**Expectancy Effects,** **Failure of Blinding Integrity, and Placebo Response in Trials of Treatments for Psychiatric Disorders: A Narrative Review**

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**Revision date: 30/11/2024**

**Word count:** 3699

**KEY POINTS**

**Question:** Whatis theimpact of expectancy effects and functional unblinding in randomized controlled trials (RCTs) of treatments in psychiatry?

**Findings:** Blinding integrity may be compromised by perceived treatment efficacy and side effects, introducing bias into outcome assessments.

**Meaning:** Expectancy can influence treatment responses in RCTs. Novel statistical methods and experimental medicine models offer strategies to address this issue.

**ABSTRACT**

**Importance**
Expectancy effects are significant confounding factors in psychiatric randomized controlled trials (RCTs), potentially affecting the interpretation of study outcomes. This narrative review is the first to explore the relationship between expectancy effects, compromised blinding integrity, and the effects of active treatment/placebo in psychiatric RCTs. Additionally, we present statistical and experimental approaches that may help mitigate the confounding impact of expectancy effects. The review concludes with recommendations to enhance the reliability of RCTs in psychiatry.

**Observations**
The placebo response comprises both specific and non-specific elements, with expectation being a key specific component. Evidence from experimental and clinical studies suggests that expectancy can influence treatment responses in RCTs. Blinding integrity may be compromised by perceived treatment efficacy and side effects, introducing bias into outcome assessments. Treatment expectations can lead to unblinding during RCTs, and meta-analytic data from studies in the fields of psychedelics and anxiety disorders indicate that this can influence effect sizes. Therefore, controlling for expectancy effects is essential when interpreting RCT results. Novel statistical methods, though still in need of further validation, offer strategies to address this issue. Another approach may involve experimental medicine models, which aim to develop objective improvement markers (readouts) less affected by expectancy effects.

**Conclusions and Relevance**
Expectancy effects represent a significant confound in psychiatric RCTs. We recommend collecting data on treatment expectations alongside monitoring blinding integrity to more accurately interpret study outcomes. Additionally, developing objective readouts that are less confounded by expectancy effects offers another promising avenue for mitigating these confounding influences in psychiatric RCTs.

**INTRODUCTION**

Randomized controlled trials (RCTs) are the gold standard when testing the effects of a treatment. However, non-specific confounding effects in RCTs can affect their interpretation.1–3 These include selection bias (i.e., systematic errors arising when the study sample is not reflective of the target population), the so-called *Hawthorne* effects (i.e., the change in behavior/performance when one knows they are being observed), regression to the mean (i.e., the statistical phenomenon by which subsequent measurements taken from an extreme group will tend to fall closer to the population mean over time), and the effects of expectations, which are related to failure of blinding integrity, and are a component of the placebo response.1

In this review, we focus on the relationship between expectations/expectancy effects, failure of blinding integrity, and effects of active treatment/placebo in RCTs of treatments in psychiatry.

**Key definitions and concepts**

*Placebos* are pharmacologically inactive agents or *sham* (i.e., false) procedures given under the pretense of active treatment. In RCTs, improvements in the placebo group are partly attributable to spontaneous remission and other non-specific effects of the care received in an RCT, including support from trial staff or other parallel interventions patients receive during a trial, such as dietary or sleep pattern changes.4,5 Nonetheless, some improvements are specifically attributable to the administration of the placebo itself.4 In fact, evidence from three-arm studies that include ‘no-treatment’ indicates that administration of placebo yields symptom improvements over and above the natural history of the disease.6 The effects on symptoms specifically attributable to placebo administration are known as ‘placebo effects’, while ‘placebo response’ comprises both non-specific and specific placebo effects.4 Likewise, regarding active treatment, ‘treatment effect’ refers to the improvement in symptoms specifically attributable to treatment mechanisms, while ‘treatment response’ comprises both ‘treatment effects’ and ‘placebo response’.4 Less well-studied than the placebo effect but increasingly recognized is the *nocebo effect,* comprising the undesirable changes observed in individuals receiving active treatment/placebo in the context of negative expectations or expectancies,7,8 which can manifest as side effects or decreased response to treatment.9–11 As with placebo *response* and *effect*, nocebo *effects* refer to changes in symptoms specifically attributable to nocebo mechanisms, while nocebo *response* refers to all sources of symptom worsening or adverse events in those administered placebo.4 The placebo effect is not a homogeneous entity. Genetic,12 functional neuroimaging,13,14 neuroendocrine, and neurotransmitter studies15 are revealing some of its neuropsychobiological underpinnings, which have led to the appreciation of its inter-personal and inter-disorder variability. Neurotransmitter systems including catecholamines, opioids, and endocannabinoids appear to be implicated in the placebo response. The main psychological mechanisms mediating placebo effects are thought to be related to implicit and explicit associative learning (i.e., conscious and unconscious learning that occurs through the coupling of an experience with other stimuli and/or its positive and negative consequences), the individual’s expectations of treatment, and the interplay between those factors.16,17 The terms ‘expectation’ and ‘expectancy’ are frequently used as equivalent in the literature. Here, consistent with what has been suggested by others, we use ‘expectancies’ to refer to *implicit* expectations, and ‘expectations’ in relation to *explicit*, verbalized constructs.18,19

Through blinding in RCTs, we assume that the treatment received, whether active or placebo, is concealed from participants and assessors for the duration of the study.20 However, blinding integrity is not always maintained in double-blinded RCTs. Breaches in blinding may occur due to factors concerning participants and assessors, such as perceived or observed treatment efficacy (‘benign unblinding’ if significant improvement leads to broken blinding), the experience of treatment-specific side-effects (‘malicious unblinding’),21–23 and/or factors related to trial design, such as ‘poor matching’, which has historically been an issue in clinical trials, where differences in appearance or taste of placebo and active treatment cause unblinding.24

