Nocebo Effects in the Treatment of Major Depression: Results From an Individual Study Participant–Level Meta-Analysis of the Placebo Arm of Duloxetine Clinical Trials

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ABSTRACT

Background: The nocebo effect, when a harmless substance creates harmful effects in a person who takes it, is a clinically salient yet seldom studied phenomenon that may be associated with poorer treatment outcomes, perceived adverse events, and treatment discontinuation. The covert presence of nocebo responders in clinical trials may contribute to outcome variance in both placebo and active treatment arms for important primary and secondary endpoints. Nocebo effects are thought to be driven by expectancy and conditioning.

Method: This study analyzed pooled clinical trial data in the placebo arms of controlled trials of antidepressant medications to investigate variables associated with the emergence of adverse outcomes in placebo-treated participants (N = 2,457). Specifically, we examined treatment-emergent adverse events (TEAEs) and discontinuation in placebo-treated individuals. Trials were commenced between 1993 and 2010 as studies of duloxetine versus active comparator and/or placebo.

Results: TEAEs were reported by 1,569 placebo-treated participants (63.9%), with 115 (4.7%) discontinuing from the studies due to TEAEs and 274 (11.2%) showing worsening of Hamilton Depression Rating Scale total score during placebo treatment. There was specifically no evidence to support the expectancy hypothesis, that reported TEAEs were influenced by adverse effects described in the clinical trials participant information and consent forms, or the conditioning hypothesis, that reported TEAEs would be influenced by adverse effect profiles of previous antidepressant medications used by these study participants. There was some evidence to suggest that people who had previously used complementary medications were more likely to report TEAEs. Variables specific to individual studies were the strongest predictors of TEAEs.

Discussion: In this study, TEAEs were very common among placebo-treated clinical trial participants. Unexpectedly, there was no evidence to associate TEAEs with adverse clinical outcomes, nor were the conditioning or expectancy hypotheses supported by these data.

Conclusions: The nocebo effect is a common, covert, and poorly understood driver of clinical outcomes that requires further investigation.

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While the importance of the placebo effect is widely understood, the parallel role of the nocebo effect is largely unrecognized in clinical practice. Nocebo effects are adverse reactions to treatment not adequately explained by the physical or pharmacologic actions of the agent,[1] being a psychological, social, or cultural reaction to treatment that either creates a de novo adverse experience or amplifies an adverse response to a genuine side effect or preexisting symptoms. Nocebo reactions may often overlap with the known side effect profile of a treatment, especially on the foundation of prior adverse effects. The nocebo effect may be an important yet covert factor contributing to adverse effects, poor clinical outcomes, and treatment nonadherence.[2]

Nocebo experiences have been postulated to be driven by 2 processes, prior conditioning and negative expectations regarding treatment.[3,4] Several factors may influence an individual's likelihood of being a nocebo responder. These include prior adverse experiences, anxiety and depression,[5,6] type A behavior pattern, and traits such as neuroticism and pessimism.[7–9] Prior experiences and learning processes, not just from information regarding adverse effects of a proposed treatment but also from previous experiences with medical treatments, especially similar classes of drugs, influence the likelihood of adverse outcomes (conditioning).[10] Not surprisingly, people with an expectation of adverse events (AEs) are more likely to experience them (expectancy).[11] Furthermore, preexisting nonspecific somatic symptoms are not infrequently reported as AEs.[10] Gender may also be a factor given that while males and females experience placebo effects at the same rate, women appear to be more prone to nocebo effects.[12]

Clinically, nocebo effects not infrequently overlay normal patient behavior. A classic example of nocebo effects was illustrated by Colloca et al,[13] who noted worse pain, motor performance, and anxiety in postoperative patients who had been told that their morphine infusion that was being administered via a computerized pump was being stopped when compared to postoperative patients whose morphine infusion was stopped surreptitiously. Indeed, there have been many reports that demonstrate positive (placebo) and negative (nocebo) reactions to inert treatments and tests.[14–17] All of these experiments involved prior conditioning or priming of study participants with information. The concept of nocebo effects is related to that of negative expectation of an outcome. Top-down control of sensory input has a

Clinical Points

- The nocebo effect is common in the placebo arm of controlled trials in major depressive disorder.
- Expectancy and conditioning are players, but more research is needed to understand what lies behind the etiology of the nocebo effect.
- The nocebo effect may explain 11.2% of Hamilton Depression Rating Scale worsening, 63.9% of treatment-emergent adverse events, and 4.7% of discontinuation in this large placebo-treated patient sample. These results suggest that further elucidation of the nocebo effect may help to improve trial designs.

paramount role in modeling perceptual experiences and operates via many sensory modalities (somatosensory, auditory, and visual), and it is a common factor whereby complex cognitive and emotional modulation can shape a patient's perception of the therapeutic effects or AEs of their treatments.

