European Archives of Psychiatry and Clinical Neuroscience
https://doi.org/10.1007/s00406-020-01103-4

ORIGINAL PAPER

Efficacy of anticonvulsant ethosuximide for major depressive disorder: a randomized, placebo-control clinical trial

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Received: 22 October 2019 / Accepted: 21 January 2020

Abstract
Results of a preclinical study suggested that the anticonvulsant drug ethosuximide may elicit ketamine-like rapid-acting antidepressant actions. We evaluated the antidepressant efficacy of ethosuximide versus placebo in non-medicated adult patients with major depressive disorder (MDD). This randomized, double-blind, placebo-controlled trial included patients at three mental health centers in China. Eighty eligible adults (aged 18–65 years) met the DSM-5 criteria for MDD. Patients in the acute single study received three doses (500, 1000, or 1500 mg) of ethosuximide or placebo. Patients in the repeated study received ethosuximide (1500 mg/day) or placebo for 2 weeks. The Hamilton Depression Rating Scale (HAM-D), the Montgomery–Åsberg Depression Rating Scale (MADRS), and the Hamilton Anxiety Rating Scale were used to assess antidepressant and antianxiety responses to ethosuximide. No significant reductions in depression and anxiety rating scale scores were observed after a single oral administration of ethosuximide, in comparison with placebo. Furthermore, patients receiving ethosuximide for 2 weeks did not show reductions in depression and anxiety rating scale scores. There were no serious adverse events. Responses to the study's primary and secondary outcome measures, the clinician-rated HAM-D and MADRS, showed no change from baseline to the end of treatment, with either ethosuximide or placebo. These results suggest that ethosuximide does not produce ketamine-like robust antidepressant actions in adult patients with MDD.

Keywords Major depressive disorder · Ethosuximide · Anticonvulsant

Introduction

Major depressive disorder (MDD) is one of the most common psychiatric disorders worldwide. Although the antidepressants currently available are moderately effective in the treatment of depression, it takes weeks to months to achieve antidepressant effects. In addition, approximately one-third of affected patients have treatment-resistant MDD [1]. There is, therefore, an unmet medical need for the development of novel rapid-acting antidepressants that are also effective against treatment-resistant MDD [2–6].

The *N*-methyl-D-aspartate receptor antagonist ketamine can produce rapid-acting and sustained antidepressant actions against MDD, including treatment-resistant depression [7–16]. Of importance is that off-label use of ketamine in the treatment of depression is popular in the United States [17, 18]. On March 5, 2019, the U.S. Food Drug Administration (2019) approved the nasal spray of esketamine in the treatment of treatment-resistant depression. However, there are serious concerns about side effects (i.e., psychotomimetic effects, dissociation, and potential for abuse) of ketamine and esketamine in the treatment of depression [2, 5, 19–24].

In 2018, Yang et al. demonstrated that the blockade of NMDAR-dependent bursting activity by ketamine in the LHb promotes its rapid-acting antidepressant effects in rodents [25]. Furthermore, LHb bursting requires both NMDAR and low-voltage-sensitive T-type calcium channels (T-VSCC). Interestingly, the T-VSCC inhibitor ethosuximide

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Published online: 01 February 2020

(200 mg/kg) could show rapid antidepressant actions in rodents. Ethosuximide has been widely used as anticonvulsant drug in the world, and it is effective in the treatment of childhood absence epilepsy [26, 27]. In addition to its effect on epilepsy, ethosuximide can affect sensory transmission and has beneficial effects on pain [28]. The side effects of ethosuximide are also generally minimal [28]. The aim of this study was, therefore, to evaluate the antidepressant efficacy of ethosuximide in comparison with placebo in adult patients with MDD.

Methods

Study design and participants

This study was a multicenter, double-blind, controlled, parallel-group study conducted in three mental health centers in China (Wuxi Mental Health Center, Wuxi; Chaohu Hospital of Anhui Medical University, Hefei; and Anhui Mental Health Center, Hefei). Patients were enrolled from January 1 to May 1, 2019. Data analysis was performed from May 18 to May 25, 2019. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization, and Good Clinical Practice guidelines. The design for this study is depicted in Fig. 1. This study was registered at https://www.chictr.org.cn (registration number ChiCTR1900022765).

