Complementary and Alternative Medicine for Major Depressive Disorder: A Meta-Analysis of Patient Characteristics, Placebo-Response Rates, and Treatment Outcomes Relative to Standard Antidepressants

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Objective: To compare patient characteristics, placebo-response rates, and outcome differences in active treatment compared to placebo in randomized controlled trials (RCTs) of complementary and alternative medicine (CAM) and standard antidepressants for major depressive disorder (MDD).

Data Sources: Eligible studies were first identified using searches of PubMed/MEDLINE, restricted to English, by cross-referencing the search term *placebo* with each of the antidepressants (those that had received letters of approval by the US, Canadian, or EU drug regulatory agencies for the treatment of MDD) and selected CAM agents. These searches were limited to articles published between January 1, 1980, and September 15, 2009 (inclusive). Reference lists from identified studies were also searched for studies eligible for inclusion.

Study Selection: We selected RCTs for MDD that included validated diagnostic assessment and baseline/outcome measures of illness severity. Assessment was limited to widely used CAM agents most frequently studied in RCTs with pill placebo: St John's wort, omega-3 fatty acids, and S-adenosyl-L-methionine (SAMe).

Data Synthesis: Of eligible publications, 173 reported results of 1 trial, and 5 included > 1 trial, representing a total of 185 RCTs. Patient variables, including illness severity, were similar across CAM and antidepressant RCTs, except for a higher proportion of women in CAM studies ($P = .0003$). Random-effects meta-analysis indicated that both antidepressant and CAM monotherapy resulted in superior response rates compared with placebo. Placebo-response rates were significantly lower for patients enrolled in CAM versus antidepressant RCTs ($P = .002$). Meta-regression analyses yielded no significant differences in the relative risk of prematurely discontinuing therapy due to any reason between active treatment and placebo for antidepressant and CAM RCTs, although discontinuation due to adverse events was higher in antidepressant RCTs compared to CAM RCTs ($P = .007$).

Conclusions: Participants in CAM trials were more likely to be female and to have a lower placebo-response rate compared to those in standard antidepressant trials for MDD. Trials of standard antidepressants and CAM therapies were composed of patients with similar depression severity.

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See also Editorial on page 667.

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Complementary and alternative medicine (CAM) has been defined as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[1] There have been relatively few rigorous randomized controlled trials (RCTs) of CAM therapies for psychiatric disorders. In treatment studies of CAM for major depressive disorder (MDD), a relatively small number have used rigorous diagnostic and outcome criteria with adequate sample sizes. At present, it is unknown whether individuals who enter RCTs of CAM are similar to those who enter RCTs of standard antidepressants in terms of patient variables and placebo-response rates. High placebo-response rates in MDD often complicate interpretation of results and increase the likelihood of dismissing potentially efficacious treatments.[2–4] In placebo-controlled trials of US Food and Drug Administration–approved antidepressants, the overall difference between antidepressants and placebo is relatively small.[5]

Complementary and alternative medicine use has increased over several decades,[6] with 40% of US adults currently using at least 1 CAM treatment annually.[7] CAM use is common among individuals with psychiatric disorders, particularly MDD.[8–12] The widespread use of CAM may complicate participant recruitment for CAM trials. Those eligible and interested may have already pursued trials on their own or with health care providers and may be disinclined to participate in a placebo-controlled trial. Although patient preferences in RCTs are an understudied topic, individuals who enter trials do not find all treatments equally acceptable.[13] In addition, patient expectations about the efficacy of the antidepressant treatment may affect outcome itself and possibly the degree of placebo response. It is also possible that individuals who pursue CAM therapies would have less tolerance for side effects and higher dropout rates than those who enter antidepressant trials. It is therefore unclear if patients who enter RCTs of CAM therapies are similar to those who enter trials of antidepressants for MDD.

Our objective was to compare patient variables from placebo-controlled trials of CAM and antidepressants for the treatment of MDD. We hypothesized that participation in RCTs of CAM may be associated with specific patient

variables, such as female gender, lower depression severity at baseline, a greater tendency to respond to placebo, and a greater likelihood of discontinuation due to adverse effects. We also sought to examine whether CAM and standard antidepressant therapy both resulted in significant differences compared with parallel placebo controls. We selected RCTs for MDD that included validated diagnostic assessments at baseline and had adequate outcome measures of depression severity. The selection of MDD as the disorder of study was based on its prevalence, its public health significance, the widespread use of CAM treatments for MDD, and the relatively large number of RCTs of CAM to allow for comparisons with standard pharmacotherapy.

