Neurotoxicity Research (2018) 33:621–633
https://doi.org/10.1007/s12640-017-9860-4

ORIGINAL ARTICLE

Add-on Treatment with Curcumin Has Antidepressive Effects in Thai Patients with Major Depression: Results of a Randomized Double-Blind Placebo-Controlled Study

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Received: 7 November 2017 / Revised: 19 December 2017 / Accepted: 20 December 2017 / Published online: 11 January 2018

Abstract

Activation of immune-inflammatory and oxidative-nitrosative (IO&NS) stress pathways plays a role in major depression (MDD). Evidence suggests that curcumin (500–1000 mg/day), a polyphenol with strong anti-IO&NS properties, may have efficacy either as monotherapy or as an adjunctive treatment for depression. Further controlled trials with extended treatment periods (> 8 weeks) and higher curcumin doses are warranted. This 12-week study was carried out to examine the effects of adjunctive curcumin for the treatment of MDD. In this double-blind, placebo-controlled trial, 65 participants with MDD were randomized to receive either adjunctive curcumin (increasing dose from 500 to 1500 mg/day) or placebo for 12 weeks. Four weeks after the active treatment phase, a follow-up visit was conducted at week 16. Assessments of the primary, i.e., the Montgomery-Asberg Depression Rating Scale (MADRS), and secondary, i.e., the Hamilton Anxiety Rating Scale (HAM-A), outcome measures were rated at baseline and 2, 4, 8, 12, and 16 weeks later. Curcumin was more efficacious than placebo in improving MADRS scores with significant differences between curcumin and placebo emerging at weeks 12 and 16. The effects of curcumin were more pronounced in males compared to females. There were no statistically significant treatment-emerging adverse effects and no significant effects of curcumin on blood chemistry and ECG measurements. Adjunctive curcumin has significant antidepressant effects in participants with MDD as evidenced by significant benefits occurring 12 and 16 weeks after treatment initiation. Curcumin administration was safe and well-tolerated even when combined with antidepressants. Future trials should include treatment-by-sex interactions to examine putative antidepressant effects of immune-modifying compounds.

Keywords Depression · Oxidative and nitrosative stress · Immune · Inflammation

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Introduction

An emerging body of evidence indicates that activation of neuro-oxidative, neuro-nitrosative, and neuro-immune pathways may underpin the pathophysiology of major depressive disorder (Maes et al. 2009, 2011a; Moylan et al. 2013). Firstly, depression is characterized by lowered levels of antioxidants, which protect against oxidative damage, including high-density lipoprotein (HDL) cholesterol, lecithin–cholesterol acyltransferase (LCAT) and paraoxonase 1 (PON1) activities, and vitamin E, coupled with oxidative damage to lipids, proteins, and DNA (Maes et al. 1994, 1997, 1999, 2000, 2011a; Peet et al. 1998; Bilici et al. 2001; Sobczak et al. 2004; Tsuboi et al. 2006; Bortolasci et al. 2014; Gomes et al. 2017; Roomruangwong et al. 2017). A recent meta-analysis has confirmed disorders in neuro-oxidative pathways in major depression (Liu et al. 2015). Secondly, major depression is accompanied by indicants of nitrosative stress as indicated by increased inducible nitric oxide (NO) synthase activity and nitration and nitrosylation of proteins (Gałecki et al. 2012; Maes 2008; Maes et al. 2011b, c; Liu et al. 2015). In depression, both neuro-oxidative and neuro-nitrosative pathways may cause neuroprogression, namely the neuronal dysfunctions caused by oxidative pathways leading to increased neurotoxicity and cytotoxicity coupled with disorders in synaptic plasticity and lowered neuroprotection (Maes et al. 2009, 2011a, c; Moylan et al. 2013).

Thirdly, there is also evidence that activated neuro-immune pathways may play a key role in depression and the neuroprogressive pathways accompanying the illness (Maes 2008; Maes et al. 2009; Leonard and Maes 2012; Moylan et al. 2013). For example, activation of cell-mediated immune (CMI) and mild inflammatory responses are consistently found in major depression (Maes et al. 1990; Maes 1995), including increased levels of neurotoxic and cytotoxic cytokines, such as interleukin (IL)-1, IL-6, and IL-17 (Maes 1995; Rizavi et al. 2016). These findings are now confirmed in different meta-analyses (Howren et al. 2009; Liu et al. 2012; Valkanova et al. 2013; Köhler et al. 2017a, b). Secondary pathways, activated by immune and oxidative responses including the tryptophan catabolite pathway (TRYCAT), may further fuel the neurotoxic burden in patients with major depression (Maes et al. 2011b; Anderson and Maes 2014). In depression, lowered levels of key antioxidants, including HDL-cholesterol, PON1, vitamin E, coenzyme Q10, and the glutathione system, not only increase oxidative burden but also neuro-immune and inflammatory responses (Maes et al. 2011a; Leonard and Maes 2012; Moylan et al. 2013). Interestingly, immune responses to environmental stress and immune-serotonin responses to inflammatory stressors may be greater in women than men, while men appear to present higher levels of reactive oxygen species than women (Maes et al. 2011a, b).

Since 2001, we treat patients with major depression with high-dose antioxidants and ω3 polyunsaturated fatty acids (PUFAs) based on the knowledge that treatments with these compounds may attenuate neuro-oxidative and neuro-immune pathways (Maes 2005; Maes et al. 2012). We have argued that selected, high-dose natural anti-inflammatory and antioxidant substances (NAIOSs) may target six pathophysiologically guided drug targets, which are associated with the pathophysiology of major depression, namely (1) activation of CMI pathways, (2) inflammation, (3) increased oxidative and nitrosative stress, (4) lowered antioxidant defenses, (5) secondary damage to mitochondria, and (6) neuroprogression including lowered neuroprotection (Maes et al. 2012; de Melo et al. 2017).