**Evidence on placebo responses to biological treatments across psychiatric disorders**

 An umbrella review25 summarizing 1,691 RCTs found that placebo response varied substantially from large effect sizes in disorders such as generalized anxiety disorder (d = 1.85) and depression (g = 1.10), to small effect sizes in disorders such as obsessive-compulsive disorder (d = 0.32) and schizophrenia spectrum disorders (standardized mean change = 0.33). These findings were similar to those reported in a meta-analysis of placebo outcomes in nine psychiatric disorders.26 The umbrella review additionally explored potential correlates of increased placebo responses within and across disorders. Some of these positive correlates included larger sample size and number of centers, which associated with higher placebo response, potentially reflecting inconsistencies introduced in larger trials in training of clinical staff, patient selection, and methodology.25

**What is the evidence that expectations causally affect placebo and treatment responses?**

*Evidence from experimental studies*

Experimental studies in healthy volunteers and in patients support the notion that manipulating expectations can causally influence treatment response. One approach to demonstrate this has been to give verbal and/or written suggestions that a ‘sham’ treatment (e.g., an inactive cream, placebo pill, or saline nasal spray) is a medication with efficacy for a specific symptom. Induction of the symptom then takes place in the laboratory, and when the ‘treatment’ is given, the symptom reduces in intensity as the experimenter suggested it would. Such approaches consistently induce placebo effects in pain,27–29 and can modulate emotional constructs, such as reducing disgust30 or improving sadness induced acutely through music or movies.31–33 However, one can prevent a placebo effect by pairing symptom relief with an alternative explanation for the improvement, such as the experimenter explicitly stating that the stimulus intensity has been reduced.28 This line of research suggests that expectations are the key mediator of placebo-induced improvement. A possible confound with this approach is the potential for demand characteristics or Hawthorne effects. Indeed, in experiments on acute sadness, the effects of the placebo were larger on subjective outcomes compared with autonomic measures,32,33 potentially suggesting responder bias.34

A more direct way of causally measuring the effect of expectations on treatment response is through the ‘open-hidden paradigm’, whereby active medication is either given to patients in plain view as would be usual clinical practice, or is given covertly, either through verbal instructions that a medication is inactive or by a machine hidden from the patient (e.g., for intravenous infusions). Multiple studies have demonstrated that hidden treatment works, but open treatment is superior in conditions such as acute pain, Parkinson’s disease, depression and social anxiety disorder.35–38 The only difference between open and hidden treatment is the knowledge that treatment is being administered, so the difference in efficacy is thought to relate to expectation effects.39,40

*Evidence from clinical studies*

There is some indirect evidence that expectations can affect efficacy of treatments in the context of clinical studies. Efficacy of a treatment is larger when administered in an open-label trial compared with the same treatment administered in double-blind fashion,41,42 presumably because there is more certainty about the treatment received. Supporting this, the more active treatment arms there are in an RCT (i.e., as probability of receiving active treatment increases), the higher the placebo response rate43,44 (although the correlation may not always be perfect, see for instance45). Additionally, recent studies appear to directly evidence a role for expectations in treatment response. In patients with post-traumatic stress disorder, enhanced expectations at baseline were associated with a higher probability of early response to sertraline and greater outcomes at 10 weeks.46 Similarly, in an observational study of patients with difficult-to-treat depression undergoing repetitive transcranial magnetic stimulation, higher positive treatment expectations at baseline were associated with greater odds of remission.47 Nevertheless, although this evidence suggests that expectations might causally moderate treatment response in the context of a RCT, to our knowledge this has yet to be empirically proven.

*Expectations and learning reinforce one another*

Expectations and learning have been shown to lead to activation of downstream biological systems such as the endogenous opioid and dopamine systems.14,48 It is likely that expectations and learning are inter-related and reinforce each other. Experimentally-induced placebo effects are stronger when verbal suggestions (to induce expectations) are combined with classical conditioning (i.e., learning).5,49 That is, expectations are important in inducing a placebo effect, which can be *enhanced or reduced* through learning.

Therefore, baseline expectations might be enhanced or attenuated by experiences that occur during an RCT. For example, a patient might notice a particular symptom, which might have been mentioned as a potential adverse effect of a treatment during the consent process. This knowledge might interact with baseline expectations to enhance the placebo-specific component of that patient’s treatment response. If so, unblinding during a trial could alter placebo-specific components of treatment response. If this were to occur to differing degrees across active and placebo arms, then estimates of efficacy could be biased. This is potentially a particular problem when outcome measures are subjective, as in many RCTs in psychiatry.50 To our knowledge, there is only one study, examining two antidepressant trials, that supports this notion.51 Patients were asked to rate what they believed their symptom burden would be at the end of treatment in each study visit. The results showed expectations were not fixed, and changes in expectations were significantly associated with response.

**Blinding integrity and expectations**

*Is blinding integrity assessed and maintained in clinical trials?*

Systematic reviews have consistently shown that assessment of blinding integrity is rarely conducted in psychiatry. Assessment of blinding had been performed in 7.1% of antidepressant RCTs between 2010 and 2020,52 3.64% of anxiolytic RCTs since 1980,50 1.6% of antipsychotic RCTs,53 and 0.6% of ADHD RCTs.54 Comparable figures are observed outside of psychiatry: only 2% of randomized trials had assessed blinding integrity in a random sample of controlled trials in 2003,55 and 7% of general medicine RCTs taken from leading medical journals between 1998 and 2001 had done so.56

Blinding integrity can be assessed by calculating correct guess rates in active treatment and placebo arms. If correct guess rates are at chance level, blinding is intact. Conversely, if correct guessing is higher than chance, or lower than chance suggesting systematic opposite guessing, this suggests blinding has been broken. In antidepressant RCTs, Lin et al. found that blinding had been either successful or slightly broken.52 This is in contrast to the conclusions of another systematic review of antidepressant RCTs, in which correct guessing was more likely in active treatment arms for both participants and assessors, suggesting unblinding.57 Further studies are needed to understand whether blinding tends to be maintained more frequently in placebo compared with active treatment arms.