METHOD

Data Sources and Search Strategy

We identified double-blind, randomized, placebo-controlled trials of either a standard antidepressant or CAM treatment used as monotherapy for MDD for possible inclusion. We defined *standard antidepressants* as pharmacologic agents that have or had received a letter of approval by the US, Canadian, or EU drug regulatory agencies for the treatment of MDD. The procedure for identifying placebo-controlled RCTs of antidepressants for MDD was described previously.[14] We defined *CAM* as health care practices not currently considered conventional medicine. We restricted CAM therapies for comparison specifically to natural pharmacologic agents that have been assessed for MDD in at least 2 RCTs with pill placebo comparisons and have been widely studied in the United States, Canada, and European Union: St John's wort (*Hypericum perforatum L.*); omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); and S-adenosyl-L-methionine (SAMe).

Eligible studies were first identified using searches of PubMed/MEDLINE, restricted to English, by cross-referencing the search term *placebo* with each of the above-mentioned agents (either antidepressant or CAM). The PubMed/MEDLINE search was limited to articles published between January 1, 1980, and September 15, 2009 (inclusive). We used 1980 as a cutoff in order to decrease diagnostic variability because the *DSM-III* was introduced in 1980. To expand our database, we reviewed the reference list of all studies identified with PubMed/MEDLINE. Final inclusion of articles was determined by consensus between the authors.

Study Selection

We selected randomized, double-blind, placebo-controlled trials of either a standard antidepressant or CAM used as monotherapy for the acute-phase treatment of MDD. We selected studies that also met all of the following criteria.

1. Required an MDD diagnosis verified by criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) editions: *DSM-III*,[15] *DSM-III-R*,[16] *DSM-IV*[17]; Research Diagnostic Criteria[18]; or Feighner's Diagnostic Criteria.[19]
2. Were at least 4 weeks in duration.
3. Used an oral preparation of active treatment and placebo.
4. Presented entirely original data.
5. Focused on the treatment of adults.
6. Did not exclusively focus on the treatment of patients with treatment-resistant depression or other depressive disorders, including bipolar disorder, depression with psychotic features, dysthymia, or neurotic or minor depression.
7. Did not exclusively focus on the treatment of MDD with comorbid alcohol or substance use disorders or a specific comorbid medical illness, or antenatal/postpartum MDD.
8. Involved the use of the Hamilton Depression Rating Scale (HDRS),[20] the Montgomery-Asberg Depression Rating Scale (MADRS),[21] or the Clinical Global Impressions-Improvement scale (CGI-I)[22] as outcome measures.

Definitions

Clinical response was defined as a ≥ 50% reduction in HDRS or MADRS scores, baseline to endpoint, or a CGI-I score < 3 at the final visit. For consistency, the HDRS was chosen over the MADRS or CGI when response rates from multiple scales were reported. For studies that reported only CGI-based response rates, the HDRS-based response rates were either obtained from the sponsor or imputed using the method of Walsh et al.[3] Discontinuation rate was defined as per each protocol. For consistency, we used intent-to-treat (ITT)–based response rates in the present analysis. Whenever ITT-based response rates were not available in the publication, the sponsor was contacted to obtain ITT-based response rates. In cases in which the sponsor could not retrieve ITT-based response rates, we utilized response rates based on completers. The probability of receiving placebo was computed from the number of treatment arms and the randomization schedule (eg, 1:1:1) of each trial. For example, a 2-arm trial with a 2:1 randomization favoring antidepressant treatment yields a 1 in 3 chance of receiving placebo.

