REVIEW

Is placebo effective? If yes, what this could mean?

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Abstract

Results of meta-analyses focused on estimation of placebo efficacy have been contradictory. The problem of large-scale meta-analyses in detecting placebo effects might be due to lumping together rather disparate health disorders, placebo-responders with nonresponders. In contrast, studies focused on a certain disorder and on individual subjects were able to detect placebo effects. The most convincing evidence for placebo effects have been brought by studies focused on biological correlates of these effects and those using modern imaging techniques. Placebo appears to be effective: (1) in some disorders (such as some depressive or pain conditions), (2) in some individuals ("placebo-reactors") and (3) in some context (e.g. in a favourable patient-doctor relationship). Placebo effects have significant implications for medical practice (e.g. it is important to inform the patient that he/she will obtain an effective treatment) and for medical research (e.g. they call attention to some limits of current EBM methodology). They have also general and philosophical implications (e.g. they call attention to the limits of knowledge which can be gained objectively in a group of individuals). Conclusion: placebo can be effective, but only under certain conditions. Placebo effects have important implications for medical practice, research and generally.

Introduction

According to some meta-analyses of a great number of clinical trials placebo may appear to be powerless (Hrobjartsson & Gotzsche 2001; Kienle & Kiene 1997). On the other hand, studies focused on biological effects of placebo in individual persons bring opposite evidence(Benedetti *et al* 2005; Wager *et al* 2004). Is placebo effective? If yes, when? If placebo is effective, what this could mean (for medical practice, research, or generally)? This short paper attempts to find answers to some aspects of these questions.

Is placebo effective?

Results of meta-analyses

Results of meta-analyses focused on estimation of placebo efficacy have been contradictory. In 1955, Henry K. Beecher published the classic work entitled "The Powerful Placebo."(Beecher 1955). The author claimed that in 15 trials with different diseases, 35% of 1082 patients were satisfactorily relieved by a placebo alone. The Beecher's article was in 1997 re-analysed and "no evidence was found of any placebo effect in any of the studies" used by Beecher (Kienle & Kiene 1997). The authors of this re-analysis concluded that the presumed placebo "effects" might had been produced by spontaneous improvement, fluctuation of symptoms, regression to the mean, additional treatment, conditional switching of placebo treatment, scaling bias,

irrelevant response variables, answers of politeness, experimental subordination, conditioned answers, neurotic or psychotic misjudgment, psychosomatic phenomena, misquotation, etc.

One of the most frequently cited meta-analysis on this subject by Hrobjartsson and Gotzsche published in New England Journal of Medicine analysed 114 clinical trials comparing placebo with no treatment in 40 diverse clinical conditions (such as hypertension, asthma, hyperglycemia, alcohol abuse, ileus, infertility, marital discord, prostatism, pain, Parkinson's disease, schizophrenia, etc.) in over 8,000 patients (Hrobjartsson & Gotzsche 2001). They found little evidence in general that placebos had powerful clinical effects.

However, a re-analysis of some Hrobjartsson's and Gotzsche's studies showed that when disorders were amenable to placebos and the design was adequate to detect the effects, the placebo effect was robust there (Wampold *et al* 2005). Hrobjartsson and Gotzsche refused this and characterized B. E. Wampold et al.'s conclusion as powerful spin (Hrobjartsson & Gotzsche 2007). In addition, they extended and updated their earlier systematic review with 52 new randomized trials comparing placebo with no treatment (Hrobjartsson & Gotzsche 2004). They found no evidence of a generally large effect of placebo interventions in this newer study. A possible small effect on patient-reported continuous outcomes, especially pain, could not be clearly distinguished from bias there. However, even meta-analyses generally regarded as the top of evidence-based medicine (EBM) are not immune to bias, for example in selection and transformation of data as was shown by these authors (Gotzsche *et al* 2007).

While meta-analyses evaluating conglomeration of very heterogenous clinical conditions have problems in detecting placebo effects, those focusing on particular kind of disorders appear to be more successful. For example The Oxford league table of analgesic efficacy which is based on meta-analyses of a great number of clinical trials of analgesics versus placebo in acute pain indicates that placebo produced at least 50% pain relief in 18% of over 10,000 placebo treated persons (Moore *et al* 2003; Oxford league table of analgesics in acute pain, 2009). Pain appears to be particularly sensitive to placebo effects, at least to some extent, as is discussed below. Placebo was reported to have a beneficial effect in 27 trials involving the treatment of pain even in the original Hrobjartsson's and Gotzsche's study, although these authors discounted effects of placebo in pain in their later publications (Hrobjartsson & Gotzsche 2006).

