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COMMENTARY

Is placebo useful in the treatment of major depression in clinical practice?

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Background: For many years, placebo has been defined by its inert content and use in clinical trials. In recent years, several studies have demonstrated its effect in the treatment of major depression. The aim of this paper is to present the conclusions of recent meta-analyses of the placebo effect in major depression, to explain the mechanism by which placebo exerts its effect, and to discuss whether placebo can be used in the treatment of patients with major depression in clinical practice. Recent meta-analyses have demonstrated that the placebo effect is estimated to account for 67% of the treatment effect in patients receiving antidepressants, and furthermore that placebo is as effective as antidepressants in patients with mild to moderate major depression (reporting a Hamilton Depression Rating Scale score lower than 25), whereas placebo is less effective than antidepressants in severely depressed patients. However, several limitations make the translation of these conclusions into clinical practice impracticable. Clinicians should learn from the "placebo lesson" to maximize the nonspecific effects of treatment when they prescribe an antidepressant, particularly in less severely depressed patients, who show a higher placebo response in randomized controlled trials. This strategy can increase the antidepressant effect and may reduce nonadherence with treatment.

Keywords: placebo effect, major depressive disorder, subthreshold depressive disorder, antidepressants

Introduction

In recent years, the placebo effect had received increasing attention in the treatment of depressive disorders, given that data from randomized controlled trials (RCTs) suggest that the placebo effect is estimated to account for 67% of the treatment effect in patients receiving antidepressants.[1]

Data from other recent RCTs confirm the clinical meaningful effect of placebo in depressed patients, and have opened up a debate as to the usefulness of antidepressants. The present paper summarizes the recent data on the placebo effect in the treatment of major depression with the aim of evaluating whether placebo can also be used successfully in clinical practice.

Materials and methods

We search the MEDLINE/PubMed database for papers published in the English language between January 2007 and December 2012, using the terms "placebo OR placebo effect" AND "depression", AND "antidepressant". The search was limited to meta-analyses and reviews, and those judged not to be pertinent or less relevant were excluded. Reference lists of reviews and meta-analyses were also hand-searched for

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further relevant reports. Using this strategy, we identified 23 papers.

Discussion

Placebo effect in major depression

The placebo effect in the treatment of patients with major depression is supported by many placebo-controlled trials, in which the rate of patients with depression showing an improvement in symptoms was estimated to be about 30%.[2] In recent years, the magnitude of the placebo effect has been suggested to be clinically relevant, particularly in mildly to moderately depressed patients. A meta-analysis of 35 short-term RCTs submitted to the US Food and Drug Administration for regulatory approval (also including unpublished studies) found little evidence for the efficacy of antidepressants in patients whose depression was not severe, unless alternative treatments had failed to provide benefit.[3] This finding was confirmed in a recent meta-analysis of six RCTs, which demonstrated that the efficacy of antidepressants, compared with placebo, increases with the severity of depressive symptoms, being minimal or null in patients with mild or moderate depression and substantial in patients with severe depression.[4] The authors found that antidepressants were superior to placebo only in patients with a pre-treatment Hamilton Depression Rating Scale (HDRS) score higher than 24.[5] This result was recently confirmed by Leucht et al who analyzed the efficacy of amitriptyline compared with placebo in the treatment of major depressive disorder.[6]

However, the results of these studies were not unanimously accepted. The conclusion of Kirsch et al was criticized by Mathew and Charney chiefly for the use, as a measure of outcome, of the mean difference in HDRS between antidepressants and placebo at the end of the studies, rather than the more clinically meaningful response or remission rate, and for the potentially severe consequences of undertreating depressed patients using placebo (risk of suicide, disability, and familial, vocational, or social dysfunction).[3,7] A recent meta-analysis on the outcome of placebo versus antidepressants in RCTs concluded that drug-placebo differences may be improved by inclusion of fewer sites and subjects, and use of better quality control in diagnostic and clinical assessments.[8]

Moreover, the data from the above-mentioned meta-analyses are contradicted by the results of a review of 14 short-term RCTs conducted in the primary care setting, in which less severely depressed patients are usually treated. The review found a higher response/remission rate in patients treated with selective serotonin reuptake inhibitors or tricyclic antidepressants than in patients receiving placebo.[9]

Collected together, these data open a scientific and clinical debate concerning the treatment of mild to moderate forms of major depression, because: these accounted for 49% of all episodes of major depression;[10] mild severity (HDRS scores less than 22) was found in 71% of depressed outpatients seeking treatment;[11] and participation in RCTs of patients with milder, briefer, and more responsive forms of depression could have contributed to the two-fold increase in the placebo response observed in clinical trials conducted from 1980 to 2005.[1,12]

The aforementioned RCT data, even where contradictory and open to criticism, suggest that placebo seems to be as effective as antidepressants in the treatment of patients with mild to moderate depression, whereas placebo is less effective than antidepressants in the treatment of patients with severe depression. However, they leave unresolved the question of whether and how the patient with mild to moderate depression might be successfully treated with placebo in clinical practice.