Quantitative Data Synthesis

Response rates between groups were compared with the use of analysis of variance. In addition to sample size, when response rates were compared between active-treatment groups (antidepressant or CAM), the probability of being randomly assigned to placebo as well as dosing (fixed vs flexible) were also entered as covariates, because they were found to predict antidepressant response rates in a previous meta-analysis.[13] Similarly, in addition to sample size, when response rates were compared between placebo-treatment groups, illness severity at baseline, year of publication, and the probability of being randomly assigned to placebo were also entered as covariates for the same reason. Random-effects meta-analysis was utilized to estimate the pooled risk ratio (RR) of responding to antidepressants versus placebo and of responding to CAM versus placebo. Finally, meta-

regression was used in order to compare RR between treatment groups. For meta-regressions comparing the RR of response between treatment groups, year of publication, illness severity at baseline, and the probability of being randomly assigned to placebo were also entered as covariates because they had also previously been found to influence the RR of clinical response following antidepressant versus placebo therapy. All tests conducted were 2-tailed, with α set at the .05 level.

RESULTS

Initially, 7,275 abstracts were identified in PubMed/MEDLINE. Of these, 6,837 were excluded for a number of reasons (other topics, reviews). The remaining 438 abstracts described clinical trials of either a standard antidepressant or CAM used as monotherapy for depressive disorders. These 438 articles were obtained and reviewed thoroughly. After the reference list of these 438 publications as well as 2 large meta-analyses were reviewed, 15 additional articles were identified. Ninety-eight articles were excluded because they presented data previously published elsewhere, 25 were excluded because they focused on children and/or adolescents, and 40 were excluded because they focused on the treatment of depressive disorders other than MDD, because they focused on perinatal MDD, because the diagnosis of MDD was based on the *DSM-II*, or because they did not state which, if any, diagnostic criteria, were used to define MDD. One study was excluded because it focused on patients with treatment-resistant depression, 27 were excluded because they focused on the treatment of patients with depression and comorbid alcohol and/or drug use disorders, and 63 were excluded because they focused on the treatment of depression and comorbid Axis III disorders. Three were excluded because they did not involve the use of an oral form of an antidepressant (selegiline); 3, because they were < 4 weeks in duration; and 2, because they did not involve the use of the HDRS, MADRS, or CGI.

Thus, a total of 191 publications were found eligible for inclusion (list available from the authors upon request). We were able to obtain antidepressant-, CAM-, and placebo-response rates for 178 (93.1%) of the 191 publications. Outcome in the remaining 13 trials was reported as a continuous measure only (change in depression severity scores), and response rates could not be obtained by contacting the study authors or sponsor. While 173 of these publications reported the results of a single trial, 5 reported results of several (a total of 12) trials. Thus, a total of 320 antidepressant versus placebo (n = 298, 93.2%) or CAM versus placebo (n = 22, 6.8%) comparisons (treatment arms) from 185 clinical trials were pooled, involving a total of 46,842 patients randomly assigned to treatment with an antidepressant (n = 28,345, 60.5%), a CAM treatment (n = 1,502, 3.2%), or placebo (n = 16,995, 36.2%). Six trials included treatment arms with both CAM and standard antidepressants compared to placebo. The mean (standard deviation) study duration was 7 (2.9) weeks, and the mean sample size per treatment arm was 92.8 (58.4) patients. The 19 studies that included 22 treatment arms of CAM therapies compared to placebo are presented in Table 1. Jadad scores[23] were assessed to provide a measure of methodological quality and are included in Table 1.

There was no statistically significant difference between antidepressant and CAM studies, respectively, in mean ± SD age per treatment arm (43.8 ± 8.6 vs 16.0 ± 4.4 years, $P = .25$), mean trial duration (7.1 ± 2.9 vs 6.4 ± 1.8 weeks, $P = .21$), or mean baseline severity in terms of HDRS-17 score per treatment arm (21.2 ± 4.3 vs 19.9 ± 3.5, $P = .13$). The proportion of women in the randomized sample was significantly lower in standard antidepressant trials than in CAM trials (61.8% vs 70.7%, respectively, $P = .0003$), as was the mean year of publication (1996 ± 7.9 vs 2002 ± 4.6, respectively, $P = .0003$) and the mean probability of receiving placebo (33.0 ± 8.4% vs 40.9 ± 8.5%, $P < .0001$). In contrast, mean sample size was greater in antidepressant-only studies than in CAM studies (95.1 ± 67.3 vs 68.2 ± 45.7 patients per treatment arm, respectively, $P = .03$). Controlling for mean trial duration, the frequency of postbaseline assessments per trial was higher for patients enrolled in antidepressant studies than CAM studies (5.5 ± 0.11 vs 3.3 ± 0.33, respectively, $P < .0001$).