*Does unblinding affect estimates of efficacy?*

Whether there is a relationship between blinding integrity and estimates of efficacy has been less explored. In the meta-analysis by Lin et al. in antidepressant trials, results were inconclusive as to whether failure of blinding relates to effect size, but this analysis only included four trials, as so few reported an assessment of blinding integrity.52 In a recent meta-analysis of anxiolytic RCTs, unblinding in placebo groups fell short of being associated with a larger treatment effect size, but no relationship was seen between unblinding in active groups and effect size.50 Meanwhile, unblinding of *clinicians* was significantly associated with increased effect sizes, but this effect might have been driven by two outlying trials.50 Overall, it is unclear if unblinding affects estimates of treatment efficacy, mostly owing to a lack of data. Nonetheless, there is evidence from trials in medicine more widely to suggest that lack of blinding does bias outcomes.58,59 At present, available data suggest the frequent occurrence of unblinding when blinding integrity is assessed.50,52–56 However, we have too few data to identify the causes of unblinding. The possibility that malicious unblinding is occurring in RCTs should be taken seriously, the effects of which likely act through changes in expectations.

*What is the evidence that expectations mediate the effect of unblinding on treatment efficacy?*

In psychiatry, valuable insights concerning this question can be obtained from the field of psychedelics, in which blinding is notably difficult to achieve given psychedelics’ prominent psychoactive effects. In this context, expectations seem to have a crucial role in the process of drug-assisted psychotherapy,21 although the mechanisms remain poorly understood (for a recent review see60). Pre-conceived ideas of psychedelic effects, possibly enhanced by media depictions,61 help to shape pre-treatment expectations and expectancies. Poor blinding integrity mediated by unbalanced expectations in treatment arms favoring active treatment has led to concerns that estimates of efficacy in psychedelic RCTs are inflated.62 This was explicitly explored in a recent Bayesian network meta-analysis63 comparing psychedelic RCTs with escitalopram RCTs for depressive symptoms. The authors found that placebo escitalopram outperformed placebo psychedelics. The only psychedelic treatment that outperformed placebo escitalopram was high-dose psilocybin, and its effect size decreased considerably when the comparator was placebo escitalopram (from 0.88 to 0.31).63 The resulting hypothesis is that, where blinding is easier to maintain, expectations in the placebo group will be higher, with a larger placebo effect and smaller drug-placebo difference. This can be exemplified by an RCT of ketamine for depression,64 in which participants underwent treatment while sedated with general anesthetic to successfully blind them to treatment allocation. Although the therapeutic response in the ketamine group was similar to that seen in other trials of ketamine for depression, similar efficacy was also seen in the placebo group, with no statistically significant difference between them. Conversely, unblinding of participants in placebo arms leads to reduced placebo responses (‘lessebo’ effect). This is supported by data from a meta-analysis of RCTs for multiple treatment modalities in anxiety disorders, where pill placebo (*d* = 1.29) outperformed psychological placebo (*d* = 0.83) and waiting lists (*d* = 0.20), presumably because the pill placebo was better blinded.65 This highlights that not all placebos are created equal, which has important implications for the interpretation of comparative evidence synthesis approaches, such as network meta-analyses.66

It is noteworthy that in the above-mentioned Bayesian network meta-analysis comparing psychedelic and escitalopram trials, although placebo escitalopram outperformed placebo psychedelic, extremely low dose psilocybin showed similar efficacy to placebo escitalopram, possibly due to participants experiencing some mild effects of psilocybin resulting in improved blinding.63 This suggests that placebo response can be enhanced (and/or made more predictable across treatments) via improved blinding through the use of *active placebos.* Active placebos differ from a regular pill placebo due to their ability to mimic a treatment’s adverse effects but not its therapeutic effects.22 However, choosing an active placebo completely devoid of therapeutic effects might be a complex task given our ever-evolving understanding of the pathophysiological mechanisms underlying psychiatric conditions.67–69 Further, the use of active placebos involves deliberate induction of side effects potentially without treatment benefits, meaning the harm-benefit analysis is skewed towards harm.

Additionally, the use of active placebo might introduce confounders, resulting in even more challenging interpretation of RCT results. Instead, it might be more fruitful to *control* for expectation effects in RCT analyses.

**Approaches to account for expectation and unblinding effects**

**Novel statistical methods**

Several statistical approaches have been considered to account for non-specific effects in RCTs. These include identifying placebo responders *post-hoc* and using covariates associated with ‘responders’ to classify patients in the treatment arm as either ‘treatment responders’ or ‘placebo responders’; or modelling the impact of ‘propensity’ to respond to placebo on treatment response via mixture modelling70 (for a review see71). These approaches assume that ‘placebo responders’ represent a stable trait measure.71 Notably, different care by different professionals in different centers might also be relevant, resulting in variable placebo responses, even within the same RCT.

