THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 26, Number 9, 2020, pp. 815–821

DOI: 10.1089/acm.2019.0252

JACM

Putative Antidepressant Effect of Chamomile (*Matricaria chamomilla* L.) Oral Extract in Subjects with Comorbid Generalized Anxiety Disorder and Depression

Jay D. Amsterdam, MD,[1] Qing S. Li, MS,[2] Sharon X. Xie, PhD,[3] and Jun J. Mao, MD, MSCE[2]

Abstract

Objectives: This exploratory analysis examined the putative antidepressant effect of *Matricaria chamomilla* L. (chamomile) extract in subjects with generalized anxiety disorder (GAD) with or without comorbid depression. It was hypothesized that chamomile extract would demonstrate similar anxiolytic activity in both subgroups, but superior antidepressant activity in GAD subjects with comorbid depression.

Design: As part of a randomized double-blind placebo-controlled trial of chamomile extract for relapse prevention of GAD, 179 subjects received initial therapy with open-label chamomile extract 1500 mg daily for 8 weeks. Linear mixed-effect models were used to identify clinically meaningful changes in anxiety and depression symptoms between diagnostic subgroups.

Settings/Location: The study took place at the University of Pennsylvania in Philadelphia, PA.

Subjects: Subjects were ≥18 years old with a primary DSM IV-TR diagnosis of GAD. They were subcategorized into two diagnostic groups: GAD without comorbid depression ($n = 100$) and GAD with comorbid depression ($n = 79$).

Interventions: Open-label chamomile extract 1500 mg was given daily for 8 weeks.

Outcome measures: Generalized anxiety disorder (GAD-7), Hamilton rating scale for anxiety, Beck anxiety inventory, Hamilton rating scale for depression (HRSD), the six-item core HRSD (items 1, 2, 3, 7, 8, and 13), and the Beck depression inventory (BDI).

Results: The authors observed similar anxiolytic effects over time in both diagnostic subgroups. However, there was a greater reduction in HRSD core symptom scores ($p < 0.023$), and a trend level reduction in HRSD total scores ($p = 0.14$) and in BPI total scores ($p = 0.060$) in subjects with comorbid depression.

Conclusions: *M. chamomilla* L. may produce clinically meaningful antidepressant effects in addition to its anxiolytic activity in subjects with GAD and comorbid depression. Future controlled trials in subjects with primary major depressive disorder are needed to validate this preliminary observation.

Keywords: chamomile, *Matricaria chamomilla* L., antidepressant, depression, anxiety, anxiolytic

Introduction

Generalized anxiety disorder (GAD) frequently occurs with symptoms of comorbid depression.[1–4] Although conventional antidepressant drug therapies have simplified the treatment of comorbid anxiety and depression, a large segment of the population goes untreated[5] or declines conventional antidepressant therapy for financial, cultural, or personal reasons. Many of these individuals seek alternative medicine remedies for their symptoms.[6] The identification of inexpensive and effective alternative therapies for anxiety and depression is, therefore, of public health relevance.[7,8]

[1]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
[2]Integrative Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[3]Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

Matricaria chamomilla L. (chamomile) has been used since antiquity as a traditional botanical remedy for anxiety symptoms.[9] A recent randomized double-blind placebo-controlled trial of pharmaceutical grade chamomile oral extract in subjects with GAD[10] demonstrated significantly greater reduction in mean anxiety symptom outcome ratings for chamomile versus placebo ($p=0.047$). Based upon these clinical observations, and findings from *in vitro* and *in vivo* animal studies,[11–22] a *post hoc* exploratory analysis examining the putative antidepressant effect of chamomile oral extract in subjects with comorbid GAD and depression was performed.[23] In that analysis, 57 subjects received either chamomile extract or placebo therapy: 19 subjects had comorbid GAD and depression, 16 had GAD and a history of depression, and 22 had GAD and no current or history of depression. A significantly greater reduction in mean total depression rating scores ($p<0.05$) and in core depression symptom scores ($p<0.05$) was observed for chamomile versus placebo in all subjects, and a trend level decline in core depression symptom scores for chamomile versus placebo in subjects with current comorbid GAD and depression ($p=0.062$).[23]

Given the prior observation of a possible antidepressant action for chamomile,[23] in the current exploratory analysis it was hypothesized that chamomile would produce a similar anxiolytic effect in GAD subjects with and without comorbid depression, but a greater reduction in depression symptoms in subjects with GAD and comorbid depression.

