

Placebo response in depression

Shamsah B. Sonawalla, MD; Jerrold F. Rosenbaum, MD



With its naturally fluctuating course, depression is a highly placebo-responsive condition: mean placebo response rates in antidepressant clinical trials are 30% to 40%. We review the history and terminology of placebo and the proposed mechanisms underlying the placebo response, including the physician–patient relationship and biological, sociocultural, and treatment situation factors. We identify the predictors and patterns of placebo response in depressed patients, both within and outside of the clinical trial context, and differentiate between true drug response and placebo pattern response. We discuss the strategies now being advanced to minimize the placebo response given the increased placebo drift reported in recent trials, and the ethical guidelines governing placebo administration. Potential areas for future research include the identification of biological markers of placebo response, such as functional neuroimaging and quantitative electroencephalography, the development and testing of more sophisticated, alternative research designs, and the design of valid biological tools to assess antidepressant efficacy.

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Address for correspondence: Shamsah B. Sonawalla, MD, Department of Psychiatry, Massachusetts General Hospital, 15 Parkman Street, WAC 812, Boston, MA 02111, USA
(e-mail: ssonawalla@partners.org)

Author affiliations: Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Mass, USA

Since depression, like chronic pain and anxiety, is characterized by fluctuations in course and spontaneous improvements and features “distress” as a key symptom, it is not surprising that it is also a placebo-responsive condition.¹ The mean response rates for placebo in antidepressant clinical trials range between 30% and 40%.^{2,3} In this review, we describe the historical views of placebo, the associated terminology, the proposed mechanisms underlying placebo response, and the predictors of placebo response in depressed patients. We further discuss patterns of placebo response in depression, placebo response in antidepressant clinical trials, the suggested strategies to minimize it, and the ethical issues associated with the administration of placebo.

History

The word placebo derives from the Latin word *placere*, which literally means “to please.”^{4,5} First used in Western medicine in the 1700s, the term placebo was defined in the 1785 edition of *Motherby's New Medical Dictionary* as a “commonplace method or medicine.”⁶ In 1811, Hooper's *Medical Dictionary* defined placebo as “an epithet given to any medicine adopted to please rather than to benefit the patient.”⁶ In 1958, the term appeared in the *English Psychiatric Dictionary* as “a preparation containing no medicine (or no medicine related to the complaint) and administered to cause the patient to believe that he is receiving treatment.”⁴ Shapiro suggested that most of the practice of medicine until the 17th century was an exploitation of placebo effects.^{5,6}

Definitions and terminology

Shapiro defined a placebo as “any therapy or component of therapy that is deliberately used for its nonspecific, psychological, or psychophysiological effects, or that is used for its presumed specific effect, but is without specific activity for the condition being treated” and

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also noted that “specific activity is the therapeutic influence attributable solely to the contents or processes of the therapies rendered [and] should be based on scientifically controlled studies.”^{6,7}

Brody defined placebo as “a form of medical therapy, or an intervention designed to simulate medical therapy, that at the time of use is believed not to be a specific therapy for the condition for which it is offered and that is used either for its psychological effect or to eliminate observer bias in an experimental setting; [or is] a form of medical therapy now believed to be inefficacious, though believed efficacious at the time.”⁸

Placebo effect

There is a distinction between a “true placebo effect” versus a “perceived placebo effect.”⁹ A true placebo effect depends on factors such as the attitudes of the physician and the patient, the suggestibility of the patient, and the type of treatment.⁹ A perceived placebo effect results from the influence of such factors as the natural course of the disease, the tendency of most measures of biological variation to regress toward the mean, and unidentified parallel interventions (eg, patients receiving extra attention during a clinical trial, becoming more aware of the problem, and taking actions that influence outcome).⁹

Placebo response

Placebo response represents the apparent improvement in the clinical condition of patients randomly assigned to placebo treatment (eg, a change within the placebo group from pretreatment to posttreatment).¹⁰ This change may be due to an effect of placebo, but not necessarily so, as in the case of spontaneous remission.⁴ Also, a substantial portion of the placebo response (the improvement that occurs in placebo-treated patients) is a result of the passage of time and the associated regression to the mean, expected fluctuations in illness course, and spontaneous remission.¹