The results of the random-effects meta-analyses indicated that treatment with either standard antidepressant (RR = 1.38; 95% CI, 1.35–1.46; $P < .0001$) or CAM (RR = 1.60; 95% CI, 1.30–1.97; $P < .0001$) monotherapy resulted in superior response rates compared to placebo (Figure 1). Response rates for antidepressants versus placebo from all clinical trials that employed the use of an antidepressant were 53.5% (15,184/28,345) versus 37.7% (6,129/16,217), respectively (number needed to treat [NNT] of approximately 1 in 6). Response rates for CAM versus placebo from all clinical trials that employed the use of a CAM were 51.3% (777/1,502) versus 31.7% (380/1,197), respectively (NNT of approximately 1 in 5). The results of the meta-regression analysis did not indicate any difference in terms of the RR of responding to active therapy versus placebo between antidepressant- and CAM-treated patients ($P = .89$).

There was also no statistically significant difference in the RR of responding to antidepressants versus placebo when comparing trials that involved antidepressant therapy alone versus those that included both an antidepressant and a CAM ($P = .76$). Response rates for antidepressants versus placebo from CAM studies were 54.3% (256/471) versus 41.0% (172/419), respectively (NNT of approximately 8). Response rates for antidepressants versus placebo from non-CAM studies were 53.5% (14,927/27,874) versus 37.7% (5,956/15,798), respectively (NNT of approximately 6).

Meta-regression analyses suggested no statistically significant difference in the risk ratio of prematurely discontinuing therapy due to any reason between active treatment and placebo for antidepressants and CAMs ($P = .89$). The proportion of patients who prematurely discontinued antidepressant therapy and placebo for any reason in studies involving the use of an antidepressant were 26.2% (7,453/28,345) versus 27.6% (4,369/15,798), respectively. The proportion of patients who prematurely discontinued CAM therapy and placebo for

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Table 1. Placebo-Controlled Trials of Complementary and Alternative Medicine

Author (year)	Duration (wk)	Arms, Dose	n	Jadad Score
Kagan (1990)	3	SAMe, 200–800 mg/d	9	5
		Placebo	6	
Salmaggi (1993)	4	SAMe, 1,600 mg/d	40	4
		Placebo	40	
Hangsen (1994)	4	*Hypericum perforatum*, 900 mg/d	42	5
		Placebo	47	
Laakmann (1998)	6	*Hypericum*, 300 mg/d (0.5% hyperforin)	49	5
		Hypericum, 300 mg/d (5% hyperforin)	49	
		Placebo	49	
Schrader (1998)	6	*Hypericum perforatum*, 500 mg/d	81	5
		Placebo	81	
Philipp (1999)	8	*Hypericum perforatum*, 1,050 mg/d	106	5
		Imipramine, 100 mg/d	110	
		Placebo	47	
Kalb (2001)	6	*Hypericum perforatum*, 900 mg/d	37	5
		Placebo	35	
Shelton (2001)	8	*Hypericum perforatum*, 900–1,200 mg/d	98	5
		Placebo	102	
Hypericum Depression Trial Study Group (2002)	8	*Hypericum perforatum*, 900–1,500 mg/d)	113	5
		Sertraline 50–100 mg/d	111	
		Placebo	116	
Lecrubier (2002)	6	*Hypericum perforatum*, 900 mg/d	186	5
		Placebo	189	
Marangell (2003)	6	DHA, 2 g/d	18	3
		Placebo	17	
Uebelhack (2004)	6	*Hypericum perforatum*, 900 mg/d	70	5
		Placebo	70	
Bjerkenstedt (2005)	4	*Hypericum perforatum*, 900 mg/d	54	4
		Fluoxetine, 20 mg/d	54	
		Placebo	55	
Fava (2005)	12	*Hypericum perforatum*, 900 mg/d	45	4
		Fluoxetine, 20 mg/d	47	
		Placebo	43	
Gastpar (2006)	6	*Hypericum perforatum*, 900 mg/d	131	5
		Citalopram, 20 mg/d	127	
		Placebo	130	
Kasper (2006)	6	*Hypericum perforatum*, 600 mg/d	123	5
		Hypericum perforatum, 1,200 mg/d	127	
		Placebo	82	
Moreno (2006)	8	*Hypericum perforatum*, 900 mg/d	20	3
		Fluoxetine, 20 mg/d	20	
		Placebo	26	
Randlov (2006)	6	*Hypericum*, 810 mg/d (0.18% hypericin)	43	2
		Hypericum, 810 mg/d (0.12% hypericin)	44	
		Placebo	42	
Mischoulon (2009)	8	EPA, 1 g/d	28	5
		Placebo	29	

