Impure placebo as an unsound concept and other problems in the paper by Howick et al.

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Howick et al. have reported the findings of a survey that addressed the use of placebos among primary care practitioners in the United Kingdom. (1) They adopted methodology similar to that used in previous studies performed in other countries; however, the use of this approach also means that they repeated the conceptual confusion of the previous surveys. (2,3,4) Therefore the findings are not useful.

First, although the authors acknowledge the conceptual problems related to placebos and placebo effects, they fail to consider the fundamental importance of these problems in their paper. They write for example: "*... placebos are often characterized as inactive and nonspecific when in fact they can be active, and have specific effects, especially for relieving pain*." The essential difference between "giving a placebo" and "the placebo effect" (3,4) is not considered in their paper.
By definition, a "placebo" means an inert substance. (5) The "placebo effect" is produced by other factors involved, such as expectancy, behavioral conditioning and the quality of the patient–physician relationship, (6) but not by the inert placebo. Inert substances and methods cannot have "specific" – or "unspecific" – effects by themselves. Because of the misleading nature of the term "placebo effect", other terms have been proposed to describe the phenomenon in clinical practice, including "care effect", (3) "contextual healing", (7) and "meaning response". (8)

Second, the authors wrote that they "*adopted a pragmatic approach and asked physicians whether they used various treatments described as placebos in other similar surveys*." They justified this approach by claiming that their "*approach has the advantage of being useful: patients, doctors, and policy makers care more about whether particular treatments are effective and ethical than whether these treatments carry the label 'placebo'*". What the authors did, however, was to survey the frequency of the usage of placebos. Frequency of usage does not tell us anything about effectiveness, and it cannot act as a guide for policy makers about whether the "use of placebos" should be increased or decreased.

Third, the authors introduced a novel concept "ethical placebo" but did not elaborate it in any respect. At the end of their paper, they concluded that "*further investigations are warranted to develop ethical and cost-effective placebos*." Given that, by definition, a "placebo" is inert, (5) it is not clear what the authors mean with their comment. Concealed use of inert substances or methods is deceiving and unethical. For example, the Council on Ethical and Judicial Affairs of the American Medical Association states that it "*may undermine trust, compromise the patient–physician relationship, and result in medical harm to the patient*". (9)

A few studies on the open-label use of placebos have indicated that a beneficial response is not necessarily limited to settings in which patients are deceived. (10,11,12) However, open-label use of pure placebos remains a special case, and no general recommendations can yet be given. Problems related to so-called impure placebos are described below.

Fourth, the only findings of the survey that make any sense are the figures describing the use of "pure placebos". However, even in this respect the findings leave many questions open. The authors wrote that pure placebos mean "*interventions such as sugar pills ... or saline injections without direct pharmacologically active ingredients for the condition being treated*." The questionnaire asked "*respondents to note how frequently (if at all) they used placebo interventions*". According to the results, 12% of the respondents reported using pure placebos at least once in their career. It is not clear what the term "using" covered. Did the respondents mean 1) writing a formal prescription for a pure placebo without informing the patient that the physician believed it to be pharmacologically ineffective, 2) giving the patient pure placebos directly from the physician's office, 3) verbally suggesting that the patient might test a treatment the physician considered ineffective, or 4) allowing the patient to use, for example, alternative medicine treatments that the physician considered useless. All of these four options are very different types of situations, and some are clearly unethical, whereas some are less so. (2) Furthermore, even though 12% of the respondents reported using pure placebos at least once in their career, only 0.9% reported using them frequently. Since the use of pure placebos implies the misleading of patients, and misleading patients is unethical, (9) we conclude that less than 1% of general practitioners in the UK are frequently unethical in this sense.

Fifth, the authors adopted the concept "impure placebo" uncritically from earlier research, and they ignored the confusion created by the use of this concept in empirical studies. (2) They defined impure placebos as "*substances, interventions or 'therapeutic' methods which have known pharmacological, clinical or physical value for some ailments but lack specific therapeutic effects or value for the condition for which they have been prescribed*". They gave examples of impure placebos, such as positive suggestions, probiotics for diarrhea, antibiotics for suspected viral infections, off-label uses of potentially effective therapies, conventional medicine whose effectiveness is not evidence-based, non-essential physical examinations, and non-essential technical examinations of the patient (blood tests, X-rays). Their list had a few more items, and, at the bottom of Table 2, they gave 11 more items that they classified as "impure placebos".

We cannot see any justification for classifying all the preceding examples under the singular heading of "impure placebo", let alone classifying all of them together with the "pure placebos" under the higher level heading "placebos". All of their examples are problematic in some sense. To save space, we will not comment on all two dozen items in the authors' lists, but a few examples follow:

a) Positive suggestions
Utterances like "*you will certainly feel better in a few days*" belong to normal good physician–patient relationships and do not "*lack ... value for the condition for which they have been prescribed*".

b) Probiotics for diarrhea
There is evidence that probiotics have preventive, as well as curative, effects on some types of diarrhea (13,14). Why have the authors ignored this evidence?

c) Antibiotics for suspected viral infections
Most respiratory infections are viral in origin, but laboratory tests are seldom made to confirm

the etiology. Many patients have both viruses and bacteria simultaneously, and it is usually not possible to determine for certain whether antibiotics are ineffective. (4,15,16) A decision to prescribe antibiotics is often based on the probability of bacterial infection, and the duration of symptoms is one of the associated factors that physicians consider. Thus the use of antibiotics for acute respiratory tract infections cannot be classified uniformly as placebo treatment.

d) Off-label uses of potentially effective therapies
The official process of approving pharmaceuticals has legal and commercial components, and it is only partly based on scientific evidence. Off-label use – prescribing for an unapproved indication or an unapproved age group – is common practice, for example, in pediatrics and intensive care. There is no justification to classify off-label treatments as placebo interventions.

e) Conventional medicine whose effectiveness is not evidence-based
"Evidence-based medicine" (EBM) is a problematic term that dichotomizes medicine artificially into two fields: EBM and non-EBM. There are many definitions of EBM, but they are vague and do not provide an unambiguous demarcation line between the EBM and non-EBM sectors of medicine. We agree with Timmermans and Mauck, who noted that "*The term is loosely used and can refer to anything from conducting a statistical meta-analysis of accumulated research, to promoting randomized clinical trials, to supporting uniform reporting styles for research, to a personal orientation toward critical self-evaluation*." (17) Thus the EBM or non-EBM division is irrelevant to the question of what is or is not a placebo.

f) Non-essential physical examinations and non-essential technical examinations of a patient (blood tests, X-rays)
It is often not obvious what physical or technical examinations are useful for a particular patient. All experienced physicians recall cases in which an examination that originally seemed non-essential unexpectedly revealed important findings. In some cases, it is the pressure of the patient that leads to an examination or X-ray being made. It is not reasonable to classify such examinations as placebo interventions.

In conclusion, the paper's main finding "*placebos are commonly used in UK primary care*" is not correct. Only 0.9% of the responding general practitioners reported using pure placebos frequently. The frequency with which impure placebos are used is irrelevant because the concept is useless, as described above.
Misleading a patient by administering inert substances without the explicit consent of the patient is unethical. The authors' proposal to "*develop ethical and cost-effective placebos*" is not possible because saving money by misleading patients is unethical. There is substantial conceptual confusion in the area of placebo and placebo-effect research, and the paper by Howick et al. does not help to reduce this confusion.

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