Hrobjartsson and Gotzsche conducted a systematic review of clinical trials in which patients were randomly assigned to either placebo or no treatment.¹¹ This review included three clinical trials of depression in a total of 152 patients. A placebo was either pharmacological (eg, a tablet), physical (eg, a manipulation), or psychological (eg, a conversation). The authors found that, compared with no treatment, placebo treatment had no significant

effect on binary outcomes, regardless of whether these outcomes were subjective or objective. For the trials with continuous outcomes, placebo offered a beneficial effect, but the effect decreased with increasing sample size, indicating a possible bias related to the effects of small trials. The pooled standardized mean effect was significant for the trials with subjective outcomes, but not for those with objective outcomes. In trials involving treatment of pain, however, placebo did have a beneficial effect, as indicated by a reduction in the intensity of pain. The authors concluded that there was little evidence in general that placebos had powerful objective clinical effects. Although placebos had no significant effects on objective or binary outcomes, they had possible small benefits in studies with continuous subjective outcomes and for the treatment of pain. They suggest that outside the setting of clinical trials, there is no justification for the use of placebos as therapeutic agents. Considering the limitations of the review, the authors note that they did not assess the effect of the patient–provider relationship, and hence could not rule out a therapeutic psychological effect of this relationship, which may be largely independent of any placebo intervention.¹¹ The physician–patient relationship, however, is an important factor, especially in the treatment of illnesses such as depression.

Nocebo effect

Nocebo literally means “I shall harm.” Nocebo responses are adverse reactions to incidental aspects of treatment; they are extremely common in patients and in healthy volunteers in drug trials, and have important implications for noncompliance with treatment.⁶ Negative expectations of treatment or transient adverse effects yielding conditioned responses to incidental factors may lead to severe adverse effects.¹²

Proposed mechanisms underlying placebo response

Several mechanisms underlying a placebo response have been proposed. These include the factors detailed below.

Sociocultural factors

These include belief systems held by patients and/or physicians/therapists, which may follow from ideas inconsistent

with Western scientific methods and thought. Historically, medical anthropologists, psychiatrists, and psychologists have studied magical, nonlogical beliefs, considering them to be the key to placebo mechanisms. When a treatment lacks a logical theory of action, the efficacy attributed to it derives from culturally derived beliefs.^{6,13}

Factors associated with the treatment situation

Features of the treatment situation that are likely to contribute to the placebo response include a thorough evaluation, an explanation for distress, an expert healer, a plausible treatment, prior experience, expectation of improvement, a healer's commitment, enthusiasm, and positive regard, and an opportunity to verbalize distress.¹ Ranga emphasizes the importance of understanding that placebo does not really mean that no treatment was delivered.¹⁴ A component of treatment includes all the contact between the investigator's team and the patient, and suggests that this itself may have a therapeutic effect. Thus, the myth that placebo suggests no treatment is not entirely accurate; placebo basically implies no specific treatment.¹⁴ Some researchers have suggested that expectations based on pill size, type, color, and number affect outcome.^{15,16} Multiple pills, larger pills, and capsules have been shown to exert stronger placebo effects than single pills, smaller pills, and tablets. Also, pill color may carry a suggestion of potency and effect without prior cues.⁶

Physician–patient relationship

The doctor–patient relationship confers significant potency to the placebo response.^{17,18} A good doctor–patient relationship may help increase compliance and maximize placebo effects, while minimizing nocebo effects.¹⁹ Transference, suggestion, guilt reduction, persuasion, cognitive dissonance, and conditioning may have a role in the placebo effect.⁴ Positive physician attitudes and good communication skills have been reported to lower malpractice claims.¹⁹ Physician conviction regarding a drug's potency conveys a powerful expectation to a hopeful patient and may be an important “mediator of therapeutic effectiveness.”^{17,18}

Biological factors

The opioid system has been implicated in placebo effects.²⁰ Sheline and colleagues also suggest that

platelet serotonin binding characteristics, but not patient clinical characteristics, may distinguish depressed patients who do and do not respond to placebo.²¹ Mayberg and colleagues reported on a patient with post-stroke depression, following an infarction of the left basal ganglia. The patient's depression remitted during a 6-week, double-blind trial, during which he received placebo. Cortical serotonin-receptor binding was measured using ¹¹C-*N*-methylspiperone and positron emission tomography (PET) before and after the trial. The authors found that cortical serotonin-receptor binding increased in the left temporal cortex by more than 25% during the trial (ie, with placebo in this case). The authors conclude that the change in serotonin-receptor binding and its relationship to the improvement in mood observed in this patient are consistent with a correlation between serotonin-receptor binding in the left temporal cortex and severity of symptoms of depression.²²

