

Does the model of additive effect in placebo research still hold true? A narrative review

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Summary

Personalised and contextualised care has been turned into a major demand by people involved in healthcare suggesting to move toward person-centred medicine. The assessment of person-centred medicine can be most effectively achieved if treatments are investigated using ‘with versus without’ person-centredness or integrative study designs. However, this assumes that the components of an integrative or person-centred intervention have an additive relationship to produce the total effect. Beecher’s model of additivity assumes an additive relation between placebo and drug effects and is thus presenting an arithmetic summation. So far, no review has been carried out assessing the validity of the additive model, which is to be questioned and more closely investigated in this review.

Initial searches for primary studies were undertaken in July 2016 using Pubmed and Google Scholar. In order to find matching publications of similar magnitude for the comparison part of this review, corresponding matches for all included reviews were sought.

A total of 22 reviews and 3 clinical and experimental studies fulfilled the inclusion criteria. The results pointed to the following factors actively questioning the additive model: interactions of various effects, trial design, conditioning, context effects and factors, neurobiological factors, mechanism of action, statistical factors, intervention-specific factors (alcohol, caffeine), side-effects and type of intervention.

All but one of the closely assessed publications was questioning the additive model. A closer examination of study design is necessary. An attempt in a more systematic approach geared towards solutions could be a suggestion for future research in this field.

Keywords

Placebo, additive effect, person-centred medicine, review

Introduction

According to the integrative approach to health, medicine should not only focus on disease and illness but also on the consequences of disease and its contextual factors, as well as the positive aspects of health, such as, for instance, quality of life.¹

Personalised and contextualised care is becoming a major demand and suggested paradigm shifts are starting to move toward person-centred medicine: from disease to patient to person. This is mainly due to the fact that a more individual-based or person-centred as well as a more integrative medicine is increasingly demanded by patients² as well as leading academic institutions such as, for instance, the Institute of Medicine; the Consortium of Academic Health Centers for Integrative Medicine, and the Integrative and Personalised Healthcare at the University Witten/Herdecke in Germany.

While ‘personalised’ medicine is mainly oriented at the molecular specifications of individuals in diagnostics, treatment and prevention, the term ‘person-oriented’ medicine refers to a more comprehensive and humanistic account of individuals in diagnosis, treatment and prevention, including biological, psychological, social, spiritual and relational aspects of health care.³ The Institute of Medicine defines patient-centred care as: ‘Providing care that is respectful of and responsive to individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions’.⁴ This includes, for instance, a better doctor–patient relationship/alliance, a regard for concrete patient needs and expectations and the context under which healthcare is delivered. In fact, there are indications for better health outcomes, when all or even only some of these issues are taken into consideration.^{5,6}

In the field of evidence-based medicine, it is necessary to investigate the efficacy of person-centred and integrative interventions in order to assess which specific contribution such types of interventions have to offer. Methodologically, this can best be achieved if treatments are investigated using ‘with versus without’ person-centredness or integrative study designs and thus the specific, additive benefit of person-centredness and integration can be statistically calculated. However, this assumes that the components of an integrative and/or person-centred intervention have an additive relationship to produce the total

effect. This is also the assumption of the gold-standard randomised clinical trial.

Randomised, double-blind, placebo-controlled clinical trials are currently held to be the best way to demonstrate the clinical effectiveness of drugs.⁷ Its methodology relies on the method of comparison of standardised group intervention through which the observed outcome difference between groups (drug/intervention versus placebo) can be attributed to the pharmacological effect of the drug/intervention being tested.⁸ The rationale behind this is the 'additive' model which was first described by Beecher in his influential explicit assumption of an additive relation between placebo and drug effects, 'The placebo effect of active drugs is masked by their active effects... The total 'drug' effect is equal to its 'active' effect plus its placebo effect' (quotes in the original).⁹ What was later called and is now referred to as 'Beecher's model of additivity', thus presents an arithmetic summation. The anesthesiologist Henry K. Beecher (1904–1976) tended to only include pills in his definition and went on to describe a placebo intervention as a dummy or placebo tablet with the same inert pharmacological substances, for instance, lactose, saline solution or starch and further remarks that the reasons these are given differ substantially but with two principal functions: to distinguish pharmacological effects from the effects of suggestion and to obtain an unbiased assessment of the results of experiment.⁹ At a later point in time, the emergence of the biopsychosocial model of Engel,¹⁰ taking into account the patient, the social context in which that person lives and the complementary system devised by society to deal with the disruptive effects of illness, that is, the physician role and the healthcare system. Its scope is determined by the historic function of the physician to establish whether the person soliciting help is 'sick' or 'well' and if sick why and in which ways and then to develop a rational programme to treat the illness and restore and maintain health.