Depression appears to be another disorder which is sensitive to placebo effects, at least at its moderate level. Placebo was nearly as effective as antidepressants at moderate levels of initial depression in a recent analysis of the Food and Drug Administration database (Kirsch *et al* 2008). Drug-placebo differences increased as a function of initial severity reaching conventional criteria for clinical significance only for patients at the upper end of the very severely depressed category. Antidepressant efficacy was attributed to decreased responsiveness to placebo among very severely depressed patients. An earlier study using Food and Drug Administration database did not find differences in rates of suicide and attempted suicide among the placebo- and antidepressants-treated groups (Khan *et al* 2000).

Results of studies focused on biological effects of placebo in individual persons

Perhaps the most convincing evidence for placebo effects have been brought by studies focused on biological correlates of these effects and those using modern imaging techniques of placebo effects in individual persons.

It was shown already more than 30 years ago that placebo analgesia could be blocked by the opioid antagonist naloxone, which indicated an involvement of endogenous opioids (Levine *et al* 1978). Placebo can reduce pain by both opioid and non-opioid mechanisms (Benedetti *et al* 2005; Benedetti 2008).The cholecystokinin antagonist proglumide enhanced placebo analgesia in a human model of experimentally induced ischemic pain (Benedetti 1996). This potentiation occurred only in placebo responders, but not in non-responders. Peak B endorphin levels were elevated in cerebrospinal fluid following placebo administration in chronic pain patients but only in those who experienced pain relief after placebo, not in those patients who fail to experience such relief (Lipman *et al* 1990).

Quite impressive and frequently cited are several studies demonstrating placebo effects on activation of some brain structures detected by modern imaging techniques such as PET (positron emission tomography) and fMRI (functional magnetic resonance imaging).

Using PET, it was found that both opioid and placebo analgesia are associated with increased activity in the rostral anterior cingulate cortex (which is presumably involved in higher order cognitive networks and endogenous opioid systems). These findings indicate a related neural mechanism in placebo and opioid analgesia (Petrovic *et al* 2002). Another PET study revealed significant placebo-induced activation of mu-opioid receptor-mediated neurotransmission in rostral anterior cingulate, the dorsolateral prefrontal cortex, the insular cortex, and the nucleus accumbens. Regional activations were paralleled by lower ratings of pain intensity, reductions in its sensory and affective qualities (Zubieta *et al* 2005). In two functional magnetic resonance imaging (fMRI) experiments, it was found that placebo analgesia was related to decreased brain activity in pain-sensitive brain regions, including the thalamus, insula, and anterior cingulate cortex, and was associated with increased activity during anticipation of pain in the prefrontal cortex (Wager *et al* 2004). Authors of this study state that their "findings provide strong refutation of the conjecture that placebo responses reflect nothing more

than report bias" claimed by authors of one of the meta-analyses (Hrobjartsson & Gotzsche 2001).

Brain imaging techniques demonstrated biological effects of placebo not only in pain but also in other disorders and even in belief and empathy. These studies have aroused a considerable interest as well. Positron emission tomography provided in vivo evidence for substantial release of endogenous dopamine in the striatum of Parkinson's disease patients in response to placebo (Fuente-Fernandez *et al* 2001). An fMRI study showed that religious believers were able to down-regulate the perceived intensity of a noxious stimulation (evaluated according to activation of the ventrolateral prefrontal cortex and other brain areas) when they were presented with a religious image (Wiech *et al* 2008). In the same group, presentation of a non-religious image had no effect on the perception of pain. Non-religious control subjects did not show a modulation of pain during presentation of either of the pictures. Another functional imaging study focused on effects of empathy with pain in loved persons on activation of brain structures. Bilateral anterior insula, rostral anterior cingulate cortex, brainstem, and cerebellum were activated when subjects received pain and also by a signal that a loved one experienced pain. The insula and cingulate cortex activation correlated with individual empathy scores (Singer *et al* 2004).

In summary, placebo seems to act, but only under certain conditions. The problem of large-scale meta-analyses in detecting placebo effects might be due to lumping together rather disparate health disorders, placebo-responders with nonresponders. In contrast, studies focused on a certain disorder and on individual subjects were able to detect placebo effects. Moreover, the obligatory design of the controlled trials lowers the placebo effect (e.g. by telling subjects who take part that they may receive the active or inactive treatment).

