ORIGINAL RESEARCH

Chamomile (*Matricaria recutita*) May Provide Antidepressant Activity in Anxious, Depressed Humans: An Exploratory Study

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ABSTRACT

Context • Anxiety and depression are the most commonly reported psychiatric conditions and frequently occur as comorbid disorders. While the advent of conventional drug therapies has simplified treatment, a large segment of the population goes untreated or declines conventional therapy for financial, cultural, or personal reasons. Therefore, the identification of inexpensive and effective alternative therapies for anxiety and depression is of relevance to public health.

Objective • The current study explores data from a 2009 clinical chamomile trial in humans to determine if chamomile provides clinically meaningful antidepressant activity versus a placebo.

Design: • In the 2009 randomized, double-blind, placebo-controlled study, the research team examined the antianxiety and antidepressant action of oral chamomile (*Matricaria recutita*) extract in participants with symptoms of comorbid anxiety and depression.

Setting • In the 2009 study, all of participants' evaluations took place at the Depression Research Unit at the University of Pennsylvania. The study drew participants from patients at the Department of Family Medicine and Community Health's primary care clinic at the University of Pennsylvania, Philadelphia.

Participants • Of the 57 participants in the 2009 trial, 19 had anxiety with comorbid depression; 16 had anxiety with a past history of depression; and 22 had anxiety with no current or past depression.

Intervention • The intervention and placebo groups in the 2009 trial received identically appearing 220-mg capsules containing either pharmaceutical-grade chamomile extract standardized to a content of 1.2% apigenin or a placebo (ie, lactose monohydrate NF), respectively.

Outcome Measures • In the current study, the research team used generalized estimating equations analysis to identify clinically meaningful changes over time in scores from the Hamilton Depression Rating (HAM-D) questionnaire among treatment groups.

Results • In the current study, the research team observed a significantly greater reduction over time in total HAM-D scores for chamomile vs placebo in all participants ($P < .05$). The team also observed a clinically meaningful but nonsignificant trend for a greater reduction in total HAM-D scores for chamomile vs placebo in participants with current comorbid depression ($P = .062$). When the team examined the HAM-D core mood item scores, it observed a significantly greater reduction over time for chamomile vs placebo in all participants ($P < .05$) and a clinically meaningful but nonsignificant trend for a greater reduction over time for chamomile vs placebo in participants without current or past depression ($P = .06$).

Conclusion • Chamomile may provide clinically meaningful antidepressant activity that occurs in addition to its previously observed anxiolytic activity. (*Altern Ther Health Med.* 2012;18(5):44-49.)

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Anxiety and depression are the most commonly reported psychiatric conditions[1-3] and frequently occur as comorbid disorders.[4-7] Both conditions can be chronic or recurrent[5,8] and can frequently require long-term therapy.[9] While the advent of conventional drug therapies has simplified treatment, a large segment of the population goes untreated or declines conventional therapy for financial, cultural, or personal reasons.[10] Many of these individuals seek complementary and alternative medicine (CAM) remedies for their symptoms.[11] Therefore, the identification of inexpensive and effective alternative therapies for anxiety and depression is of relevance to public health.[12,13] Researchers need to perform rigorous testing of candidate CAM therapies to expand available therapeutic options for anxiety and depression.

The use of chamomile as an herbal remedy dates back to ancient Greece and Rome. Practitioners have used chamomile (*Matricaria recutita*) as a traditional herbal remedy for its calming effect. While many varieties of chamomile exist, Roman (*Anthemis nobilis*) and German (*M recutita*) are the most widely used. These types are members of the Compositae (Asteracae) family. Practitioners consider *M recutita* to be the more potent variety and use it widely for medicinal purposes. Researchers have documented use of *M recutita* for relief of depressive and anxiety symptoms in a number of regions in southern Italy,[14] Sardinia,[15] Morocco,[16] and Brazil.[17] *M recutita* is grown as a cash crop in Argentina, Egypt, Hungary, Slovakia, and Germany.[18] In addition, practitioners have used other varieties of chamomile to treat the symptoms of depression and anxiety, including *Anthemis arvensis* and *Tanacetum parthenium* in Tuscany[19] and *Chamaemelum fuscatum* in Spain.[20] In spite of these uses, only one randomized controlled study has explored the effects of chamomile on mood in the past. This randomized, double-blind, placebo-controlled trial of oral chamomile extract for generalized anxiety disorder (GAD) found a significantly greater reduction in mean ratings for anxiety symptoms for chamomile vs placebo ($P = .047$) and a nonsignificant (albeit clinically meaningful) reduction in depression ratings[21] with chamomile vs placebo ($P = .136$).[22]