However, this additive model can be questioned in the event of statistical interactions between the pharmacological and the placebo effects. Such statistical interactions can be presented in a statistical model in which the combined effect of several factors is the sum of the effects produced by each of the factors in the absence of the others. For example, if one factor increases risk by a% and a second factor by b%, then the additive combined effect of the two factors is (a + b) %. Evidence in different domains has shown that the placebo effect can influence the clinical effect of the active principle.¹¹ For instance, two decades ago already Kleijnen et al. rebutted the idea of the additive model when they reviewed the evidence

of placebo effects' interactions with medicine in double-blind clinical trials.¹² Their results suggested that 'specific as well as non-specific effects are sometimes synergistic, and others antagonistic'. The researchers conclude in their paper that the implicit additive model of the randomised clinical trials is therefore too simplistic. Furthermore, they recommend that all interventions ought to be tested within their optimal context.

Kirsch also asked the question whether drug and placebo effects in depression are additive.¹³ He argues that data on drugs other than antidepressants indicate that placebo and drug effects are not always additive. However, because drug effects are estimated as the difference between the drug response and the placebo response, the assumption of additivity is implicit in conventional clinical trials. Furthermore, he suggests that if effects from/of antidepressant medication are found not to be additive, alternative designs will be needed to assess drug effects.

In its end result, combining the effect of an intervention with that of the placebo effect, the actual effect can either be arithmetically additive or not. However, for basic assumptions – specifically for that of randomised clinical trials – this arithmetic additivity is of importance. When investigating clinical studies that have looked at the placebo effect phenomenon, it becomes evident that, due to context-dependent variability of the placebo effect, an arithmetic additivity/summation of various context – and intervention factors – is rather unlikely, which in turn should have consequences for the interpretation of randomised clinical trials.¹⁴ A variety of studies have refuted the hypothesis that 'drug' effects and placebo effects are necessarily additive, but instead have suggested that mutually exclusive mechanisms may be operating in the two arms of a randomised clinical trial.^{15–17}

The design of the randomised clinical trial cannot take into account other, more individual-based factors which play a defining role in the extent of the placebo response, using the placebo effect.

So far, no review has been carried out assessing the validity of the additive model.

This review intends to provide an overview of this criticism and is posing the question whether the model of additivity in placebo research is similar to what Beecher proposed 60 years ago; it is critically discussed and debated in the field of healthcare. It was precisely the large amount of literature on placebo since 1955 which made us want to categorise and summarise some of this vast sea of publications. This we have done in a previous publication (Katja Boehm, Bettina Berger, Thomas Ostermann, Peter Heusser. Placebo effects in medicine: A

bibliometric analysis. *JRSM Open* July 2016 vol. 7 no. 7. Published July 1, 2016, doi: 10.1177/2054270416643890). What we attempted to show in this follow-up publication was to pick one issue which we have repeatedly come across during our bibliometric analysis, which is to assess how other researchers have dealt with the validity of the assumption of additivity of the placebo model, which specifically assumes an additive relation between placebo and drug effects and is thus presenting an arithmetic summation.

Thus, the objective of this study is to systematically retrieve the available literature on clinical or experimental studies and reviews that explicitly deal with the additive model, to compare them with similar publications and to reflect on their content in relation to argumentation for or against the additive model in placebo research.

Methodology

In order to attain publications eligible for inclusion in this review, a search strategy was determined and followed. Preliminary searches in Pubmed aimed at both identifying existing systematic reviews and assessing the volume of potentially relevant studies. Search terms were kept very broad, included different types of population, intervention, outcomes and study designs. Boolean AND was used.

Initial searches for primary studies were undertaken until July 2016 using the electronic, medical database Pubmed and Google Scholar. However, this was not deemed sufficient. Thus, other sources of evidence included reference lists from relevant primary studies and review articles and the Internet. Experts and researchers working in the area were contacted and asked whether they knew of any unpublished results. No exclusions based on language were applied.

Search terms

Search terms consisted of the phrases ‘placebo AND additive model’.

