TECHNICAL COMMENTARY

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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 antipsychotic being tested. Placebo effects can substantially influence conclusions about the efficacy of antipsychotic medications as they minimise any differences in response to the antipsychotic and the placebo.

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 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version 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, which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% of items checked 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 eight systematic reviews that met our inclusion criteria[3-10].

- Moderate to high quality evidence finds less variability in response to antipsychotics than in response to placebo, with older studies, those with younger patients, higher dose treatments, and greater mean-difference in symptom-change being associated with less variability.
- Moderate to high quality evidence finds a small to medium-sized improvement in overall symptoms with placebos. The response was greatest in studies with more efficacious drugs, younger samples, shorter illness duration, more severe baseline symptoms, shorter study duration, increased

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number of study sites, and non-university or non-Veteran Affairs settings.

- For people with stable schizophrenia and predominant negative symptoms, moderate to high quality evidence also finds a small placebo response which is most apparent in studies with larger numbers of arms in the trial, larger numbers of study sites, and industry sponsorship (vs. academic settings).
- Moderate quality evidence suggests improvement is greater for those taking antipsychotics than for those taking placebo.
- Moderate quality evidence suggests increased improvement in symptoms from baseline to follow-up in placebo arms of clinical trials over time (1960 to 2014). Conversely, there is decreased improvement in symptoms from baseline to follow-up in treatment arms of clinical trials over time. This may be explained by enrolment of less severely ill patients at baseline and higher expectations that medications will improve symptoms.
- Moderate quality evidence suggests greater improvement in PANSS total scores in the placebo arm of studies using last observation carried forward (LOCF) methods than in studies using mixed-effect models for repeated measures (MMRM). Studies involving more countries and studies in outpatient settings had greater placebo response in the analysis of MMRM methods, while studies with shorter study duration showed greater placebo response in the analysis of LOCF methods.
- Moderate to high quality evidence finds around 66% of people receiving placebo report an adverse event. These corresponded to the same type of adverse events found with antipsychotics. 27% reported nervous system disorders, 13% reported gastrointestinal disorders, and 30% reported psychiatric disorders (anxiety, depression, agitation etc). A higher level of schizophrenia symptoms at baseline was associated with more adverse events.

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Agid O, Siu CO, Potkin SG, Kapur S, Watsky E, Vanderburg D, Zipursky RB, Remington G

Meta-Regression Analysis of Placebo Response in Antipsychotic Trials, 1970–2010

American Journal of Psychiatry 2013; 170:1335–1344

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Comparison	**Level of placebo response and factors influencing this response.**
Summary of evidence	**Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests there is a significant placebo response over 12 weeks of treatment which is most apparent in studies with more efficacious drugs, younger samples, shorter illness duration, more severe symptoms, shorter study duration, increased number of study sites, and non-university or non-Veteran Affairs settings.**
Change in overall symptom severity between baseline and up to 12 weeks, and factors influencing response	
A small to medium-sized improvement in symptoms from baseline to follow-up in the placebo group; 50 RCTs, N = 6,672, SMC = -0.33, 95%CI -0.44 to -0.22, $p < 0.001$, Q = 387.83, $p < 0.001$ Authors state that all studies were of adequate quality. Meta-regression investigating significant heterogeneity revealed that studies with larger placebo responses were independently associated with; greater mean improvement in the study drug arms, younger samples and/or shorter illness duration, higher baseline symptom severity, shorter trial duration, and more recent studies, although recency could be explained by study design factors such as an increase in the number of study sites and a decrease in the percentage of university or Veteran Affairs sites over time.	
Consistency in results‡	Inconsistent for overall analysis, although this is explained by variances across studies in efficacy of the drug tested, age/ illness duration, severity of symptoms, trial duration, number of study sites and study setting.
Precision in results§	Precise
Directness of results‖	Direct

Chen YF, Wang SJ, Khin NA, James Hung HM. and Laughern TP.

Trial issues and treatment effect modelling in multi-regional schizophrenia trials

Pharmaceutical Statistics 2010; 9: 217-229

View review abstract online

Comparison	**Relationships between baseline symptom severity, weight and age and improvements in symptoms over time in both placebo and antipsychotic groups.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests there was a placebo response evident for symptom improvement (measured by PANSS) over time, and although this improvement appears greatest for those taking antipsychotics, the placebo effect may increase over time. Lower baseline symptom severity and higher baseline weight and age may result in more improved symptoms, particularly for those taking antipsychotics.**

Change in symptoms severity

31 RCTs with most trials being 4 to 6 weeks duration, N = 12,585

For both groups, there are significant negative correlations with higher baseline weight and age measurements indicating lower PANSS baseline scores (lower scores = less severe symptoms);

Drug group: weight $r = -0.08$ $p < 0.01$, age: $r = -0.06$, $p < 0.01$

Placebo group, weight $r = -0.07$, $p < 0.01$, age: $r = -0.05$, $p < 0.01$

For both groups there are significant negative correlations with higher PANSS baseline scores (higher scores = more severe symptoms) indicating lower PANSS change scores (lower change scores = less improvement over time);