Curcumin, a food additive in Indian culinary and a plant polyphenol, is one of those NAIOSs that may possess clinical efficacy by targeting these six pathophysiologically guided drug targets (Maes et al. 2012; Lopresti et al. 2012; Lopresti 2017). An early randomized controlled trial (RCT) showed that curcumin, taken orally, was significantly more effective than placebo in improving depressive symptoms (Lopresti et al. 2014). Two recent meta-analyses that included six studies showed that treatment of depression with curcumin (orally 500–1000 mg/day) significantly improves depressive and anxiety symptoms (Al-Karawi et al. 2016; Ng et al. 2017). Nevertheless, more investigations with treatment periods longer than 8 weeks and with higher curcumin dosages are required (Lopresti et al. 2014). Moreover, approved antidepressant agents supposedly act through the modulation of serotonergic pathways, but evidence indicates that only approximately a third of patients with major depression achieve remission after a trial with a first-line antidepressant agent (Carvalho et al. 2014). Therefore, the discovery of mechanistically novel antidepressants is a priority in the field of psychiatry.

Thus, the aim of the study was to conduct a 12–16-week RCT to examine the clinical efficacy of a higher dose of curcumin (orally, 1500 mg/day) versus placebo as an add-on treatment for major depression. The a priori hypothesis was that add-on treatment with this higher dose of curcumin would be significantly more effective than placebo in reducing depressive symptoms and that after discontinuation the clinical effects of curcumin would be maintained until 1 month later. The secondary hypothesis is that adjunctive treatment with curcumin would be superior to placebo for reducing anxiety.

Experimental Procedures

Participants

In this double-blind, randomized controlled study, we recruited 92 patients from September 2015 to February 2017.

All participants were outpatients admitted to the Department of Psychiatry, King Chulalongkorn Hospital, Bangkok, Thailand. This study was a 12-week RCT (see Fig. 1). We included male and female patients, ages 18 to 63 years, with a major depressive episode as assessed using the Mini International Neuropsychiatric Interview 6.0 (MINI 6.0) (Sheehan et al. 1998) in a validated Thai translation (Kittirathanapaiboon and Khamwongpin 2005). The diagnoses were made by BK, a senior research psychiatrist. Patients were eligible when they showed a baseline Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg 1979) score > 20. Exclusion criteria were axis 1 DSM-IV-TR diagnoses other than major depression, including but not limited to bipolar disorder, anxiety disorders, schizophrenia, psycho-organic syndromes, eating disorders, substance abuse, or dependence disorders. We also excluded participants with major depression with psychotic features and patients who had a significant risk of suicide (as assessed with a score > 6 on item suicidal thoughts of the MADRS), pregnant women, women who were breastfeeding, or women who intended to fall pregnant. Also participants suffering from major medical illness were excluded to participate, including neurodegenerative/neuroinflammatory disorders, such as Alzheimer's disease, stroke, Parkinson's disease, or multiple sclerosis, autoimmune disorders, diabetes, inflammatory bowel disease, chronic obstructive pulmonary disease, etc. We also excluded subjects who were treated with glucocorticoids, antibiotics, anticoagulant medications, antioxidant supplements (including curcumin), herbal supplements, or ω3 polyunsaturated fatty acids. Use of analgesics (once a week) or contraceptive pills was permissible.

All participants were treated with care as usual, that is, fluoxetine ($n = 12$; 10–50 mg/day), other selective serotonin reuptake inhibitors (SSRIs, $n = 13$), mainly sertraline (40–125 mg/day), other antidepressants (including mianserin, trazodone) combined or not with psychotherapy, and mood stabilizers (five subjects were treated with sodium valproate 200–1000 mg/day and one patient with lamotrigine 200 mg/day). First-line approved antidepressants as well as their dosages were stable for at least 8 weeks prior to trial initiation and during the study. Likewise, psychotherapy was started at least 8 weeks prior to the study and continued during the study. No additional treatments were provided during the study period. One patient was treated with propranolol (20 mg/day) and one patient with enalapril (5 mg/day).

Moreover, all women recruited to participate in the study had urine pregnancy tests and were excluded when positive. All patients had blood tests at baseline for the number of white blood cells (WBC) and platelets, hematocrit (Hct), hemoglobin (Hb), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AlkP), total (TBil) and direct bilirubin (DBil), and blood urea nitrogen (BUN) as well as ECG measurements, including heart rate and PR and QRS interval. Patients with abnormal results on those tests were excluded from the study.

This project was registered at Thai Clinical Trial Registry (TCTR), clinicaltrials.gov TCTR ID: TCTR20170803002. All participants gave written informed consent prior to participation in this study. The study was conducted according to Thai and international ethics and privacy laws. Approval for the study was obtained from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB ID298/57). The study was conducted in compliance with the International Guideline for Human Research protection as required by the Declaration of Helsinki, The Belmont Report, CIOMS Guideline, and International Conference on Harmonization in Good Clinical Practice.

