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Placebo response

Introduction

Placebo effects in pharmaceutical trials vary widely, with response rates varying from 20% to 70%. The placebo response can include improvement in symptoms and even adverse reactions that have been associated with the medication being tested. Placebo effects can substantially influence conclusions about the efficacy of medications as they minimise any differences in response.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, the most recent and/or comprehensive review was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found five reviews that met our inclusion criteria[3-7].

- Moderate quality evidence suggests greater response to active medications than to placebo for both mania and depression symptoms. Response rates to active medications was around 49% for mania and 52% for depression. Response rates to placebo was around 32% for mania and 39% for depression.
- Greater response to active medications for mania, but not for depression, was related to greater relative efficacy (comparing active medications to placebo). Greater response to placebo for mania, but not for depression, was related to decreased relative efficacy.

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- Moderate to low quality evidence suggests longer treatment duration increased the likelihood of placebo response for depression. Greater depression symptom severity at baseline (start of treatment) increased the likelihood of response to active treatment for depression.
- People with mania and psychotic symptoms, and people who completed the trials, were more likely to have active drug-associated improvements in mania symptoms. People with mixed-state diagnoses were less likely to have active drug-associated improvements in mania symptoms. Increased placebo response for mania was associated with older patients' age, and female sex.
- Studies conducted in the USA or Europe (vs. other regions), and studies conducted over three or more regions (vs. fewer regions) were more likely to report greater placebo response.

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Bartoli F, Clerici M, Di Brita C, Riboldi I, Crocamo C, Carra G

Effect of clinical response to active drugs and placebo on antipsychotics and mood stabilizers relative efficacy for bipolar depression and mania: A meta-regression analysis

Journal of Psychopharmacology 2018; 32: 416-22

View review abstract online

Comparison	**Associations between levels of placebo response to antipsychotics and mood stabilizers and clinical study results.**
Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct, large samples) suggests greater response to active medications than placebo for mania and depression symptoms. Response to active drugs was around 49% for mania, and 52% for depression. Response to placebo was around 32% for mania, and 39% for depression.** **For mania symptoms, increased response to active drugs was related to increased relative efficacy (active drug vs. placebo). Increased response to placebo was not related to relative efficacy.** **For depression symptoms, increased response to active drugs was not related to increased relative efficacy (active drug vs. placebo). Increased response to placebo was related to decreased relative efficacy.**

Mania

Response = ≥ 50% reduction in Young Mania Rating Scale scores

Increased response to active drugs was significantly related to increased efficacy (active drugs vs. placebo);

Overall response to active drugs: 31 RCTs, N = 9,758, 49.3%, 95%CI 46.2% to 52.4%, I^2 = 83.7%

Relative efficacy: RR = 1.48, 95%CI 1.38 to 1.58, $p < 0.05$

Correlation: $\beta = 1.83$, $p = 0.002$

Increased response to placebo was not significantly related to efficacy (active drugs vs. placebo);

Overall response to placebo: 31 RCTs, N = 9,758, 32.3%, 95%CI 29.6% to 35.0%, I^2 = 66.4%

Relative efficacy: RR = 1.48, 95%CI 1.38 to 1.58, $p < 0.05$

$\beta = -0.86$, $p = 0.60$

Subgroup analysis of antipsychotics (aripiprazole, olanzapine, haloperidol, quetiapine, asenapine, cariprazine, risperidone and paliperidone) found response to antipsychotics was related to

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increased relative efficacy (β = 1.13; p = 0.008), and response to placebo was related to lower relative efficacy (β = -2.24; p < 0.001). Subgroup analysis of mood stabilisers (lithium, valproate, topiramate and carbamazepine) found that response to mood stabilisers was related to increased relative efficacy (β = 1.13; p = 0.008), but response to placebo was not significantly related to relative efficacy (β = -4.34; p = 0.15). Authors report a significant risk of publication bias.
Depression **Response = ≥ 50% reduction in Montgomery-Asberg Depression Rating Scale scores**
Increased response to active drugs was not significantly related to increased efficacy (active drugs vs. placebo); Overall response to active drugs: 22 RCTs, N = 7,988, 52.5%, 95%CI 48.1% to 56.8%, I^2 = 89.3% Relative efficacy: RR = 1.28, 95%CI 1.19 to 1.37, p < 0.05 Correlation: β = -0.03, p = 0.98 *Increased response to placebo was related to decreased efficacy (active drugs vs. placebo);* Overall response to placebo: 22 RCTs, N = 7,988, 38.7%, 95%CI 34.7% to 42.8% I^2 = 81.1% Relative efficacy: RR = 1.28, 95%CI 1.19 to 1.37, p < 0.05 β = -1.39, p = 0.047 Subgroup analyses of antipsychotics (aripiprazole, olanzapine, quetiapine, cariprazine, ziprasidone and lurasidone) and mood stabilisers (lithium, lamotrigine, valproate) found similar results. Authors report non-significant trend for risk of publication bias

