatment with pharmaceutical-grade chamomile extract 1500 mg/day for up to 8 weeks. Primary outcomes were the frequency of clinical response and change in GAD-7 symptom scores by week 8. Secondary outcomes included the change over time on the Hamilton Rating Scale for Anxiety, the Beck Anxiety Inventory, and the Psychological General Well Being Index. Frequency of treatment-emergent adverse events and premature treatment discontinuation were also examined.
Results: Of 179 subjects, 58.1% (95% CI: 50.9% to 65.5%) met criteria for response, while 15.6% prematurely discontinued treatment. Significant improvement over time was also observed on the GAD-7 rating ($\beta = -8.4$ [95% CI = −9.1 to −7.7]). A similar proportion of subjects demonstrated statistically significant and clinically meaningful reductions in secondary outcome ratings of anxiety and well-being. Adverse events occurred in 11.7% of subjects, although no serious adverse events occurred.
Conclusion: Chamomile extract produced a clinically meaningful reduction in GAD symptoms over 8 weeks, with a response rate comparable to those observed during conventional anxiolytic drug therapy and a favorable adverse event profile. Future comparative effectiveness trials between chamomile and conventional drugs may help determine the optimal risk/benefit of these therapies for patients suffering from GAD.

Introduction

Generalized anxiety disorder (GAD) is a common form of anxiety with manifestations including excessive worry, poor concentration, restlessness, muscle tension, irritability, fatigue, and sleep difficulties that have occurred for ≥6 months (American Psychiatric Association, 2000). Lifetime prevalence for GAD ranges from 3.7–9.0% of the population in Europe and the United States (Asnaani et al., 2010; Kessler et al., 2012; Wittchen et al., 2011). It is also one of the most common psychiatric disorders in primary care (Davidson et al., 2010; King et al., 2008). While around 46–56% of GAD patients qualify for remission over the course of 8–12 years, 36–43% of patients will experience relapse (Bruce et al., 2005; Francis et al., 2012; Penninx et al., 2011; Yonkers et al., 2003). Although patients with GAD do experience a decline in psychiatric severity

Abbreviations: BAI, Beck Anxiety Inventory self-report scale; CGI-S, Clinical Global Impression–Severity; GAD, Generalized Anxiety Disorder; HAM-A, Hamilton Rating Scale for Anxiety observer scale; PGWB, Psychological General Well Being self-report scale.

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over time, the absolute magnitude of that improvement is modest if untreated (Ramsawh et al., 2008).

One of the most commonly prescribed psychopharmacological therapies for GAD symptoms are benzodiazepine tranquilizers (Baldwin et al., 2012; Reinhold and Rickels, 2015; Rickels and Rynn, 2002; Stahl, 2002). Although effective as a short-term therapy, extended use of benzodiazepines can result in tolerance, habituation, and withdrawal syndrome (Ashton, 2005; Bateson, 2002; Biggio et al., 2003; Bonavita et al., 2002). Furthermore, benzodiazepines result in relatively non-specific suppression of autonomic arousal, causing many to experience neurocognitive impairments (e.g., memory consolidation deficits) while the drug is active (Barker et al., 2004; Lader, 2011; Stewart, 2005), which may make benzodiazepine use prohibited in particular situations of cognitive alertness.

Other classes of medication (e.g. serotonin-1_A receptor partial agonists, serotonin reuptake inhibitors) also demonstrate anxiolytic activity (Baldwin et al., 2011; Gelenberg et al., 2000; Mitte et al., 2005). However, the commonly used selective serotonin reuptake inhibitors are often associated with weight gain, insomnia, daytime somnolence, jitteriness, agitation, and sexual side effects (Ferguson, 2001; Goethe et al., 2007). Concerns over side effects may influence a patient's attempts to treat their anxiety, with around half of treatment-seeking GAD patients tolerating qualifying symptoms for at least 2 years prior to pursuing medical attention (median delay between 6 to 14 years), and a third of those patients ignoring given psychiatric referrals (Baldwin et al., 2012; Kessler et al., 1998). By contrast, many individuals with anxiety and severe depression report attempts to use a complementary or alternative therapy to treat their problem, and endorse a high acceptability of the treatment modality (Kessler et al., 2001; McIntyre et al., 2016).