Using expectations as a proxy for ‘placebo responsiveness’ within a specific RCT might be less problematic than other methods due to reduced assumptions about stability. Recently, statistical methods have been proposed to allow estimation of treatment efficacy while ‘correcting’ for expectations in a given RCT. In a series of neurostimulation trials for depression and ADHD, comparing models that included both patients' beliefs about their treatment and their actual treatment assignment helped determine whether improvements in symptoms were due entirely to expectation effects.72 That is, if the model fit was improved by the inclusion of actual treatment assignment *in addition to* subjective beliefs, this suggested there was a true, specific effect of treatment on symptoms. If not, this suggested symptom improvement was more due to expectations. Another approach involves modelling patients’ ‘treatmentality’ (i.e., a patient’s post-hoc beliefs about the treatment they received in an RCT ) as a construct derived from expectations.73 Specific treatment effects can then be assessed via contrasts of patients with similar ‘treatmentality’.71,73 An additional method that uses post-treatment beliefs about group assignment aims to estimate outcomes in a perfectly blinded trial from data in an imperfectly blinded trial.74 This involves separating patients into 4 strata: guessed placebo/received placebo, guessed active/received placebo, guessed placebo/received active, guessed active/received active. Then, each stratum is transformed into a continuous distribution via kernel density estimation. Random samples of outcome values are taken from these distributions to match the original sample size in a weighted fashion such that outcome data now represents a perfectly blinded trial (for a practical example, see74). Theoretically, one could also test how outcomes would look in a perfectly unblind trial.

Such statistical methods need further validation in external studies, especially as the causal relationships between expectations at baseline, unblinding during the trial, their interactions, and treatment outcomes, remain unknown.72 Additionally, it is unclear whether expectations affect treatment outcome to the same degree in active treatment and placebo arms. Furthermore, these methods do not consider the role that unblinding or expectations in *clinician raters* might have on estimates of treatment effects.71 Overall, more research is needed to understand how to statistically account for these effects.

**Approaches from experimental medicine models**

A different approach to accounting for expectation effects in RCTs could be to identify outcomes that are not or less confounded by expectations or unblinding (i.e., objective markers of improvement as opposed to questionnaires of symptoms). Notably, the above-mentioned umbrella review found evidence in disorders such as panic disorder and primary insomnia that placebo effect size is smaller when objective outcome measures are used, compared with subjective outcomes.25 However, such objective measures are rare in psychiatry.

Experimental medicine models, inducing features resembling a disorder in healthy volunteers in the laboratory, could be used to develop and test such measures.2 Examples of experimental medicine models of psychiatric disorders include the Oxford Emotional Test Battery (ETB)75,76 for affective disorders, administration of ketamine to model psychosis,77 inhalation of air enriched with high concentrations of CO2 (e.g. 35%) for panic disorder,78 and lower concentrations of CO2 (e.g. 7.5%) for generalized anxiety disorder.79–81 ‘Symptoms’ in these models are often responsive to standard treatments, and therefore these models can be used at a ‘proof-of-concept’ stage of novel treatment development or when repurposing already licensed treatments.79

There is evidence that while standard treatments reduce ‘symptoms’ in these models, placebos or expectation effects might not. For example, in the Oxford ETB, placebo treatment showed no effect on emotional processing compared with no treatment in healthy volunteers.76 More recently, in an experimental study in which we successfully induced positive expectations for a sham ‘intranasal lorazepam spray’ in healthy volunteers, these expectations did not translate into reduced anxiety in the 7.5% CO2 inhalational model of generalized anxiety.82

Through the use of such models, we might be able to develop objective assays that are less confounded by expectation effects. The use of these readouts in RCTs would therefore be less affected by unblinding.

**Recommendations for future research**

In light of the data that we have discussed on the relationship of treatment and placebo effects to failure of blinding integrity and expectation effects, here we make recommendations to improve our understanding and, ultimately, the outcomes, of RCTs in psychiatric disorders.

First, more data are needed regarding blinding integrity in RCTs in psychiatric disorders, whether blinding fails for patients or clinician raters, and if so, why. It is imperative to understand whether ‘benign’ or ‘malicious’ unblinding is taking place and whether there are impacts of this on expectations. If so, we need to understand whether changes in expectations causally affect estimates of treatment efficacy. We have highlighted signals to suggest that maintaining blinding in placebo arms might be more important for an accurate estimate of treatment efficacy, but this needs to be formally assessed. This is particularly pertinent where treatments are difficult to blind effectively, such as psychedelics or neuromodulation. For these reasons, we recommend that data regarding expectations and blinding integrity are routinely collected in psychiatric RCTs, e.g. through the use of the ‘Guess of Treatment Questionnaire’, a 5-item questionnaire that assesses a participant’s guess of treatment and the reasons behind each guess.74 An important factor to consider here is *equipoise*, an ethical principle guiding clinical research which states that an investigator must not believe in the therapeutic superiority of any of the trial arms, although this may be difficult to achieve.83 We therefore recommend that these data be collected by an independent researcher not involved in rating clinical outcomes.

 Second, more data regarding the success of blinding and regarding expectations would allow assessments of whether statistical methods to ‘correct’ for expectancy or placebo effects in RCTs are valid and accurate. At present, the methods described here are not in use as it is unclear how much of an improvement they provide over standard statistical approaches such as mixed models with repeated measures. We need to empirically test these methods with real data.

Finally, we recommend development of readouts that are objective or resistant to expectation effects in psychiatric disorders. Examples of such readouts might include cognitive/behavioral measures, psychophysiological readouts such as heart rate, skin conductance or quantitative electroencephalography, or neuroimaging measures such as estimates of network connectivity. We have highlighted early evidence that development of such readouts for psychiatric disorders is possible. Evidence suggests that experimental medicine models with healthy volunteers may be less confounded by expectation effects, and might be a vehicle to develop such readouts.

Through these recommendations, we believe that we can improve our understanding of non-specific effects that impact treatment response. By better understanding these effects, we can reduce the variability in treatment and placebo responses within and between RCTs in psychiatric disorders, to better estimate treatment efficacy. Improving the testing and development of treatments is most constructively seen as a collective effort, and regulatory agencies could influence this by considering the measurement of expectancies and blinding integrity as requirements. Doing so will enhance the development and testing of potential new treatments for psychiatric disorders.