Materials and Methods

Subjects

Data for this exploratory analysis were derived from the open-label phase of a randomized double-blind placebo-controlled peer-reviewed trial of chamomile oral extract therapy for relapse prevention of GAD (ClinicalTrials.gov identifier: NCT01072344). The full study protocol and primary study outcomes have been published previously.[24–26]

In brief, subjects were ≥18 years old with a primary DSM-IV-TR diagnosis of GAD, ascertained using the structured clinical interview for DSM-IV-TR Axis I Disorders (SCID-I/P).[27] Baseline GAD severity was at least moderate with a GAD-7 rating[28,29] ≥10 and a clinical global impression severity (CGI/S)[30] score ≥4 (i.e., moderately ill). Exclusion criteria were known sensitivity to chamomile, plants of the Asteraceae family, mugwort, or birch pollen; primary DSM-IV-TR diagnosis of a mood disorder (comorbid depression symptoms were not a study exclusion if they did not constitute the primary study diagnosis); panic disorder, phobic disorder, obsessive–compulsive disorder, post-traumatic stress disorder, acute stress disorder, substance-induced anxiety disorder; psychosis; dementia; substance abuse or dependence within the preceding 3 months; unstable medical condition; pregnant or breastfeeding; renal and/or hepatic insufficiency; malignancy; or concurrent use of antidepressants, anxiolytics (e.g., benzodiazepines, buspirone, and serotonin reuptake inhibitors), mood stabilizers, and/or other integrative therapies (e.g., hypericum, valerian root, ginseng, and chamomile tea).

Procedures

The study design included an initial 8-week open-label phase of chamomile extract therapy with response defined as a ≥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). Nonresponse was defined as a <50% reduction in total GAD-7 score or a CGI/S score ≥4 (i.e., moderate) at study week 8. Responders at week 8 continued open-label consolidation chamomile therapy for an additional 4 weeks. For this open-label phase of the study, the primary protocol-designated continuous outcome measure was change in GAD-7 scores. Subjects who continued to respond to open-label chamomile therapy were then enrolled into a randomized-double-blind comparison of chamomile versus placebo for relapse prevention of GAD. For the current exploratory analysis, the data from all subjects who received open-label chamomile extract for up to 8 weeks were analyzed.

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 family medicine outpatient clinic at Penn Medicine in the University of Pennsylvania Health System. All study-related procedures were performed at the Depression Research Unit of the Perelman School of Medicine, University of Pennsylvania. Subjects provided informed consent in accordance with the ethical standards of the University of Pennsylvania's IRB. The study was conducted using the Principles of Good Clinical Practice Guidelines, with oversight by the local office of human research and by an independent Data & Safety Monitoring Board.

Before the baseline study visit, all subjects underwent a detailed evaluation that included a medical and psychiatric history, physical examination, and laboratory tests (including complete blood count, electrolytes, hepatic, renal and thyroid panel, pregnancy test in women of child-bearing potential, urinalysis, and urine drug screen for drugs of abuse).

Treatment

Clinical management was conducted in a structured manner.[31] Fixed-flexible dosing with chamomile oral extract 500 mg capsules totaling 1500 mg daily was administered. The total daily dose was based upon prior efficacy and tolerability observations.[10] The fixed-flexible dosing strategy afforded subjects the opportunity to reduce the daily dose of chamomile to a minimum of 500 mg (if warranted). Study drug accountability and capsule counts were ascertained at weeks 2, 4, and 8 of study visits.

Study drug

Each capsule contained 500 mg of pharmaceutical grade dry extract of *M. chamomilla* L. flowers (equivalent to 2.0 g of German chamomile flowers). This corresponded to 6 mg of flavonoids, with total apigenin-7-glycosides (calculated as apigenin-7-glycoside; Api-7Glc). The extraction solvents were ethanol 70%, v/v, and water (for the second extraction). German chamomile dry extract SHC-1 (DER 4:1, batch no. 50,053 (Swedish Herbal Institute AB, Vallberga, Sweden) was standardized to a content of 1.2% Api-7Glc and 0.2%–0.6% tetra coumaroyl spermine . The content of Api-7Glc in the herbal substance and herbal preparation was analyzed according to the European Pharmacopoeia 8.8 monograph 04/2016:0404 and the United States Pharmacopeia-30.