When is placebo effective?

Placebo appears to be effective: (1) in some disorders (mostly in those markedly influenced by psychological factors, such as some depressive or pain conditions), (2) in some individuals ("placebo-reactors") and (3) in some context (e.g. a favourable patient-doctor relationship). Placebo effects may have further limitations – they may be transitory (Craggs *et al* 2008).

What are implications of placebo effects?

Implications for medical practice

Some held view that „Outside the setting of clinical trials, there is no justification for the use of placebos."(Hrobjartsson & Gotzsche 2001) because „Clinical placebo interventions are unethical, unnecessary, and unprofessional."(Hrobjartsson 2008). On the other hand, some practitioners argue that the use of placebos is sometimes justified because it will do no harm and may do some good, but others warn that this may decrease credibility in health providers(Wikipedia Placebo 2009).

In my opinion the discussion should focus on utilization of conditions which enhance placebo-like effects of treatment rather than on the use of placebo as such. Placebo effects can be desirable in clinical practice to optimize the total therapeutic effect. Psychological theories explain that enhanced expectation and motivation and classical conditioning of the patient determine the degree of the placebo effect. These directly influence neurobiological systems such as the endogenous opioids. The context effect of each therapeutic intervention should be maximized towards an improved therapeutic effect (Oeltjenbruns & Schafer 2008).

One of the specific advices for clinical practice which can be derived from the research of placebo effects is to inform the patient that he/she will obtain an effective treatment. Response expectancies have been proposed as the major determinant of placebo effects. When the patient is completely unaware that a treatment is being given, the treatment is less effective than when it is given overtly. In one study thoracotomized patients were treated with buprenorphine infusions together with a basal intravenous infusion of saline solution. The patients were allocated into three groups. The first group was told nothing about any analgesic effect (natural history). The second group was told that the basal infusion was: either a powerful painkiller or a placebo (classic double-blind administration). The third group was told that the basal infusion was a potent painkiller. It was found that the double-blind group showed a reduction of buprenorphine requests compared to the natural history group. However, this reduction was even larger in the deceptive administration group (Colloca *et al* 2004; Pollo *et al* 2001).

Placebo effects might be increased when the drug has an excellent reputation and is given by an authority. However, the latter attribute may be in contradiction with the currently emphasized and advocated need of partnership between the patient and doctor.

Implications for medical science

There is general agreement that placebo control groups are an important tool for distinguishing placebo effects from true biological/pharmacological effects of a particular treatment in clinical trials. Government regulatory agencies approve new drugs only after tests establish not only that patients respond to them, but also that their effect is greater than that of a placebo.

The effects of placebo can be estimated only as the difference between placebo and no-treatment in randomized trials (Hrobjartsson 2002). Sometimes it could be important to pre-screen potential test populations, and treat those manifesting a placebo-response as a special group, or remove them altogether from the test population (Wikipedia Placebo 2009).

In my opinion, one of the major implications of the meta-analyses which failed to detect placebo effects (mentioned above) is calling attention to some limits of current EBM methodology. If an effect of a particular treatment has not been proved in a particular meta-analysis, does it mean that this treatment is always ineffective? Meta-analyses (regarded for the top criterion of EBM) are a very useful and important tool in separating facts from myths but their current methodology have limits due to some factors such as: (1) focusing on the group means rather than on individuals (their differences/characteristics), (2) lumping together highly mixed group of conditions and (3) ignoring the context of treatment (e.g. the patient-doctor relationship).

General and philosophical implications

Placebo effects depend on higher order cognition (Higher Nervous Activity – Activitas Nervosa Superior) and seem to be specific for humans. They involve phenomena and concepts such as belief, hope, positive personal relationship, trust which are seldom considered and investigated in experimentally oriented biomedical sciences. Yet, they may have biological manifestations as shown above.

Research on placebo effects calls attention to the limits of knowledge which can be gained objectively in a group of individuals. This way of gaining knowledge is very important and useful but it can lead to a fallacy that something which cannot be objectively evoked and detected cannot exist. From this assumption proceed therapeutic guidelines, are determined financial covers of medicines from health insurance. This is the rational and useful approach. But we should accept/be aware of the fact that for a particular person it can be meaningful something which can be known only by him/her and which resists to scientific knowledge. This is not a sufficient reason, however, for indulging oneself in any treatment which is not provable by EBM.

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