The placebo effect has been shown to have a neurobiological basis that includes the release of endorphins.[18,19] Neurobiological correlates for the nocebo effect are less well understood, although the possibility of down-regulation of important neurotransmitters including cholecystokinin, dopamine, and endorphins has been postulated.[14] Enck et al[20] linked the nocebo effect with deactivation of dopamine and opioid brain reward circuitry induced by negative expectations. Johansen at al[21] demonstrated that increased cortisol release was induced in study participants administered intravenous isotonic saline who had been informed that the substance being injected would increase pain.

As well as being of clinical importance, the nocebo effect may also be a key confound in clinical trials of drug safety and efficacy, with nocebo responders potentially demonstrating poorer rates of improvement or even symptomatic worsening with treatment and reporting more AEs. For instance, participant information and consent forms (PI&CFs), which disclose in detail the AE profile of a study treatment, provide negative and potentially anxiogenic information to study participants prior to the initiation of treatment that could condition expectancy and may thereby precipitate a nocebo effect.[22] There is likely to be considerable interindividual variability in the way clinical trial participants understand, react, or further explain AE information included in PI&CFs. For example, it is common for people to search for additional information about potential benefits or AEs on the Internet.[23] Higher study discontinuation rates due to nocebo responses may lead to lower sample sizes and consequently to higher false-negative trial results.[24] The nocebo effect may potentially influence the progress of new drugs through to regulatory approval.

In this study, we explored the nocebo effect in the placebo arm of clinical trials of antidepressants for the treatment of major depression and its influence on treatment-emergent adverse events (TEAEs) and clinical outcomes. To investigate predictors of the nocebo response, correlations between health outcome measures, demographics, previous treatments, adverse effects described in PI&CFs, dropout rates, and characterization of the reported adverse effect profile were examined. The specific hypotheses tested were that participants treated with placebo

1. will report TEAEs resembling those listed in the PI&CF (the expectancy hypothesis),
2. will report AEs similar to the AE profiles of their previous treatment (the conditioning hypothesis), and
3. who report TEAEs will have worse clinical outcomes (treatment discontinuation) than those who do not report AEs.

METHOD

Studies Included in the Meta-Analysis

Placebo-arm data were obtained from 20 industry-sponsored, multisite, randomized, clinical trials of antidepressant treatment for acute episodes of major depression. All placebo-controlled data were included irrespective of inclusion and exclusion criteria. Trials were commenced between 1993 and 2010 as studies of duloxetine versus active comparator and/or placebo. (Trial registration information is as follows: IMPACT clinical trial number 3327; IMPACT clinical trial number 4091; IMPACT clinical trial number 4689; IMPACT clinical trial number 4298; ClinicalTrials.gov identifiers: NCT00071695; NCT00062673; NCT00036335; NCT00067912; NCT00073411; NCT00489775; NCT00536471; NCT00666757. Note that trials with IMPACT numbers predate mandatory clinical trial registration requirements; see lillytrials.com/results/cymbalta.pdf for clinical trial summaries.)

Sixteen different study designs were included, with 4 trials having duplicate study designs to comply with US requirements. Treatment length was 4, 7, 10, and 36 weeks for 1 trial each; 9 weeks for 2 trials; 8 weeks for 12 trials; and 12 weeks for 2 trials. The 17-item Hamilton Depression Rating Scale (HDRS-17)[25,26] was the primary outcome measure for 17 of the trials, where participants had a HDRS-17 total score at baseline of 15 or greater. Adverse event data were recorded for all 20 clinical trials. Where individual studies are mentioned, they are labeled using industry identifier codes of 4- or 5-letter format.

Only study participants allocated to the placebo arm were included in the analyses. *Baseline* refers to the visit at which the placebo treatment was started, which is usually the randomization visit. However, some studies included placebo lead-in periods. For these studies, the baseline was not the randomization visit, but the visit at which study participants received placebo medication. Study participant data were only included in the analysis during the time of placebo treatment.

Worsening of clinical symptoms was defined by (1) worsening of symptoms from baseline to endpoint, defined as any increase >0 in HDRS total score (if HDRS was not

available, Montgomery-Asberg Depression Rating Scale [MADRS] was used; if MADRS was not available, Clinical Global Impressions-Severity of Illness scale [CGI-S] was used); (2) worsening of symptoms from baseline to any visit, defined as any increase > 0 in HDRS total score (if HDRS was not available MADRS was used, if MADRS was not available CGI-S was used); (3) worsening of symptoms from baseline to endpoint, defined as any increase > δ in HDRS total score (values of 0, 1, 2, and 3 were used for δ); or (4) worsening of symptoms from baseline to any visit, defined as any increase > δ in HDRS total score.