Patterns of response in depression

A challenge in the treatment of depressive disorders is to differentiate treatment-specific response from spontaneous remission or nonspecific response. Pattern analysis has identified two types of response patterns to antidepressants: true drug response (TDR) and placebo pattern response (PPR).²³ TDR is characterized by a 2-week delay in onset followed by persistent improvement and PPR is characterized by early, transient, or nonpersistent improvement.^{23,24} Patients with major depressive disorder who have PPR are more likely to experience relapse compared with those with TDR, and antidepressant continuation appears to be no more effective in preventing depressive relapse than placebo.²³

Biological and cognitive differences in depressed patients with TDR and PPR

We conducted two studies at our center assessing differences in biological and cognitive factors between patients with TDR and PPR. In the first study, we evaluated the relationship between basal ganglia choline-creatine ratios, as measured by *in vivo* localized proton magnetic resonance spectroscopy (MRS), among patients with TDR compared with those without TDR following antidepressant treatment.²⁵ We found a significant difference in the degree of change from baseline to week 8 in choline-creatine ratios between the TDR

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group (N=8) and the PPR/nonresponse group (N=7); patients with TDR had a 20% increase in choline-creatine ratios, and those with PPR/nonresponse had a 12% decrease in choline-creatine ratios. Our data suggest that TDR to fluoxetine treatment in depression may be associated with an increase in choline-creatine ratios in the basal ganglia.²⁵

In the second study, we examined the relationship between cognitive factors and TDR (N=134) and PPR (N=66) to antidepressant treatment.²⁶ We found that after 8 weeks of treatment with an antidepressant, patients with PPR had significantly lower scores on the Perceived Stress Scale (PSS) and the Beck Hopelessness Scale (BHS) ($P<0.001$ and $P<0.05$, respectively) compared with patients with TDR. Our preliminary data suggest that significant changes in cognitive/psychological factors accompany PPR with antidepressant treatment and differentiate it from the TDR pattern.

Predictors of placebo response in depression

Illness factors

Predictors of placebo response in depression include a relatively short illness duration, a precipitating event, depression of mild-to-moderate severity, and a good response to previous antidepressant treatment.²⁷ Bialik and colleagues²⁸ found that the placebo response rate was the highest for women with a single episode of depression (66.7%) and lowest for women with recurrent depressive episodes (13.3%). These authors also found that, among patients experiencing their first episode, placebo responders had lower Hamilton Rating Scale for Depression (HAM-D) total scores at baseline and lower ratings of psychomotor retardation than nonresponders. For patients with a recurrence of an episode, placebo responders had lower baseline ratings of somatic anxiety.²⁸ Stewart and coworkers²⁹ found that the presence of a psychosocial stressor in the context of a depressive episode predicted a higher rate of placebo response. Brown and colleagues²⁶ noted that improvement with placebo was associated with a relatively short illness, a precipitating event, depression of only moderate global severity, and a good response to previous antidepressant treatment.

Assessments of severity of depression can predict placebo response; mild depressive episodes are more likely to

respond to placebo (rates as high as 70%) compared with severe depressive episodes (rates closer to 30%).^{1,30,31} The chronicity of the presenting episode is associated with a low placebo response rate.¹ Depressed patients who are ill for more than a year have lower placebo response rates (usually less than 30%), and those with depressive episodes of less than 3 months' duration have placebo response rates closer to 50%.³² Klein proposed that the relationship between placebo response and episode duration suggests that some of the placebo response may merely represent spontaneous remission.³³

Patient factors

Patient demographic and personality attributes do not consistently distinguish placebo responders and nonresponders in antidepressant trials.³⁴ Fairchild and colleagues³⁵ have proposed that the tendency to respond while receiving placebo should be viewed as normally distributed in the population: a smaller percentage of patients never respond while receiving placebo, another subset consistently do, and the majority of patients respond under specific conditions of disease or treatment.