Consistency in results‡	Inconsistent
Precision in results§	Precise
Directness of results‖	Direct

Iovieno N, Nierenberg AA, Parkin SR, Hyung Kim DJ, Walker RS, Fava M, Papakostas GI

Relationship between placebo response rate and clinical trial outcome in bipolar depression

Journal of Psychiatric Research 2016; 74: 38-44

View review abstract online

Comparison	**Placebo vs. active drug response rates for depression in people with bipolar disorder.**

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Summary of evidence	**Moderate quality evidence (inconsistent, precise, direct, large sample) suggests a small effect of greater response to active medications rather than placebo for depression, with response to active drugs being around 55% of the sample, and the response to placebo being around 39%.**
Depression **Response = ≥ 50% reduction in Hamilton Depression Rating Scale scores**	
Small, significant effect of greater response with drugs vs. placebo; Active drug response = 55.1%, placebo response = 39.2% 17 RCTs, N = 6,578, RR = 1.29, 95%CI 1.18 to 1.34, $p < 0.001$ Pharmacotherapy and placebo response rates were highly positively correlated within studies.	
Consistency in results	Authors report that the relative efficacy of the active drug compared to placebo was highly heterogeneous across studies.
Precision in results	Precise
Directness of results	Direct

Nierenberg AA, Ostergaard SD, Iovieno N, Walker RS, Fava M, Papakostas GI

Predictors of placebo response in bipolar depression

International Clinical Psychopharmacology 2015; 30: 59-66

View review abstract online

Comparison	**Predictors of placebo response for depression in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, direct, large sample) suggests longer treatment duration increased the likelihood of response to placebo, and increased depression severity at baseline increased response to active treatment rather than placebo.**
Predictors of placebo response for depression **Response = ≥ 50% reduction in Hamilton Depression Rating Scale scores**	
17 RCTs, N = 6,578 Longer treatment duration increased the likelihood of response to placebo, and increased	

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depression severity at baseline increased response to active treatment rather than placebo.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Welten CC, Koeter MW, Wohlfarth T, Storosum JG, van den Brink W, Gispen-de Wied CC, Leufkens HG, Denys DA

Placebo response in antipsychotic trials of patients with acute mania: Results of an individual patient data meta-analysis

European Neuropsychopharmacology 2015; 25: 1018-26

View review abstract online

Comparison	**Placebo vs. active drug response rates for mania, and predictors of placebo response for mania, in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, direct, large sample) suggests greater response to active medications (32.8%) than placebo (27.9%) for mania.** **Less severe illness and an absence of psychotic features at baseline, studies conducted in the USA or Europe (vs. other), and studies covering three or more regions (vs. one or two) significantly predicted increased placebo response.**
Placebo and active response rates for mania and predictors of placebo response **Response = ≥ 50% reduction in Young Mania Rating Scale scores**	
10 studies, N = 1,019 *There was greater response with drugs vs. placebo;* Active drug response = 32.8%, placebo response = 27.9% Less severe illness and an absence of psychotic features at baseline, studies conducted in the USA or Europe (vs. other), and studies covering three or more regions (vs. one or two) significantly predicted increased placebo response.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.

Directness of results	Direct

Yildiz A, Vieta E, Tohen M, Baldessarini RJ

Factors modifying drug and placebo responses in randomized trials for bipolar mania

International Journal of Neuropsychopharmacology 2011; 14: 863-75

View review abstract online

Comparison	**Predictors of placebo and active drug response for mania in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (unable to assess consistency or precision, direct, large sample) suggests increased placebo response for mania and fewer significant drug/placebo differences were associated with more study sites, older patients' age, and female sex. Studies with more patients with initial psychotic features and more trial completion in drug arms were associated with greater drug-associated improvement and drug/placebo differences, whereas more mixed-state diagnoses decreased both measures.**

Predictors of placebo and active response rates for mania

Response = ≥ 50% reduction in Young Mania Rating Scale scores

32 studies, N = 10,800

Increased placebo response and fewer significant drug/placebo differences were associated with more study sites, older patients' age, and female sex. Studies with more patients with initial psychotic features and more trial completion in drug arms were associated with greater drug-associated improvement and drug/placebo differences, whereas more mixed-state diagnoses decreased both measures.

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no measure of precision is reported.
Directness of results	Direct

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Explanation of acronyms

β = correlation coefficient, CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, p = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCTs = randomised controlled trials, RR = relative risk, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[8].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[8].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[8];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[10].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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