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The Placebo Attributable Fraction in General Medicine: Protocol for a meta-epidemiological Study of Cochrane Reviews

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INTRODUCTION

Placebo has long been used as dummy treatment in the “control group” in randomized controlled trials to ensure methodological validity (1,2). Placebo-controlled group may show similar response to active treatment especially for subjective outcomes. This is known as placebo response and, sometimes, placebo response may reach up to about 40% of active treatment response (3–5).

Placebo response consists of placebo effect and other factors such as natural course of the disease and regression to the mean (6). Among these, placebo effect is the change of the status caused by placebo and the existence and degree of this effect was controversial (7–9). No matter how much placebo effect exists, the magnitude of placebo response attributable to active treatment response, which called the placebo-attributable fraction, is highly important for the implications of clinical trials and treatment choice in clinical setting.

In this study, we will systematically review Cochrane reviews to examine the placebo-attributable fraction in all fields of medicine and reveal the difference of the size of the placebo-attributable fraction according to specialties and intervention methods.

METHODS

Types of studies included

We will select all the systematic review of randomized placebo-controlled trials published in the Cochran Database of Systematic Reviews. Among selected studies, we will include reviews which showed the significant beneficial effect of intervention arm compared to placebo for their first primary outcome. If there are multiple comparison regarding the first primary outcome due to multiple intervention arms, we will select the first comparison.

We will define placebo-attributable fraction (P-AF) as follows:
For dichotomous beneficial outcome,

$$\frac{the\ proportion\ of\ beneficial\ event\ in\ the\ \ placebo\ arm}{the\ proportion\ of\ beneficial\ event\ in\ the\ intervention\ arm}$$

For dichotomous harmful outcome,

$$\frac{1-the\ proportion\ of\ harmful\ event\ in\ the\ \ placebo\ arm}{1-the\ proportion\ of\ harmful\ event\ in\ the\ intervention\ arm}$$

For continuous beneficial outcome

$$\frac{the\ change\ of\ score\ or\ scale\ in\ the\ placebo\ arm}{the\ change\ of\ score\ or\ scale\ in\ the\ placebo\ arm}$$

We will exclude interventions whose aim is to prevent deterioration in the continuous score (i.e. either increase in bad outcome scale or decrease in good outcome scale, as this would complicate interpretation of placebo-attributable fraction.

To calculate the P-AF defined above, we will use the average proportion or change score in the control group in the numerator, and the event rate or the change score in the intervention group based on the pooled OR or SMD/MD in the denominator. Therefore, we will exclude reviews that did not perform meta-analysis, did not report the change of score (if first primary outcome is continuous), did not report the number of participants and events for each arm (if first primary outcome is dichotomous), using outcome measure other than MD or SMD for first primary outcome. We will also exclude systematic reviews of studies other than pill placebo-controlled trials (e.g. sham-controlled trials, non-randomized controlled trials, diagnostic test accuracy studies and prognostic studies), overview of reviews, or methodological reviews.

Search strategy

We will search Cochrane Central Register Controlled Trials (CENTRAL) using “placebo” as keyword in Title, Abstract, Keywords in Cochrane Reviews

Study selection

Two authors will independently perform the initial screening of the titles and abstracts of all studies identified by the search and will examine the potential eligibility for inclusion. After initial screening, same authors will assess the eligibility based on a full-text review. We will resolve disagreements by discussion between the authors, with another author acting as an arbiter.

Data extraction

Two authors will use structured data extraction form to independently collect the data from included studies. If the review reported RR, we will extract pooled RR of each review. If the review reported MD, we will extract the change of the outcome and the number of participants for each of intervention and placebo arm of included trials separately. If the review reported SMD, we will extract the change of the outcome with standard deviation and the number of participants for each of intervention and placebo arm of included trials separately. We will also extract the following information: number of participants and trials in meta-analysis of first primary outcome, sample size of intervention and placebo arm, outcome data type (dichotomous or continuous), outcome type, medical specialty, Intervention type (pharmacological or non-pharmacological) and Cochrane review group.

We will categorize outcome types as below: (10–12)

Objective outcome

·All-cause mortality,

Semi objective outcomes

· Major morbidity event

· Obstetric outcomes

· Resource use and Hospital stay/process measures

· Internal and external structure related outcomes

· Biological markers

· Other semi-objective outcomes including cause-specific mortality, composite (mortality / morbidity only), and withdrawals/dropouts

Subjective outcomes

·Pain

·Quality of life/functioning

·Mental health outcomes
·Various subjectively measured outcomes including consumption, satisfaction with care, composite (at least 1 non-mortality/morbidity) and surgical/device related success/failure
·General health-related outcomes including general physical health and adverse events
·Signs/symptoms reflecting continuation/end of condition and Infection/onset of new acute/chronic disease
Others
·Other outcomes
We will categorize medical specialty as follows: cancer, cardiovascular, central nervous system/ musculoskeletal, digestive system, infectious disease, mental health and behavioral conditions, obstetrics and gynecology, pathological conditions, respiratory disease, urogenital and others (10–12).

Statistical analysis
First, we will calculate P-AF for each review as described above. Next, we will compute the weighted mean of P-AF of each review to show the overall P-AF across general clinical condition.
Additionally, we will perform sub-group analyses and meta-regression analyses to examine any heterogeneity of P-AF across outcome types, intervention types, medical specialty, overall risk of bias and Cochrane review groups.

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