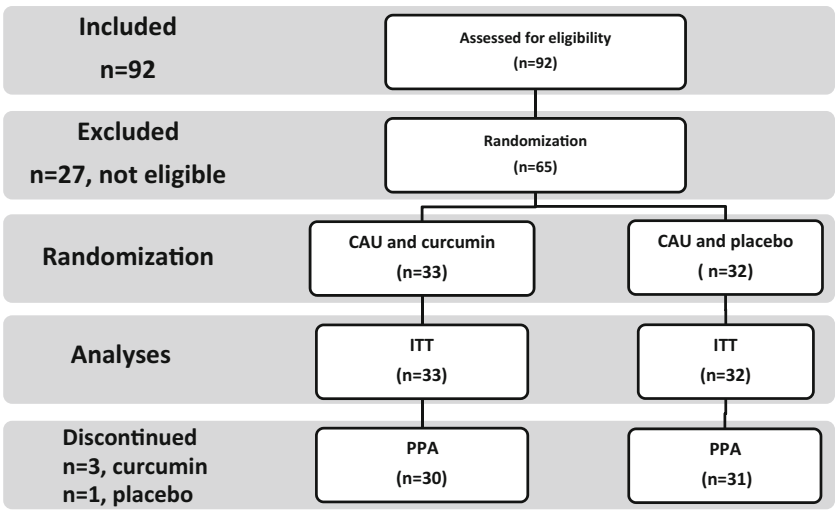

Fig. 1 CONSORT flow diagram. This figure shows the CONSORT flow diagram with the progress of the patients through the randomized controlled trial

Procedures

Randomization

Curcumin was supplied by the Government Pharmaceutical Organization (GPO), Bangkok, Thailand. Curcumin was delivered in 250-mg capsules together with indistinguishable placebo capsules. The GPO compound preparation consisted of curcuminoids 100%, namely curcumin 77%, demethoxycurcumin 17%, and bisdemethoxycurcumin 6%. The trial pharmacist labeled the 250-mg curcumin capsules, which were identical in appearance as the placebo (cellulose) capsules, by code numbers and packed the capsules in identical containers. Curcumin was used at a dose of 500–1500 mg/day. At baseline, patients were directed to take one capsule, 250 mg curcumin, or indistinguishable placebo twice a day, one before breakfast and one before dinner for 1 week. After this, they were asked to increase the dose every week by 250 mg/day (before breakfast or dinner). Thus, after 4 weeks (t4), patients were taking 1500 mg curcumin/day or placebo. Patients were randomly and equally assigned to treatment with curcumin or placebo in a double-blind fashion. A random allocation sequence was performed by the trial pharmacist according to CONSORT guidelines and using a block randomization method. The trial pharmacist kept the treatment code double-blinded and supplied the trial medication to the outpatient clinic and clinical psychiatrist. Returned medication containers were audited to measure medication compliance and checked with volunteer-reported pill count at t4, t8, and t12. As such, patients were randomized in two treatment groups: (a) the active intervention group treated with curcumin + care as usual and (b) the control group treated with placebo and care as usual.

Assessments

Assessments were made by the principal investigator, a senior clinical psychiatrist (BK) and a research psychologist (ST), using semistructured interviews. At baseline (t0) sociodemographic (including age, sex, education, social status, income) and clinical (including age at onset, smoking behavior, use of antidepressants) data were collected by BK, while the research psychologist (ST) scored two efficacy measurements, namely the MADRS (primary outcome measurement) (Montgomery and Asberg 1979) and Hamilton Anxiety Rating Scale (HAM-A) (secondary outcome measurement; Hamilton 1959) rating scales. The same rater (ST) completed the MADRS and HAM-A at baseline (t0) and weeks 2 (t2), 4 (t4), 8 (t8), 12 (t12), and 16 (t16, namely 4 weeks after discontinuation of treatment). At t2, t4, t8, t12, and t16, BK also measured putative treatment-related adverse effects (see Table 4 for the adverse effects rated in this study). In addition, BK recorded any other treatment-emergent adverse events, defined as newly emerging side effects or adverse effects worsening the pretreatment status. At t0, we measured body mass index (BMI) as weight (kg) / squared length (meters).

Biological Measurements

Fasting blood samples were taken at 8.00–8.30 a.m. at t0 and t12 for the assay of WBCs, platelets, Hct, Hb, creatinine, AST, ALT, AlkP, TBil, DBil, and BUN. ECG measurements were performed to assess heart rate and PR and QRS intervals. The number of WBCs, platelets, Hct, and Hb was assayed by the Central Laboratory, Department of Laboratory Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand, using the MindRay-BC-6800 (Auto Hematology Analyzer; Nanshan, Shenzhen 518057, People's Republic of China). Creatinine, AST, ALT, AlkP, TBil, DBil, and BUN were assayed by the clinical biochemistry laboratory of the same university hospital using the Architect C16000 (Abbott Laboratories, Abbott Park, IL, USA). All inter-assay CV values were < 5.7%. Resting ECG measurements, including PR and QRS interval, were measured using the electrocardiograph ECG-2250 (Nihon Kohden, Irvine, CA, USA).

Statistics

Baseline data, including socio-demographic and clinical data, were checked for balance between the curcumin and placebo treatment groups using analyses of contingency tables (X^2 test) to assess associations between nominal variables and analyses of variance (ANOVAs) to assess differences in scale variables between treatment groups. The primary outcome analysis is a linear mixed model (LMM) repeated measures analysis to assess responsivity of the MADRS to treatment with curcumin from t2 to t16. The secondary outcome measurements are (a) repeated measurements design ANOVA with all time points as dependent variables and considering sex effects (2) and univariate General Linear Model (GLM) analyses to assess differences between the two treatment modalities in t12–t2 and t16–t2 responses, t0 covaried. We used an intention-to-treat (ITT) analysis, namely analyses were performed on all randomized patients ($n = 65$). This study also performed a per protocol approach (PPA) including patients who completed all MADRS measurements. The pre-specified LMM repeated measures analyses included fixed categorical effects of treatment, assessment time, time-by-treatment interaction, sex, sex-by-treatment and sex-by-treatment-by-time interactions, care as usual (fluoxetine versus other antidepressants), and use of clonazepam or clorazepate and continuous fixed covariates, namely baseline MADRS (or HAM-A) scores, age, and age at onset, while we have also explored the effects of age at onset and age groups (q25 and q75 split), BMI, current, and past suicidal