Study selection criteria

Inclusion criteria for study selection were clinical studies, experimental studies as well as reviews which were published after 1955 and which would discuss the placebo effect or placebo response in relation to the so called ‘additive model’ and either try and dispute or agree with it. It was deemed of necessary importance that the paper referred to the phenomenon of additivity.

Excluded reviews were clinical studies which used the term ‘additional’ merely in a statistical sense, not referring to placebo effects or clinical studies that were merely referring to additive drug effects but which were also identified during the search due to their inclusion of a placebo arm.

Included reviews were narrative without exception, meaning they were carried out far from systematically and therefore no measurement tool to assess the quality of the included reviews could be applied.

Study selection process

Initially, selection criteria were interpreted liberally. Unless studies identified by electronic searches could be clearly excluded based on titles and abstracts, full copies of the article were obtained. Final inclusion/exclusion decisions were made after the full texts had been retrieved.

In order to find matching publications for the comparison part of this review, corresponding matches for all included reviews were found using Pubmed by

1. searching in the same journal as original publication,
2. using the first MeSH term as an identifier and
3. having been published in the same year.

If nothing in the same year or journal was available, we identified the next best, e.g. a year or two later, or, for instance, a publication in another BioMedCentral journal.

Results

The results from the Pubmed literature search resulted in 110 hits. Google Scholar showed about 80,000 hits. For the latter, abstracts of the Google Scholar results were read, and the inclusion criteria applied up to the point where meaningful findings thinned out, which was after page 19 of the Internet display.

General overview

A total of 26 reviews^{13,15–41} and 3^{26,27,42} clinical and experimental studies fulfilled the inclusion criteria. Clinical entities of the included publications were not always clear-cut as the authors of the reviews often generalised their findings and opinions. Controlled studies investigating how placebo effects can be used as additive effects in clinical practice are still scarce. The experimental studies all included healthy subjects.^{26,27,42} One review specialised in neurological disorders such as Parkinson.³⁸ Two of

them focused on depression.^{13,40} Of those that specified them, discussed or applied interventions included acupuncture,^{32,41} psychotherapy,²⁴ surgery,²⁵ caffeine^{13,23} and pain killer (saline).¹⁹ Included publications critically assessed the additive model to some extent and results pointed to the factors described in the following section, all but one¹⁵ of which are questioning the additive model. These were categorised into the following: interactions of various effects, trial design, conditioning, context effects and factors, neurobiological factors, mechanism of action, statistical factors, intervention-specific factors (alcohol, caffeine), side-effects and type of intervention. The comparing publications found no critical debate regarding the placebo effect, leave alone the additive effect of the placebo phenomenon (see Table 1). In the following section, we will discuss the following 15 reviews which critically examine the above mentioned additive effect.

General publication topic: 1. Interactions of effects

Researchers suggest that the placebo effect associated with the simple act of ingesting a pill (either placebo or verum) may possibly potentiate the actual physiological effect of the drug (positive interaction).¹⁸

Placebo effect could diminish the physiological response to the drug, especially in patients with a strong placebo effect (negative interaction).¹⁸ Researchers suggest that the extent of such interactions may also depend on the study design (parallel vs. cross-over) and that such interactions may jeopardise the randomised clinical trial if they are ignored in the statistical analysis.¹²

Other research teams suggest an alternative to the additive model: the interactive model, which assumes that drug-specific effects may interact with the placebo responses to result in unequal placebo effects in the two study groups.²¹

Psychological and physical effects may interact with one another, and thus researchers suggest that treatment components may have a more complex relationship.²⁵ They further elaborate that, for instance, an optimistic outlook may enhance the efficacy of a physical effect, and a physical effect may buoy a patient's optimism that a treatment is in fact working. They concluded that this multiplicative relationship between treatment components would tend to undercut the ability of a trial to focus on particular components in isolation.²⁵

One review concluded that controlled studies investigating how placebo effects can be used as additive effects in clinical practice are still scarce and warned that taking advantage of placebo effects as

additive effects in clinical practice should not be confounded with deception.³⁹ The research team suggested that it is possible to benefit from placebo effects in clinical practice by using them as effects additive to those of documented and effective treatments and conclude that the total effect of a documented treatment will partly depend on how well the placebo effects have been activated.³⁹