Because this was the first controlled trial of ethosuximide for treatment of MDD in China, and because the effect size with regard to the intervention is unclear, the appropriate sample size could not be estimated on the basis of statistical considerations. On the basis of results of animal studies, we assumed that a total sample size of 20 in each group would be adequate for this exploratory study.

We recruited adults aged 18–65 years for whom the diagnosis of MDD was confirmed by MiniInternational Neuropsychiatric Interview (MINI), as a single or recurrent episodes. A patient met inclusion criteria if the current episode was scored at least 18 on the 17item Hamilton Depression Rating Scale (HAM-D) and if the patient had not received antidepressant treatment during the previous 6 months. Exclusion criteria included substance abuse or dependence in the previous 3 months, active suicidal intent, pregnancy, bipolar disorder, any psychotic disorder or current psychotic symptoms, an unstable medical illness, substantial neurological illness, and abnormal serologic findings.

Ethics approval was granted by the research ethics boards of all three institutions (201901-kyxm-01, 2019-05, and WUXIMHCIRB2019-002). A local data and safety monitoring board oversaw the study. All participants provided written, informed consent.

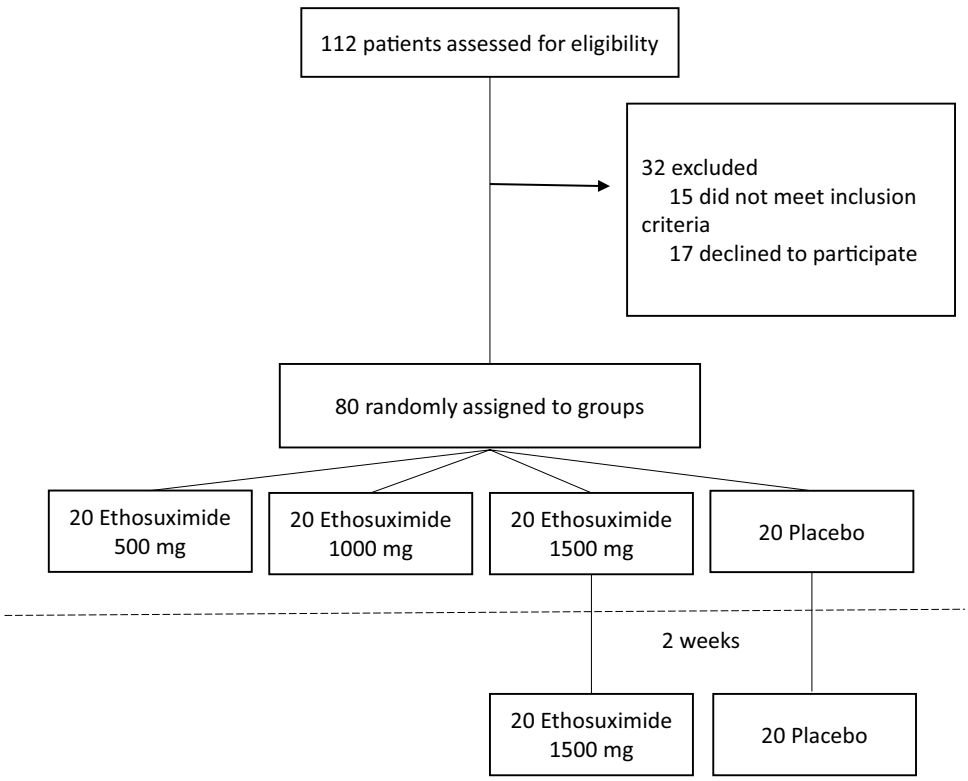

Fig. 1 CONSORT flow diagram

Randomization and masking

Patients were randomly assigned to permuted groups of ten in which they received ethosuximide (500, 1000, or 1500 mg) or placebo, administered once or repeatedly. All investigators and patients were unaware of intervention assignment, information about which was kept only in the database and known only by the pharmacy administrators.

Study drug and administration

Ethosuximide was purchased from Eisai Pharmaceutical Company (Tokyo, Japan). The placebo was purchased from Hunan Erkang Pharmaceutical Company (Changsha, Hunan, China). The patients receiving single doses were given 500 mg, 1000 mg, or 1500 mg of ethosuximide only on the first day of treatment. The patients receiving repeated doses were given 1500 mg of ethosuximide daily for 2 weeks; the highest dose was anticipated to produce the maximum effect. The patients in the control group received the placebo daily for 2 weeks.