Collection of AEs and TEAEs from the 20 industry-sponsored clinical trials followed international guidelines and was harmonized across sponsors. Tolerability was assessed by open-ended questioning for AEs. Treatment-emergent adverse events were analyzed and were defined as any events occurring or worsening during placebo treatment. Endpoints analyzed were (1) any AE; (2) any treatment-related AE; (3) any severe AE; (4) any serious AE—discontinuation due to AE; and (5) discontinuation for any reason.

Disposition was analyzed in terms of number of studies included, number of study participants included in the analysis overall and by study and mean number of study participants per study, time on placebo overall and by study, proportion of placebo study participants per protocol design, number of studies using HDRS for measuring symptoms longitudinally, number of studies using MADRS for measuring symptoms longitudinally, and number of studies using CGI-S for measuring symptoms longitudinally.

Statistical Analyses

The data analysis for this article was generated using SAS software version 8.2 or higher (SAS Institute Inc; Cary, North Carolina). Baseline characteristics of the study participants were analyzed with respect to (1) demographics: age, gender, and race/ethnicity; (2) symptom severity: CGI-S score, MADRS total score, and HDRS total score; and (3) disease characteristics: prior treatment for depression (any, with selective serotonin reuptake inhibitor [SSRI], with selective norepinephrine reuptake inhibitor [SNRI]), number of previous episodes of major depressive disorder (MDD), duration of current MDD episode, and time since first episode of MDD. Safety and tolerability endpoints were analyzed descriptively overall and by study together with confidence intervals based on Clopper and Pearson.[27] Heterogeneity was assessed visually using a funnel plot, that is, plotting the rate of each endpoint by study including the 95% CI versus the sample size of placebo study participants in this study. The influence of study and other variables was analyzed using a logistic regression with the following models containing the fixed effects for study only and for the following study characteristics: age, gender, baseline HDRS total score, prior treatment for depression (any, with SSRI, with SNRI), number of previous episodes of MDD, duration of current MDD episode, and time since first episode of MDD. A Cochran-Mantel-Haenszel test was performed to explore the influence of study level. A Breslow-Day test was used to explore the variability of the nocebo effect across studies.

RESULTS

Disposition

This individual study participant–level meta-analysis contained data from 20 clinical studies of placebo-controlled studies for duloxetine in the treatment of MDD. Overall, 2,457 study participants were treated with placebo. For 692 (28.2%) of the study participants, no HDRS postbaseline values were available, as some studies used the MADRS as the primary efficacy parameter (Table 1). TEAEs were reported by 1,569 study participants (63.9%), 115 study participants (4.7%) discontinued due to an AE, and 274 (11.2%) had worsening of the HDRS total score during placebo treatment. The characteristics of the studies included in this analysis are listed in Table 1. Table 2 lists the most frequently recorded TEAEs; however, these TEAEs cover only a small part of the 560 preferred terms that were mentioned. The median frequency that a preferred term was mentioned was 2, and the upper quartile (75th percentile) was 5, whereas the mean was 8.1 occurrences. This skewed distribution is shown in Figure 1.

Baseline Characteristics

Baseline characteristics can be split into study participant–level characteristics (Table 3) and study design characteristics, reported in Table 1 and elsewhere.[28,29]

Relationship Between Participant Characteristics and Adverse Outcomes in Placebo-Treated Study Participants

Analyses were conducted to determine if there was any relationship between previous antidepressant use by study participants and adverse outcomes for placebo-treated participants. No significant differences were found regarding overall TEAE rates for study participants who had been previously treated with antidepressants (n = 1,174; 64.5% with at least 1 TEAE) compared to those who were antidepressant treatment naive (n = 1,283; 63.3% with at least 1 TEAE) ($P = .4411$). None of the TEAEs occurring in more than 1% of the study participants differed significantly between these 2 groups. When this comparison was restricted to previous SSRI use, no significant difference was found (odds ratio = 0.94 [95% CI, 0.69–1.28; $P = .41$]), with no significant heterogeneity across studies (Breslow-Day test, $P = .60$). Similarly, for previous tricyclic antidepressant use, the association was not significant (odds ratio = 1.12 [95% CI, 0.65–1.95; $P = .24$]), with no significant heterogeneity across studies (Breslow-Day test, $P = .65$). For other antidepressant use, no significant association was found (odds ratio = 1.49 [95% CI, 0.81–2.74; $P = .56$]), with no significant heterogeneity across studies (Breslow-Day test, $P = .18$). These results suggest that previous treatment with an antidepressant was not a significant determinant of TEAE rates in placebo-treated patients.