Api-7Glc was present in the botanical product in both free and esterified forms. For the measurement of total apigenin-7-glucosides, the herb and extracts were separately

subjected to alkaline hydrolysis, in which various acetylated derivatives of Api-7Glc were converted to Api-7Glc. The hydrolysates were then subjected to high-performance liquid chromatography using a Waters Empower system.

The content of the genuine Matricaria flower extract (DER_{native}–6.2:1) in the SHC-1 comprised 65% of the product, whereas the other 35% of the product comprised maltodextrin as a carrier. Samples of the herbal substance and herbal preparations were retained at the manufacturer's quality control laboratory. A certificate of analysis of purity and suitability for human use was provided to the study investigators and was submitted to the United States Food and Drug Administration for approval of a new drug application (IND 107,206) on December 17, 2009.

Chamomile capsules were prepared and packaged by the University of Pennsylvania Investigational Drug Service under *Good Manufacturing Practice Guidelines*, in a high-efficiency particulate air (HEPA)-filtered ISO-8 production facility. A dose of 500 mg of dry extract SHC-1 was filled into a gelatin capsule shell without any additional filler.

Outcome measures

Protocol-designated and *post hoc* outcome measures included in this analysis were the 7-item generalized anxiety disorder (GAD-7) rating,[28,29] Hamilton rating scale for anxiety (HRSA),[32] Beck anxiety inventory (BAI),[33] 17-item Hamilton rating scale for depression (HRSD),[34] the six-item core HRSD (comprising HRSD items #1 (depressed mood), #2 (guilt), #3 (suicide ideation), #7 (work and interest), #8 (retardation), and #13 (somatic symptoms general)),[23,35] and the Beck depression inventory (BDI).[36] GAD subjects underwent a *post hoc* categorization into two groups: (1) GAD without comorbid depression and (2) GAD with comorbid depression.

Sample size justification

The sample size for the open-label phase of the study by the estimated sample size required to detect a chamomile versus placebo difference during the relapse-prevention phase of the trial was determined. A screen failure rate of 10% and a nonresponse rate of 40% in the open-label study phase were estimated. Thus, a total of 180 subjects received open-label chamomile extract (of which 179 subjects had at least one repeat outcome measurements performed). This sample size permitted us to test the primary (i.e., relapse prevention) hypothesis with 80% power to detect a difference between treatment conditions at the 0.05 level. It was noted that the current exploratory analysis was not specifically powered to detect statistically significant differences in depression rating outcomes between GAD subgroups.

Statistical procedures

Statistical analysis followed intent-to-treat principals. The objective of this exploratory analysis was a two-group comparison of the mean change in outcomes (i.e., GAD-7, HRSA, BAI, core HRSD, 17-item HRSD, and BDI ratings) between GAD subjects without comorbid depression and GAD subjects with comorbid depression taking chamomile extract for 8 weeks.

A chi-square test was used to compare categorical baseline variables and two-sample *t*-test to compare continuous baseline variables between the diagnostic subgroups. Differences in outcomes over time from baseline to week 8 were examined using a linear mixed-effect model. The fixed effects in the linear mixed-effect model for each outcome were comorbid depression status, time, comorbid depression status × time interaction, and baseline outcome. Subject-specific

Table 1. Demographic and Clinical Characteristics of Participants

	All subjects (n = 179)	*GAD without comorbid affective disorder (n = 100)*	*GAD with comorbid affective disorder (n = 79)*	p[a]
Age (mean/SD)	45.7 ± 15.3	44.7 ± 16.5	46.9 ± 13.5	0.32
Gender (*N*, %)				0.26
Male	60 (34)	30 (30)	30 (38)	
Female	119 (66)	70 (70)	49 (62)	
Age GAD onset (mean/SD)	21.5 ± 15.4	18.6 ± 14.1	25.1 ± 16.2	**0.0045**
Episode length (years) (mean/SD)	8.4 ± 13.9	10.1 ± 16.1	6.2 ± 10.1	0.081
HRSA total (mean/SD)	14.7 ± 3.6	14.2 ± 3.3	15.5 ± 3.8	**0.012**
GAD-7 (mean/SD)	13.7 ± 2.8	13.3 ± 2.6	14.2 ± 2.9	**0.029**
Age depression onset (mean/SD)	23.6 ± 14.5	20.4 ± 11.1	25.7 ± 16.1	0.089
HRSD 17 total (mean/SD)	13.7 ± 4.0	12.3 ± 3.4	15.5 ± 3.9	**<0.001**
HRSD total (mean/SD)	16.5 ± 5.5	14.3 ± 4.5	19.3 ± 5.4	**<0.001**
HRSD core score[b] (mean/SD)	2.2 ± 1.5	1.7 ± 1.2	2.9 ± 1.6	**<0.001**
HRSD extended core score[c] (mean/SD)	5.0 ± 2.5	4.0 ± 2.1	6.3 ± 2.4	**<0.001**
BDI total (mean/SD)	19.5 ± 10.1	16.0 ± 8.1	23.9 ± 10.7	**<0.001**
BAI total (mean/SD)	16.8 ± 9.4	16.2 ± 9.5	17.6 ± 9.2	0.33