ideation and current smoking. This statistical method allows us to control for the effects of relevant covariates and interactions when examining treatment effects at the subject level, while minimizing biased imputations due to incomplete assessments. Adverse effects were compared between the two treatment groups at t2, t4, t8, t12, and t16 using the phi coefficient for nominal by nominal data. The differences in the sums of all positive adverse effects between curcumin and placebo were examined using a LMM repeated measures analysis including a fixed categorical effect of treatment, assessment time, time-by-treatment interaction, sex and sex-by-treatment interaction, care as usual groups, use of clonazepam and clorazepate, and one continuous fixed covariate, namely age. Differences in blood assays and ECG measurements between t0 and t12 were examined using repeated measurement design ANOVAs with blood assays or ECG measurements as dependent variables and the time-by-treatment interaction as outcome variable (including other effects as described above). Tests were two-tailed and a p value of 0.05 was used for statistical significance. All statistical analyses were performed using IBM SPSS Windows version 22. Statistical analyses were conducted in accordance with the International Conference on Harmonisation E9 statistical principles (November 2005). Using a two-tailed test at $\alpha = 0.05$ and assuming a power of 0.80 and an effect size of 0.48, it is indicated that the required sample size is around 130 participants and therefore the protocol included 130 subjects. Unfortunately, the study was stopped before we were able to recruit 130 participants because grant support was limited in time. Therefore, no new patients could be randomized, although enrolled patients completed the study.

Results

CONSORT Flow Diagram

Figure 1 shows the CONSORT flow diagram with the progress of the patients through the RCT. Of the 92 patients included in the study, 12 cases were excluded because of abnormal baseline blood tests or because they did not have a t0 MDRS > 20, while 15 patients declined to participate in the study, most of them being unable to follow the study schedule for practical reasons. Therefore, 65 patients were randomized to enter the study and were treated with care as usual and curcumin or placebo. One patient belonging to the placebo group and three patients allocated to the active intervention group discontinued the study. Finally, 61 patients completed the study without any violations of the study protocol. Accordingly, we analyzed data of 33 participants treated with curcumin and 32 with placebo using a classical ITT analysis and 30 participants treated with curcumin and 31 with placebo using a PPA, with ITT and PPA showing similar results. Here we show the ITT results.

Baseline Characteristics of the Curcumin and Placebo Treatment Groups

Table 1 compares the socio-demographic and clinical data between the curcumin and placebo group. We found no significant differences between both treatment groups in age, sex, BMI, education, t0 MADRS, t0 HAM-A, care as usual, clonazepam, chlorazepate, age at onset of illness, duration of illness, smoking, or current suicidal ideation, although there was a modest difference in past suicidal ideation. There were no significant differences in any of the blood measurements, heart rate, and PR and QRS intervals between patients treated with curcumin versus placebo.

Effects of Curcumin on MADRS

Table 2 (LMM no. 1) shows the outcome of the primary LMM analysis with MADRS as dependent variable and treatment, assessment time (t2, t4, t8, t12, and t16), time-by-treatment interaction, sex, sex-by-treatment and sex-by-treatment-by-time interactions, care as usual groups, use of clonazepam, and use of chlorazepate as fixed categorical effects and t0 MADRS and age and age at onset as continuous fixed covariates. We found significant effects of trial drugs (mean ± SE MADRS in placebo = 14.8 ± 1.1 versus curcumin 12.6 ± 1.3), t0 MADRS, time, time-by-treatment, and sex-by-treatment. Figure 2 displays that curcumin treatment induces an improvement in MADRS score over time from t0 to t12 and that it is maintained at t16. We reran the same analysis but without care as usual groups, use of clonazepam and clorazepate, and age at onset and found similar results. LMM no. 4 and no. 5 show a significant effect of current and past suicidal ideation on MADRS responsivity with higher mean ± SE MADRS values in patient with current (15.3 ± 1.3 versus 12.7 ± 1.2) and past suicidal ideation (15.2 ± 1.2 versus 12.2 ± 1.2) versus those without suicidal ideation. There were no significant effects of suicidal-ideation-by-treatment interaction, age groups (LMM no. 2), BMI (LMM no. 3), or smoking (LMM no. 6) on MADRS responsivity.

The secondary analyses showed the following results. Firstly, repeated measurement design ANOVA (tests for within-subject effects) showed a significant effect of time-by-treatment ($F = 2.80$, $df = 5/105$, $p = 0.017$) but no significant effects of time-by-sex ($F = 0.27$, $df = 5/15$, $p = 0.928$) or time-by-treatment-by-sex ($F = 1.98$, $df = 5/74$, $p = 0.082$). Secondly, univariate GLM analyses with t0 MADRS as covariate showed a significantly greater reduction in Δ t12–t2 MADRS (means ± SE = − 14.1 ± 1.6 versus − 8.6 ± 1.6; $F = 6.77$, $df = 1/56$, $p = 0.012$) and Δ t16–t2 MADRS (means

Table 1 Socio-demographic and baseline clinical and biological data in participants allocated to the active intervention (curcumin) and control (placebo) study groups