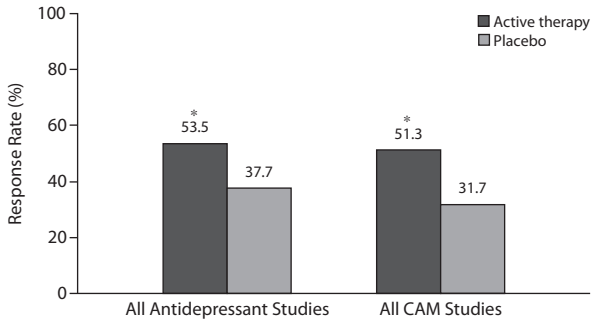
Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, SAMe = S-adenosyl-L-methionine.

any reason in studies involving the use of a CAM were 14.1% (212/1,502) versus 15.9% (190/1,197), respectively.

However, the relative risk of discontinuing active therapy versus placebo due to adverse events for patients treated with antidepressants was significantly higher than for CAM-treated patients ($P = .007$, Figure 2). The proportions of patients who prematurely discontinued antidepressant therapy and placebo specifically due to adverse events in studies involving the use of only an antidepressant or an antidepressant and a CAM were, respectively, 9.6% (2,672/27,874) versus 6.3% (998/15,798) (number needed to harm [NNH] of approximately 1 in 30) and 7.4% (35/471) versus 5.2% (22/419) (number needed to harm (NNH) of approximately 1 in 46). The proportion of patients who prematurely discontinued CAM therapy and placebo specifically due to adverse events in studies involving the use of a CAM were 4.2% (64/1,502) versus 4.0% (48/1,197) (NNH of approximately 1 in 500).

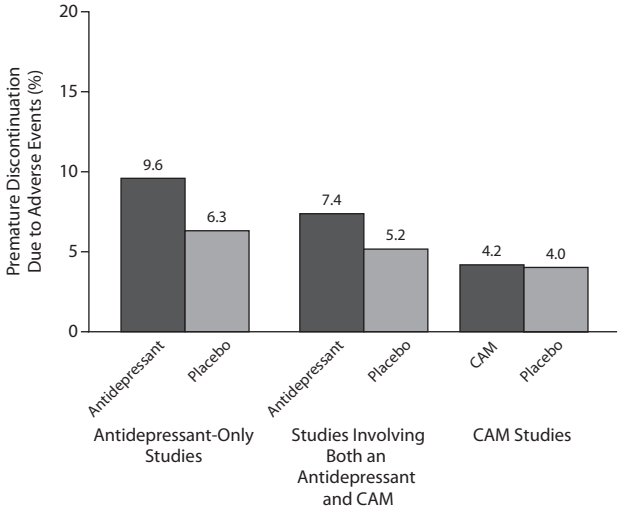
There was a trend toward statistical significance ($P = .051$) for lower response rates for patients treated with a CAM than an antidepressant. However, placebo- response rates were significantly lower for patients enrolled in CAM (31.7%, 380/1,197) versus antidepressant-only (37.7%, 5,956/15,798) studies ($P = .002$). This was true even when studies that included both a CAM and an antidepressant were not pooled along with the CAM-only trials (26.6%, 207/778) ($P < .0001$). In fact, placebo-response rates were significantly higher for CAM studies that also included

Figure 1. Efficacy of Antidepressants and CAM in Major Depressive Disorder[a]