A review team providing a description of a conceptual framework assessing the causes of placebo response in clinical trials in order to develop strategies for minimising placebo response in clinical trials, maximising placebo response in clinical practice and talking with depressed patients about the risks and benefits of antidepressant medications suggested that the simplest and most common way to understand the nature of a combination of expectancy-based placebo effects, effects of the therapeutic setting, measurement factors and natural history factors is to assume that medication effects are additive with placebo response (i.e. placebo response is the same in the medication and placebo groups).⁴⁰ However, they found that there is little or no evidence in the pharmacologic treatment of major depressive disorder to prove that medication effects and the placebo response are additive. The team concluded that it appears likely that the specific effect of a medication is at least partially additive with that of the placebo response, although its precise magnitude cannot be determined without knowing whether there are significant medication effect by placebo response interactions.

General publication topic: 2. Trial design

In regard to trials design, various researchers believe that the extent of interactions may depend on the design selected for the randomised clinical trial (e.g. parallel-group vs. cross-over design).¹⁸ A number of various consequences of different types of study designs on placebo effect are claimed to be expected.¹⁸ For instance, a standard two-group randomised clinical trial investigating the placebo effect can be expected to show that the placebo effect is not measured directly and that the comparison with baseline values gives inaccurate estimates of the effect. Additionally, it is to be expected that in other two-group and standard three-group randomised clinical trials, the placebo effect is underestimated, whereas in multigroup randomised clinical trials, it is potentially overestimated.

One argument against the additive model is incomplete blinding with many drugs, so that patients/subjects may be aware of the experimental condition by taking adverse events into account.¹⁹ This awareness,

the researchers suggest, would increase the placebo response in the drug group and reduce the placebo response in the placebo group.

Other researchers suggest that studies using the balanced placebo design would be of help, as these have been shown to diminish the ability of subjects to discover the condition to which they have been assigned.²⁰

General publication topic. 3: Conditioning responses

Hypothetically speaking, some researchers suggest that the placebo effect could be conditioned in either direction by the presence of an active treatment,¹⁸ which would be considered a statistical interaction, but the causal link would be in the opposite direction. For example, the magnitude of the placebo response may vary according to the circulating concentration of the active drug. Researchers of one study investigating whether stimuli associated with the use of caffeine (i.e. smell, taste) elicited a conditioned increase in arousal showed a non-significant tendency towards an additive effect of the conditioned arousal on the unconditioned arousal to caffeine as seen in some dependent variables.²⁶ In a study investigating the development of autoimmune disease in female, New Zealand hybrid mice was dramatically modified by classical conditioning of immunosuppression.⁴³ Groups of animals received each week a solution of sodium saccharin (conditioned stimulus). One group of conditioned animals received an injection of cyclophosphamide (the unconditioned stimulus) after half of the weekly occasions when they received the saccharin solution. The rate of development of proteinuria and mortality were significantly retarded in these conditioned mice relative to untreated controls and non-conditioned animals that received unpaired treatment with saccharin and cyclophosphamide.

General publication topic. 4: Content effects/factors

In laboratory research, a number of experimental designs have been employed that may help to identify and characterise predictors of the placebo response in the future. Some of these models have already been tested in laboratory settings, while others are based on theoretical considerations and wait for their empirical approval. Some reviews, for instance, discuss the fact that as opposed to clinical trials, experimental designs allow control over some of the factors that are believed to drive the placebo response, e.g. the wording and timing of information provided,⁴⁴

the gender and social status of the experimenter and the subject,⁴⁵ their emotional state⁴⁶ and psychological and genetic traits.^{19,47,48}

Other researchers remark that under conditions of high placebo response rates (such as in depression, functional disorders, pain), meta-analyses and re-analyses of trial data have identified some factors that contribute to the placebo response, e.g. lower symptom severity at study onset^{49–52} or improvement of symptoms during drug-free run-in.^{20,50,51}

Some researchers argue that treatment components may have a more complex than additive relationship (multiplicative relationship between treatment components), e.g. an optimistic outlook may enhance the efficacy of a physical effect, and a physical effect may buoy a patient's optimism that a treatment is in fact working.²⁵

General publication topic. 5: Neurobiological factors/mechanism of action

Placebo is different from specific treatment with a prefrontal top-down influence on opioid-receptor-rich rostral anterior cingulate cortex in pain studies⁵³ and doubts about the validity of the additive model derive from neurobiological evidence.^{20,53} Researchers demonstrated that separate mechanisms have to account for the placebo response in an (open) drug trial (with an opioid agonist) and following application of placebo in an expectancy trial. While the drug caused greater activation than placebo in the rostral anterior cortex, placebo caused a greater increase in the lateral orbitofrontal and the ventrolateral prefrontal cortex; both, however, were effective in reducing experimental pain.