Based upon prior observations from in vivo and in vitro animal studies suggesting that chamomile may possess antidepressant activity,[23-27] the research team conducted the current secondary, exploratory analysis of its prior, clinical chamomile trial in humans[22] to examine whether chamomile demonstrated antidepressant activity in conjunction with its antianxiety effects. The team hypothesized that chamomile would show clinically meaningful, antidepressant activity (vs placebo) as measured by change over time in ratings for depression symptoms.

METHODS

Participants

The Department of Family Medicine and Community Health's primary care clinic at the University of Pennsylvania, Philadelphia referred patients to the study. These individuals were ≥18 years old and had a primary *DSM IV* Axis I diagnosis of GAD that the research team confirmed using the *Structured Diagnostic Interview for DSM IV* (SCID).[28] Participants had mild-to-moderate symptoms of depression and a minimum baseline score ≥9 on the Hamilton Anxiety Rating (HAM-A)[29] questionnaire.

The research team did not exclude individuals from the trial if they had a comorbid DSM IV Axis I dysthymic disorder nor if they had a depressive disorder not otherwise specified (NOS) where the comorbid condition did not constitute the primary disorder. The team did exclude individuals from the trial if they had a current diagnosis of major depressive disorder, bipolar disorder, panic disorder, phobic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, substance-induced anxiety disorder, psychosis, dementia, or substance abuse or dependence within the preceding 3 months. Other exclusion criteria were (1) an unstable medical condition, (2) hepatic or renal insufficiency, (3) malignancy, or (4) known sensitivity to chamomile, plants of the asteraceae family, mugwort, or birch pollen. The study did not permit concurrent use of anxiolytics, antidepressants, mood stabilizers, sedatives, or herbal remedies (including chamomile preparations). Women with childbearing potential had to employ a medically proven form of contraception and had to have a negative pregnancy test before starting therapy.

To assign participants to groups, the research team performed blocked randomization with varying block sizes. First, the team randomly selected a block size from among a small set of block sizes and randomly permuted the group numbers within that block. The team continued the procedure until it had randomized all participants into the groups. The team permuted the random numbers within each block using the random number generator and user code in Stata 10.0 software (StataCorp LP, College Station, Texas).

Evaluation Procedures

Participants provided informed consent in accordance with the ethical standards of the Institutional Review Board of the University of Pennsylvania. The research team conducted the study using the *Principles of Good Clinical Practice Guidelines* with oversight by the local office of human research (OHR) and by an independent data and safety monitoring board. At the screen and baseline visits for the study, the research team obtained a participant's psychiatric

history using the SCID format.[28] The team performed a medical history, physical examination, and laboratory evaluation that included a complete blood count; a test of electrolyte levels; hepatic, renal, and thyroid panels; a pregnancy test (in women with childbearing potential); urinalysis; and a urine drug screen. At weeks 2, 4, 6, and 8 during the study, a research doctor or nurse obtained structured outcome ratings using the Hamilton Depression Rating Scale (HAM-D) questionnaire[29] and a treatment-emergent, side-effects profile (TESS).[30] The data on side effects included the date of onset and cessation of any adverse event, its severity, its relationship to treatment or the study's procedure, and the outcome.[30] The research team obtained sitting and standing blood pressure, pulse, and weight at each of the study's visits. All of participants' evaluations took place at the Depression Research Unit at the University of Pennsylvania.