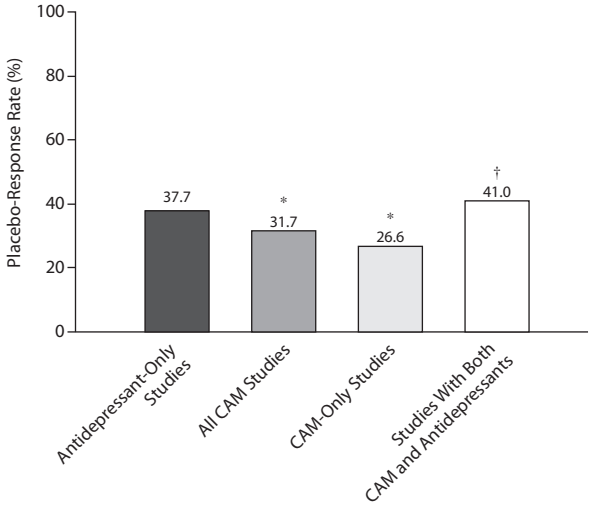
[a]$P = .89$ for risk ratio of response to antidepressants vs placebo compared to CAM vs placebo.
*$P < .001$ vs placebo.
Abbreviation: CAM = complementary and alternative medicine.

Figure 2. Tolerability of Antidepressants and CAM in Major Depressive Disorder[a,b]



[a]$P = .007$ for risk ratio of discontinuation due to adverse events of antidepressants vs placebo (all antidepressant studies) compared to CAM vs placebo.
[b]$P = .502$ for risk ratio of discontinuation due to adverse events of antidepressants vs placebo in non-CAM studies compared to studies with both an antidepressant and CAM.
Abbreviation: CAM = complementary and alternative medicine.

Figure 3. Placebo-Response Rates From Antidepressant and CAM Studies of Various Design



*$P < .05$ vs antidepressant-only studies.
†$P > .05$ vs antidepressant-only studies.
Abbreviation: CAM = complementary and alternative medicine.

an antidepressant treatment arm (41.0%, 172/419) than for CAM-only studies ($P = .005$), but not antidepressant-only studies ($P = .23$). For a summary, see Figure 3.

A post hoc analysis was conducted to examine whether the difference in placebo-response rates between antidepressant and CAM studies observed remained statistically significant after the frequency of assessment of depression was controlled for. Adding frequency of assessment as an independent variable in the multiple regression also resulted in a statistically significant difference in placebo-response rates between the 2 study types ($P = .002$).

DISCUSSION

To our knowledge, this is the first meta-analysis to assess differences between participants in RCTs of CAM therapies and standard antidepressants for the treatment of MDD. We were particularly interested in whether participants in CAM trials had less severity of symptoms at baseline and whether they demonstrated different placebo-response rates from those in studies of standard antidepressants.

We found a significantly higher proportion of women in the CAM trials than in standard antidepressant trials. This finding is consistent with the epidemiologic studies of CAM use and surveys of clinical populations that indicate more prevalent use of CAM therapies among women.[7,11,12,24] In fact, we found that the majority of participants in both standard antidepressant and CAM RCTs were female, which was also expected, as women have a higher lifetime prevalence of MDD than men.[25] We did not find any other patient demographic or clinical variables, including severity of depression at baseline, to differ between CAM and standard antidepressant trials. Overall, we found that both CAM therapies and antidepressants were superior to placebo. It is important to assess depression severity at baseline when comparing studies, as depression severity at baseline is an independent predictor of the differential response between active antidepressant and placebo response.[13] There has been controversy due to inconsistent results with St John's wort across large studies as to whether it is effective for moderate to severe depression.[26,27] A recent meta-analysis did not find a difference in response rates between St John's wort and selective serotonin reuptake inhibitors.[28] While our analysis was not designed to assess the efficacy of specific CAM therapies, our results do not support that trials assessing CAM therapies are composed of patients with less severe depression. This is an important finding, as it challenges the view that CAM therapies should be reserved for only those with mild to moderate illness.