All statistical tests were two-sided. Bold indicates statistical significance set at 0.05.
[a]Chi-square or two-sample *t*-test *p* values.
[b]Item 1, 2, and 3.
[c]Item 1, 2, 3, 7, 8, and 13.
BAI, Beck anxiety inventory; BDI, Beck depression inventory; GAD, generalized anxiety disorder; HRSD, Hamilton rating scale for depression; SD, standard deviation.

random intercepts to account for the correlation between repeated measures of each outcome were used. Given the exploratory nature of the study, preplanned hypotheses, and the fact that the study was not specifically powered to identify statistically significant differences between the diagnostic groups, the authors chose not to apply Bonferroni corrections for multiple outcome analyses.

Analyses were conducted using STATA (version 12.0; STATA Corporation, College Station, TX) and SAS (version 9.4; SAS Institute, Cary, NC). All statistical tests were two sided. The statistical significance level was set at 0.05.

Results

Study enrollment occurred between March 2010 and June 2015, with 394 subjects evaluated and 179 subjects enrolled: the mean (standard deviation) age was 45.7 (15.3) years and 119 (66%) were female. Demographic and clinical variables of the subject sample are displayed in Table 1.

Subjects were subcategorized into two diagnostic groups: (1) GAD without comorbid depression ($n=100$) and (2) GAD with comorbid depression ($n=79$). At baseline, there were no clinically meaningful differences between diagnostic subgroups for most sociodemographic characteristics. However, the mean age of first GAD onset was significantly older for GAD subjects with comorbid depression (mean 25.1 years) versus subjects without comorbid depression (mean 18.6 years) ($p=0.0045$). In addition, subjects with comorbid depression had a significantly higher mean total HRSA score ($p=0.012$), higher mean GAD-7 score ($p=0.029$), higher mean total HRSD score ($p<0.001$), higher mean core HRSD scores ($p<0.001$), and higher mean BDI score ($p<0.001$) (Table 1).

There was no statistically significant difference in change over time in any of the anxiety symptom outcome measures between diagnostic subgroups during 8 weeks of chamomile therapy. In contrast, GAD subjects with comorbid depression demonstrated significant reductions over time for the core HRSD score versus GAD subjects without comorbid depression ($p=0.023$) (Table 2). Similarly, GAD subjects with comorbid depression demonstrated a greater trend level reduction over time in total HRSD ($p=0.14$) and BDI scores ($p=0.060$) (Table 2).

Discussion

In a prior study of the putative antidepressant effects of chamomile extract in GAD subjects with or without comorbid depression, a greater, although trend level, reduction of total HRSD scores was observed while taking chamomile (vs. placebo) in GAD subjects with comorbid depression ($p=0.062$).[23] These preliminary observations suggested that chamomile extract may exert an antidepressant effect distinct from its anxiolytic activity. The authors, therefore, undertook the current exploratory analysis to examine the putative antidepressant effect of chamomile extract on a new, and substantially larger, sample of GAD subjects with or without comorbid depression. The authors hypothesized