Clinical assessment

We collected all participants' general demographic data, such as age, gender, years of education, height, weight, and length of episode. We administered the HAM-D and the Montgomery–Åsberg Depression Rating Scale (MADRS) to assess depressive symptoms. Anxiety symptoms were assessed with the Hamilton Anxiety Rating Scale (HAM-A). In addition, we examined the dependent symptoms using the Visual Analog Scale (VAS) [29].

In a previous study of healthy male adults, the peak plasma levels of ethosuximide reached 15 μg/mL 3–5 h after a single oral 750-mg dose and remained at this level for 24 h [28]. The patients in our study who received ethosuximide (500, 1000, or 1500 mg) and those who received the placebo were administered the HAM-D, MADRS, and HAM-A at baseline and 1 and 5 h after a single oral administration. Patients also responded to the VAS 1 and 5 h after a single dose.

In the repeated (2 week) administration study, the patients receiving ethosuximide (1500 mg) and those receiving the placebo were administered the HAM-D, MADRS, and HAM-A at baseline, the end of the first week. We wanted to know the antidepressant effect of repeated ethosuximide therapy, so we also measured the HAM-D, MADRS, and HAM-A at the end of the second week of drug administration. The VAS was also measured at baseline, at the end of the first week, and at the end of the second week of drug administration.

Statistical analysis

The data were calculated as means ± standard deviations. The analysis was performed with PASW Statistics 20 (formerly SPSS Statistics; SPSS, Tokyo). Baseline characteristics among the four groups were compared using the Pearson χ^2 test for categorical variables and one-way analyses of variance (ANOVAs) for continuous variables. The primary outcome measure was the HAM-D score. The secondary outcome measures included the MADRS and HAM-A scores and the VAS rating. Changes from baseline in the HAM-D, MADRS, HAM-A, and VAS results were assessed with repeated measures one-way ANOVAs, followed by post hoc Fisher's least significant difference test. To correct violations of sphericity, we adjusted the degrees of freedom in the ANOVA using the Greenhouse–Geisser correction. *P* values of less than 0.05 were considered statistically significant.

Results

Participants

Of 112 volunteers screened, 32 were excluded for several reasons. The 80 patients who participated (20 in each group) received the drug or placebo and completed the final assessment (Fig. 1). Demographic information, clinical characteristics, and treatment parameters for the four groups are presented in Table 1. There were no differences in depression (MADRS and HAM-D) and anxiety (HAM-A) rating scores among the four groups (Table 1).

Primary outcome: Hamilton Depression Rating Scale

The primary outcome was HAM-D score change. Figure 2a shows changes in HAM-D scores from baseline to 5 h after a single dose. We observed no significant difference at 5 h between the patients given ethosuximide and those given placebo ($F_{3,76} = 1.421$; $P = 0.243$). Figure 3a shows changes in HAM-D scores from baseline to 2 weeks after the repeated administration. We observed no significant difference at 2 weeks between the patients given ethosuximide and those given placebo ($F_{1,38} = 1.290$; $P = 0.263$).

Secondary outcomes: MADRS

Figure 2b shows changes in MADRS scores from baseline to 5 h after a single administration. We observed no significant difference 5 h between the patients given ethosuximide and those given placebo ($F_{3,76} = 1.530$; $P = 0.214$). Figure 3b shows changes in MADRS scores from baseline to 2 weeks after repeated administration. We observed no significant at 2 weeks between the two groups ($F_{1,38} = 1.305$; $P = 0.260$).