Materials

The research team dispensed chamomile product and lactose monohydrate (placebo) under an Investigational New Drug (IND) exemption. The team prepared identically appearing 220-mg capsules containing either pharmaceutical-grade chamomile extract standardized to a content of 1.2% apigenin (Spectrum Pharmacy Products, New Brunswick, New Jersey) or placebo (ie, lactose monohydrate NF, Spectrum Pharmacy Products, New Brunswick, New Jersey).

Treatment Procedures

The research team initiated chamomile or placebo therapy at one capsule daily for the first week and increased it to two capsules daily during the second week of therapy. For participants with a ≤50% reduction in total HAM-A scores vs the baseline, the team increased the dosage to three capsules daily during week 3 of therapy and then to four capsules daily during week 4. For participants who continued to have a ≤50% reduction in baseline HAM-A scores at week 4, the team increased the dosage to five capsules daily during weeks 5 through 8 of the study. Dose reductions could occur at any time based upon drug tolerability.

Outcome Measurement

The research team obtained additional outcome measurements at baseline and after 2, 4, 6, and 8 weeks of treatment, including structured Hamilton Depression Rating (HAM-D)[21] scores for the test's total of 17 items, the HAM-D core mood items score (ie, depressed mood, guilt, suicidal ideation), and individual HAM-D symptom item scores. An experienced research doctor or research nurse from the Depression Research Unit assigned outcome ratings. The team analyzed results under blinded conditions.

Statistical Procedures

The research team conducted analyses using the xtgee procedure for Stata 10.0.[31] The team implemented generalized estimating equations (GEE) with 2-sided tests of hypotheses and a P-value $< .05$ as the criteria for statistical significance. Exploratory analysis examined the subgroups of those subjects in the chamomile and placebo treatment arms to see whether the impact of chamomile therapy was dependent upon group status (ie, current comorbid depression, past history of depression, or no current or past depression).

Given the available sample size, the team fit GEE models for all participants individually and for individual participants in the subgroups to identify trends that may inform future hypotheses. The GEE models included the total HAM-D score, HAM-D core depression items scores, and individual HAM-D item scores as the main outcome variables. The GEE models also included the covariates of time, baseline value for each HAM-D outcome measure, an indicator variable for chamomile, and a chamomile x-time interaction term. If the chamomile x-time interaction was significant, this finding indicated that the change over time with chamomile differed from placebo. The GEE models allowed for a variable number of measurements per participant so that information on all participants was available for the analysis. Finally, given the exploratory nature of this study, the team did not control for multiple comparisons.

The research team used the lincom procedure in Stata 10.0 to estimate (with 95% CI) the difference in overall changes between groups. In addition, the team calculated effect sizes as the absolute value of the estimated difference between groups divided by the standard deviation (SD) of the outcome variable under consideration.

RESULTS

Enrollment

Sixty-one participants enrolled in the trial: 73.7% Caucasian, 12.3% African American, and 14.0% other. The mean (SD) age of the chamomile participants was 45.5 (14.53) years and the mean (SD) age of the placebo participants was 45.9 (10.88) years ($P = .98$). Table 1 gives the full descriptions of participants. Fifty-seven participants had a baseline visit plus at least one post-baseline measurement: chamomile (n = 28) and placebo (n = 29).

The research team performed exploratory analyses on the entire group of participants and on subgroups that included participants with current comorbid depression (n = 19), with a history of depression but no current depression (n = 16), and with no past or current depression (n = 22). Table 1 displays clinical and demographic variables for each subgroup. Participants with current comorbid depression had a secondary diagnosis of depressive disorder NOS (n = 15) or dysthymic disorder (n = 4). Participants with a past history of depression had a prior diagnosis of major depressive disorder (n = 2), dysthymic disorder (n = 2), depressive disorder NOS (n = 11), or postpartum depression (n = 1). Of the 57 randomized participants whom the team evaluated, eight (14.03%) discontinued treatment prematurely: two for adverse events (one for allergic reaction from placebo and one for abdominal discomfort from chamomile), three for withdrawn consent, two lost to follow-up,