**Acknowledgements**

Nathan TM Huneke is Deputy Director of Education for the British Association for Psychopharmacology, for which he receives an honorarium, and an NIHR Clinical Lecturer. Guilherme F Veronesi is an NIHR Academic Clinical Fellow. Professor Baldwin receives a Stipend from Wiley Publishers for editorial work (Human Psychopharmacology) and has received editorial fees from Elsevier publishers (Medicine). He is supported by NIHR grants NIHR 1171206 and NIHR 165425, and his employer will receive a grant from Idorsia pharmaceutical company, for work outside the scope of this article. He is a Medical Patron of Anxiety UK. Samuele Cortese, NIHR Research Professor (NIHR303122) is funded by the NIHR for this research project. Samuele Cortese is also supported by NIHR grants NIHR203684, NIHR203035, NIHR130077, NIHR128472, RP-PG-0618-20003 and by grant 101095568-HORIZONHLTH-2022-DISEASE-07-03 from the European Research Executive Agency. Prof. Cortese has declared reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, the Canadian AADHD Alliance Resource, the British Association of Psychopharmacology, and from Healthcare Convention for educational activity on ADHD, and has received honoraria from Medice. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS or the UK Department of Health and Social Care.

Nathan TM Huneke and Guilherme F Veronesi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**ROLE OF FUNDER/SPONSOR STATEMENT**

Not applicable

**NON-AUTHOR CONTRIBUTIONS**

Not applicable

**ACCESS TO DATA AND DATA ANALYSIS**

Not applicable

**MEETING PRESENTATION**

Not applicable

**FIGURES TITLES AND CAPTIONS**

**Title Figure 1**: Placebo response and treatment response.

**Caption Figure 1**: Some of the specific and non-specific components of the placebo and treatment responses and the factors which mediate them. Non-specific components comprise numerous factors. Only the ones that we deemed the most prominent are included in this figure.

**Title Figure 2:** Expectancy and unblinding in different study arms over the course of a randomized trial.

**Caption Figure 2**: Potential interactions between expectancies, blinding and treatment effects in a simplified, hypothetical randomized trial composed of three arms: treatment, active placebo and regular placebo. The hypothetical treatment in this graph can lead to obvious side effects early on and overwhelming treatment effects at the one-week mark. In practice, even regular placebo groups may display side effects (i.e., the nocebo effect) and show response to treatment (i.e., the placebo response), which would also contribute to mediation of expectancies and add to the complexity of the expectancy-treatment effect interaction. This schematic representation was kept to an idealized scenario to highlight theoretical concepts and relationships. (See Figure 3 for a dedicated view of the potential dynamic relationship between placebo and expectations).

**Title Figure 3:** The potential dynamic relationship between placebo and expectations.

**Caption Figure 3:** Example graph illustrating how expectations may theoretically affect placebo response over time during a trial according to hypothetical predictors such as patient-doctor encounters. Contrary to static measures of ‘placebo responsiveness’ such as ‘placebo responders’ and ‘treatment responders’, expectations dynamically influence the placebo response during an RCT and may therefore be an appropriate proxy for ‘placebo responsiveness’ in trials.

**References**

 1. Huneke NTM, Van Der Wee N, Garner M, Baldwin DS. Why we need more research into the placebo response in psychiatry. *Psychol Med*. 2020;50(14):2317-2323. doi:10.1017/S0033291720003633

2. Huneke NTM. Is superiority to placebo the most appropriate measure of efficacy in trials of novel psychotropic medications? *Eur Neuropsychopharmacol*. 2022;62:7-9. doi:10.1016/j.euroneuro.2022.06.003

3. Stahl SM, Greenberg GD. Placebo response rate is ruining drug development in psychiatry: why is this happening and what can we do about it? *Acta Psychiatr Scand*. 2019;139(2):105-107. doi:10.1111/acps.13000

4. Evers AWM, Colloca L, Blease C, et al. Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. *Psychother Psychosom*. 2018;87(4):204-210. doi:10.1159/000490354

5. Ashar YK, Chang LJ, Wager TD. Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. *Annu Rev Clin Psychol*. 2017;13(1):73-98. doi:10.1146/annurev-clinpsy-021815-093015

6. Krogsbøll LT, Hróbjartsson A, Gøtzsche PC. Spontaneous improvement in randomised clinical trials: meta-analysis of three-armed trials comparing no treatment, placebo and active intervention. *BMC Med Res Methodol*. 2009;9(1):1. doi:10.1186/1471-2288-9-1

7. Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device *v* inert pill: randomised controlled trial of two placebo treatments. *BMJ*. 2006;332(7538):391-397. doi:10.1136/bmj.38726.603310.55

8. Webster RK, Weinman J, Rubin GJ. A systematic review of factors that contribute to nocebo effects. *Health Psychol*. 2016;35(12):1334-1355. doi:10.1037/hea0000416

9. Barsky AJ. Nonspecific Medication Side Effects and the Nocebo Phenomenon. *JAMA*. 2002;287(5):622. doi:10.1001/jama.287.5.622

10. Bingel U, Wanigasekera V, Wiech K, et al. The Effect of Treatment Expectation on Drug Efficacy: Imaging the Analgesic Benefit of the Opioid Remifentanil. *Sci Transl Med*. 2011;3(70). doi:10.1126/scitranslmed.3001244

11. Amanzio M, Mitsikostas DD, Giovannelli F, Bartoli M, Cipriani GE, Brown WA. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. *Lancet Reg Health - Eur*. 2022;12:100253. doi:10.1016/j.lanepe.2021.100253

12. Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. *Trends Mol Med*. 2015;21(5):285-294. doi:10.1016/j.molmed.2015.02.009

13. Zunhammer M, Spisák T, Wager TD, et al. Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nat Commun*. 2021;12(1):1391. doi:10.1038/s41467-021-21179-3

14. Huneke NTM, Aslan IH, Fagan H, et al. Functional Neuroimaging Correlates of Placebo Response in Patients With Depressive or Anxiety Disorders: A Systematic Review. *Int J Neuropsychopharmacol*. 2022;25(6):433-447. doi:10.1093/ijnp/pyac009

15. Benedetti F, Frisaldi E, Shaibani A. Thirty Years of Neuroscientific Investigation of Placebo and Nocebo: The Interesting, the Good, and the Bad. *Annu Rev Pharmacol Toxicol*. 2022;62(1):323-340. doi:10.1146/annurev-pharmtox-052120-104536

16. Jepma M, Koban L, Van Doorn J, Jones M, Wager TD. Behavioural and neural evidence for self-reinforcing expectancy effects on pain. *Nat Hum Behav*. 2018;2(11):838-855. doi:10.1038/s41562-018-0455-8

17. Peciña M, Chen J, Karp JF, Dombrovski AY. Dynamic Feedback Between Antidepressant Placebo Expectancies and Mood. *JAMA Psychiatry*. 2023;80(4):389. doi:10.1001/jamapsychiatry.2023.0010

18. Kube T, Rief W. Are placebo and drug-specific effects additive? Questioning basic assumptions of double-blinded randomized clinical trials and presenting novel study designs. *Drug Discov Today*. 2017;22(4):729-735. doi:10.1016/j.drudis.2016.11.022

19. Corsi N, Colloca L. Placebo and Nocebo Effects: The Advantage of Measuring Expectations and Psychological Factors. *Front Psychol*. 2017;8. doi:10.3389/fpsyg.2017.00308

20. Day SJ. Statistics Notes: Blinding in clinical trials and other studies. *BMJ*. 2000;321(7259):504-504. doi:10.1136/bmj.321.7259.504

21. Szigeti B, Heifets B. Expectancy effects in psychedelic trials. *Biol Psychiatry Cogn Neurosci Neuroimaging*. Published online 2024.

22. Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Common Mental Disorders Group, ed. *Cochrane Database Syst Rev*. 2004;2012(10). doi:10.1002/14651858.CD003012.pub2

23. Shah E, Triantafyllou K, Hana AA, Pimentel M. Adverse events appear to unblind clinical trials in irritable bowel syndrome. *Neurogastroenterol Motil*. 2014;26(4):482-488. doi:10.1111/nmo.12289

24. Bello S, Wei M, Hilden J, Hróbjartsson A. The matching quality of experimental and control interventions in blinded pharmacological randomised clinical trials: a methodological systematic review. *BMC Med Res Methodol*. 2016;16(1):18. doi:10.1186/s12874-016-0111-9

25. Huneke NTM, Amin J, Baldwin DS, et al. Placebo effects in randomized trials of pharmacological and neurostimulation interventions for mental disorders: An umbrella review. *Mol Psychiatry*. Published online June 24, 2024. doi:10.1038/s41380-024-02638-x

26. Bschor T, Nagel L, Unger J, Schwarzer G, Baethge C. Differential Outcomes of Placebo Treatment Across 9 Psychiatric Disorders: A Systematic Review and Meta-Analysis. *JAMA Psychiatry*. 2024;81(8):757. doi:10.1001/jamapsychiatry.2024.0994

27. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *PAIN*. 1999;83(2):147. doi:10.1016/S0304-3959(99)00081-0

28. Huneke NTM, Brown CA, Burford E, et al. Experimental Placebo Analgesia Changes Resting-State Alpha Oscillations. Mouraux A, ed. *PLoS ONE*. 2013;8(10):e78278. doi:10.1371/journal.pone.0078278

29. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain*. 2006;124(1):126-133. doi:10.1016/j.pain.2006.04.005

30. Schienle A, Übel S, Schöngaßner F, Ille R, Scharmüller W. Disgust regulation via placebo: an fMRI study. *Soc Cogn Affect Neurosci*. 2014;9(7):985-990. doi:10.1093/scan/nst072

31. Glombiewski JA, Rheker J, Wittkowski J, Rebstock L, Rief W. Placebo mechanisms in depression: An experimental investigation of the impact of expectations on sadness in female participants. *J Affect Disord*. 2019;256:658-667. doi:10.1016/j.jad.2019.06.070

32. Göhler AC, Haas JW, Sperl MFJ, Hermann C, Winkler A. Placebo nasal spray protects female participants from experimentally induced sadness and concomitant changes in autonomic arousal. *J Affect Disord*. 2021;295:131-138. doi:10.1016/j.jad.2021.07.037

33. Friehs T, Rief W, Glombiewski JA, Haas J, Kube T. Deceptive and non-deceptive placebos to reduce sadness: A five-armed experimental study. *J Affect Disord Rep*. 2022;9:100349. doi:10.1016/j.jadr.2022.100349

34. Hróbjartsson A, Kaptchuk TJ, Miller FG. Placebo effect studies are susceptible to response bias and to other types of biases. *J Clin Epidemiol*. 2011;64(11):1223-1229. doi:10.1016/j.jclinepi.2011.01.008

35. Faria V, Gingnell M, Hoppe JM, et al. Do You Believe It? Verbal Suggestions Influence the Clinical and Neural Effects of Escitalopram in Social Anxiety Disorder: A Randomized Trial. *eBioMedicine*. 2017;24:179-188. doi:10.1016/j.ebiom.2017.09.031