Variables	Placebo $n = 32$	Curcumin $n = 33$	F/X^2	df	p
Age (years)	46.2 (13.4)	42.6 (13.6)	1.12	1/63	0.294
Age groups (< 38, 38–54, > 54 years)	8/11/13	13/9/11	1.54	2	0.463
Sex (male/female)	10/22	9/27	0.12	1	0.724
BMI (kg/m^2)	23.9 (3.9)	25.0 (4.1)	1.24	1/62	0.271
T0 MADRS	27.8 (4.4)	27.6 (5.7)	0.02	1/63	0.890
T0 HAM-A	28.0 (11.3)	28.7 (10.1)	0.08	1/63	0.776
Single/married/divorced/widow	11/8/3/4	10/13/3/3	–	–	–
Education (years)	13.7 (4.7)	12.5 (4.8)	0.86	1/51	0.357
Care as usual groups[a]	12/13/7	12/14/7	0.02	1	0.989
Clonazepam (no/yes)	25/7	24/9	0.26	1	0.614
Chlorazepate (no/yes)	23/9	28/8	0.13	1	0.722
Age at onset (years)	38.1 (13.3)	33.8 (14.3)	1.51	1/62	0.224
Duration of illness (years)	8.1 (10.0)	9.3 (9.9)	0.25	1/62	0.616
Current suicidal ideation (no/yes)	17/15	20/13	0.37	1	0.543
History of suicidal ideation (no/yes)	18/14	10/23	4.46	1	0.035
Smoking (no/yes)	29/3	32/2	$\Psi = -0.062$	–	0.616
White blood cells (10^9/L)	7.35 (2.61)	7.75 (1.92)	0.48	1/63	0.491
Platelets (10^9/L)	265 (73)	288 (71)	1.77	1/63	0.189
Hemoglobin (g/dL)	13.37 (1.69)	13.67 (1.49)	0.54	1/63	0.464
Hematocrit (%)	40.8 (4.7)	41.1 (4.4)	0.10	1/63	0.755
Creatinine (mg/dL)	0.81 (0.20)	0.78 (0.22)	0.17	1/62	0.685
Aspartate aminotransferase (U/L)	21.7 (5.9)	24.0 (10.8)	1.14	1/62	0.290
Alanine aminotransferase (U/L)	22.9 (13.5)	25.4 (12.4)	0.59	1/62	0.445
Alkaline phosphatase (U/L)	77.7 (20.6)	71.8 (17.5)	1.46	1/60	0.232
Total bilirubin (mg/dL)	0.53 (0.24)	0.56 (0.34)	0.15	1/62	0.704
Direct bilirubin (mg/dL)	0.18 (0.1)	0.19 (0.1)	0.05	1/62	0.826
Blood urea nitrogen (mg/dL)	12.2 (3.8)	11.6 (3.4)	0.39	1/63	0.537
Heart rate (bpm)	65.9 (9.3)	69.1 (10.7)	1.58	1/62	0.213
PR interval (ms)	170.7 (50.7)	162.8 (39.0)	0.51	1/62	0.479
QRS interval (ms)	87.1 (18.2)	94.2 (18.4)	2.44	1/62	0.123

All data are shown as mean (±SD)

F results of analyses of variance, X^2 results of analyses of contingency tables, Ψ phi coefficient for nominal by nominal data

[a] Care as usual groups: fluoxetine/other selective serotonin reuptake inhibitors (SSRIs)/other antidepressants. These treatments were combined with psychotherapy and mood stabilizers in six patients

± SE = − 18.7 ∀1.8 versus − 12.9 ± 1.7; $F = 4.67$, $df = 1/56$, $p = 0.035$) in patients treated with curcumin versus those treated with placebo. No such differences were detected at the other time points. Nevertheless, introduction of the treatment-by-sex interaction (e.g., for Δ t12–t2, t0 covaried) shows significant effects of treatment ($F = 10.60$, $df = 1/54$, $p = 0.002$) as well as the interaction ($F = 4.35$, $df = 1/54$, $p = 0.042$). Analyses of simple effects showed a significant effect in males ($F = 10.42$, $df = 1/54$, $p = 0.002$) but not in females ($F = 1.05$, $df = 1/54$, $p = 0.311$). In males treated with placebo, the Δ MADRS is − 5.1 (± 2.6) and in males treated with curcumin − 17.6 (± 2.9), whereas in females treated with placebo, the Δ was − 10.3 (± 1.83) and in females treated with curcumin − 12.9 (± 1.8).

Effects of Curcumin on HAM-A

Table 3 (LMM no. 1) shows the outcome of a LMM analysis with the HAM-A as a dependent variable. We found significant effects of time, sex-by-trial drug interaction, and T0 HAM-A. The sex-by-treatment interaction showed that in males, curcumin decreased HAM-A scores more than placebo (mean ± SE HAM-A levels = − 9.1 ± 4.4 versus − 5.5 ± 3.9), whereas in females, curcumin increased HAM-A scores more than the placebo (mean ± SE HAM-A levels = − 4.4 ± 2.8 versus − 7.4 ± 2.8). Nevertheless, the secondary statistical tests (including repeated measures GLM and univariate GLM analysis) did not show any significant effects of treatment or sex-by-treatment interactions.

Table 2 Results of Linear Mixed Model (LMM) analyses with MADRS (t2, t4, t8, t12, t16) as dependent variables and treatment modality as primary explanatory variable, while adjusting for age, sex, and other putative confounding variables

LMM	Explanatory variables	Wald	*df*	*p*
LMM no. 1	Trial drugs	7.52	1/183	0.007
	Time	28.80	4/90	< 0.001
	Time-by-treatment	3.20	4/90	0.017
	Sex-by-treatment	13.69	1/201	< 0.001
	Sex	0.88	1/183	0.351
	Time-by-sex-by-treatment	1.44	8/90	0.190
	T0 MADRS	43.03	1/156	< 0.001
	Age	1.65	1/155	0.200
	Age at onset	2.54	1/157	0.113
	Care-as-usual	1.58	2/156	0.209
	Clonazepam	0.68	1/149	0.413
	Clorazepate	1.74	1/154	0.189
LMM				
No. 2	Age groups (instead of age)	1.45	1/154	0.238
No. 3	BMI	0.04	1/161	0.834
No. 4	Past suicidal ideation	6.07	1/157	0.015
No. 5	Current suicidal ideation	6.59	1/153	0.011
No. 6	Smoking	3.11	1/155	0.080

Putative Adverse Effects

We did not observe any treatment-emergent adverse events. Table 4 shows putative adverse effects at t2, t4, t8, t12, and t16. There were no significant differences in incidence in any of the side effects between curcumin and placebo at any of the time points using phi coefficient for nominal by nominal data performed at the $p = 0.05$ level without p corrections. Table 4 shows also the total number of possible side effects at the different time points in both patient groups. LMM repeated measures analysis (with treatment, assessment time, time-by-treatment interaction, sex, sex-by-treatment, and fluoxetine-by-treatment interactions as fixed categorical variables and age as fixed continuous covariate) showed that there were no significant differences in total numbers of possible adverse effects among those treated with curcumin or placebo ($F = 0.01$, $df = 1/262$, $p = 0.925$; mean ± SE for placebo = 1.60 ± 0.13 and for curcumin = 1.59 ± 0.14).