Table 1. Clinical and Demographic Characteristics of Participants' Subgroups[b]

	Comorbid Depression(n = 19)	Past History of Depression (n = 16)	No Depression (n = 22)
Chamomile/placebo	7/12	8/8	13/9
Gender, men/women	9/10	8/8	6/16
Age at consent (y)[a]	43.7 (16.5)	48.6 (12.5)	42.2 (9.8)
Age at consent, range (y)	29-78	22-70	25-62
Age GAD onset (y)[a]	23.0 (14.9)	24.9 (8.3)	30.8 (11.9)
Age GAD onset, range (y)	12-75	14-47	18-58
Illness length (y)[a]	19.9 (14.7)	23.5 (14.3)	11.8 (11.3)
Illness length, range (y)	0.5-51	3-54	0.3-33
Episode length (mo)[a]	56.2 (67.9)	41.3 (64.8)	47.2 (53.7)
Episode length, range (mo)	2-240	6-256	3-240
Prior episodes (no.)[a]	4.7 (7.0)	7.2 (11.3)	1.4 (2.0)
Prior episodes, range	0-10	0-43	0-6
Baseline HAM-A[a]	16.1 (4.1)	13.7 (3.1)	14.5 (3.3)
Baseline HAM-A, range	11-26	10-21	9-22
Baseline HAM-D[a]	12.2 (3.5)	10.13 (3.3)	9.8 (3.5)
Baseline HAM-D, range	5-19	5-18	3-15

[a]Mean ± standard deviation
[b]All scores come from data obtained in a 2009 study.[22]
Abbreviations: GAD, generalized anxiety disorder; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression.

and one for noncompliance. Please note that one subject withdrew consent after taking a single dose of the study's drug. To be conservative, however, in the interpretation of its observations, the team retained all efficacy data for this participant in its analyses. The average number of adverse events per participant was greater with placebo (0.77) vs chamomile (0.39) ($P = .26$). Amsterdam et all have provided a detailed description of the safety profile of chamomile vs placebo previously.[22]

Antidepressant Activity

Table 2 displays quasi-least squares (QLS) analyses of individual HAM-D symptom scores, HAM-D core mood scores, and total HAM-D scores. After controlling for baseline values, the research team observed a significantly greater reduction over time in total HAM-D scores for chamomile vs placebo in all participants ($P < .05$). The team also observed a clinically meaningful but nonsignificant trend for a greater reduction in total HAM-D scores for chamomile vs placebo in participants with current comorbid depression ($P = .062$). When the team examined the HAM-D core mood item scores, it observed a significantly greater reduction over time for chamomile vs placebo in all participants ($P < .05$) and a clinically meaningful but nonsignificant trend for a greater reduction over time for chamomile vs placebo in participants without current or past depression ($P = .06$).

DISCUSSION

The observation of a significantly greater reduction in total HAM-D scores with chamomile (vs placebo) in all participants ($P < .05$) and a clinically meaningful trend for a greater reduction in total HAM-D scores for chamomile (vs placebo) in participants with current comorbid anxiety and depression ($P = .062$), suggests that chamomile may exert an antidepressant effect in conjunction with its previously reported antianxiety effects in the same population. While the research team did not power this secondary, exploratory study specifically to detect statistically significant differences between treatment conditions for HAM-D outcome measures or between participants' subgroups, it did expect to find clinically meaningful changes over time in HAM-D outcome measures that would favor chamomile vs placebo. Chamomile's mode of antidepressant action is unknown, although it may be independent of its anxiolytic activity.[22] Several lines of evidence suggest that one or more of chamomile's flavanoid constituents may exert an antidepressant effect via modulation of central noradrenalin (NA), dopamine (DA), serotonin (5-HT), and γ-amino butyric acid neurotransmission.[23-27] In addition, chamomile also appears to modulate hypothalamic-pituitary-adrenocortical (HPA) axis activity.[32,33] For example, Lorenzo et al[34] found that apigenin increased NA activity in an isolated rat atria model and inhibited monoamine-oxidase activity in rat atria homoge-