36. Amanzio M, Pollo A, Maggi G, Benedetti F. Response variability to analgesics: a role for non-specific activation of endogenous opioids. *Pain*. 2001;90(3):205-215. doi:10.1016/S0304-3959(00)00486-3

37. Benedetti F, Maggi G, Lopiano L, et al. Open versus hidden medical treatments: The patient’s knowledge about a therapy affects the therapy outcome. *Prev Treat*. 2003;6(1):No Pagination Specified-No Pagination Specified. doi:10.1037/1522-3736.6.1.61a

38. Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD. Dissociable Influences of Opiates and Expectations on Pain. *J Neurosci*. 2012;32(23):8053-8064. doi:10.1523/JNEUROSCI.0383-12.2012

39. Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. *Nat Rev Neurosci*. 2015;16(7):403-418. doi:10.1038/nrn3976

40. Petrie KJ, Rief W. Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects. *Annu Rev Psychol*. 2019;70(1):599-625. doi:10.1146/annurev-psych-010418-102907

41. Jensen KB, Kirsch I, Pontén M, et al. Certainty of genuine treatment increases drug responses among intellectually disabled patients. *Neurology*. 2017;88(20):1912-1918. doi:10.1212/WNL.0000000000003934

42. Rutherford BR, Wall MM, Brown PJ, et al. Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials. *Am J Psychiatry*. 2017;174(2):135-142. doi:10.1176/appi.ajp.2016.16020225

43. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009;19(1):34-40. doi:10.1016/j.euroneuro.2008.08.009

44. Woods SW, Gueorguieva RV, Baker CB, Makuch RW. Control Group Bias in Randomized Atypical Antipsychotic Medication Trials for Schizophrenia. *Arch Gen Psychiatry*. 2005;62(9):961-970. doi:10.1001/archpsyc.62.9.961

45. Lidstone SC, Schulzer M, Dinelle K, et al. Effects of Expectation on Placebo-Induced Dopamine Release in Parkinson Disease. *Arch Gen Psychiatry*. 2010;67(8):857. doi:10.1001/archgenpsychiatry.2010.88

46. Graham B, Garcia NM, Burton MS, et al. High expectancy and early response produce optimal effects in sertraline treatment for post-traumatic stress disorder. *Br J Psychiatry*. 2018;213(6):704-708. doi:10.1192/bjp.2018.211

47. Mollica A, Ng E, Burke MJ, et al. Treatment expectations and clinical outcomes following repetitive transcranial magnetic stimulation for treatment-resistant depression. *Brain Stimulat*. 2024;17(4):752-759. doi:10.1016/j.brs.2024.06.006

48. Benedetti F, Carlino E, Pollo A. How Placebos Change the Patient’s Brain. *Neuropsychopharmacology*. 2011;36(1):339-354. doi:10.1038/npp.2010.81

49. Colloca L, Tinazzi M, Recchia S, et al. Learning potentiates neurophysiological and behavioral placebo analgesic responses. *PAIN*. 2008;139(2):306. doi:10.1016/j.pain.2008.04.021

50. Haq R, Molteni L, Huneke NTM. The relationship between blinding integrity and medication efficacy in randomised‐controlled trials in patients with anxiety disorders: A systematic review and meta‐analysis. *Acta Psychiatr Scand*. Published online August 10, 2024:acps.13741. doi:10.1111/acps.13741

51. Zilcha-Mano S, Brown PJ, Roose SP, Cappetta K, Rutherford BR. Optimizing patient expectancy in the pharmacologic treatment of major depressive disorder. *Psychol Med*. 2019;49(14):2414-2420. doi:10.1017/S0033291718003343

52. Lin YH, Sahker E, Shinohara K, et al. Assessment of blinding in randomized controlled trials of antidepressants for depressive disorders 2000–2020: A systematic review and meta-analysis. *eClinicalMedicine*. 2022;50:101505. doi:10.1016/j.eclinm.2022.101505

53. Tajika A, Furukawa TA, Shinohara K, et al. Blinding successfulness in antipsychotic trials of acute treatment for schizophrenia: a systematic review. *BMJ Ment Health*. 2023;26(1):e300654. doi:10.1136/bmjment-2023-300654

54. Fusetto Veronesi G, Huneke NTM, Shah M, Cortese S. Systematic Review: Assessment of Blinding Integrity in 161 Randomized Controlled Trials of Attention-Deficit/Hyperactivity Disorder Medications. *J Am Acad Child Adolesc Psychiatry*. Published online September 2024. doi:10.1016/j.jaac.2024.07.926

55. Hrobjartsson A, Forfang E, Haahr M, Als-Nielsen B, Brorson S. Blinded trials taken to the test: an analysis of randomized clinical trials that report tests for the success of blinding. *Int J Epidemiol*. 2007;36(3):654-663. doi:10.1093/ije/dym020

56. Fergusson D. Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. *BMJ*. 2004;328(7437):432-0. doi:10.1136/bmj.37952.631667.EE

57. Scott AJ, Sharpe L, Colagiuri B. A systematic review and meta-analysis of the success of blinding in antidepressant RCTs. *Psychiatry Res*. 2022;307:114297. doi:10.1016/j.psychres.2021.114297

58. Juni P. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ*. 2001;323(7303):42-46. doi:10.1136/bmj.323.7303.42

59. Hróbjartsson A, Thomsen ASS, Emanuelsson F, et al. Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *CMAJ*. 2013;185(4):E201-E211. doi:10.1503/cmaj.120744

60. Heifets BD, Olson DE. Therapeutic mechanisms of psychedelics and entactogens. *Neuropsychopharmacology*. 2024;49(1):104-118. doi:10.1038/s41386-023-01666-5

61. Aday JS, Heifets BD, Pratscher SD, Bradley E, Rosen R, Woolley JD. Great Expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology (Berl)*. 2022;239(6):1989-2010. doi:10.1007/s00213-022-06123-7