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Because CAM therapies are widely used and have good apparent acceptability among the general population, we expected that placebo-response rates might be higher in CAM than antidepressant studies. Interestingly, there was a lower placebo-response rate for patients enrolled in CAM studies compared with antidepressant studies. This was true even when studies that included a CAM therapy arm and an antidepressant arm were compared to antidepressant studies alone. One possible explanation for the lower placebo-response rate in CAM trials is that participants in CAM studies may have more modest expectations compared to those randomized into trials of antidepressants. Also, the mean probability of receiving a placebo was higher in CAM trials than in antidepressant trials, which, in part, may explain the finding.[29] Lack of higher placebo-response rates compared to standard therapies is consistent with RCTs of CAM therapies for other indications, which have found placebo-response rates in CAM trials to be similar but not greater than placebo-response rates of conventional treatments.[30]

It has been previously demonstrated that the likelihood of receiving active therapy influences patient expectations and response rates.[29] Specifically, Papakostas and Fava[14] demonstrated that the likelihood of receiving placebo influences trial outcomes in MDD. Placebo-response rates have been reported as increasing over time in trials of MDD.[3,4,31] The later mean year of publication in CAM trials might have led us to expect a higher placebo-response rate rather than lower in comparison to the antidepressant trials. However, despite those study characteristics, we found lower placebo-response rates in CAM studies. Also, patient preferences for specific interventions have been demonstrated in MDD to improve treatment response in an open trial design.[32] It is unclear how expectations may influence placebo-response rates in CAM trials at this time, but it does not appear that they are inflated in CAM trials for MDD.

There were no significant differences in the risk ratio of response to active therapy versus placebo between patients enrolled in antidepressant and CAM trials, suggesting equivalent efficacy in relation to placebo for antidepressants and CAM therapies. We did find a trend toward statistical significance for lower response rates with the CAM therapies than with antidepressants. This may be due to the lower placebo-response rates observed in CAM studies. Both CAM therapies and antidepressants resulted in significantly higher response rates than placebo. There were no significant differences in response rates to antidepressant versus placebo in studies of antidepressant alone or in studies in which patients were randomly assigned to either a CAM or antidepressant. We found the response to antidepressant compared with placebo consistent, whether or not there was a parallel CAM treatment arm in the study. In terms of dropout rates, the overall differential discontinuation rate between active therapy and placebo was not different in CAM and antidepressant studies. However, the relative risk of discontinuing active therapy compared to placebo due to adverse events was significantly higher in standard antidepressant RCTs than CAM RCTs. Participants may have different expectations in trials of CAM therapies compared to standard antidepressant trials. It is possible that expectations about treatment and side effects influenced dropout rates beyond the contribution of the actual experience of side effects. Higher study completion rates could have implications for the ability to detect a significant difference between active treatment and placebo.

The main strength of this study is the novel comparison of patient characteristics and placebo-response rates among placebo-controlled trials of antidepressants and CAM therapies. Only studies meeting the a priori criteria, with validated diagnostic criteria, validated outcome measures, and adequate duration, were included in the meta-analysis. This study also had important limitations. Because we applied stringent inclusion and exclusion criteria to the trials selected for analysis, the number of studies was limited. Also, limitation of the literature search to English-language publications is a notable constraint of the analysis. We focused on CAM therapies that were comparable to antidepressants, specifically those available in an oral preparation and with which an oral placebo comparison arm was included. Therefore, our results are not generalizable to all CAM therapies. CAM therapies differ broadly in terms of amount of study for the treatment of MDD and biologic plausibility for use in MDD. The findings of these analyses specifically pertain to St John's wort, SAMe, and omega-3 fatty acids used as monotherapy in placebo-controlled trials for the treatment of MDD. Additionally, as we limited our study to trials for MDD, it is not possible to know if our findings would extend to mood disorders other than MDD or other psychiatric disorders.

It has been argued that rigorous RCTs for CAM interventions are urgently needed from a public health perspective and that placebo-controlled trials should be utilized to assess efficacy and safety when feasible.[33] Our findings suggest that the studied CAM therapies may have similar efficacy and better tolerability than standard antidepressants. The current analysis supports further assessment of CAM treatments for MDD in adequately powered placebo-controlled randomized trials.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), selegiline (EMSAM), sertraline (Zoloft and others).

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