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Chamomile (*Matricaria recutita*) May Have Antidepressant Activity in Anxious Depressed Humans - An Exploratory Study

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Abstract

Objective—As part of a randomized, double-blind, placebo-controlled study, we examined the antidepressant action of oral chamomile (*Matricaria recutita*) extract in subjects with co-morbid anxiety and depression symptoms. We hypothesized that chamomile may demonstrate a clinically meaningful antidepressant activity versus placebo.

Methods—57 subjects received either chamomile extract or placebo therapy. Nineteen subjects had anxiety with co-morbid depression, 16 had anxiety with past history of depression, and 22 had anxiety with no current or past depression. Generalized estimating equations analysis was used to identify clinically meaningful changes over time in Hamilton Depression Rating (HAM-D) rating outcome measures among treatment groups.

Results—We observed a significantly greater reduction in mean total HAM-D scores ($p<0.05$) and HAM-D core depression item score ($p<0.05$) for chamomile versus placebo in all subjects,

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and a non-significant trend for a greater reduction in HAM-D core depression score for chamomile versus placebo in subjects with anxiety with current co-morbid depression (p=0.062).

Conclusion—Chamomile may have clinically meaningful antidepressant activity that occurs in addition to its previously observed anxiolytic activity.

Keywords

Antidepressant; Chamomile; Depression; Complementary & Alternative Medicine; Matricaria recutita

INTRODUCTION

Anxiety and depression are the most commonly reported psychiatric conditions (1,2,3), and frequently occur as co-morbid conditions (4,5,6,7). Both conditions can be chronic or recurrent (5,8) and can frequently require long-term therapy (9). While the advent of conventional drug therapies for anxiety and depression has simplified their 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). The identification of inexpensive and effective alternative therapies for anxiety and depression is therefore of public health relevance (12,13). Rigorous testing of candidate CAM therapies is also needed to expand available therapeutic options for anxiety and depression.

The use of chamomile as an herbal remedy dates back to ancient Greece and Rome. Chamomile (*Matricaria recutita*) has been used as a traditional herbal remedy for its calming effect. While there are many varieties of chamomile, Roman (A. nobilis) and German (M. recutita) are the most widely used. These are members of the Compositae (Asteracae) family. M. recutita is considered the more potent variety and is most widely used for medicinal purposes. M. recutita use for relief of depressive and anxiety symptoms is documented 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, other chamomile varieties have been used to treat the symptoms of depression and anxiety including A. arvensis and T. parthenium in Tuscany (19) and C. fuscatum in Spain (20). In spite of these uses, there has been on one randomized controlled study that has explored the effects of chamomile on mood. A randomized, double-blind, placebo-controlled trial of oral chamomile extract for generalized anxiety disorder (GAD) found a significantly greater reduction in mean anxiety symptom ratings for chamomile versus placebo ($60\widehat{\beta}_3 = -3.17$, 95% CI= −6.29 to −0.45) (p=0.047), and a non-significant (albeit clinically meaningful) reduction in depression ratings (21) with chamomile versus placebo ($60\widehat{\beta}_3 = -3.22\,(95\%\quad \mathrm{CI} = -7.44, 1.00)$ (p=0.136) (22).

Based upon prior observations from in vivo and in vitro animal studies suggesting that chamomile may possess antidepressant activity (23,24,25,26,27), we conducted this secondary, exploratory analysis of our prior clinical chamomile trial in humans to examine whether chamomile demonstrated antidepressant activity (22) along with its antianxiety effects. We hypothesized that chamomile would show clinically meaningful antidepressant activity (versus placebo) as measured by change over time in depression symptom ratings.

METHODS

Subjects

Subjects were referred from the Department of Family Medicine & Community Health primary care clinic at the University of Pennsylvania. Subjects were ≥ 18 years old and had a primary DSM IV Axis I diagnosis of GAD, that was confirmed using the *Structured Diagnostic Interview for DSM IV* (SCID; 28). Subjects had mild to moderate symptom severity with a minimum baseline Hamilton Anxiety Rating (HAM-D; 29) score ≥ 9. Subjects with co-morbid DSM IV Axis I dysthymic disorder or depressive disorder NOS were not excluded from the trial if their co-morbid condition did not constitute the primary disorder. Subjects were excluded from the trial if they had a current diagnosis of major depressive disorder, bipolar disorder, panic disorder, phobic disorder, obsessive-compulsive disorder, post-traumatic 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 an unstable medical condition, hepatic or renal insufficiency, malignancy, or known sensitivity to chamomile, plants of the asteraceae family, mugwort, or birch pollen. Concurrent use of anxiolytic, antidepressant, mood stabilizer, sedative, or herbal remedies (including chamomile preparations) were not permitted. Women of child-bearing potential employed a medically proven form of contraception and had a negative pregnancy test before starting therapy.