Table 1. Studies and Design Parameters Included in the Nocebo Analyses

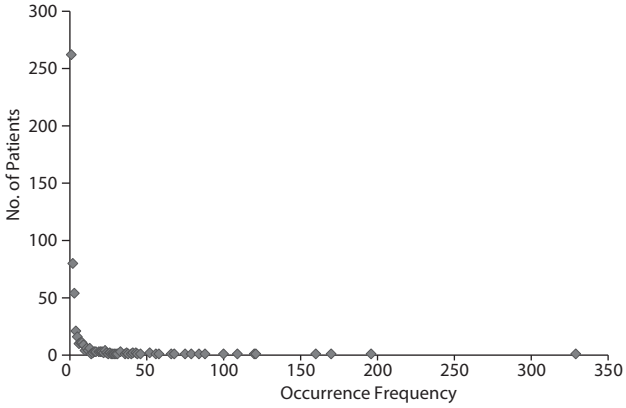
Study ID	Protocol Title	Year of Protocol	Development Phase	Study Design	Placebo Lead-In?	Titration of Duloxetine?	Length of Acute Phase (wk)[a]	No. of Postbaseline Visits	HDRS Data Available?	Cross-Regional Study?[b]
HMAG	Duloxetine/Placebo in MDD	1993	1b/2	Parallel	Yes	No	12	11	Yes	No
HMAH	Duloxetine 20/30 mg vs Placebo in Major Depression	1993	2	Parallel	Yes	No	10	10	Yes	No
HMAI	A Double-Blind, Placebo- and Clomipramine-Controlled Study of Duloxetine in Patients With Major Depression	1993	2	Parallel	Yes	No	8	9	Yes	No
HMAQA	Duloxetine vs Placebo in the Treatment of Major Depression	1998	2	Parallel	Yes	Yes	8	8	Yes	No
HMAQB	Duloxetine vs Placebo in the Treatment of Major Depression	1998	2	Parallel	Yes	Yes	8	8	Yes	No
HMATA	Duloxetine vs Placebo and Paroxetine in the Acute Treatment of Major Depression	2000	3	Parallel	Yes	Yes	8	5	Yes	No
HMATB	Duloxetine vs Placebo and Paroxetine in the Acute Treatment of Major Depression	2000	3	Parallel	Yes	Yes	8	5	Yes	No
HMAYA	Duloxetine vs Placebo and Paroxetine in the Treatment of Major Depression	2000	3	Parallel	Yes	Yes	8	5	Yes	No
HMAYB	Duloxetine vs Placebo and Paroxetine in the Treatment of Major Depression	2000	3	Parallel	Yes	Yes	8	5	Yes	No
HMBHA	Duloxetine Once-Daily Dosing vs Placebo in the Acute Treatment of Major Depression	2000	3	Parallel	Yes	No	9	6	Yes	No
HMBHB	Duloxetine Once-Daily Dosing vs Placebo in the Acute Treatment of Major Depression	2000	3	Parallel	Yes	No	9	6	Yes	No
HMBV	Duloxetine vs Placebo in the Treatment of Elderly Patients with MDD	2002	4	Parallel	Yes	No	8	4	Yes	Yes
HMCB	Duloxetine Once-Daily Dosing vs Placebo in Patients With Major Depression and Pain	2001	3b	Parallel	No	No	7	5	Yes	No
HMCR	Duloxetine vs Escitalopram and Placebo in the Treatment of Patients With Major Depression	2003	3b	Parallel	Yes	No	8	6	Yes	No
HMDH	A Ten-Week, Randomized, Double-Blind Study Evaluating the Efficacy of Duloxetine 60 mg Once Daily vs Placebo in Outpatients With MDD and Pain (EU-Pain Enriched Study)	2005	3b	Parallel	No	Yes	8	6	No	No
HMFA	Cymbalta vs Placebo in Long-Term Treatment Late-Life MDD	2006	4	Parallel	Yes	Yes	12	5	Yes	Yes
HMFS	MDD Efficacy in Depressive Symptom Improvements and Usual Function	2007	4	Parallel	No	Yes	36	11	Yes	Yes
HMGR	MDD and Associated Painful Physical Symptoms	2009	4	Parallel	No	Yes	8	4	No	Yes
HMGU	MDD—Pain Replication Study	2010	4	Parallel	No	Yes	8	4	No	Yes
HQAC	Validation of Daily Telephone Self-Assessment in the Study of Antidepressant Treatment Outcome	2002	2	Parallel	Yes	No	4	4	Yes	No

[a]Without placebo lead-in.
[b]Cross-regional studies are those performed in the United States and in other regions (Europe and others).
Abbreviations: HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder.

Table 2. Treatment-Emergent Adverse Events in the Placebo Group With an Incidence of > 3%

Preferred Term	Frequency (N = 2,457)	Incidence (%)
Headache	329	13.4
Nausea	196	8.0
Dry mouth	170	6.9
Diarrhea	160	6.5
Insomnia	121	4.9
Dizziness	120	4.9
Constipation	109	4.4
Fatigue	100	4.1
Nasopharyngitis	88	3.6
Dyspepsia	84	3.4
Upper respiratory tract infection	79	3.2
Back pain	75	3.1