62. Muthukumaraswamy SD, Forsyth A, Lumley T. Blinding and expectancy confounds in psychedelic randomized controlled trials. *Expert Rev Clin Pharmacol*. 2021;14(9):1133-1152. doi:10.1080/17512433.2021.1933434

63. Hsu TW, Tsai CK, Kao YC, et al. Comparative oral monotherapy of psilocybin, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, ayahuasca, and escitalopram for depressive symptoms: systematic review and Bayesian network meta-analysis. *BMJ*. Published online August 21, 2024:e078607. doi:10.1136/bmj-2023-078607

64. Lii TR, Smith AE, Flohr JR, et al. Randomized trial of ketamine masked by surgical anesthesia in patients with depression. *Nat Ment Health*. 2023;1(11):876-886. doi:10.1038/s44220-023-00140-x

65. Bandelow B, Reitt M, Röver C, Michaelis S, Görlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. *Int Clin Psychopharmacol*. 2015;30(4):183-192. doi:10.1097/YIC.0000000000000078

66. Nikolakopoulou A, Chaimani A, Furukawa TA, Papakonstantinou T, Rücker G, Schwarzer G. When does the placebo effect have an impact on network meta-analysis results? *BMJ Evid-Based Med*. 2024;29(2):127-134. doi:10.1136/bmjebm-2022-112197

67. Salamone JD. A critique of recent studies on placebo effects of antidepressants: importance of research on active placebos. *Psychopharmacology (Berl)*. 2000;152(1):1-6. doi:10.1007/s002130000509

68. Hegvik TA, Waløen K, Pandey SK, Faraone SV, Haavik J, Zayats T. Druggable genome in attention deficit/hyperactivity disorder and its co-morbid conditions. New avenues for treatment. *Mol Psychiatry*. 2021;26(8):4004-4015. doi:10.1038/s41380-019-0540-z

69. McCutcheon RA, Weber LAE, Nour MM, Cragg SJ, McGuire PM. Psychosis as a disorder of muscarinic signalling: psychopathology and pharmacology. *Lancet Psychiatry*. 2024;11(7):554-565. doi:10.1016/S2215-0366(24)00100-7

70. Tarpey T, Petkova E. Modelling Placebo Response via Infinite Mixtures. *JP J Biostat*. 2010;4(2):161-179.

71. Kessels R, Mozer R, Bloemers J. Methods for assessing and controlling placebo effects. *Stat Methods Med Res*. 2019;28(4):1141-1156. doi:10.1177/0962280217748339

72. Fassi L, Hochman S, Daskalakis ZJ, Blumberger DM, Cohen Kadosh R. The importance of individual beliefs in assessing treatment efficacy. *eLife*. 2024;12:RP88889. doi:10.7554/eLife.88889

73. Zhang Z, Kotz RM, Wang C, Ruan S, Ho M. A Causal Model for Joint Evaluation of Placebo and Treatment-Specific Effects in Clinical Trials. *Biometrics*. 2013;69(2):318-327. doi:10.1111/biom.12005

74. Szigeti B, Nutt D, Carhart-Harris R, Erritzoe D. The difference between ‘placebo group’ and ‘placebo control’: a case study in psychedelic microdosing. *Sci Rep*. 2023;13(1):12107. doi:10.1038/s41598-023-34938-7

75. Huneke NT, Walsh AE, Brown R, Browning M, Harmer CJ. No evidence for an acute placebo effect on emotional processing in healthy volunteers. *J Psychopharmacol (Oxf)*. 2017;31(12):1578-1587. doi:10.1177/0269881117739552

76. Murphy SE, Downham C, Cowen PJ, Harmer CJ. Direct effects of diazepam on emotional processing in healthy volunteers. *Psychopharmacology (Berl)*. 2008;199(4):503-513. doi:10.1007/s00213-008-1082-2

77. Lahti AC, Weiler MA, Tamara M, Parwani A, Tamminga CA. Effects of Ketamine in Normal and Schizophrenic Volunteers. *Neuropsychopharmacology*. 2001;25(4):455-467. doi:10.1016/S0893-133X(01)00243-3

78. Leibold NK, van den Hove DLA, Viechtbauer W, et al. CO2 exposure as translational cross-species experimental model for panic. *Transl Psychiatry*. 2016;6(9):e885-e885. doi:10.1038/tp.2016.162

79. Baldwin DS, Hou R, Gordon R, Huneke NTM, Garner M. Pharmacotherapy in Generalized Anxiety Disorder: Novel Experimental Medicine Models and Emerging Drug Targets. *CNS Drugs*. 2017;31(4):307-317. doi:10.1007/s40263-017-0423-2

80. Garner M, Attwood A, Baldwin DS, James A, Munafò MR. Inhalation of 7.5% Carbon Dioxide Increases Threat Processing in Humans. *Neuropsychopharmacology*. 2011;36(8):1557-1562. doi:10.1038/npp.2011.15

81. Bailey JE, Kendrick A, Diaper A, Potokar JP, Nutt DJ. A validation of the 7.5% CO 2 model of GAD using paroxetine and lorazepam in healthy volunteers. *J Psychopharmacol (Oxf)*. 2007;21(1):42-49. doi:10.1177/0269881106063889

82. Huneke NTM, Cross C, Fagan HA, et al. Placebo Effects Are Small on Average in the 7.5% CO2 Inhalational Model of Generalized Anxiety. *Int J Neuropsychopharmacol*. 2024;27(4):pyae019. doi:10.1093/ijnp/pyae019

83. Freedman B. Equipoise and the Ethics of Clinical Research. *N Engl J Med*. 1987;317(3):141-145. doi:10.1056/NEJM198707163170304.