Evaluation Procedures

Subjects provided informed consent in accordance with the ethical standards of the Institutional Review Board of the University of Pennsylvania. 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. At the screen and baseline study visits, a psychiatric history was obtained using the SCID format (28). A medical history, physical examination, and laboratory evaluation was performed that included complete blood count, electrolytes, hepatic, renal and thyroid panel, pregnancy test (in women of child-bearing potential), urinalysis, and urine drug screen was obtained. Structured outcome ratings that included the Hamilton Depression Rating Scale (HAM-D) (29) and the treatment emergent side effects profile (that included the date of onset and cessation, severity, relationship of adverse event to treatment or study procedure, and outcome) (30) were obtained at study weeks 2, 4, 6, and 8 by a research doctor or nurse. All subject evaluations took place at the Depression Research Unit at the University of Pennsylvania. Sitting and standing blood pressure, pulse, and weight were obtained at each study visit.

Outcome Measurement

Structured total 17-item Hamilton Depression Rating (HAM-D)[21] score, HAM-D core mood items (i.e., depressed mood, guilt, suicide ideation) score, and individual HAM-D symptom item scores were obtained at each study visit. Outcome ratings were conducted by an experienced research doctor or research nurse and took place in the Depression Research Unit.

Materials

Chamomile product and lactose monohydrate (placebo) were dispensed under an IND exemption granted to the investigators by the local OHR at the University of Pennsylvania. Identically appearing capsules containing either pharmaceutical grade chamomile extract standardized to a content of 1.2% apigenin (Spectrum Pharmacy Products, New Brunswick, NJ) or placebo (i.e., lactose monohydrate NF, Spectrum Pharmacy Products, New

Brunswick, NJ) were prepared. Chamomile was prepared as 220 mg capsules. Randomization was performed using blocked randomization with varying block sizes (22). First, we randomly selected a block size from among a small set of block sizes. Then, we randomly permuted the group numbers within that block. We continued this procedure until all subjects were randomized into each of the two conditions. Random numbers were permuted within each block using the random number generator and user code in Stata software. All study results were analyzed under blinded conditions.

Treatment Procedures

Chamomile or placebo therapy was initiated at one capsule daily for the first week and increased to 2 capsules daily during the second week of therapy. Subjects with a ≤ 50% reduction in total HAM-A score (versus baseline) were increased to 3 capsules daily during week 3, and then to 4 capsules daily during week 4 of therapy. Subjects who continued to have a ≤ 50% reduction in baseline HAM-A score were increased to 5 capsules daily during study weeks 5 through 8. Dose reductions could occur at any time based upon drug tolerability. Outcome measurements were obtained at baseline and after 2, 4, 6, and 8 weeks of treatment.

Statistical Procedures

Analyses were conducted using the xtgee procedure for Stata 10.0 (31).Generalized estimating equations (GEE) was implemented with 2-sided tests of hypotheses and a p-value <0.05 as the criterion for statistical significance. Exploratory analysis examined subject subgroups to see whether the impact of chamomile therapy was dependent upon group status (i.e., current co-morbid depression, past history of depression, or no current or past depression). Given the available sample size, we fit GEE models in all subjects and within subgroups of subjects to identify trends that may inform future hypotheses. The GEE models included total HAM-D score, HAM-D core depression items scores, and individual HAM-D item scores as the main outcome variables. 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 indicated that the change over time with chamomile differed from placebo. The GEE models allowed for a variable number of measurements per subject, so that information on all subjects was available for the analysis. Finally, given the exploratory nature of this study, we did not control for multiple comparisons. The lincom procedure in Stata 10.0 was used to estimate (with 95% confidence intervals) the difference in overall changes between groups. In addition, effect sizes were calculated as the absolute value of the estimated difference between groups divided by the standard deviation of the outcome variable under consideration.

RESULTS

Enrollment

61 subjects enrolled in the trial: 73.7% Caucasian, 12.3% African American, and 14.0% other. Mean (SD) age of the chamomile subjects was 45.5 (14.53) years and mean age of the placebo subjects was 45.9 (10.88) years (p=0.98). (the full subject description is given in Table 1. Fifty-seven subjects had a baseline visit plus at least one post-baseline measurement: chamomile (n=28) and placebo (n=29). Exploratory analyses were performed on the entire group of subjects and on subgroups that included subjects with current co-morbid depression (n=19), history of depression but no current depression (n=16), and no past or current depression (n=22). Clinical and demographic variables of each subgroup are displayed in Table 1. Subjects with current co-morbid depression had a secondary diagnosis of depressive disorder NOS (n=15) or dysthymic disorder (n=4). Subjects 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 post-partum depression (n=1). Of the 57 randomized subjects who were evaluated, 8 (14.03%) discontinued treatment prematurely: 2 for adverse events (1 for allergic reaction from placebo, and 1 for abdominal discomfort from chamomile); 3 for withdrawn consent, 2 lost to follow up, and 1 for noncompliance. [Note: One subject withdrew consent after taking a single dose of study drug. However, to be conservative in the interpretation of our observations, all efficacy data from this subject were retained in our analyses]. The average number of adverse events per subject was greater with placebo (0.77) versus chamomile (0.39) (p=0.26). A detailed description of the safety profile of chamomile versus placebo was described previously (22).