Placebo effect in subthreshold depression

The advent of operational criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* and its subsequent editions for the diagnosis of major depression has brought patients with subthreshold major depression to clinical attention. Even though this approach was criticized for the risk of treating normal emotional states as illness and challenging the model's credibility, subthreshold major depression had received increasing attention, particularly in depressed patients with medical illness (eg, cardiovascular disease), for the recognized negative effect of depression on the outcome of medical conditions.[13–20] Moreover, subthreshold major depression can represent the residual symptoms of major depression, increasing the risk of recurrence, which needs to be adequately prevented. Therefore, in the conditions mentioned above, the treatment of subthreshold major depression has become a matter of clinical interest. Placebo is expected to exert a meaningful clinical effect in the treatment of such depressed patients, according to the point of view that the mild forms of major depression are responsive to placebo. A recent meta-analysis confirmed that there is no evidence of superiority for antidepressants compared with placebo in the treatment of patients with subthreshold major depression.[21] However, use of placebo in the treatment of subthreshold depression should be considered with caution in patients with severe medical illness and in patients with a history of severe

major depression, because placebo would be ineffective in these patients (see below).

How does placebo exert an antidepressant effect?

The placebo effect should not be confused with other causes of healing, such as spontaneous improvement, the Hawthorne effect (ie, the subject improves simply in response to the fact that she/he is being studied and not in response to any particular experimental manipulation), regression to the mean, patient or doctor evaluation bias, and possibly unidentified effects of cointervention.[22,23] The placebo effect can be defined as a biologic or psychologic response induced by administration of pills, liquids, or injections of substances without a specific effect in relation to the disease needing treatment.[24,25]

One of the more considered explanations of the placebo effect is the "expectation theory", which considers the placebo effect to be the result of the subject's expectation that a treatment will be effective for her/his illness.[26] This expectation is based on personal beliefs, previous experiences, conditioning, the context of treatment, and a positive relationship with the doctor.[27–31] Hence a better definition of placebo would be the one proposed by Brody, ie, "a change in patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacological or physiological property".[32]

The role of expectation in the placebo response is also demonstrated in RCTs. In a recent review of 90 clinical trials, which included patients with nonpsychotic unipolar depression, the placebo response was influenced by the probability of receiving an active treatment, and the placebo response rates were higher in RCTs using a three-arm design, with two groups receiving antidepressants and one group receiving placebo, than in RCTs using a two-arm design (one receiving antidepressants and one receiving placebo).[33] The opposite was observed for antidepressants, in that response rates to antidepressants were lower in studies including a placebo arm. Also, in a previous report, response rates to antidepressants were lower in placebo-controlled trials (46%) than in trials comparing the effect of two antidepressants (60%).[34] These studies suggest that the patient's expectation of receiving an antidepressant increases the placebo response, whereas the expectation to receive placebo decreases the response to an antidepressant.

Further, the investigator's expectations can be involved in the placebo effect, in that the increased placebo response observed from 1980 and 2005 in RCTs was found only in trials using rating scales completed by an observer and not in those using self-reported rating scales, suggesting that investigators tended to overestimate positive changes in patients, perhaps because enthusiasm about the efficacy of a new antidepressant can induce high expectations for improvement.[1]

Interestingly, expectation of improvement can play a role in treatment regardless of the type of treatment administered, as suggested by Miller and Colloca, who found that expectation-induced therapeutic effects could enhance the patient response to placebo and to pharmacologic and nonpharmacologic treatments.[35] Alleviation of demoralization might be a possible explanation for this effect, ie, if the patient accepts that her/his stressful condition is overwhelming their abilities to cope (demoralization) and decides to seek help, their demoralization improves and the condition ameliorates.[36] This mechanism might also be involved in the treatment of depressed patients, who are often demoralized. Demoralization can be viewed as a step in a sequence, starting with loss of interest and pleasure, and if the loss of pleasure and interest becomes pervasive, demoralization can follow.[37,38] Therefore, any kind of treatment (placebo, antidepressants, psychotherapy) alleviating demoralization can improve a depressive disorder to some extent.

Although there is a lack of data on the neurobiology of the placebo effect in depression, some authors have reported that placebo induces release of dopamine in the ventral striatum in patients with Parkinson's disease.[39] Interestingly, the amount of dopamine release was associated with the level of expectation.[40] It cannot be excluded that this effect could be also active when a placebo induces improvement in depressive symptoms, since a reward deficit mediated by dysfunction of the dopaminergic pathways is believed to be present in major depression.[41–43]

Is placebo useful in clinical practice?

Care provided in the clinical practice setting is significantly different from that in RCTs, so conclusions about the placebo effect derived from RCTs cannot be automatically transferred to treatment provided in clinical practice.