Table 2. Changes in Outcomes

	Mean change from baseline (95% CI)		*Between-group difference (95% CI)*	
Variables	*GAD without comorbid affective disorder*	*GAD with comorbid affective disorder*	*GAD with comorbid affective disorder versus GAD without comorbid affective disorder*	p[a]
HRSA				0.75
Week 2	−5.08 (−5.8 to −4.3)	−5.26 (−6.1 to −4.4)	−0.17 (−1.3 to 1.0)	
Week 4	−7.32 (−8.1 to −6.5)	−7.82 (−8.7 to −6.9)	−0.50 (−1.7 to 0.7)	
Week 8	−8.90 (−9.7 to −8.1)	−9.48 (−10.4 to −8.6)	−0.59 (−1.8 to 0.6)	
HRSD 17				0.14
Week 2	−3.89 (−4.7 to −3.1)	−3.73 (−4.7 to −2.8)	0.16 (−1.1 to 1.4)	
Week 4	−5.63 (−6.5 to −4.8)	−6.23 (−7.2 to −5.3)	−0.60 (−1.9 to 0.7)	
Week 8	−6.86 (−7.7 to −6.0)	−8.09 (−9.0 to −7.1)	−1.23 (−2.5 to 0.05)	
GAD-7				0.34
Week 2	−4.78 (−5.6 to −4.0)	−4.65 (−5.5 to −3.8)	0.12 (−1.1 to 1.3)	
Week 4	−6.26 (−7.1 to −5.4)	−7.15 (−8.1 to −6.2)	−0.89 (−2.1 to 0.3)	
Week 8	−7.54 (−8.4 to −6.7)	−8.05 (−9.0 to −7.1)	−0.50 (−1.7 to 0.7)	
HRSD extended core				**0.023**
Week 2	−1.15 (−1.6 to −0.7)	−1.23 (−1.7 to −0.7)	−0.075 (−0.7 to 0.6)	
Week 4	−1.68 (−2.1 to −1.2)	−2.32 (−2.8 to −1.8)	−0.64 (−1.3 to 0.03)	
Week 8	−2.19 (−2.6 to −1.7)	−3.10 (−3.6 to −2.6)	−0.90 (−1.6 to −0.2)	
BAI				0.87
Week 2	−4.80 (−6.1 to −3.4)	−4.59 (−6.1 to −3.0)	0.21 (−1.8 to 2.2)	
Week 4	−7.30 (−8.7 to −5.9)	−7.06 (−8.6 to −5.5)	0.24 (−1.8 to 2.3)	
Week 8	−8.86 (−10.3 to −7.4)	−9.44 (−11.0 to −7.8)	−0.58 (−2.7 to 1.5)	
BDI				0.060
Week 2	−6.05 (−7.5 to −4.6)	−7.76 (−9.4 to −6.1)	−1.71 (−3.9 to 0.4)	
Week 4	−7.51 (−9.0 to −6.0)	−9.36 (−11.0 to −7.7)	−1.85 (−4.0 to 0.3)	
Week 8	−9.20 (−10.7 to −7.7)	−12.26 (−13.9 to −10.6)	−3.06 (−5.3 to −0.8)	

All statistical tests were two-sided. Bold indicates statistical significance set at 0.05.
[a]Mixed-effect *p*-value of the interaction term.
CI, confidence interval; HRSA, Hamilton rating scale for anxiety.

that chamomile extract would demonstrate a similar anxiolytic effect over time for both GAD subgroups, but would show a greater antidepressant effect over time in GAD subjects with comorbid depression. Although the current exploratory analysis was not specifically powered to detect statistically significant differences between diagnostic subgroups for changes over time in depressive symptom scores, the authors did expect to find clinically meaningful changes between depressed versus nondepressed GAD subjects.

Although chamomile's mode of antidepressant action in humans is unknown, it may be independent of its anxiolytic activity. For example, several constituents of dried chamomile extract possess neurokinin-1 receptor (NK1r) antagonist activity.[37] NK1r antagonists appear to block production of substance P resulting in a potent anti-inflammatory and putative antidepressant action in humans,[38–40] and this mechanism of action may contribute to chamomile's antidepressant activity.

Chamomile extract constituents may also affect hypothalamic-pituitary-adrenocortical (HPA) axis activity that modulates GAD and depressive symptoms. For example, lower cortisol awakening levels have been observed in GAD subjects, as has lower HPA axis activity during chronic stress with subsequent enhanced cortisol activation in depression.[41,42] In addition, other studies suggest that chamomile may exert an antidepressant effect by modulating HPA axis activity.[20,21] For example, Yamada et al.[20] found that chamomile oil vapor reduced restriction stress-induced increases in adrenocorticotropic (ACTH) levels in ovariectomized rats. Moreover, plasma ACTH levels further decreased when diazepam was administered with chamomile oil vapor. In contrast, the ACTH decrease was blocked when flumazenil was given with chamomile oil vapor. In a bovine behavioral study, Reis et al.[21] examined the effects of chamomile on ''handling stress'' in Nellore calves fed dietary *M. chamomilla* CH12 ($n=30$) or no chamomile ($n=30$) for 30 days. The calves were stressed on days 31, 38, 45, and 60. Cortisol levels were significantly lower after stress immobilization in chamomile-fed calves on day 45, suggesting that chamomile may exert both an anxiolytic and antidepressant effect through modulation of the HPA axis.