Drug group; $r = -0.20$, $p < 0.01$

Placebo group; $r = -0.12$, $p < 0.01$

For the drug group only, there is a significant positive correlation between higher baseline weight and higher PANSS change scores;

Drug group; $r = 0.12$, $p < 0.01$

Placebo group; $r = 0.04$, $p > 0.05$

For the drug group only, there is a significant positive correlation between higher baseline age and higher PANSS change scores;

Drug group; $r = 0.08$, $p < 0.01$ Placebo group; $r = 0.04$, $p > 0.05$ Note: Authors state that the placebo response may increase over time, but for the US trials only which span a greater time period and may reflect improvements in trial blinding methods. They report similar dropout rates between the treated and the placebo groups in 73% of trials, with the remaining trials reporting more dropouts in the placebo groups.	
Consistency in results	No measure of consistency is reported.
Precision in results	No measure of precision is reported.
Directness of results	Direct

Fraguas D, Diaz-Caneja CM, Pina-Camacho L, Umbricht D, Arango C

Predictors of Placebo Response in Pharmacological Clinical Trials of Negative Symptoms in Schizophrenia: A Meta-regression Analysis

Schizophrenia Bulletin 2019; 45: 57-68

View review abstract online

Comparison	**Level of placebo response and factors influencing this response in people with stable schizophrenia and predominant negative symptoms.**
Summary of evidence	**Moderate to high quality evidence (large sample, precise, inconsistent, direct) suggests there is a significant placebo response over 14 weeks of treatment which is most apparent in studies with larger numbers of arms in the trial, larger numbers of study sites, and industry sponsorship (vs. academic settings).**
Change in negative symptoms severity and factors influencing response	
Placebo response from baseline to follow-up (mean 14 weeks) was large; 18 RCTs, N = 998, $d = 2.91$, 95%CI 2.05 to 3.77, $p < 0.001$, $I^2 = 98\%$, $p < 0.001$ *However, a small effect showed antipsychotics reduced negative symptoms more than placebo;* 18 RCTs, N = 998, $d = 0.21$, 95%CI 0.03 to 0.38, $p = 0.02$, $I^2 = 66\%$, $p < 0.001$ Authors report a high risk of publication bias Multivariable meta-regression analyses showed that larger numbers of arms in the trial, larger	

numbers of study sites, and industry sponsorship (vs. academic settings) were associated with greater placebo response.	
Consistency in results	Inconsistent
Precision in results	Imprecise for pairwise comparison, precise for placebo response
Directness of results	Direct

Matsusaki A, Kaneko M, Narukawa M

Meta-analysis of Placebo Response in Randomized Clinical Trials of Antipsychotic Drugs Using PANSS Focusing on Different Approaches to the Handling of Missing Data

Clinical Drug Investigation 2018; 38: 751-61

View review abstract online

Comparison	**Level of placebo response and factors influencing this response.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests greater improvement in PANSS total scores in the placebo arm of studies using last observation carried forward (LOCF) methods than in studies using mixed-effect models for repeated measures (MMRM) methods. Studies involving more countries and studies in outpatient settings had greater placebo response in the analysis of MMRM methods, while studies with shorter study duration showed greater placebo response in the analysis of LOCF methods.**

Change in symptoms

A significant effect of greater improvement in PANSS total scores in the placebo arm with last observation carried forward (LOCF) methods than with mixed-effect models for repeated measures (MMRM) methods;

6 RCTs, N = 686, MD = -11.0 vs. -9.0, $p = 0.032$

Multivariate meta-regression found moderating effects of studies involving more countries and studies in outpatient settings had greater placebo response in the analysis of MMRM methods. In the analysis of LOCF methods, studies with shorter study duration showed greater placebo

response. The multivariate analysis found no moderating effects of publication year, number of study sites, enrolment speed, rater training, diagnosis, placebo lead-in, or active comparator.	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

McCutcheon RA, Pillinger T, Mizuno Y, Montgomery A, Pandian H, Vano L, Marques TR, Howes OD

The efficacy and heterogeneity of antipsychotic response in schizophrenia: A meta-analysis

Molecular Psychiatry 2019; doi: 10.1038/s41380-019-0502-5.

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Comparison	**All antipsychotics vs. placebo.**
Summary of evidence	**Moderate to high quality evidence (large sample, appears inconsistent, precise, direct) finds a medium-sized effect of greater total symptoms improvement with antipsychotics. There was less variability in response to antipsychotics than in response to placebo, with older studies, those with younger patients, higher dose treatments, and greater mean-difference in symptom-change being associated with less variability.**
Symptoms	
A medium-sized significant effects of greater total symptom improvement with antipsychotics; 66 RCTs, N = 17,202, $g = 0.47$, 95%CI 0.42 to 0.51, $p < 0.001$ Authors report that there was less variability in symptomatic improvement in antipsychotic-response relative to placebo. Less variability was associated with older studies, younger patients, higher dose treatments, and greater mean-difference in symptom-change.	
Consistency in results	Forest plot appears inconsistent.
Precision in results	Precise
Directness of results	Direct