Figure 1. Frequency of the Occurrence of MedDRA Preferred Terms



Analyses were conducted to determine if previous use of antidepressants was associated with reporting overlapping AE patterns specifically associated with those antidepressants when subsequently receiving placebo treatment. No significant difference was found between study participants who had or had not previously used mirtazapine, mianserin, amitriptyline, nortriptyline, imipramine, doxepin, clomipramine, trazodone, or nefazodone and who reported TEAEs of sedation, fatigue, sluggishness, or lethargy ($P = .56$). Similarly, no significant difference was found between study participants who had or had not previously used amitriptyline, nortriptyline, desipramine, imipramine, doxepin, or clomipramine and reported TEAEs of dry mouth or constipation ($P = .24$). No significant difference was found between study participants who had or had not previously used paroxetine, fluoxetine, sertraline, citalopram, escitalopram, or fluvoxamine and reported TEAEs of nausea, sexual dysfunction, libido decreased, loss of libido, abnormal orgasm, decreased orgasmic sensation, delayed ejaculation, ejaculation disorder, ejaculation failure, and erectile dysfunction ($P = .41$).

Analyses were conducted to determine if there was a relationship between previous use of an individual antidepressive agent and adverse outcomes. A significant result was observed for previous treatment in which *Hypericum perforatum* was associated with a greater likelihood of reporting any TEAE ($P = .02$). A greater likelihood of reporting any TEAE was also seen with those individuals who had previously received clomipramine ($P = .005$). However, previous treatment with sertraline, citalopram, or trazodone was significantly associated with discontinuing the trial due to adverse effects ($P < .05$), whereas *Hypericum perforatum* was not ($P = .52$).

Placebo-treated study participants who reported or experienced HDRS worsening, study discontinuation, or TEAEs were studied to identify participant variables that were associated with these adverse outcomes. Results of the logistic regressions are displayed in Figure 2. HDRS worsening occurred in 274 (11.2%) of placebo-treated study participants. When comparing the patients with and without HDRS worsening using *t* test or χ^2 tests, HDRS worsening was significantly associated with preexisting apathy (3.6% vs 1.2% for those with vs without HDRS worsening; $P = .007$), greater number of previous episodes (mean [SD] of 6.3 [13.13] vs 4.1 [8.87]; $P = .0038$), longer duration of current episode (mean [SD] months: 27.7 [71.76] vs 13.4 [30.74]; $P < .0001$), previous antidepressant treatment (57.7% vs 45.5%; $P = .0002$), smaller CGI-S score at study baseline (mean [SD]: 4.17 [0.73] vs 4.28 [0.67]; $P = .0151$), and study participant location in the United States (92.0% vs 76.9%; $P < .0001$). The gender factor was only significant for nocebo effect for women in these studies for the outcome "TEAE" but not for "HDRS worsening" or "discontinuation." The proportion of women among placebo-treated participants with TEAEs was 67.7% versus 61.8% among placebo-treated participants without TEAEs ($P = .0033$).

Relationship Between Study Design Characteristics and Adverse Outcomes in Placebo-Treated Study Participants

Analyses were conducted to determine if there was any relationship between the design aspects of a study and adverse outcomes for placebo-treated participants. Overall, no significant difference was found when comparing TEAE rates from placebo-treated study participants in 2-arm studies (ie, duloxetine or placebo; n = 1,683), in which 63.8% reported at least 1 TEAE, to placebo-treated study participants in 3-arm studies (duloxetine, another antidepressant, or placebo; n = 744), in which 64.1% reported at least 1 TEAE ($P = .8753$). Further analyses revealed that placebo response increased for the outcome measure "TEAE" with the variable "year of protocol" ($P < .0001$), whereas the nocebo response is evident in earlier studies for TEAEs. This result suggests that there is an inverse pattern between placebo and nocebo response with "year of protocol" (Figure 2C).

Heterogeneity Between Individual Studies for Prognostic Factors for Adverse Outcomes

Considerable heterogeneity was observed across the different studies for prognostic value for the variables. Homogeneity testing showed that heterogeneity was

Table 3. Demographic and Study Characteristics of Placebo-Treated Participants From the 20 Studies Used in This Analysis

Characteristic	Total (N = 2,457)	Any TEAE (n = 1,569)	Discontinuing Due to TEAE (n = 115)	HDRS Total Score Worsening (n = 270)[a]
Female, n (%)	1,611 (65.6)	1,062 (67.7)	85 (73.9)	177 (64.6)
Age, mean ± SD, y	46.2 ± 15.03	45.7 ± 14.87	48.3 ± 16.22	48.2 ± 16.46
Geographical region, n (%)				
United States	1,791 (72.9)	1,250 (79.7)	90 (78.3)	252 (92.0)
Europe	495 (20.1)	214 (13.6)	18 (15.7)	12 (4.4)
Other	171 (7.0)	105 (6.7)	7 (6.1)	10 (3.6)
Year of protocol, n (%)				
< 1998	261 (10.6)	200 (12.7)	16 (13.9)	39 (14.2)
1998–2003	1,189 (48.4)	801 (51.1)	52 (45.2)	192 (70.1)
> 2003	1,007 (41.0)	568 (36.2)	47 (40.9)	43 (15.7)
Placebo lead-in, n (%)	1,432 (58.3)	969 (61.8)	72 (62.6)	240 (87.6)
Titration with duloxetine in active arm of the study, n (%)	1,521 (61.9)	875 (55.8)	70 (60.9)	110 (40.1)
Length of acute phase of study, mean ± SD, wk	10.6 ± 7.55	11.1 ± 8.15	12.4 ± 9.61	10.4 ± 6.81