Other evidence suggests that chamomile's flavonoid constituents may exert antidepressant activity through modulation of central neurotransmitter activity.[13–16,20] For example, Lorenzo et al.[11] found that apigenin increased noradrenalin (NA) activity in an isolated rat atria model, and inhibited monoamine oxidase activity in rat atria homogenates. Morita et al.[12] found that apigenin stimulated the uptake of L-[^{14}C]-tyrosine, a dopamine (DA) precursor, into cultured adrenal chromaffin cells, whereas flavone produced an increase in [^{14}C]-catecholamine production without altering [^{14}C]-tyrosine turnover. Nakazawa et al.[13] found an antidepressant-like activity of apigenin on NA and DA turnover in the amygdala and hypothalamus in mice exposed to the forced swim test (FST), whereas Anjaneyulu et al.[14] found that quercetin reduced the immobility of mice during the FST in a dose-dependent manner comparable with fluoxetine and imipramine. Yi et al.[15] found that apigenin reduced immobility during the FST in mice; reversed FST-induced reduction in sucrose intake in rats; lowered stress-induced alterations in serotonin (5-HT), DA, and their metabolites; and reversed FST-induced increases in HPA axis activity.

Finally, several recent studies of chamomile therapy in depressed humans and animals with depression-like symptoms have lent additional support to the possibility that chamomile may produce antidepressant effects.[43–45]

Several caveats should be considered in the interpretation of the current findings. For example, the study was not powered to detect statistically significant differences in any of the depression outcome ratings between diagnostic subgroups. Moreover, the *post hoc* categorization of subjects into separate diagnostic subgroups necessarily produced smaller sample sizes and may have altered the authors' ability to detect small to moderate differences in HRSD and BDI ratings between groups. Diagnostic subcategorization also produced some unbalance in baseline clinical and demographic variable distributions that could have influenced the current findings. Furthermore, given the exploratory nature of the analysis, the authors did not correct for multiple outcome comparisons. Thus, it is possible that the statistically significant and clinically meaningful reductions in HRSD and BDI scores observed in GAD subjects with comorbid depression represent type 1 errors. Furthermore, given the *a priori* presence of higher depression scores at baseline for the subgroup of GAD subjects with comorbid depression, it is possible that the current observation of antidepressant activity could represent a placebo effect. It is also possible that the apparent effects of chamomile extract on depression symptoms were not due to antidepressant action *per se*, but rather the result of chamomile's primary anxiolytic activity. In this regard, the antidepressant outcomes may have been different if the primary disorder of the study was major depressive disorder. Similarly, it is possible that the antidepressant outcome may have been different if a greater chamomile dose or treatment duration had been selected, or if a different chamomile species or chamomile extract standardization had been employed.

Furthermore, the authors acknowledge that the absence of an active or placebo control group and/or differences in some baseline variables between diagnostic subgroups may have limited their ability to evaluate the contribution of a ''placebo effect'' on outcome. Moreover, possible uncertainty of the validity of the HRSD core symptom scale, which was the only outcome measure demonstrating a significant difference between subgroups in this study, could possibly raise questions about the putative antidepressant action of chamomile. In this regard, however, the authors note that the BDI measure in this study also showed a meaningful, although trend-level, significance of $p<0.06$.

Finally, it is acknowledged that the current analyses were exploratory and only suggest the possibility of an antidepressant activity for chamomile. Future prospective trials will need to be conducted in subjects with primary major depressive disorder to validate the presence of antidepressant activity of chamomile.

Conclusions

In addition to its primary anxiolytic activity in subjects with GAD, *M. chamomilla* L. oral extract may also demonstrate a substantial reduction of depressive symptoms in subjects with comorbid GAD plus depression. Thus, it is possible that *M. chamomilla* L. may also possess primary antidepressant activity. Future controlled clinical trials of subjects with primary depression are needed to validate this observation.

Acknowledgments

The authors are grateful to Dr. Alexander Panossian for providing his botanical expertise in the formulation and production of the pharmaceutical grade chamomile extract product used in this study, and for his invaluable assistance in the preparation and submission of the regulatory documentation of the chamomile product for NIH and FDA regulatory approval. The authors thank Kenneth Rockwell Jr, PharmD, MS, Director of Research Pharmacy, Perelman School of Medicine, University of Pennsylvania, and the Penn Investigational Drug Service for study drug preparation and dispensing. The Swedish Herbal Institute is thanked for producing, processing, and providing the standardized chamomile extract product.