Biological factors

The dexamethasone suppression test is the only biological variable that has been reported to predict placebo response.¹ Patients who suppress cortisol secretion in response to dexamethasone are found to be more likely to respond to placebo (approximately 50%) than non-suppressors (approximately 10%).¹

A recent study used quantitative electroencephalography (QEEG) to examine brain function in 51 depressed subjects receiving either an antidepressant (fluoxetine or venlafaxine) or placebo, and sought to detect differences between medication and placebo responders.³⁶ The study assessed both QEEG power and cordance, a new measure that reflects cerebral perfusion and is sensitive to the effect of antidepressant medication. There were no significant pretreatment differences in clinical or QEEG measures among the four outcome groups. Placebo responders, however, showed a significant increase in prefrontal cordance starting early in treatment that was not seen in medication responders (who showed decreased cordance) or in medication nonresponders or placebo nonresponders (who showed no significant change). The authors conclude that "effec-

tive” placebo treatment induces changes in brain function that are distinct from those associated with antidepressant medication. If these results are confirmed, concordance may be useful for differentiating between medication and placebo responders.³⁶

Placebo response in antidepressant clinical trials

Double-blind, randomized, placebo-controlled, clinical trials are recognized as the standard for establishing a drug’s safety, efficacy, and dose–response relationships for most major psychiatric disorders.³⁷⁻³⁹ Justifications for using placebo control groups include the fluctuating natural course of most psychiatric illnesses, the wide variability in placebo response across patient groups, and the influence of psychosocial factors on treatment response.³⁷ The response rates for placebo in antidepressant clinical trials range from 30% to 40%.^{2,3} Among patients with milder forms of depression and a relatively short episode duration, the placebo response rate is close to 50% and often indistinguishable from the response rate to antidepressants.² Recent antidepressant clinical trials have seen a “placebo drift” in that the placebo response rate is higher than in trials conducted 30 years ago, with a slight lowering of the response to antidepressants and a substantial narrowing of the drug–placebo difference.¹ Possible explanations for this observation include the fact that patient samples in recent trials are more likely to have milder forms of depression than those in the older studies. Also, since the newer antidepressants have fewer side effects than the older ones, recent studies are more truly double-blind; hence a positive bias toward the active agents on the part of both patients and clinicians has less influence over the outcome.¹ Rush⁴⁰ points out that individuals most likely to enter placebo-controlled trials may well be those most likely to respond to placebo, ie, patient self-selection is a key factor (into or out of placebo-controlled studies). He further explains that individuals most likely to agree to participate in placebo-controlled trials are those who have less severe, less complicated, less chronic, less disabling, and less treatment-resistant illnesses, hence those more likely to respond to placebos.⁴⁰

Strategies to minimize placebo response in antidepressant clinical trials

The substantial placebo response in depression reduces

the power of clinical trials and confounds treatment decisions and the assessment of new therapies.⁴¹ The development of new antidepressant drugs is complicated by high placebo response rates, since new drugs are required to demonstrate superior effectiveness to placebo or else they may be abandoned.^{42,43} Due to the paucity of objective outcome measures in depression, it is particularly difficult to prove efficacy that is superior to placebo. Thase⁴⁴ argues that since a third of antidepressant published trials fail to demonstrate efficacy, new strategies are needed to systematically reduce the sources of variance. He suggests recruiting subjects with moderate and severe illnesses, and implementing a 4-week lead-in phase during which subjects receive psychoeducation about handling depression; these are both steps aimed at reducing the number of patients still likely to respond to placebo once the proper trial has begun.⁴⁴ The 1- to 2-week, single-blind, placebo run-in period prior to randomization was designed to lower the placebo response in clinical trials; however, unfortunately, it provides no advantage in acute-phase efficacy trials.³ Some researchers suggest that a variable duration, double-blind, placebo run with raters who are independent of the design may reduce placebo responses both in the week after randomization and over the course of the study.⁴⁵ Using raters who can reliably administer specific instruments over time, and assessing interrater reliability over sequential assessments with other sites is important.¹⁰

Researchers have proposed potential alternatives to the use of a placebo control group. These include add-on studies, variable dose designs, establishing a priori threshold effect sizes with an active comparison control, and comparisons with historical controls.⁴⁶ Although add-on designs do not obviate the need for placebo, they eliminate placebo monotherapy. However, substantially larger study populations are needed for sufficient power to establish a drug–placebo difference because of the contribution of the primary agent(s) to both drug and placebo effects. Also, the use of add-on designs could influence the duration of the trial.⁴⁶ Variable dose designs allow for the possibility of establishing dose–response relationships; however, it must be clearly specified in the informed consent process that some doses may not exert a therapeutic effect. Data regarding effect sizes of drug versus placebo suggest that establishing a threshold effect size that an investigational drug must reach or exceed in a trial with an active con-