Antidepressant Activity

QLS analyses of individual HAM-D symptom scores, HAM-D core mood score, and total HAM-D scores are displayed in Table 2. After controlling for baseline values, we observed a significantly greater reduction over time in total HAM-D scores for chamomile versus placebo in all subjects ($p<0.05$). We also observed a clinically meaningful (albeit non-significant) trend for a greater reduction in total HAM-D scores for chamomile versus placebo in subjects with current co-morbid depression (p=0.062). When the HAM-D core mood item score were examined, we observed a significantly greater reduction over time for chamomile versus placebo in all subjects ($p<0.05$), and a clinically meaningful (albeit non-significant) trend for a greater reduction over time for chamomile versus placebo in subjects without current or past depression (p=0.06).

DISCUSSION

The observation of a significantly greater reduction in total HAM-D scores with chamomile (versus placebo) in all subjects ($p<0.05$), and a clinically meaningful trend for a greater reduction in total HAM-D scores for chamomile (versus placebo) in subjects with current co-morbid anxiety and depression (p=0.062) suggests that chamomile may exert an antidepressant effect along with its previously reported antianxiety effects in this same population. While this secondary, exploratory study was not specifically powered to detect statistically significant differences between treatment conditions for HAM-D outcome measures or between subject subgroups, we did expect to find clinically meaningful changes over time in HAM-D outcome measures (if they occurred) that would favor chamomile versus 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 (GABA) neurotransmission (23,24,25,26,27). 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 (MAO) activity in rat atria homogenates. Morita et al. (23) found that apigenin stimulated the uptake of L-[^{14}C]-tyrosine (a DA precursor) into cultured adrenal chromaffin cells, while 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.

Several caveats should be considered in the interpretation of the current findings. The study was not powered to detect statistically significant differences between treatment conditions for HAM-D outcome measures or between subject subgroups. The small sample size necessarily limits our ability to identify small to moderate differences in HAM-D outcome measures between treatment conditions.

The post hoc division of subjects into subgroups necessarily resulted in unbalanced distribution of baseline clinical and demographic variables that could have increased the likelihood of a type I or type II error. Similarly, given the exploratory design of the study, we 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). This possibility could be evaluated in a future study. It is possible that the antidepressant outcome would have been different if the primary diagnosis in these subjects was 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 a greater chamomile dose or treatment duration had been employed. It is also possible that another chamomile species or chamomile extract with a different standardization, may have produced different results.

Finally, we note 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 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 ($p<0.05$) and a reduction in HAM-D core mood symptom scores ($p<0.05$) for chamomile versus placebo in all subjects, and a clinically meaningful trend for a reduction in total HAM-D scores for chamomile versus placebo in anxious subjects with current co-morbid depression ($p=0.062$), suggests that chamomile may produce a clinically meaningful antidepressant effect in humans. Future controlled clinical trials in patients with depression as their primary diagnosis will be needed to confirm these exploratory findings.

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Table 1

Clinical & demographic characteristics of subject subgroups.

	Co-morbid 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 (yrs) *	43.7 (16.5)	48.6 (12.5)	42.2 (9.8)
Age at Consent – range	29 – 78	22 - 70	25 - 62
Age GAD Onset (yrs) *	23.0 (14.9)	24.9 (8.3)	30.8 (11.9)
Age GAD Onset - range	12 – 75	14 - 47	18 - 58
Illness Length (yrs) *	19.9 (14.7)	23.5 (14.3)	11.8 (11.3)
Illness Length - range	0.5 – 51	3 - 54	0.3 – 33
Episode Length (mos) *	56.2 (67.9)	41.3 (64.8)	47.2 (53.7)
Episode Length – range	2 – 240	6 - 256	3 - 240
Prior Episodes (#) *	4.7 (7.0)	7.2 (11.3)	1.4 (2.0)
Prior Episodes – range	0 – 10	0 - 43	0 - 6
Baseline HAM-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 *	12.2 (3.5)	10.13 (3.3)	9.8 (3.5)
Baseline HAM-D Range	5 – 19	5 - 18	3 - 15

* Mean ± standard deviation (SD)

Table 2

Difference in change in HAM-D symptoms (with 95% CI and effect size[**]) for chamomile versus placebo

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

[*] ($p<0.05$)

[#] ($p=0.062$)

[†] ($p=0.06$)

[**] Effect size = ES