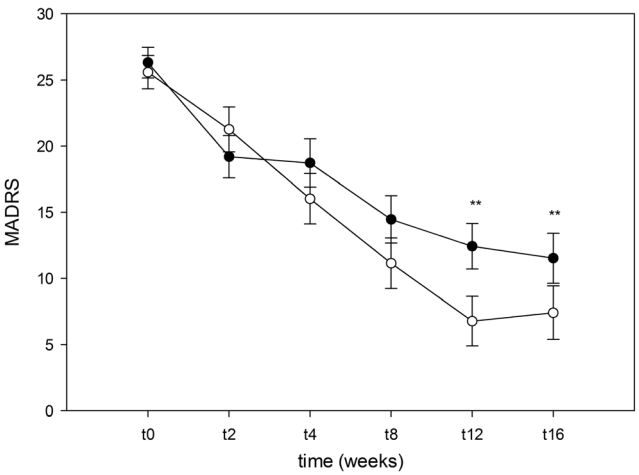

Fig. 2 Effects of curcumin versus placebo. This figure displays that curcumin treatment induces an improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score over time from baseline (t0) to 12 weeks later (t12) and that it is maintained at week 16 (t16)

Table 3 Results of Linear Mixed Model (LMM) analyses with HAM-A (t2, t4, t8, t12, t16) as dependent variables and treatment modality as primary explanatory variable, while adjusting for age, sex, and other putative confounding variables

LMM	Explanatory variables	Wald	*df*	*p*
LMM no. 1	Trial drugs	0.11	1/202	0.144
	Time	5.92	1/86	< 0.001
	Time-by-treatment	0.87	1/87	0.488
	Sex-by-treatment	10.04	2/219	0.002
	Sex	0.00	1/212	0.997
	Time-by-sex-by-treatment	0.79	8/86	0.609
	T0 HAM-A	120.06	1/201	< 0.001
	Age	0.73	1/202	0.238
	Age at onset	0.16	1/201	0.393
	Care-as-usual	0.16	2/203	0.850
	Clonazepam	0.07	1/196	0.795
	Clorazepate	0.49	1/199	0.487

Table 5 shows the measurements of blood assays and ECG at t0 and t12. Repeated measurement design ANOVAs with blood assays or ECG measurements as dependent variables and the time-by-treatment interaction as primary outcome variable showed that there were no significant effects of the interaction on any of the blood or ECG variables (not even at the $p = 0.05$ levels even without adjustment for multiple testing).

Discussion

The first major finding of this randomized study is that add-on treatment with curcumin significantly improved the MADRS score and that this effect was significant 12 weeks after starting treatment and that, after discontinuation of curcumin, the improvement was maintained 4 weeks later. Importantly, the outcome of the primary LMM and secondary GLM analysis reached the same conclusions thereby increasing confidence in the results that curcumin significantly improves depressive symptoms. Moreover, the effects of curcumin on depressive symptoms are greater in males than females, although the primary LMM and secondary GLM analyses are not concordant with regard to this interaction.

Table 4 List and frequency of adverse events at different time points in individuals treated with curcumin (Cur) and placebo (Pl)

Putative side effects	t2 (32/31)	t4 (30/31)	t8 (30/29)	t12 (30/29)	t16 (30/28)
Dizziness (Pl/Cur)	2/0	0/0	1/0	1/2	1/4
Nausea/vomiting (Pl/Cur)	1/3	1/1	2/0	0/1	0/0
Flatulence (Pl/Cur)	1/1	3/1	1/1	0/0	0/2
Stomachache (Pl/Cur)	0/0	0/0	0/0	0/0	0/0
Diarrhea (Pl/Cur)	0/1	1/0	1/0	0/1	0/0
Constipation (Pl/Cur)	3/0	1/3	0/0	0/1	2/0
Hungry (Pl/Cur)	1/0	0/0	0/1	0/2	0/1
Rash (Pl/Cur)	0/1	0/0	0/0	0/0	0/0
Sleepy (PL/Cur)	1/1	1/0	1/0	1/1	2/1
Insomnia (PL/Cur)	4/2	2/3	4/2	2/2	1/1
Headache (PL/Cur)	3/2	1/1	0/2	0/0	1/2
Ataxia (PL/Cur)	0/0	0/0	1/0	0/0	0/1
Weight gain (PL/Cur)	3/2	2/6	5/5	4/7	1/3
Weight loss (PL/Cur)	3/2	2/0	0/3	1/1	0/0
Other (PL/Cur)	6/6	3/4	2/3	2/0	3/4
Overall	1.9 (0.9)	1.7 (0.9)	1.4 (0.8)	1.6 (0.9)	1.7 (0.9)
Pl Cur	1.7 (0.9)	1.8 (0.9)	1.8 (0.9)	1.6 (0.9)	1.8 (0.9)