There also seems to be evidence showing that placebos and antidepressants, while exerting nearly equal benefits, exhibit different effects on the brain.^{24,54–56}

Others claim that the effect of a treatment (vis-à-vis the natural course of a disorder) may be due to the physiochemical properties of the characteristic ingredient entirely, or this effect may be larger than the difference between the treatment and placebo outcomes.²⁴ This may be so in the case where the treatment and placebo have equivalent outcomes, and the treatment is beneficial because of the physiochemical ingredients and the placebo because of hope, expectation, or re-moralisation. It has also been suggested that the placebo effect may increase active drug terminal half-life, which would be a novel mechanism of placebo action and may be due in part to modulation of the bioavailability of the active drug.²⁷

General publication topic: 6. Statistical factors

Researchers who developed a theoretical statistical modeling approach proposed to differentiate between four virtually exclusive types of participants in placebo-controlled trials⁵⁷ rather than using the conventional separation in drug responders/drug non-responders and placebo responders and non-responders. Patients who would respond only with drug, patients who would respond only with placebo, patients who would respond both with drug and placebo ('always responder') and patients who would not respond to drug and placebo ('never responder').²⁰

There exists a basic assumption that minimising placebo responses per se would improve the assay sensitivity. However, other associations between the size of placebo effects and the potential to detect significant drug-placebo differences are possible under certain circumstances.¹² Some researchers hypothesise that a defined window representing an optimised consideration of placebo mechanisms in clinical trial designs could exist, which could facilitate the detection of drug efficacy. Accordingly, both over-enriched paradigms (activating many placebo mechanisms) and impoverished study designs (with very limited placebo mechanisms) could hinder the detection of specific treatment effects and thereby impede drug discovery.²¹

Others remark that the underlying hypothesis that the placebo response is equal in size irrespective of whether an active drug or a placebo was given (also known as the assumption of additivity) has never been thoroughly tested.^{15,22}

When answering the questions whether the likelihood of receiving an active treatment affect may affect the placebo response, some evidence for a dependency of the placebo response on the likelihood of receiving active treatment derives from a recent paper by Lidstone et al.⁵⁸ who claim that the clinical response to varying likelihood of active treatment showed maximal response for 50% and 75% chances of receiving active treatment compared to 25% and 100%. Some clinical data also suggest that the number of study arms in a trial, e.g. with various dosages of the drug against placebo, codetermines the size of the placebo and the drug response.²² In two meta-analyses of depression trials,^{59,60} it was shown that the lower the likelihood of receiving active treatment (as compared to placebo), the lower the response to placebo and to drug. Similar findings were made for migraine⁶¹ and for schizophrenia treatment⁶²: with trial designs that randomised 50% of patients to either drug or placebo (called 1:1 ratio trials here), the placebo response would be lower compared to trials with two or more drug arms and higher numbers of patients assigned to

active treatment compared to placebo (called 2:1 or $\geq 2:1$ ratio trials) in trials with parallel group design.

Some evidence from comparative effectiveness research trials suggests an increase of the placebo response without being able to control for it.²² For instance, Rutherford et al.⁴⁰ compared the efficacy of various antidepressants in 48 placebo-controlled studies with patients treated to the efficacy of the same drugs with 42 comparative effectiveness research studies. They found on average a 15% higher response rate of the drugs in the comparator trials that they attributed to expectancy responses, meaning that patients knew they would receive an active treatment anyway. Since the average placebo response in the placebo-controlled trials was 35%, they calculate a total of 50% placebo response in comparator trials.

