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Review article

# Placebo and nocebo reactions in randomized trials of pharmacological treatments for persistent depressive disorder. A meta-regression analysis

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ABSTRACT

*Background:* We aimed to investigate placebo and nocebo reactions in randomized controlled trials (RCT) of pharmacological treatments for persistent depressive disorder (PDD).
*Methods:* We conducted a systematic electronic search and included RCTs investigating antidepressants for the treatment of PDD. Outcomes were the number of patients experiencing response and remission in placebo arms (=placebo reaction). Additional outcomes were the incidence of patients experiencing adverse events and related discontinuations in placebo arms (=nocebo reaction). A priori defined effect modifiers were analyzed using a series of meta-regression analyses.
*Results:* Twenty-three trials were included in the analyses. We found a pooled placebo response rate of 31% and a placebo remission rate of 22%. The pooled adverse event rate and related discontinuations were 57% and 4%, respectively. All placebo arm outcomes were positively associated with the corresponding medication arm outcomes. Placebo response rate was associated with a greater proportion of patients with early onset depression, a smaller chance to receive placebo and a larger sample size. The adverse event rate in placebo arms was associated with a greater proportion of patients with early onset depression, a smaller proportion of females and a more recent publication.
*Conclusions:* Pooled placebo and nocebo reaction rates in PDD were comparable to those in episodic depression. The identified effect modifiers should be considered to assess unbiased effects in RCTs, to influence placebo and nocebo reactions in practice.
*Limitations:* Limitations result from the methodology applied, the fact that we conducted only univariate analyses, and the number and quality of included trials.

## 1. Background

Placebo reactions refer to positive reactions to a nonspecific treatment (e.g. response), while nocebo reactions refer to negative reactions to a nonspecific treatment (e.g. adverse events). Besides methodological biases and natural course of disease, psychological factors contribute to placebo and nocebo reactions including experiences gained from prior treatments (conditional learning) and expectancy towards the effects of a treatment (Benedetti et al., 2003; Shedden Mora et al., 2011).

Placebo and nocebo reactions have been documented in all medical fields including surgery and other invasive procedures (Jonas et al., 2015), but are particularly prevalent in mental health. Both placebo and nocebo reactions account for a considerable proportion of the reactions that can be found in active treatment arms of randomized controlled trials and are therefore highly relevant for estimating the true medication effect (Rief et al., 2008; Shedden Mora et al., 2011).

Among antidepressant trials for major depressive disorder, a mean response rate of 30–40% has been found in placebo arms, while in medication arms on average about 50% of the patients responded (Furukawa et al., 2016; Walsh et al., 2002). Consequently, a large portion of the improvements in the medication arms were attributable to the placebo effect (Rief et al., 2009b; Walsh et al., 2002). Similar findings exist for adverse events in placebo arms. A meta-analysis revealed that 64% of the patients treated in placebo arms of antidepressant trials reported adverse events and 5% therefore discontinued treatment (Dodd et al., 2015). However, the size of both placebo and nocebo reactions varied substantially between trials (Dodd et al., 2015; Rief et al., 2009b; Walsh et al., 2002). Factors that may contribute to the variability were investigated, and it was found that the placebo response rate was higher

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in trials with a longer duration (Andrews, 2001; Furukawa et al., 2016; Rief et al., 2009b; Walsh et al., 2002) and in multicenter trials compared to single-center trials (Furukawa et al., 2016). Moreover, placebo response was shown to be significantly greater in major depression than in dysthymia (Rief et al., 2009b). Inconsistent findings exist for the influence of the baseline severity of depression on placebo response rates (Kirsch et al., 2008; Rabinowitz et al., 2016; Rief et al., 2009b; Walsh et al., 2002) as well as for the publication year (Furukawa et al., 2016; Rief et al., 2009b; Walsh et al., 2002). Earlier studies found an increase of the placebo response rate with increasing publication year (Rief et al., 2009b; Walsh et al., 2002). Though, a recent systematic review revealed that the average placebo response remained constant since the year 1991 (Furukawa et al., 2016). With regard to adverse events, it was shown that the incidence rate of adverse events in placebo groups increased with decreasing publication year of the study protocol (Dodd et al., 2015) and an increasing proportion of male patients (Nestoriuc and Rief, 2010). Moreover, adverse event rates in the placebo arms were found to be influenced by the medication administered in the medication arm, the study quality, and the assessment method (Rief et al., 2009a, 2006).