Authors' Contribution

Dr. Amsterdam and Dr. Mao designed the study and wrote the protocol. Ms. Li and Dr. Xie managed the literature searches and analyses. Ms. Li and Dr. Xie undertook the statistical analysis. All authors contributed to the first draft of the article and have approved the final article.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This study was supported by grants from the National Institutes of Health (NIH)/National Center for Complementary and Integrative Health (Grant Number R01 AT005074), and NIH/National Cancer Institute (Cancer Center Support Grant Number P30 CA008748 to Memorial Sloan Kettering Cancer Center). Additional support for the preparation of this article was provided by the Translational and Integrative Medicine Research Fund at Memorial Sloan Kettering Cancer Center. The funding agencies had no role in study design; in the collection, analysis, or interpretation of the data; in the writing of the report; or in the decision to submit the article for publication.

References

1. Brown TA, Campbell LA, Lehman CL, et al. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. J Abnorm Psychol 2001;110:585–599.
2. Schoevers RA, Deeg DJ, van Tilburg W, Beekman AT. Depression and generalized anxiety disorder: Co-occurrence and longitudinal patterns in elderly patients. Am J Geriatr Psychiatry 2005;13:31–39.
3. Dunlop BW, Davis PG. Combination treatment with benzodiazepines and SSRIs for comorbid anxiety and depression: A review. Prim Care Companion J Clin Psychiatry 2008;10:222–228.
4. Bruce SE, Yonkers KA, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: A 12-year prospective study. Am J Psychiatry 2005; 162:1179–1187.
5. Wang PS, Lane M, Olfson M, et al. Twelve-month use of mental health services in the United States: Results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:629–640.
6. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. Adv Data 2004:1–19.
7. Givens JL, Houston TK, Van Voorhees BW, et al. Ethnicity and preferences for depression treatment. Gen Hosp Psychiatr 2007;29:182–191.
8. Givens JL, Katz IR, Bellamy S, Holmes WC. Stigma and the acceptability of depression treatments among African Americans and Whites. J Gen Intern Med 2007;22:1292–1297.
9. Salamon I. Production of Chamomile, *Chamomilla recutita* (L.) Rauschert, in Slovakia. J Herb Spic Med Plants 1992;1: 37–45.
10. Amsterdam JD, Li Y, Soeller I, et al. A randomized, double-blind, placebo-controlled trial of oral *Matricaria recutita* (chamomile) extract therapy for generalized anxiety disorder. J Clin Psychopharmacol 2009;29:378–382.
11. Lorenzo PS, Rubio MC, Medina JH, Adler-Graschinsky E. Involvement of monoamine oxidase and noradrenaline uptake in the positive chronotropic effects of apigenin in rat atria. Eur J Pharmacol 1996;312:203–207.
12. Morita K, Hamano S, Oka M, Teraoka K. Stimulatory actions of bioflavonoids on tyrosine uptake into cultured bovine adrenal chromaffin cells. Biochem Biophys Res Commun 1990;171:1199–1204.
13. Nakazawa T, Yasuda T, Ueda J, Ohsawa K. Antidepressant-like effects of apigenin and 2,4,5-trimethoxycinnamic acid from *Perilla frutescens* in the forced swimming test. Biol Pharm Bull 2003;26:474–480.
14. Anjaneyulu M, Chopra K, Kaur I. Antidepressant activity of quercetin, a bioflavonoid, in streptozotocin-induced diabetic mice. J Med Food 2003;6:391–395.
15. Yi LT, Li JM, Li YC, et al. Antidepressant-like behavioral and neurochemical effects of the citrus-associated chemical apigenin. Life Sci 2008;82:741–751.
16. Pinto SA, Bohland E, Coelho Cde P, et al. An animal model for the study of Chamomilla in stress and depression: Pilot study. Homeopathy 2008;97:141–144.
17. Marder M, Paladini AC. GABA(A)-receptor ligands of flavonoid structure. Curr Top Med Chem 2002;2:853–867.
18. Paladini AC, Marder M, Viola H, et al. Flavonoids and the central nervous system: From forgotten factors to potent anxiolytic compounds. J Pharm Pharmacol 1999;51:519–526.
19. Awad R, Levac D, Cybulska P, et al. Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. Can J Physiol Pharmacol 2007;85:933–942.
20. Yamada K, Miura T, Mimaki Y, Sashida Y. Effect of inhalation of chamomile oil vapour on plasma ACTH level in ovariectomized-rat under restriction stress. Biol Pharm Bull 1996;19:1244–1246.
21. Reis LS, Pardo PE, Oba E, et al. *Matricaria chamomilla* CH12 decreases handling stress in Nelore calves. J Vet Sci 2006;7:189–192.
22. Dimpfel W. Rat electropharmacograms of the flavonoids rutin and quercetin in comparison to those of moclobemide and clinically used reference drugs suggest antidepressive and/or neuroprotective action. Phytomedicine 2009;16: 287–294.
23. Amsterdam JD, Shults J, Soeller I, et al. Chamomile (*Matricaria recutita*) may provide antidepressant activity in anxious, depressed humans: An exploratory study. Altern Ther Health Med 2012;18:44–49.