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trol might obviate the need for a placebo control; however, the possibility of a robust placebo effect in both treatment groups still cannot be excluded from such trials. Comparing the efficacy results of an investigational agent with historical data from previous trials has been suggested as an alternative to placebo control groups. The limitations of this approach include variability in rating scales used, changes in diagnostic criteria, and different patient demographic and clinical characteristics over time.⁴⁶

Some researchers suggest switching from placebo trials to comparison trials as an alternative.⁴⁷ A double-masked discontinuation trial with the new treatment as an add-on or as a monotherapy has also been suggested as an alternative.⁴⁰ Having established add-on efficacy against placebos, and/or discontinuation efficacy in an add-on or monotherapy trial, one could then proceed to the classic randomized, double-masked, placebo-controlled trial with the new treatment as a monotherapy versus placebo. During the course of the add-on or discontinuation trials, one could attempt to identify specific clinical, historical, demographic, or other features that appear to be associated with a high likelihood of drug response.⁴⁰ Brown, however, suggests that the initial treatment for selected depressed patients should be 4 to 6 weeks of placebo. Patients so treated should be informed that the placebo pill contains no drug but that this treatment can be helpful.³²

Ethical issues

Several ethical issues have been debated regarding the use of placebo controls in clinical trials when effective treatments are available.⁴⁸ Andrews emphasizes that placebo-controlled trials are only appropriate when there is no existing treatment for a disorder, otherwise comparison trials are indicated.⁴¹ Cochrane argues that no new treatments should be introduced into medicine unless they have been shown, in randomized controlled trials, to be superior, or equivalent, to existing treatments, and cheaper or safer.⁴⁹ The Declaration of Helsinki appears to restrict the use of placebos if an effective treatment is known.⁵⁰

Quitkin and colleagues systematically reviewed the methodological issues raised by such critiques, and concluded that, despite the large response in the placebo group, antidepressants produce specific additional benefit.⁵¹ Khan and colleagues found that in clinical trials,

depressed patients who were assigned to placebo were not at a greater risk for suicide or suicide attempts than those assigned to active treatment.⁵² Miller⁵³ suggests that four ethical standards must be satisfied for the legitimate use of placebo controls in clinical research: (i) placebo-controlled trials should have scientific and clinical merit; (ii) risks should be minimized and justified by the anticipated benefits of generating clinically relevant scientific knowledge and the expected benefits, if any, to individual research subjects; (iii) patient volunteers should give informed consent; and (iv) investigators should offer short-term individualized treatment optimization to patient volunteers after completion of research participation. Miller⁵³ further concludes that if scientific progress leads to the development of psychiatric medications that are highly effective with minimal side effects, placebo-controlled trials that withhold such treatment will become more difficult to justify. In that case, the use of placebo-controlled trials will have helped produce improvements in treatment that obviate the need and rationale for continued use of this research design.

Clinical applications

Understanding the origin and mechanisms of placebo response in depression has clinical implications. As Andrews points out: “The size of response to the placebo might well be a bane to researchers and to the drug industry, but properly handled, it is surely a boon to busy clinicians and their patients.”⁷⁴¹ Considering that depression is the fourth major illness in the world in terms of disease burden,⁵⁴ many patients and clinicians benefit from any tool that maximizes therapeutic outcome.

Dago and Quitkin⁴ suggest that, before deciding on whether or not to prescribe an antidepressant, clinicians should monitor the elements of the physician–patient relationship that may affect the patient’s expectation or hope of being helped by the medication. These authors also recommend that a clinician follow those patients who demonstrate an early clinical improvement without antidepressant treatment until they have two unimproved weeks, and only then prescribe an antidepressant. Systematic identification of a true drug response pattern in patient samples, moreover, may help identify the mechanism of action of medication and help clarify ambiguous results derived from exclusive reliance on end-point analyses in clinical trials.²⁴ In addition, differ-

entiation of TDR from PPR may help guide clinical decisions regarding long-term antidepressant treatment and the approach to depressive relapses and recurrences.^{24,55}

Future research

Potential areas for research include identification of biological markers of placebo response in depression, and developing and testing more sophisticated, alternative research designs in clinical trials. Development of valid biological tools to assess the efficacy of an antidepressant, eg, functional neuroimaging, could also help greatly toward minimizing placebo response.