[a]Seventeen studies (n = 1,765) with information available.
Abbreviations: HDRS = Hamilton Depression Rating Scale, SD = standard deviation, TEAE = treatment-emergent adverse event.

observed across all studies, with 1 study, HMAI, an outlier (Figure 3A and 3B). Interestingly, in some studies, age was protective against TEAE occurrence (HMBHB), whereas in other studies it was a risk factor for TEAEs (HMAYB) (Figure 3C; also see Supplementary eFigure 1 at PSYCHIATRIST.COM).

DISCUSSION

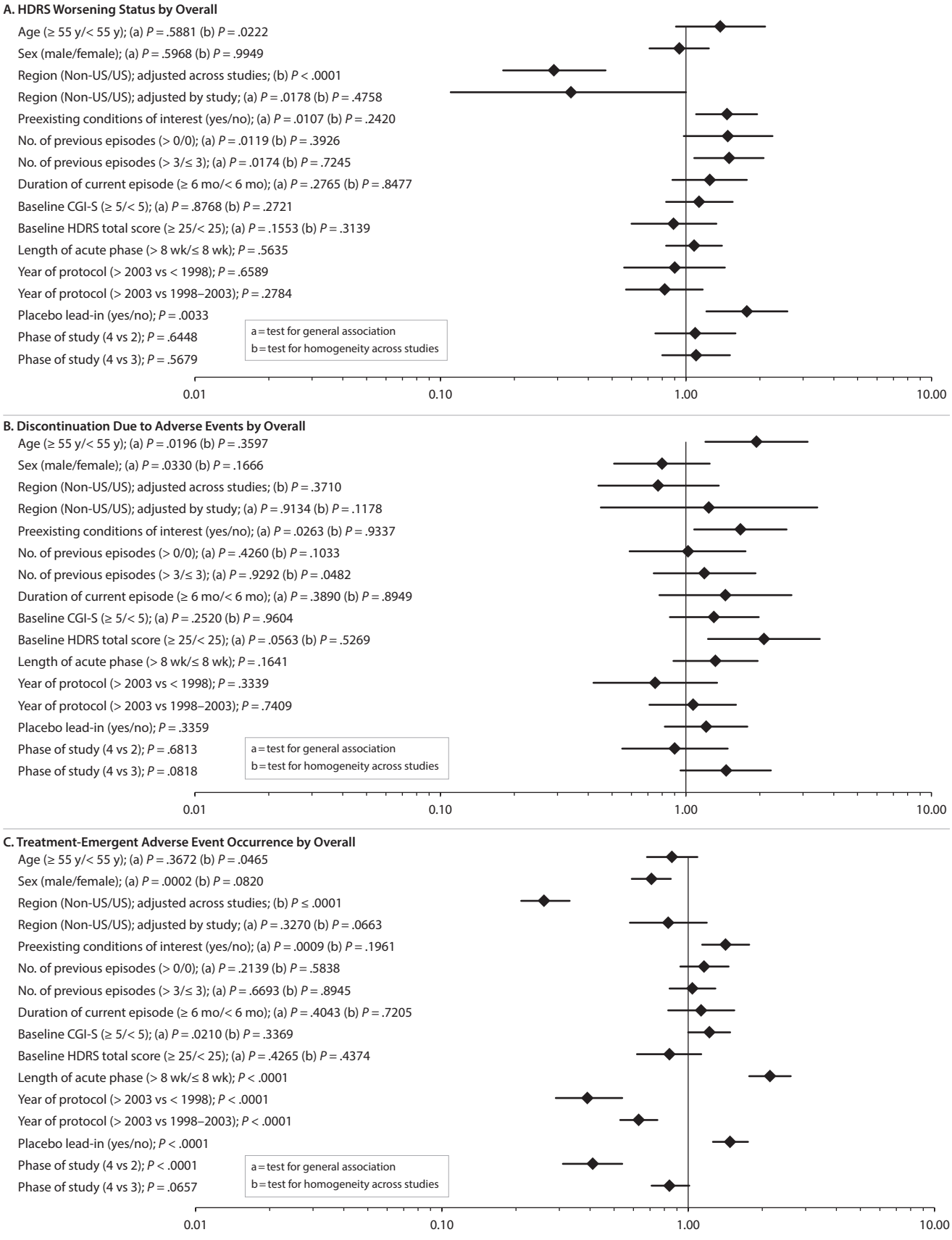
A nocebo response occurs when a harmless substance creates harmful effects in a person who takes it, leading to a phenomenon whereby a treatment expected to have a beneficial effect for a patient actually has a detrimental effect. That it may be a substantial driver of outcomes in clinical practice and trials is suggested by very high rates of TEAEs in this study. There are 2 hypothesized pathways to the nocebo effect, classical conditioning and expectancy. As an exemplar of conditioning, in a study of people given chemotherapy who did or did not receive a lemon-lime beverage together with chemotherapy, more nausea was induced in those with a preconditioned stimulus.[30] An example of expectancy can be seen in a study[31] in which people were informed that they might receive either an herbal or inert compound, while all participants actually received the inactive compound. Both placebo and nocebo reactions in that study were common.[31] In blinded trials, conditioning and expectancy also occur in the active arm. However, while on active treatment, it is not possible to objectively distinguish between events related to the compound and those related only to conditioning and expectancy.