Table 1 Clinical and demographic data for the 80 participants included in the analyses

	Control	500 mg group	1000 mg group	1500 mg group	F/χ^2	P
Participants, *n*	20	20	20	20		
Age (years)	33.65 ± 14.09	36.75 ± 12.32	32.00 ± 10.79	31.75 ± 9.55	0.76	0.52
Gender (M/F)	11/9	12/8	12/8	13/7	0.42	0.94
BMI	22.65 ± 3.23	25.15 ± 4.79	23.95 ± 3.98	25.60 ± 4.73	1.96	0.13
Education (years)	12.55 ± 2.86	13.15 ± 2.50	12.15 ± 2.35	12.65 ± 2.01	0.57	0.64
Length of episode (months)	20.85 ± 10.21	16.85 ± 8.15	22.70 ± 7.85	19.65 ± 8.72	1.56	0.21
HAM-D	25.20 ± 5.75	26.15 ± 6.56	23.95 ± 4.37	26.85 ± 4.06	1.13	0.34
MADRS	26.90 ± 5.71	28.20 ± 6.84	26.00 ± 4.65	28.90 ± 4.19	1.14	0.34
HAM-A	10.35 ± 2.18	11.30 ± 2.60	10.95 ± 2.63	10.65 ± 2.01	0.59	0.62

HAM-D Hamilton Depression Rating scale, *MADRS* Montgomery–Åsberg Depression Rating Scale, *HAM-A* Hamilton Anxiety Rating Scale

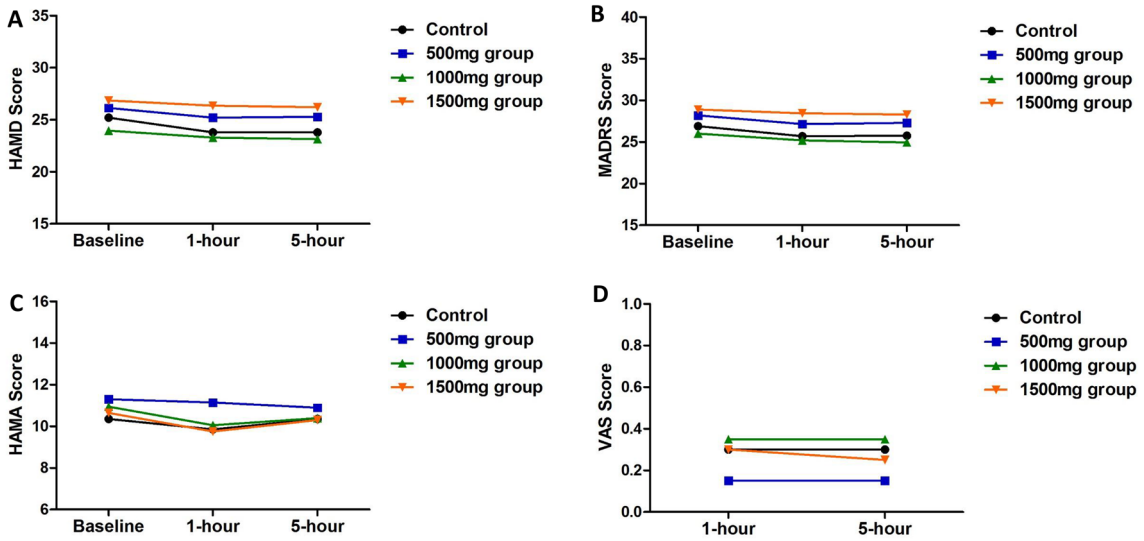

Fig. 2 Change in scale scores after single-dosage drug administration. Mean changes in Hamilton Depression Rating Scale (HAM-D), Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A) and Visual Analogue Scales (VAS) scores from baseline to 5 h after drug administration. No difference was observed on the primary and secondary outcome measures, the clinician-rated HAM-D and MADRS score change from baseline to 5 h after a single dose, between ethosuximide vs placebo

Anxiety and dependence symptoms

Figure 2c shows changes in HAM-A scores from baseline to 5 h after single-dose drug administration. We observed no significant difference at 5 h between the patients given ethosuximide and those given placebo ($F_{3,76} = 0.954$; $P = 0.425$). Figure 3c shows changes in HAM-A scores from baseline to 2 weeks after repeated administration. We observed no significant difference at 2 weeks between the two groups ($F_{1,38} = 0.050$; $P = 0.824$).

Figure 2d shows changes in VAS scores from baseline to 5 h after single-dose administration. We observed no significant difference at 5 h between the patients given ethosuximide and those given placebo ($F_{3,76} = 0.844$; $P = 0.474$). Figure 3d shows changes in VAS scores from baseline to 2 weeks after repeated administration. We observed no significant difference 2 weeks between the patients given ethosuximide and those given placebo ($F_{1,38} = 0.245$; $P = 0.623$).