24. Mao JJ, Li QS, Soeller I, et al. Long-term chamomile therapy of generalized anxiety disorder: A study protocol for a randomized, double-blind, placebo-controlled trial. J Clin Trials 2014;4:5.
25. Keefe JR, Mao JJ, Soeller I, et al. Short-term open-label chamomile (*Matricaria chamomilla* L.) therapy of moderate to severe generalized anxiety disorder. Phytomedicine 2016;23:1699–1705.
26. Mao JJ, Xie SX, Keefe JR, et al. Long-term chamomile (*Matricaria chamomilla* L.) treatment for generalized anxiety disorder: A randomized clinical trial. Phytomedicine 2016;23:1735–1742.
27. First MB. User's Guide for the Structured Clinical Interview for DSM-IV-TR Axis I Disorders: SCID-I. New York, NY: Biometrics Research Department, New York State Psychiatric Institute, 2002.
28. Löwe B, Decker O, Müller S, et al. Validation and standardization of the Generalized Anxiety Disorder Screener (GAD-7) in the general population. Med Care 2008;46:266–274.
29. Lowe B, Spitzer RL, Williams JB, et al. Depression, anxiety and somatization in primary care: Syndrome overlap and functional impairment. Gen Hosp Psychiatry 2008;30:191–199.
30. Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976.
31. Fawcett J, Epstein P, Fiester SJ, et al. Clinical management—Imipramine/placebo administration manual. NIMH Treatment of Depression Collaborative Research Program. Psychopharmacol Bull 1987;23:309–324.
32. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55.
33. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: Psychometric properties. J Consult Clin Psychol 1988;56:893–897.
34. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 1988;45: 742–747.
35. Maier WP, M. Improving the assessment of severity of depressive states: A reduction of the Hamilton depression scale. Pharmacopsychiatry 1985;18:114–115.
36. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571.
37. Yamamoto A, Nakamura K, Furukawa K, et al. A new nonpeptide tachykinin NK1 receptor antagonist isolated from the plants of Compositae. Chem Pharm Bull 2002;50: 47–52.
38. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 1998;281:1640–1645.
39. Kramer MS, Winokur A, Kelsey J, et al. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. Neuropsychopharmacology 2004;29:385–392.
40. Rupniak NMJ, Kramer MS. NK1 receptor antagonists for depression: Why a validated concept was abandoned. J Affect Disord 2017;223:121–125.
41. Chida Y, Steptoe A. Cortisol awakening response and psychosocial factors: A systematic review and meta-analysis. Biol Psychol 2009;80:265–278.
42. Staufenbiel SM, Penninx BWJH, Spijker AT, et al. Hair cortisol, stress exposure, and mental health in humans: A systematic review. Psychoneuroendocrinology 2013;38:1220–1235.
43. Kong Y, Wang T, Wang R, et al. Inhalation of Roman chamomile essential oil attenuates depressive-like behaviors in Wistar Kyoto rats. Sci China Life Sci 2017;60:647–655.
44. Chang SM, Chen CH. Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: A randomized controlled trial. J Adv Nurs 2016;72:306–315.
45. Yeung KS, Hernandez M, Mao JJ, et al. Herbal medicine for depression and anxiety: A systematic review with assessment of potential psycho-oncologic relevance. Phytother Res 2018;32:865–891.

Address correspondence to:
Jay D. Amsterdam, MD
P.O. Box 1931
Cherry Hill
New Jersey 08034
USA

E-mail: jamsterd@pennmedicine.upenn.edu