The results extend those of previous open-label, single-blind, or double-blind add-on studies indicating that curcumin (500–1000 mg/day) may augment the efficacy of antidepressants (Yu et al. 2015; Panahi et al. 2015; Sanmukhani et al. 2014). Our results also extend the results of Lopresti et al. (2014) who reported that monotherapy with curcumin may have antidepressant effects in major depressive disorder as detected by benefits occurring 4 to 8 weeks after starting add-on treatment. More recently, Lopresti and Drummond (2017) reported the outcome of an RCT with four treatment arms in major depressed patients, namely placebo, low-dose curcumin extract (500 mg/day), higher dose curcumin (1000 mg/day), or combined low-dose curcumin + saffron (30 mg/day). They found that all active curcumin treatments significantly improved severity of depression although there were no significant differences between the three active treatment conditions. In another study, Esmaily et al. (2015) reported that monotherapy with curcumin had no significant effects on depression in a 4-week trial performed in obese subjects with depression. Recently, a mini meta-analysis of curcumin treatment in depression showed that curcumin administration significantly reduced depression (Al-Karawi et al. 2016). Another meta-analysis performed on

Table 5 Putative side effects of the trial drug on blood tests: results of Repeated Measurements Design Analyses of Variance (RMA)

Dependent variables	t0	t12	F^a	*Df*	*p*
White blood cells (10^9/L)	7.41 (2.28)	7.21 (2.00)	0.36	1/57	0.552
Platelets (10^9/L)	275 (73)	265 (58)	1.80	1/57	0.185
Hemoglobin (g/dL)	13.58 (1.62)	13.23 (1.60)	1.02	1/57	0.317
Hematocrit (%)	41.13 (4.60)	40.58 (4.47)	0.01	1/57	0.909
Creatinine (mg/dL)	0.80 (0.22)	0.81 (0.19)	1.13	1/56	0.293
Aspartate aminotransferase (U/L)	22.1 (6.0)	21.5 (5.9)	0.00	1/56	0.980
Alanine aminotransferase (U/L)	23.7 (11.8)	21.4 (11.9)	1.72	1/56	0.195
Alkaline phosphatase (U/L)	72.4 (19.3)	68.4 (23.7)	2.35	1/53	0.134
Total bilirubin (mg/dL)	0.55 (0.31)	0.48 (0.24)	0.28	1/56	0.596
Direct bilirubin (mg/dL)	0.18 (0.09)	0.18 (0.1)	0.38	1/56	0.543
Blood urea nitrogen (mg/dL)	12.1 (3.6)	11.7 (3.7)	0.02	1/57	0.882
Heart rate (bpm)	68.3 (10.1)	66.3 (14.7)	0.01	1/55	0.920
PR interval (ms)	167.6 (50.0)	169.7 (42.9)	0.19	1/55	0.663
QRS interval (ms)	91.2 (19.01)	92.7 (14.6)	1.55	1/55	0.218

[a] Results of repeated measurement design analyses of variance examining time-by-treatment interaction

6 studies and 377 patients showed that curcumin has significant clinical efficacy in major depression (Ng et al. 2017).

While putative treatment-by-sex interactions, indicating a greater effect on depression in men than women, were not reported in previous studies, our primary outcome LMM analyses also found a significant treatment-by-sex interaction effect on the HAM-A. Thus, in men, there is a very modest curcumin effect on the HAM-A, while this effect is reversed in women. Nevertheless, this interaction could not be validated in secondary GLM analyses and thus these results have lower confidence. The meta-analysis by Ng et al. (2017) reported that a significant anti-anxiety effect of curcumin was detected in three of the six trials. For example, the 4-week RCT in obese adults showed that curcumin had significantly more efficacy in reducing anxiety than placebo, while there were less pronounced effects on depressive symptoms (Esmaily et al. 2015). Lopresti and Drummond (2017) showed that curcumin treatment has anti-anxiety effects, while Lopresti et al. (2014) found a trend toward a significant effect of curcumin on anxiety levels as measured with the another anxiety rating scale. Overall, the effects of curcumin on anxiety may be less pronounced than its effects on depression.

Lopresti (2017) reviewed the effects of 41 animal studies showing that curcumin administration, oral or intraperitoneal, and alone or in combination with antidepressants, attenuates depressive- and anxiety-like behaviors induced by a variety of stressors, including chronic mild stress, forced swimming test, and administration of glucocorticoids and lipopolysaccharides. As reviewed previously, curcumin has a broad spectrum of activities which could explain its clinical efficacy (Maes et al. 2012; Kaufmann et al. 2016; Farooqui 2016; Lopresti 2017). These activities targeted at the six pathophysiologically guided drug targets described in the introduction comprise: (1) attenuation of activated CMI as indicated by lowered production of interferon-γ and IL-12 and increased IL-10 production; (2) strong anti-inflammatory properties targeting nuclear factor κB (NFκB) and production of pro-inflammatory cytokines, including IL-1, IL-6, and IL-17; (3) protection against lipid, protein, and DNA oxidation and increased nitric oxide production thereby attenuating nitro-oxidative and nitrosative stress; (4) enhancing antioxidant defenses through effects on antioxidants and antioxidant enzymes, including HDL functionality-associated enzymes, such as PON1 and LCAT, catalase, glutathione *S*-transferase, glutathione, and nuclear factor (erythroid-derived 2)-like 2 (Nrf2); (5) restoring mitochondrial functions and dynamics; and (6) suppression of neuroprogression by activating neurotrophic effects thereby promoting neuroprotection and neuronal growth, while attenuating neurotoxic effects of neuro-immune and neuro-oxidative pathways including IFNγ-induced activation of indoleamine 2,3-dioxygenase (IDO) and thus the synthesis of neurotoxic TRYCATs (Jeong et al. 2009; Jurrmann et al. 2005; Maes et al. 2012; Kaufmann et al. 2016; Farooqui 2016; Lopresti 2017; Banji et al. 2013; Ghandadi and Sahebkar 2017; Slyepchenko et al. 2016; Ciftci et al. 2015; González-Reyes et al. 2013; Ganjali et al. 2017; Soto-Urquieta et al. 2014; de Oliveira et al. 2016). A recent meta-analysis suggests that approved antidepressants decrease peripheral levels of pro-inflammatory cytokines and chemokines although the role of immune activation in treatment responsivity remains unclear (Köhler et al. 2017a, b). Furthermore, available evidence indicates that a subgroup of patients with depression may benefit from anti-inflammatory agents (Köhler et al. 2014). The gender-related differences in curcumin responsivity found in the current study could perhaps be explained by sex-related differences in immune functions as reviewed in the introduction. On the other hand, men show increased production of reactive oxygen species as compared to women, although damage biomarkers do not differ between both sexes (Maes et al. 2011a). Future research should consider possible treatment-by-sex interactions on IO&NS biomarkers in association with the clinical response.