Adverse events

There were no serious adverse events during this trial.

Discussion

This was the first randomized, double-blind, placebo-controlled trial to evaluate the antidepressant efficacy of ethosuximide in a sample of un-medicated patients with MDD. The patients given ethosuximide and those given placebo revealed no differences in the primary and secondary

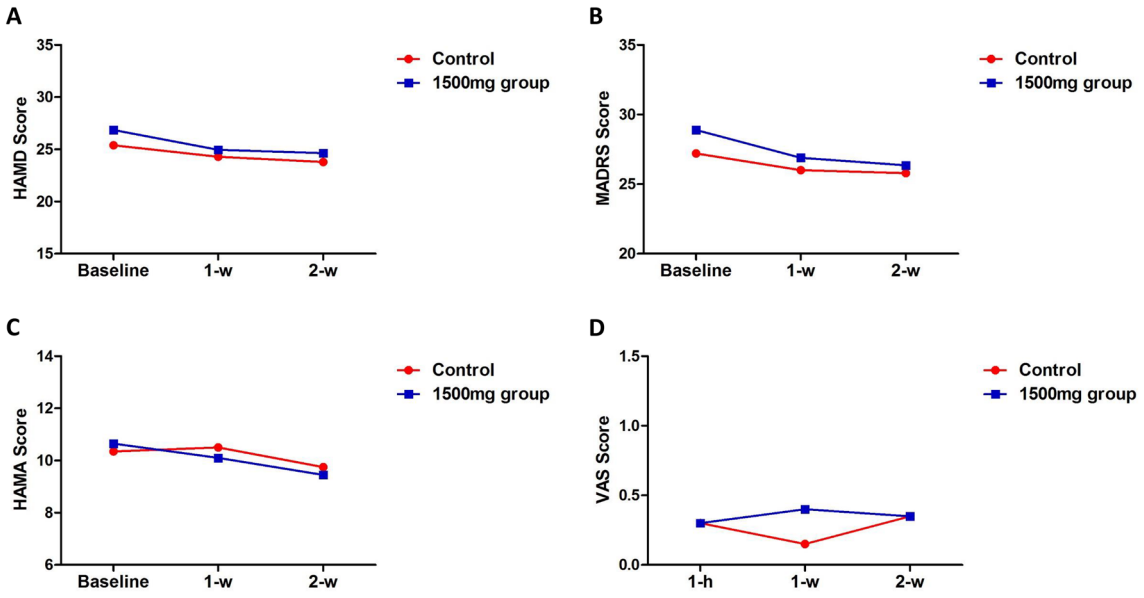

Fig. 3 Change in scale scores after repeated dosage drug administration. Mean changes in Hamilton Depression Rating Scale (HAM-D), Montgomery–Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), and Visual Analogue Scale (VAS) scores from baseline to 2 weeks after drug administration. No difference was observed on the primary and secondary outcome measures, the clinician-rated HAM-D and MADRS score change from baseline to 2 weeks after repeated drug administration, between ethosuximide vs placebo

outcome measures, and the clinician-rated HAM-D and MADRS scores did not change significantly from baseline to 5 h after a single oral dose for either patients receiving ethosuximide or those receiving placebo. Furthermore, ethosuximide did not improve anxiety in patients with MDD after a single oral dose. A single administration of any dose (500, 1000, or 1500 mg) of ethosuximide was no more effective than placebo, which indicates that ethosuximide had no antidepressant action in patients with MDD. Furthermore, patients given ethosuximide for 2 weeks and those given placebo for 2 weeks showed no changes in the primary and secondary outcome measures or in the clinician-rated HAM-D and MADRS scores from baseline to 2 weeks. Ethosuximide also did not improve anxiety in patients with MDD after repeated doses. All these results indicate that ethosuximide does not have antidepressant actions in non-medicated patients with MDD.