Although a large monotherapy placebo-treated population (N = 2,457) was included in this study and participants reporting any TEAE were common (n = 1,569), a clear profile of nocebo responders did not emerge. In particular, the results of this study did not strongly support either the expectancy hypothesis that suggested TEAEs would be influenced by adverse effects described in the clinical trials participant information and consent forms, or the conditioning hypothesis that suggested TEAEs would be influenced by adverse effect profiles of previous antidepressant medications used by these study participants. There was indirect evidence supporting the expectancy hypothesis, in that protocols from earlier years had more detailed adverse advents described. There were more TEAEs reported by placebo-treated participants in earlier phase 2 studies compared to later phase 3 studies.

Curiously, previous treatment with *Hypericum perforatum* was associated with a greater likelihood of reporting a TEAE, suggesting that previous treatment with this complementary medication was associated with more TEAEs. It is possible that a prior choice of a complementary therapy may be based on distrust of conventional pharmacotherapy, offering limited support for the expectancy hypothesis. However, this finding is moderated by the observation that of 16 antidepressant treatments investigated, only *Hypericum perforatum* and clomipramine were significantly associated with a greater likelihood of reporting any TEAE. Regarding the hypothesized role of conditioning, where individuals may have been more despondent about the prospects of treatment based on their prior experiences, tentative support was suggested by the odds ratio data presented in Figure 2. However, other factors, including type I error or the neuroprogression of the core biology of the illness, could be confounding factors.[32]

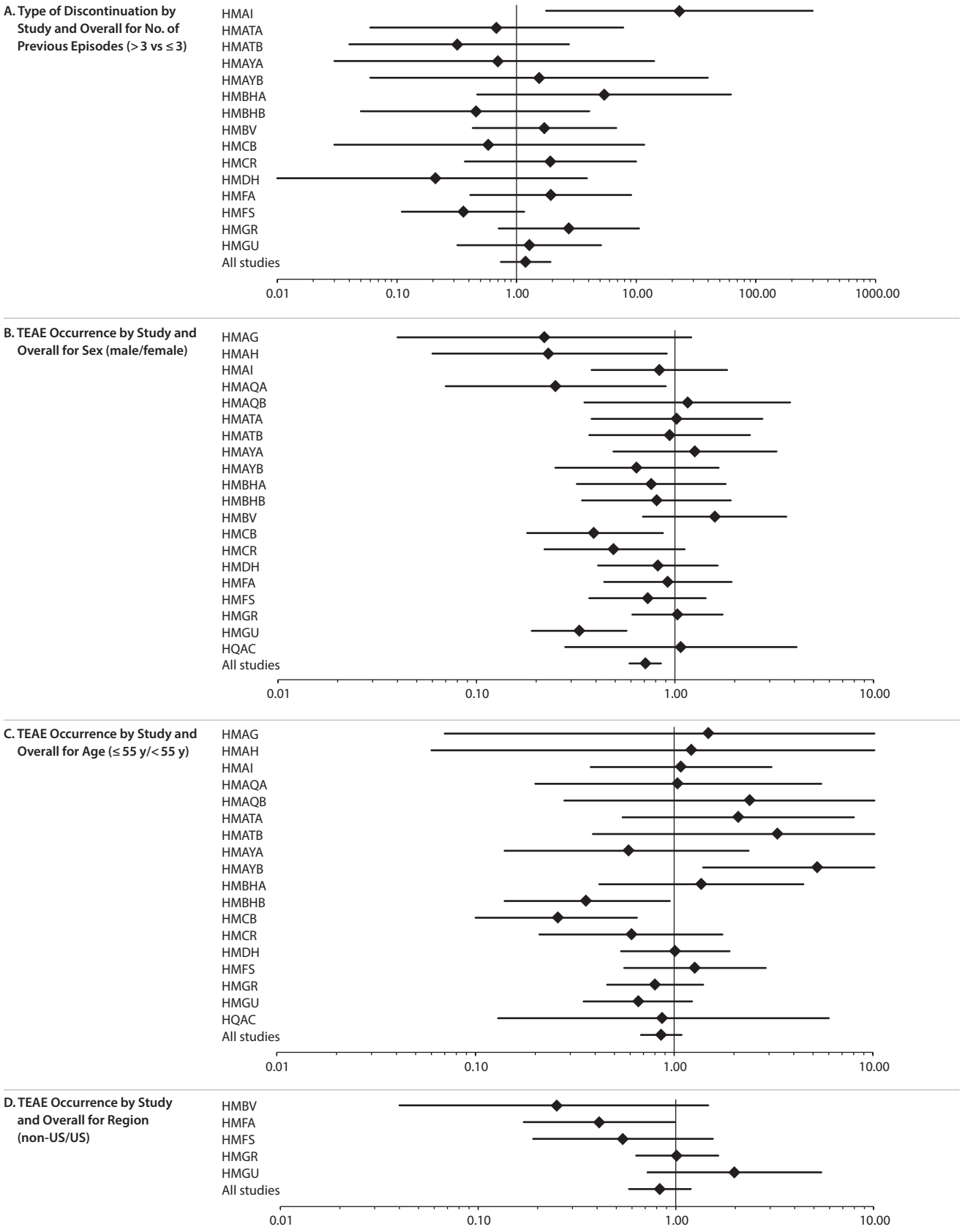
This study investigated clinical drug trial participants and used data collected during the course of the trial, and consequently the variables analyzed pertain only to data collected in the clinical trials (eg, the expectation of the patients itself was not measured) and a study population recruited in accordance with strict inclusion and exclusion criteria. Personality disorders, for example, were an exclusion criterion for all trials, with only 1 case of an emergent personality disorder reported. Other important factors, such as cultural issues and education level, were also not available as covariates to the nocebo response. As the study population in this study were participants diagnosed with MDD, it is not possible to generalize to other disorders. However, strengths of the study include the robust sample