In humans, there are only few studies that examined biomarker predictors of a good clinical response to curcumin treatment and the effects of curcumin on these biomarkers. For example, increased levels of plasma endothelin-1 and leptin are associated with greater reductions in depression severity in patients treated with curcumin (Lopresti et al. 2015). Yu et al. (2015) observed that the clinical activity of curcumin is accompanied by decreases in plasma levels of IL-1β and TNF-α and with increased plasma levels of brain-derived neurotrophic factor. These findings suggest that the effects of curcumin may be related to changes in leptin resistance and attenuation of immune-inflammatory and oxidative processes (for which ET-1 is a biomarker) (Lopresti et al. 2015; Yu et al. 2015). Future studies should examine the potential antidepressant mechanisms of action of curcumin, including its effects on biomarkers of CMI pathways, inflammation, increased oxidative and nitrosative stress, mitochondrial functions, and neuroprotection. These measurements may also help to clarify the biomarker features of curcumin treatment responders.

The current study found important modifiers of a clinical response to add-on treatment with curcumin and/or care as usual. We found that the effects of curcumin on the MADRS score became significant only after 12 weeks, whereas at week 8, no significant differences were observed. The meta-analysis of Al-Karawi et al. (2016) also reported stronger effects of curcumin for longer treatment periods. Interestingly in the meta-analysis published by Al-Karawi et al. (2016), the strongest effects of curcumin were observed in middle-aged patients. In our study, we found no significant effect of age on curcumin responsivity, and additionally, we were unable to detect significant differences in MADRS or HAM-A responses between age groups (divided in three groups using ages 38.0 and 54.0 years as threshold values). Also, current

suicidal ideation and a history of past suicidal ideation were associated with a lower responsitivity to curcumin, suggesting that when suicidal ideation is present, a more severe pathophysiology may interfere with the clinical response to treatment. Previously, it was indeed shown that suicidal ideation in depressed patients is accompanied by increased oxidative stress (Vargas et al. 2013). On the other hand, we could not find any significant effects of age at onset of depression, care as usual type (psychotherapy versus SSRIs), current use of benzodiazepines, BMI, and smoking on the responsivity to treatment. Also, part of our patients could be treatment resistant at least to an initial treatment. Therefore, future research should examine the effects of curcumin in drug-resistant depression.

In this study, we have also evaluated the safety and tolerability of curcumin treatment as well as treatment-emergent side effects. We observed that curcumin when combined with antidepressants is a very safe and well-tolerated treatment without any unwanted reactions or potential side effects, including diarrhea, upset stomach and nausea, rash, dizziness, ataxia, headache, sleep disorders, or weight gain/loss, while no allergic reactions were observed. Moreover, we could not find any effects of curcumin on blood chemistry and ECG measurements. This extends the meta-analysis results of Ng et al. (2017) reporting that curcumin is safe and well-tolerated in depressed patients.

Another important point is the ideal dosage for curcumin as previous studies investigated doses of 500 to 1000 mg/day for 5–8 weeks, while we used a higher dose for a longer period (up to 1500 mg/day, 12 weeks). Nevertheless, in our study, curcumin dose was increased after week 1 and continued to increase until 4 weeks later. Therefore, we cannot conclude whether an increase in curcumin dose was necessary to obtain a maximal response at week 12. Another limitation of curcumin is its poor oral bioavailability and short retention time in the body due to its rapid breakdown in the liver (Ng et al. 2017; Hewlings and Kalman 2017). Therefore, curcumin is often combined with piperine or formulated as a patented combination of curcuminoids and turmeric essential oils (Ng et al. 2017). As a consequence, there are unresolved concerns surrounding the use of curcumin with regard to appropriate dose, duration of effect, and effects of variation in preparations.

A limitation of the study is that we had to stop the study earlier than planned after randomizing 50% of the computed sample size. A recent systematic review and meta-regression analysis shows that early termination of RCTs may overestimate clinical efficacy in trials stopped early for benefit (Bassler et al. 2010). Nevertheless, we did not stop the study based on early beneficial treatment effects of the trial drug. Truncated trials stopped for reasons that are independently of the clinical findings are unlikely to introduce bias in the results (Psaty and Rennie 2003). The sample size was rather small and did not achieve adequate power. Most available clinical trials on curcumin are also hampered by small sample sizes. In addition, we did not collect data on treatments received during previous episodes.

In conclusion, curcumin was significantly more effective than placebo in improving depressive symptoms in major depression with significant differences between curcumin and placebo at weeks 12 and 16. A greater efficacy of curcumin is found in males as compared with females. The effects of curcumin on anxiety rating are less clear. There are no significant differences in safety and tolerability between curcumin treatment and placebo, while no treatment-emergent side effects were registered.

Acknowledgements This research has been supported by the Agricultural Research Developmental Agency (ARDA), Bangkok, Thailand. The funding agency played no role in dada reporting. The authors would like to thank Supaksorn Thika (ST) for her valuable help completing the rating scales.

Author's Contributions All the contributing authors have participated in the manuscript. BK and MM designed the study. BK recruited patients and completed diagnostic interviews. All authors contributed to interpretation of the data and writing of the manuscript. MM carried out the statistical analyses.

Compliance with Ethical Standards

Conflict of Interest The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

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