Conclusions

Depression is a placebo-responsive condition and the mean response rates for placebo in antidepressant trials range between 30% and 40%. It is important to understand the differences between placebo response, placebo effect, and PPR. Biological and cognitive differences have been identified in patients with TDR versus those with PPR. Mechanisms proposed for placebo response in depression include sociocultural factors, factors associated with the treatment situation, the physician–patient relationship, and biological factors. Predictors of placebo response include duration and severity of the depressive episode, the presence of

a precipitating event, a good response to previous antidepressant treatment, and suppression of cortisol secretion in response to dexamethasone. Recent antidepressant clinical trials have seen a placebo drift, ie, a higher placebo response rate compared with those conducted earlier. Strategies suggested to lower the placebo response in antidepressant clinical trials include the use of alternative designs, such as add-on studies, variable dose designs, and discontinuation studies, establishing a priori threshold effect sizes with an active comparison control, and comparisons with historical controls. Ethical issues have been debated regarding the use of placebo controls in antidepressant clinical trials when effective treatments are available; it is recommended that clinical trials including a placebo should meet certain ethical standards. Clinical applications include monitoring placebo response to maximize therapeutic outcome, and differentiating TDR from PPR, and using it to guide clinical decisions regarding long-term antidepressant treatment. Identification of biological markers of placebo response, development and testing of more sophisticated, alternative research designs, and development of valid biological tools to assess the efficacy of an antidepressant are some potential areas for future research. □

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La respuesta al placebo en la depresión

Con su curso natural fluctuante, la depresión constituye una condición con una alta respuesta al placebo: las frecuencias promedio de respuesta al placebo en ensayos clínicos de antidepresivos son entre el 30% y el 40%. Nosotros revisamos la historia y la terminología del placebo y los mecanismos propuestos que subyacen a la respuesta al placebo, incluyendo la relación médico-paciente, los factores biológicos y socioculturales y las situaciones en que se da el tratamiento. Nosotros identificamos los predictores y patrones de la respuesta al placebo de los pacientes depresivos, ambos dentro y fuera del contexto de los ensayos clínicos, y diferenciamos entre la verdadera respuesta al fármaco y el patrón de respuesta al placebo. Nosotros discutimos las estrategias que se están desarrollando actualmente para minimizar la respuesta al placebo, dado el aumento en la varianza del placebo que ha sido referido en ensayos recientes y las orientaciones éticas que rigen la administración del placebo. Las áreas potenciales para futuras investigaciones incluyen la identificación de marcadores biológicos de la respuesta al placebo, tales como neuroimágenes funcionales y electroencefalografía cuantitativa, el desarrollo y evaluación de diseños de investigación alternativos más sofisticados y el diseño de herramientas biológicas válidas para evaluar la eficacia de los antidepresivos.

La réponse placebo dans la dépression

L'évolution fluctuante par nature de la dépression en fait une maladie dont la réponse au placebo est importante : les taux moyens de réponse dans les études cliniques sur les antidépresseurs se situent entre 30 et 40 %. Dans cet article, nous passons en revue l'histoire et la terminologie du placebo ainsi que les mécanismes proposés pour expliquer la réponse placebo, qu'il s'agisse des relations patient-médecin ou des facteurs biologiques, socioculturels et des caractéristiques de la conduite thérapeutique. Nous identifions les facteurs prédictifs et les types de réponse placebo chez les patients dépressifs, à la fois dans et en dehors du contexte de l'essai clinique et nous différencions les réponses au traitement réel des réponses au placebo. Nous discutons des stratégies proposées actuellement pour diminuer la dérive de la réponse placebo dont les taux augmentent régulièrement comme le montrent des essais récents, et nous discutons des recommandations éthiques sur les conditions d'administration du placebo. Les orientations potentielles de la recherche future sont l'identification des marqueurs biologiques de la réponse placebo, telles l'imagerie neurologique fonctionnelle et l'électroencéphalographie quantitative, le développement et la mise à l'épreuve de schémas de recherche alternatifs, plus sophistiqués, et de modèles d'outils biologiques valides afin d'évaluer l'efficacité antidépressive.

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