It is known that a high placebo response during the trial may have undermined the ability to detect a significant statistical difference in the primary end point of clinician-rated scores of the patients receiving placebo and those receiving active compound. In a meta-analysis [30] of the magnitude of the placebo response rates across different studies of adjunctive therapy in depressed patients, differences between the active drug recipients and the placebo recipients became obscured when placebo response rates were higher than 40%. In our study, the response scores on the clinician-rated HAM-D and MADRS in the placebo group were very low because the patients enrolled in this study had not taken medication for at least 6 months. It seems that a low placebo response does not influence the antidepressant effect of the active compound. Nevertheless, in this trial, we did not confirm the superiority of ethosuximide over placebo. Overall, ethosuximide was safe and well tolerated in patients with MDD in this study. There were no severe adverse events in any group.

Because the primary and secondary end points were not met, it is possible that ethosuximide does not produce robust antidepressant actions in patients with MDD. Furthermore, ethosuximide did not alter HAM-A scores in patients with MDD after a single administration or after repeated oral administration. In addition, repeated oral administration of ethosuximide did not alter VAS ratings by patients with MDD, which suggests that ethosuximide has low potential for abuse in humans. A recent proof-of-concept study failed to demonstrate any analgesic effect of ethosuximide on neuropathic pain after 6 weeks of treatment [31]. In that study, ethosuximide was administered in the morning and evening during meals for 6 weeks and as add-on therapy. Subsequently, the dosage was increased gradually by 5 mL (250 mg) every 4 days until the maximum dosage, 30 mL (1500 mg) per day, was reached [32].

In 2018, Yang et al. [33] demonstrated that the burst in the lateral habenula of rodents with depression-like behaviors was dependent on T-VSCC and that a single dose of the T-VSCC blocker ethosuximide (200 mg/kg) abolished

burst firing and relieved depression-like behaviors in mice subjected to chronic restraint stress. In WAG/Rij rats—a genetically based model of absence epilepsy and depression-like comorbidity—chronic treatment with ethosuximide (300 mg/kg/day from P21 to 5 months) prevented the onset of depression-like phenotypes [32]. Furthermore, ethosuximide (300 mg/kg/day for 17 days) was shown to produce antidepressant-like effects in WAG/Rij rats [34]. Thus it seems that antidepressant-like effects of ethosuximide are limited to WAG/Rij rats, which suggests a link between absence seizures and depressive-like behaviors in this strain of rats [32, 34].

In contrast, previous studies demonstrated that a single dose of ethosuximide (100, 200, or 400 mg/kg) did not show rapid and sustained antidepressant effects in a stress model of chronic social defeat, although the rapid-acting antidepressant candidate (*R*)-ketamine [33, 35, 36], the (*R*)-enantiomer of ketamine, produced rapid-acting and sustained antidepressant actions in the same model [37]. Collectively, our clinical study strongly supports the negative data from the preclinical findings [37]. All these findings indicate that it is unlikely that a single dose of ethosuximide produces rapid-acting antidepressant actions in patients with MDD. At the time of this writing, a clinical trial of ethosuximide in patients with treatment-resistant MDD is under way at Zhejiang University in China (NCT03887624) [38].

This study had some limitations. First, we investigated the antidepressant effect of ethosuximide in only 80 patients. Because of the small sample size, the results have to be considered as preliminary. To verify our results, larger samples will be recruited in a future study. Second, we used relatively strict inclusion criteria, and it is unclear whether findings will generalize to all patients with treatment-resistant MDD.

In conclusion, we could not find any antidepressant effect of ethosuximide on the clinician-reported HAM-D and MADRS scores after single and repeated oral administration. Therefore, it is unlikely that ethosuximide elicits ketamine-like rapid-acting antidepressant actions in patients with MDD, but the negative findings need to be replicated by other research groups.

Acknowledgements We thank all the patients who volunteered to participate in the study. This study was supported by the National Nature Science Foundation of China (81801341), the Medical and Public Health Technology Research Projects of Wuxi Technology Bureau (CSE31N1723), the Wuxi Municipal Health and Family Planning Commission research project (MS201704), and AMED, Japan (to K.H., JP19dm0107119).

Compliance with ethical standards

Conflict of interest Dr. Hashimoto is an inventor on a filed patent application on "Application of R-ketamine and salt thereof as pharmaceuticals" by Chiba University. Dr. Hashimoto has received research support from Otsuka, Sumitomo-Dainippon, and Taisho. The other authors report no financial relationships with commercial interests.

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