Figure 2. Odds Ratios With 95% Confidence Intervals for Prognostic Variables for Adverse Outcomes



Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder.

Figure 3. Heterogeneity of the Events Across Different Studies for Placebo-Treated Study Participants[a]



[a]The number of studies included varies, as identical event information was not collected in all 20 studies used in this project. Four selected examples are presented to highlight heterogeneity.
Abbreviation: TEAE = treatment-emergent adverse event.

size and the pooling of diverse populations. Moreover, this study provides new data about the nocebo effect that can provide new insights and a better understanding of this clinically salient phenomenon. Also, the lack of evidence regarding the conditioning hypothesis is not evidence that there is no conditioning. Further prospective assessments focusing on the collection of variables possibly associated with the nocebo response could provide more insights. It is, of course, difficult to disentangle nocebo reactions from the somatic symptoms of depression, as well as comorbid medical disorders. A better understanding of the nocebo phenomenon may be helpful in future drug development, and it is relevant to clinical practice, where individuals who are more likely to have a nocebo response can be identified.

CONCLUSION

The factors contributing to the nocebo effect remain elusive and are inherently difficult to profile and characterize. A better understanding of the nocebo effect may assist in disentangling the pharmacologic and nonpharmacologic drivers of the experience and reporting of adverse effects of treatment. This increased understanding may inform and improve clinical trial design and refine clinical treatment by identifying individuals who are more likely to have worse outcomes with standard pharmacotherapy. TEAEs are very common among antidepressant clinical trial participants treated with placebo; however, defining robust predictors of a potential nocebo effect in participants from baseline data was not achievable in this large study. This study was able to find only limited support for the role of expectancy and tenuous support for conditioning in the genesis of the nocebo effect. While the nocebo response may be a common yet latent driver of the emergence of both AEs and clinical deterioration in clinical practice, it remains incompletely understood. Clarification of the role, impact, and operative pathways of the nocebo effect is necessary in order to develop appropriate clinical interventions. Repetition of analyses presented here for different compounds and indications would help to better understand nocebo effects.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Oleptro and others).

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Supplementary Material

Article Title: Nocebo Effects in the Treatment of Major Depression: Results From an Individual Study Participant-Level Meta-Analysis of the Placebo Arm of Duloxetine Clinical Trials

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List of Supplementary Material for the article

1. eFigure 1 Variability Across Studies Demonstrated by (a) the Percentage of Patients With HDRS Worsening by Study, (b) Discontinuation due to AE by Study, and (c) any TEAEs by Study

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eFigure 1. Variability across studies demonstrated by (a) the percentage of patients with HAMD worsening by study, (b) discontinuation due to AE by study and (c) any TEAEs by study. AE, adverse event; HAMD, Hamilton depression rating scale; TEAE, treatment-emergent adverse event.