In clinical practice, many factors could reduce the placebo effect seen in RCTs, including: severity of illness, ie, patients with severe major depression (and suicide risk) are excluded from RCTs but need to be treated in clinical practice, so the severity of major depression influences the choice and setting of treatment; baseline patient characteristics, ie, in a naturalistic study, patients eligible for an RCT and patients not eligible differ significantly

on several baseline measures;[44] the context of treatment, ie, visits and evaluations are frequent in RCTs, and the increasing number of follow-up assessments enhances the placebo response, even though this effect is observed for antidepressants too,[45,46] and more time is dedicated to the patient at each visit so motivation is high, whereas comparable characteristics cannot be easily obtained in clinical practice; the role of patient and clinician expectations of a placebo effect, ie, the placebo effect is increased in RCTs due to the expectation to receive (patient) or to prescribe (doctor) an active treatment, whereas this situation is not yet feasible in clinical practice, due to the impossibility of prescribing a placebo without deception (see below);[34] the outcome of treatment, ie, the chance to respond to antidepressant treatment is better in patients enrolled in a RCT than in patients treated in clinical practice, as demonstrated in the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) naturalistic cohort for patients eligible for a RCT compared with patients not eligible, and by a recent review, in which the antidepressant efficacy estimates in RCTs were larger than those in observational studies.[47,48]

Among the above-mentioned variables, the condition which makes placebo clinically impractical, even in the treatment of patients with mild to moderate depression (the only patients who respond to placebo in RCTs), is the question of how to obtain from the patient an expectation to be treated with an active compound. The "watchful waiting" procedure is not comparable with administration of placebo, given that less expectation is created by this practice because no treatment is prescribed, and may even be detrimental to the patient.[49] The greatest barrier to use of placebo is its prescription without deception, since informing patients accurately that they are being given a placebo should prevent its effect. A possible solution is suggested by Kirsch: "if a convincing rationale can be presented, perhaps placebo can be prescribed openly without deception."[50] The method consists of telling the patients that placebo has been shown to be effective for their condition, that its effect is induced at least in part by a well-known mechanism (classical conditioning), and that for this reason, taking a placebo pill could work as a new treatment. This strategy ameliorates symptoms in patients with irritable bowel syndrome and its effect has been shown to be superior to no treatment and as large as that produced by commonly prescribed medication for the syndrome.[51]

Even though this strategy is interesting from a scientific point of view, its effect has not yet been evaluated in the treatment of patients with mild to moderate depression, and therefore it should not be recommended in clinical practice. Moreover, clinicians should keep in mind the following issues. All the international guidelines for treatment of major depression, even though recognizing the relevance of the placebo effect, do not recommend placebo (instead of antidepressants or psychotherapy) in the acute treatment of nonsevere forms or in the prevention of recurrence,[52–55] and there is evidence that placebo is not as effective as antidepressants in mildly depressed patients with medical comorbidity.[18] For example, in mildly depressed patients with myocardial infarction, the risk of cardiac death is reduced by use of a selective serotonin reuptake inhibitor, such as citalopram, but not by usual care or psychotherapy, suggesting that antidepressants have superior efficacy compared with alternative treatments in these patients.[56–58] In patients with subthreshold depression and a previous history of severe major depression (subthreshold depression being a risk factor for a new episode), placebo seems not to be as effective as antidepressants in the prevention of recurrence, and a recent guideline recommends use of antidepressants in these patients.[55]

Finally, from a cost-benefit point of view, the widespread use of generic antidepressant formulations reduces the cost of antidepressant therapy, and thereby also the attractiveness of less costly alternatives (placebo) for health services, which may be concerned with better expenditure of resources.

For the reasons outlined above, placebo is not recommended in the treatment of major depression in clinical practice, because of patient peculiarities, frequent medical comorbidities, and for now, the impossibility of administering it without deception.

Conclusion

Even though contradictory and criticized, the RCT data suggest that placebo is as effective as antidepressants in the acute treatment of patients with mild to moderate depression, but is less effective than antidepressants in the treatment of severely depressed patients. Even though these findings deserve attention due to the possible clinical implications, their translation into clinical practice is impracticable for the following reasons: patients seeking treatment in daily practice are different from those enrolled in RCTs; the inefficacy of treatment, other than antidepressants, in preventing the negative effect of mild-moderate depression on medical comorbidity (which suggests placebo may be ineffective where comorbidity is concerned); and the impossibility of administering placebo without deception, even though a

strategy to overcome this barrier has been proposed but not as yet tested in depressed patients.[51]

However, clinicians should learn from the "placebo lesson" that expectation is a relevant mechanism that should be utilized and optimized in clinical practice, given that the nonspecific effects of treatment can also act during prescription of an active treatment. Therefore, clinicians should maximize the nonspecific effects of treatment when they prescribe an antidepressant, particularly for less severely depressed patients, who show a higher placebo response in RCTs. This strategy can increase the antidepressant effect and perhaps also reduce nonadherence with treatment, which is estimated to be around 40% or even higher, especially in outpatients with mild to moderate depression treated in clinical practice.[49]

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