Palermo S, Giovannelli F, Bartoli M, Amanzio M

Are patients with schizophrenia spectrum disorders more prone to manifest nocebo-like-effects? A meta-analysis of adverse events in placebo groups of double-blind antipsychotic trials

Frontiers in Pharmacology 2019; 10: 502

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Comparison	**Nocebo (adverse) effects in placebo groups.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, appears precise, direct) finds around 66% of patients receiving placebo report an adverse event, which correspond to those adverse events found in the antipsychotic groups. 27% reported nervous system disorders, 13% reported gastrointestinal disorders, and 30% reported psychiatric disorders. A higher level of schizophrenia symptoms at baseline was associated with more adverse events with placebo.**

Nocebo effects

Proportion of patients receiving placebo reporting any adverse effect;

N = 5,523, prevalence = 66.3%, 95%CI 62.7% to 69.8%, I^2 = 88%

Proportion of patients reporting nervous system disorders;

N = 6,281, prevalence = 27.6%, 95%CI 22.9% to 32.2%, I^2 = 97%

Proportion of patients reporting gastrointestinal disorders;

N = 5,370, prevalence = 12.9%, 95%CI 10.8% to 15%, I^2 = 93%

Proportion of patients reporting overall psychiatric symptoms (anxiety, depression, agitation etc);

N = 6,298, prevalence = 30.4%, 95%CI 24.8% to 36%, I^2 = 98%

Proportion of withdrawal of patients treated with placebo because of adverse effects;

N = 6,097, prevalence = 7.2%, 95%CI 5.9% to 8.4%, I^2 = 84%

The adverse effects in the placebo arms corresponded to those of the antipsychotic-atypical-medication-class against which the placebo was compared.

There was an association between the higher level of schizophrenia symptomatology and more adverse effects.

Consistency in results	Inconsistent
Precision in results	Appears precise
Directness of results	Direct

Rutherford BR, Pott E, Tandler JM, Wall MM, Roose SP, Lieberman JA

Placebo Response in Antipsychotic Clinical Trials. A Meta-analysis

JAMA Psychiatry 2014; 71(12): 1409-1421

View review abstract online

Comparison	**Changes in placebo and treatment response in clinical trials over time (1960 to 2014).**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests decreased improvement in symptoms from baseline to follow-up in treatment arms over time, and increased improvement in symptoms from baseline to follow-up in placebo arms over time. This may be explained by enrolment of less severely ill patients at baseline and higher expectations that medications will improve symptoms.**

Changes in symptom improvements over time

Improvement in symptoms from baseline to follow-up in effective-dose medication arms decreased significantly over time;

105 RCTs, N = 17,147, r = -0.26, $p < 0.001$, I^2 = 91.8%

Improvement in symptoms from baseline to follow-up in placebo arms increased significantly over time;

N = 2,882, r = 0.52, p = 0.001, I^2 not reported

There were no associations between low-dose or intramuscular medications and publication year.

Authors report significant interactions that indicate changes in randomised clinical trials are leading to inflation of baseline symptom scores, enrolment of less severely ill patients, and higher expectations of patients, which all may be responsible for the changes in symptom improvements reported here.

Consistency in results	Inconsistent

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

Welge JA, Keck PE, Jr

Moderators of placebo response to antipsychotic treatment in patients with schizophrenia: a meta-regression

Psychopharmacology 2003; 166(1): 1-10

View review abstract online

Comparison	**Antipsychotic vs. placebo response.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, unable to assess consistency or precision, direct) suggests there is a placebo response for symptom improvement, and that shorter trial duration results in higher placebo response, with the placebo response lessening over time. Symptom severity at baseline, patient age, duration of illness, trial drop-out rates and trial sex ratio have no impact on placebo response.**
Average placebo and antipsychotic response	
32 RCTs (N = total not reported) The average symptom improvement on placebo = -1.84 BPRS total score points. The average symptom improvement on antipsychotics (any type) = -8.08 BPRS total score points.	
Moderators of placebo response	
Trial duration significantly affected placebo response; BPRS scores increased (showing worsening symptoms) by approximately 1 BPRS total score point per week of trial duration (b = 1.05 ± 0.32, p = 0.003). No significant relationships were observed between placebo response and symptom severity at baseline, patient age, duration of illness, trial drop-out rates and trial sex ratio.	
Consistency in results	Consistency measure is not reported.
Precision in results	Imprecision measure is not reported.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, *b* = regression co-efficient, CI = confidence interval, *d* = Cohen's d standardised mean difference, I^2 = degree of heterogeneity index, MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Symptom Scale, Q = statistic for the test of heterogeneity, *r* = Pearsons correlation coefficient, RCT = randomised control trial, SMC = standardised mean change

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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[11].

† 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).

Weighted 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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect[11].

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[12]. 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 are an 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[11];

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

§ 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[13].

‖ 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, which 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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