Table 2. Differences in Change in Hamilton Depression Rating Symptoms With 95% Confidence Interval and Effect Size for Chamomile vs Placebo

HAM-D Item	All Participants (n=57)	Comorbid Depression (n=19)	Pas Depression (n=16)	No Depression (n=22)
Depressed mood (#1)	−0.13 (−0.44, 0.18)	−0.09 (−0.75, 0.58)	−0.10 (−0.56, 0.35)	−0.11 (−0.62, 0.39)
	ES=0.18	ES=0.11	ES=0.19	ES=0.17
Guilt (#2)	−0.55 (-0.85, −0.25)[a]	−0.29 (−0.88, 0.29)	−0.78 (−1.36, −0.18)[a]	−0.62 (−1.03, −0.21)[a]
	ES=0.72	ES=0.36	ES=1.08	ES=1.07
Suicide ideation (#3)	−0.12 (−0.27, 0.03)	−0.25 (−0.66, 0.16)	−0.10 (−0.30, 0.11)	−0.04 (−0.14, 0.06)
	ES=0.26	ES=0.35	ES=0.33	ES=0.33
Insomnia, early (#4)	0.03 (−0.26, 0.32)	0.21 (−0.34, 0.75)	−0.70 (−1.29, −0.12)[a]	0.49 (0.10, 0.88)[a]
	ES=0.04	ES=0.25	ES=0.86	ES=0.66
Insomnia, middle (#5)	−0.09 (−0.40, 0.21)	−0.29 (−0.86, 0.28)	0.27 (−0.34, 0.89)	−0.33 (−0.77, 0.12)
	ES=0.12	ES=0.41	ES=0.34	ES=0.42
Insomnia, late (#6)	−0.53 (−0.86, −0.20)[a]	−0.90 (−1.4, −0.41)[a]	0.10 (−0.61, 0.80)	−0.83 (−1.32, −0.33)[a]
	ES=0.69	ES=1.16	ES=0.12	ES=1.10
Work/activities (#7)	−0.03 (−0.40, 0.30)	−0.22 (−0.90, 0.47)	−0.34 (−1.0, 0.36)	0.32 (−0.21, 0.84)
	ES=0.04	ES=0.24	ES=0.46	ES=0.42
Retardation (#8)	0.02 (−0.14, 0.17)	0.07 (−0.28, 0.43)	−0.38 (−0.61, −0.15)[a]	0.16 (−0.04, 0.37)
	ES=0.04	ES=0.15	ES=1.02	ES=0.60
Agitation (#9)	0.06 (−0.22, 0.34)	−0.08 (−0.47, 0.31)	0.12 (−0.40, 0.64)	−0.19 (−0.64, 0.27)
	ES=0.09	ES=0.12	ES=0.17	ES=0.31
Anxiety, psychic (#10)	−0.30 (−0.62, 0.01)	−0.23 (−0.86, 0.40)	−0.25 (−0.74, 0.25)	−0.32 (−0.85, 0.21)
	ES=0.42	ES=0.31	ES=0.40	ES=0.43
Anxiety, somatic (#11)	−0.07 (−0.36, 0.23)	−0.39 (−0.95, 0.17)	0.37 (−0.19, 0.93)	−0.05 (−0.49, 0.38)
	ES=0.10	ES=0.54	ES=0.50	ES=0.08
Gastrointestinal (#12)	−0.01 (−0.20, 0.19)	0.03 (−0.44, 0.50)	0.26 (0.02, 0.51)[a]	−0.27(−0.52, −0.01)[a]
	ES=0.01	ES=0.05	ES=0.71	ES=0.70
Somatic, general (#13)	−0.32 (−0.59, −0.05)[a]	−0.34 (−0.79, 0.11)	−0.55 (−1.02, −0.09)[a]	−0.10 (−0.58, 0.37)
	ES=0.52	ES = 0.53	ES=0.94	ES=0.16
Somatic, libido (#14)	−0.21 (−0.42, −0.002)[a]	−0.53 (−0.94, −0.12)[a]	−0.43 (−0.67, −0.20)[a]	0.15 (−0.21, 0.51)
	ES=0.33	ES = 0.72	ES=0.96	ES=0.22
HAM-D core (#1, #2, #3)	−0.71 (−1.33, −0.10)[a]	−0.25 (−1.54, 1.04)	−0.98 (−2.02, 0.06)	−0.78 (−1.60, 0.03)[c]
	ES=0.47	ES = 0.14	ES=0.78	ES=0.71
HAM-D total	−2.11(−4.17, −0.06)[a]	−3.74 (−7.7, 0.19)[b]	−2.03 (−5.62, 1.56)	−1.47 (−4.68, 1.73)
	ES=0.42	ES = 0.65	ES=0.47	ES=0.32