Placebo responders seem to react or not capriciously⁶³ and for the same disease (peptic ulcer disease) but in other patients the placebo effect can vary between 0% and 100%, when compared with identical drugs.^{17,64,65}

Some researchers even suggest we are dealing with an 'efficacy paradox'⁶⁶ since some treatments may fail to prove superiority above placebo even though their total effects are of clinical relevance and exceed the effect achieved by standard care as has been shown recently in two large acupuncture trials.^{15,67,68}

Many of the elements of the healthcare encounter (characteristic elements: specific factors which are distinct but not divisible as well as incidental elements: placebo, non-specific such as empathy and focused attention) that are categorised as incidental in the context of drug trials are integral to complex non-pharmaceutical interventions. For instance, the use of placebo- or sham-controlled trial designs will not therefore detect the whole characteristic effect and may generate false-negative results.¹⁶

Intervention-specific factors

Alcohol. Drug and placebo responses are not always additive. Alcohol and stimulant drugs, for example, produce at least some drug and placebo effects that are not additive. Placebo alcohol produces effects that are not observed when alcohol is administered surreptitiously, and alcohol produces effects that are not duplicated by placebo alcohol.^{23,69} A meta-analysis on the subject showed that alcohol expectancy had strong effects on relatively deviant social behaviours and minimal effects on non-social behaviours. Alcohol consumption showed the opposite pattern of effects. The principal effects associated with alcohol expectancy involved increased alcohol

consumption and increased sexual arousal in response to erotic stimuli.

Caffeine. Research showed that the placebo and pharmacological effects of caffeine are additive for feelings of alertness but not for feelings of tension and similarly mixed results have been reported for other stimulants.^{23,70,71}

Placebo effects may vary considerably both between treatment arms and across studies.¹⁵ For example, it has been suggested that there is mounting evidence that an increased likelihood to receive active treatment (expectation) is associated with better outcome in the respective placebo groups, thereby potentially affecting conclusions about the efficacy of active treatment.^{59–61,72}

One randomised clinical trial assessing the interaction between drug and placebo effects in 180 adults who were randomised to caffeine (300 mg) or placebo groups concluded that drug and placebo effects of a medication may be less than additive, which would influence the interpretation of clinical trials.²⁷

Side-effects. Studies with participants diagnosed with depression that used an ‘active’ placebo (containing atropine), which mimics some of the side-effect profile of the drug and thus may help to counteract any potential bias, increased the response in the placebo group in comparison with an inert placebo that does not exhibit side-effects, as a meta-analysis of trials comparing placebos versus antidepressants for depression showed.^{15,73}

Type of intervention. Finally, it has been found that physical placebos, such as for instance sham acupuncture, are associated with larger placebo effects than pharmacological placebos.^{15,74–77} For instance, one study comparing a sham acupuncture device with placebo pills for arm pain due to a repetitive strain injury showed that the sham device had greater effects than the placebo pill on self-reported pain and severity of symptoms over the entire course of treatment but not during the two-week placebo run in.⁷⁷ Furthermore, a review assessing the effect of placebo acupuncture over no-treatment suggested a simple model incorporating the placebo and nocebo effects and concluded that the current additive model incorporating the placebo and nocebo effects is the simplest form.⁴¹ Nonetheless, the review suggests that this model reveals that these two effects can play important roles in determining the effect of placebo acupuncture over no-treatment and that in some cases, the effect of placebo acupuncture over no-treatment has been found to be above zero, thus resulting in significance of the conventional placebo or nocebo effects.

Discussion

In recent years, there has been accumulating evidence indicating that the basic assumptions that placebo effects in the placebo group are identical to the placebo effects in the drug group and that both combine in an additive manner may not be true under all conditions. Indeed, it is claimed that placebo responses can differ between drug groups and placebo groups,⁷⁸ and thus the components of an integrative/person-centred intervention have an additive relationship to produce the total effect has been challenged during the past few decades.

Statement of principal findings and future research

This review aimed to assess the validity of the additive model in a plethora of specifically selected publications and to reflect on their content in relation to argumentation for or against the additive model in placebo research. It was not our intention to systematically gather solutions for an alternative opposing the additive model but only to summarise approaches found in the investigated literature. Future research in this field could attempt a more systematic approach geared towards solutions, for instance, to identify opportunities to integrate more contextual factors into study designs, to think about the relevance they might have for study outcomes and to investigate how far they influence each other.

Our results showed that all but one²⁴ included publication were questioning the additive model. Interactions of various effects, trial design, conditioning, context effects and factors, neurobiological factors, mechanism of action, statistical factors, intervention-specific factors (alcohol, caffeine), side-effects and type of intervention were all bringing forth arguments against the simplistic model of additivity.