So far, little is known about placebo and nocebo reactions in trials investigating persistent forms of depression. PDD combines all forms of depressive conditions that persists for at least two years including (1) a continuing mild depressive mood (dysthymia), (2) a state meeting all criteria for major depression continuously (chronic major depression), (3) a recurrent major depression with incomplete remission between episodes, and (4) a superimposition of a major depressive episode on an antecedent dysthymia (double depression) (American Psychiatric Association, 2013). Sporadic findings suggest that placebo response might be lower in persistently depressed patients. Kocsis and collogues, for example, reported a placebo-response rate of 12% for this group of patients (Kocsis et al., 1988). The lower placebo response rate may be explained by negatively biased expectation and conditioning processes that may be more pronounced in persistently depressed patients due to their long-lasting medical and treatment history. The same processes, however, may contribute to a high prevalence of adverse events in placebo arms of trials investigating persistent depressive disorder (PDD). The objectives of the present study are to investigate (1) placebo and nocebo reactions in randomized controlled trials of pharmacological treatments for PDD and (2) to identify associated clinical and methodological characteristics.

## 2. Methods

Methodological details has been reported in the study protocol and in comprehensive meta-analyses on the benefits and harms of active treatments for PDD (Kriston et al., 2014, 2010; Meister et al., 2016a).

### 2.1. Eligibility criteria

We included randomized controlled trials that investigated antidepressants compared to placebo for the treatment of PDD in adults. Reliance upon standardized criteria for the diagnosis was required. As the distinction between subtypes of PDD is controversial, inclusion was primarily driven by the duration of the existing depressive disorder of at least two years. Trials that investigated patients with episodes of mania or hypomania were excluded. Outcomes were the number of patients that experienced (1) response and (2) remission in the placebo arm. Additional outcomes were the incidence of experiencing (3) any adverse event and (4) related treatment discontinuations in the placebo arm.

### 2.2. Search strategy

We systematically searched the following databases from inception through 2016: Medline, Embase, PsycINFO, ISI Web of Science, the Cumulative Index to Nursing and Allied Health (CINAHL), BIOSIS, and the Cochrane Central Register of Controlled Trials (CENTRAL). We performed a primary search in 2010 and updates in 2013, 2014, and 2016. Additionally, we searched all volumes of JAMA Psychiatry, the Journal of Consulting and Clinical Psychology, and the Journal of Affective Disorders by hand, contacted the first author of each included study, and accomplished forward and backward citation tracking. See eAppendix for the complete electronic data base search strategy including the exact date of each search.

### 2.3. Study selection and data collection

One of two reviewers screened the titles and abstracts of all identified articles. Subsequently, two of six reviewers independently examined the full texts of all the potentially relevant articles according to predefined eligibility criteria. We then extracted data on trial characteristics including outcomes and a priori defined modifiers using a structured extraction form. We assessed the methodological quality of the included trials in accordance with the Cochrane Collaboration's Risk of Bias tool. Two of five reviewers conducted the data extraction and performed the assessment of methodological quality. Disagreements that occurred both during the study selection and the data collection process were resolved through discussion.

### 2.4. Statistical analysis

Outcomes were response rates and remission rates as well as the rates of patients experiencing adverse events and related discontinuations in the placebo arms. We followed the definition for response and remission provided by the authors of each trial. Response was mostly defined as a 50% reduction from baseline on the HRSD; remission was mostly defined as falling below a pre specified cutoff on the HRSD. Response and remission criteria of each trial are summarized in Table 1. If response and remission rates were not reported, we approximated them from continuous rating scale scores (mostly HRSD) (Furukawa et al., 2005; Meister et al., 2015). We summarized the outcomes in the placebo arms using odds with corresponding 95% confidence intervals. Odds were calculated following the intention-to-treat principle, except for the number of patients experiencing any adverse event. For this outcome, we calculated the odds on the basis of the safety sample provided by the authors. The odds were log-transformed for all analyses and back transformed afterwards. We conducted random effects meta-analyses using the restricted maximum likelihood estimator. For each meta-analysis, we quantified the extent of heterogeneity by means of the $I^2$ statistic. Possible publication bias was investigated using visual examination of funnel plots for each outcome.

To examine the impact of possible effect modifiers on all four outcomes, we used a series of meta-regression analyses. As clinical effect modifiers, we considered mean age, proportion of women, of dysthymic patients, and of patients with early onset depression, as well as mean treatment duration and mean baseline severity of depression on the Hamilton Rating Scale for Depression (HRSD) (Miller et al., 1985). To make baseline scores comparable across trials using different measures, we converted scores obtained from other versions of the HRSD or from other observer rating scales (e.g. MADRS) to HRSD-17 according to the recommendations by Carmody et al. (2006). As methodological effect modifiers, we considered sample size of the trial, publication year, chance to receive placebo (33% in 3-arm trials and 50% in 2-arm trials), type of pharmacological treatment in the medication arm (tricyclic antidepressants, selective serotonin reuptake inhibitors, other antidepressants, and multiple antidepressants for multi-arm trials), proportion of patients that respectively experienced response, remission, any adverse event, and discontinuations due to adverse event in the medication group, as well as aspects of methodological quality (allocation generation, allocation concealment, and blinding). For the analysis of adverse event rates, additionally the assessment method of adverse events was considered (open questions, checklists, unprompted reports, and unclear assessment). We performed meta-regression analysis using the restricted maximum likelihood estimate method. Due to power considerations, we only used univariate meta-regression analyses. Since we