[a]($P < .05$); [b]($P = .062$); [c]($P = .06$)
Abbreviations: Ham-D, Hamilton Rating Scale for Depression; ES, effect size.

nates. Morita et al[23] found that apigenin stimulated the uptake of L-[^{14}C]-tyrosine (a DA precursor) into cultured adrenal chromaffin cells, and flavone produced an increase in [^{14}C]-catecholamine production without altering [^{14}C]-tyrosine turnover. Nakazawa et al (2003)[24] 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), while Anjaneyulu et al[25] found that quercetin reduced the immobility of mice during the FST in a dose-dependent fashion comparable to fluoxetine and imipramine. Yi et al[27] found that apigenin reduced immobility during the FST in mice; reversed FST-induced reduction in sucrose intake in rats; lowered stress-induced alterations in 5-HT, DA, and their metabolites; and reversed FST-induced increases in HPA-axis activity.

Researchers should consider several caveats in the interpretation of the current findings. The research team did not power the study to detect statistically significant differences between treatment conditions for HAM-D outcome measures or between participants' subgroups. The small sample size necessarily limited the team's ability to identify small-to-moderate differences in HAM-D outcome measures between treatment conditions.

The post hoc division of participants into subgroups necessarily resulted in an unbalanced distribution of baseline clinical and demographic variables that could have increased the likelihood of a type 1 or type 2 error. Similarly, given the exploratory design of the study, the research team did not control for multiple comparisons. It is possible that the reduction in HAM-D outcome scores was not the result of an antidepressant action per se but may have resulted from chamomile's anxiolytic activity as previously described.[22] A future study could evaluate this possibility. It is possible that the team would have found a different antidepressant outcome if the primary diagnosis in these participants had been depression rather than anxiety or if the baseline HAM-D scores had been higher. It is also possible that the antidepressant outcome may have been different if the team had employed a greater chamomile dose or a longer treatment duration. It is also possible that another chamomile species or chamomile extract with a different standardization may have produced different results.

Finally, the research team notes that the current analyses were exploratory and only suggest the possibility of an antidepressant activity for chamomile. Researchers will need to conduct future prospective trials in participants with primary depression to confirm the putative antidepressant activity of chamomile.

CONCLUSION

The identification of safe and effective CAM therapies for depression would be of public-health relevance for many individuals unable or unwilling to use conventional antidepressant therapy. The observation of a significant reduction over time in total HAM-D scores ($P<.05$) and a reduction in HAM-D core mood symptom scores ($P<.05$) for chamomile vs placebo in all participants and of a clinically meaningful trend for a reduction in total HAM-D scores for chamomile vs placebo in anxious participants with current comorbid depression ($P=.062$), suggests that chamomile may produce a clinically meaningful antidepressant effect in humans. Researchers will need to conduct future controlled clinical trials in patients who have depression as their primary diagnosis to confirm these exploratory findings.

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