Hypotheses in this field are expressed high and low. Regarding the interaction of effects, one team of researchers suggest that the placebo effect associated with the act of ingesting a pill may possibly potentiate the actual physiological drug effect or that the placebo effect could possibly diminish the physiological response to the drug, especially in patients with a strong placebo effect. Furthermore, it is being proposed that the result of psychological and physiological effects interacting could result in the treatment components interacting and thus a more complex, multiplicative relationship than a merely additive one is established.

Regarding the trial design, one issue is the incomplete blinding of trial participants and even more so the fact that the placebo effect cannot be measured

directly in the standard two-arm randomised clinical trial.

Regarding the conditioning of responses, it is suggested that the placebo effect could be conditioned in either direction by the presence of an active treatment, but that the causal link would then be in the opposite direction of the outcome.

Regarding the content effects/factors, it has been recommended apply experimental as opposed to clinical research designs in the future of placebo effect research. This is due to the fact that experimental designs allow to control over some of the factors that are believed to drive the placebo response such as the wording and timing of information provided, the gender and social status of the experimenter and participants, their emotional state and psychological and genetic traits. Furthermore, under conditions of high placebo response rates, meta-analyses and re-analyses of trial data have identified some factors (lower symptom severity at study onset, improvement of symptoms during drug-free run-in) that can certainly contribute to the placebo response.

When investigating neurobiological factors which could explain the mechanism of action of the placebo effect, it has been suggested that the effect of a treatment may be due solely to the physiochemical properties of the characteristic ingredient. This effect may then be larger than the difference between the treatment and placebo outcomes. In the specific case of antidepressants, a variety of studies suggest that while exerting nearly equal benefits, placebos and antidepressants often exhibit different effects on the brain. Finally, placebo is different from specific treatment with a prefrontal top-down influence on opioid-receptor-rich rostral anterior cingulate cortex in pain studies which also challenges the additive model.

Proposed solutions and meaning of the review

Taking a more statistical approach to the issue of the additive model in placebo research, it was found that the distribution of the placebo effect between treatment and placebo group is being questioned and a new 'growth mixture model' is introduced in which placebo responders are equally and fairly distributed amongst various study arms.⁷⁸ Growth mixture modeling has the potential of uncovering important information about classes of responders and non-responders in clinical trials extending existing models to longitudinal settings where not only the end point outcome is considered but the trajectory throughout the trial.

Similarly, the suggested 'interactive model' assumes that drug-specific effects may interact with

the placebo responses to result in unequal placebo effects in the two study groups.

Alternatively, one research team developed a theoretical statistical modelling approach proposed to differentiate between four virtually exclusive types of participants in placebo-controlled trials (patients who would respond only with drug, patients who would respond only with placebo, patients who would respond both with drug and placebo ('always responder') and patients who would not respond to drug and placebo ('never responder')) rather than using the conventional separation in drug responders/drug non-responders and placebo responders and non-responders. This is also referred to as the 'balanced placebo design' and is an experimental method created to simultaneously evaluate expectancy and drug effects.

The review has indicated a strengthening of the existing perception that patients are providing various assumptions and requirements for an intervention. However, the fact that this factor can strongly influence the efficacy of the drug as well as that of the placebo effect was only investigated or even implied in only very few studies, for instance, in cases where patient expectation can influence both.

Limitations of this review

No grey literature or conference proceedings were searched for relevant studies. Additionally, as this was a narrative review, not all relevant literature was included and discussed but instead only that literature was selected which was deemed most relevant to the focus. Furthermore, the inclusion of a diverse number of study designs and patient populations is likely to introduce potential for unmeasured confounding or bias.

Conclusion

All but one of the closely assessed publications was questioning the additive model. Factors such as interactions of various effects, trial design, conditioning, context effects and factors, neurobiological factors, mechanism of action, statistical factors, intervention-specific factors (alcohol, caffeine), side-effects and type of intervention (acupuncture) were brought forth as arguments against the simplistic model of additivity.

Declarations

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Guarantor: PH.

Contributorship: Substantial contributions to the conception or design of the work (PH, KB); or the acquisition (KB), analysis (BB, KB), or interpretation of data for the work (KB, BB, UW, PH) AND drafting the work or revising it critically for important intellectual content (KB, BB, UW, PH); AND final approval of the version to be published (KB, BB, UW, PH); AND reaching an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved was carried out involving all 4 co-authors (KB, BB, UW, PH).

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