As one of the most established herbal remedies, chamomile (*Matricaria chamomilla* L. or *Matricaria recutita*) has been employed as a carminative (anti-colic), antiseptic, and anxiolytic (Blumenthal et al., 1998; Bruni et al., 1997; Di Stasi et al., 2002; Merzouki et al., 2000; Pieroni et al., 2002; Singh et al., 2011; Srivastava et al., 2010). Although substantial animal data support the anxiolytic properties of chamomile and several of its flavonoid constituents (Avallone et al., 1995; Nakazawa et al., 2003; Paladini et al., 1999; Reis et al., 2006; Yamada et al., 1996; Zanoli et al., 2000), few clinical trials have been undertaken in humans. To date, there has been one randomized, double-blind, placebo-controlled trial of chamomile safety and efficacy in individuals with GAD (Amsterdam et al. 2009). In this small proof-of-concept study, patients experienced a significantly greater reduction in anxiety symptoms when randomly assigned to chamomile versus placebo ($p = 0.047$).

Building upon its biological plausibility as an active anxiolytic and demonstrated preliminary controlled effects (Amsterdam et al., 2009), we hypothesized that treatment with pharmaceutical grade oral chamomile extract would result in a significant reduction in GAD severity ratings and be associated with a favorable adverse event and tolerability profile. We report acute-phase open-label findings here to allow effect comparisons with the placebo-controlled findings from the original clinical trial of chamomile (Amsterdam et al., 2009), as the open-label conditions in the present trial better resemble how chamomile would be administered in clinical practice. In addition, we decided to separately examine the open-label findings as active drug effects tend to be underestimated in placebo-controlled trials of anxiety and depression. This is due to lowered patient expectancies of treatment efficacy that stem from the knowledge of possibly being treated with an inert compound (Rutherford et al., 2015; Rutherford et al., 2014; Rutherford et al., 2009). We provide results on long-term safety and effectiveness with subsequent continuation chamomile therapy versus placebo among responders who remained well for an additional 4 weeks of consolidation therapy after this open-label phase in a related paper (Mao et al., 2016).

Methods

Subjects

A detailed description of the study design and procedures (Trial Registration Number NCT01072344) is available (Mao et al., 2014). Subjects were recruited from media and print advertisements approved by the Institutional Review Board (IRB) of the University of Pennsylvania, and from subjects referred from the outpatient Family Medicine clinic at the University of Pennsylvania Medical Center. All study-related procedures were performed at the Depression Research Unit of the University of Pennsylvania Medical Center.

Subject enrollment occurred from March 2010 to November 2014. Inclusion and exclusion criteria are described in the associated continuation-phase randomized controlled trial (RCT) paper (Mao et al., 2016).

Study drug

M. chamomilla L. 500 mg dry extract per capsule was pharmaceutical grade. A complete description of active constituents, extraction methods used, certificate of analysis, figure of the High Performance Liquid Chromatography fingerprint, and details on preparation, packaging, and quality control for consistent production of the study drug is provided in our related paper (Mao et al., 2016). Product approval for use in GAD was further granted in a "Safe to Proceed" letter by the Food and Drug Administration on December 17, 2009 (IND 107,206).

Study procedures

After a description of the study was provided to subjects, written informed consent was obtained in accordance with the ethical standards of the IRB of the University of Pennsylvania. The study was conducted using Good Clinical Practice guidelines with oversight by the local Office of Human Research and an independent Data and Safety Monitoring Board.

Psychiatric diagnoses were verified using the *Structured Clinical Interview for DSM-IV-TR Axis I Disorders* (SCID-I) (First et al., 2001). The best estimate of the number of prior GAD episodes (as defined by DSM-IV criteria) that occurred since onset of the disorder were obtained from subjects at their initial interview using the SCID interview format. Medical history, physical examination, weight and blood pressure, and laboratory tests (including hepatic, renal, and thyroid panels, pregnancy test in women, urine screen for drug abuse, and electrocardiogram) were performed.

Outcome measures

Outcome measures were obtained at baseline and after treatment weeks 2, 4, and 8. The protocol-designated primary outcome was frequency of response at week 8 defined as a $\geq$50% reduction in baseline GAD-7 score plus a final CGI-S score of 1 (i.e., normal), 2 (i.e., borderline), or 3 (i.e., mild symptoms). Responders at week 8 continued on consolidation chamomile therapy for an additional 4 weeks. Non-response was defined as a $<$50% reduction in total GAD-7 score or a CGI-S score $\geq$4 at study week 8. The primary continuous outcome measure was change in GAD-7 scores.

Secondary outcome measures included: change from baseline on the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959); change in Beck Anxiety Inventory (BAI) (Beck et al., 1988) score; and change in baseline Psychological General Well Being