Introduction

Placebo

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Since the publication of Henry K. Beecher's article »The Powerful Placebo« (Beecher 1955) it has been discussed in the health sciences and neighbouring disciplines whether and to what extent treatments have a »placebo effect« - that is, an effect that cannot be attributed to an active ingredient applied or a specific treatment technique. Intertwined with these discussions are debates about the mechanisms that might lie behind a placebo effect. Every now and then, a public debate on the issue of placebo occurs. For example, in October 2015, professor of general practice at Aarhus University, Frede Olesen, gave a presentation on placebo and the doctor-patient relationship for more than 1000 medical doctors at the annual conference of the Royal College of General Practitioners in the UK. The topic of the conference was: The future of general practice. Placebo thus seems to be a recurrent theme of discussion and we are pleased to be able to present a selection of articles on placebo in this special issue of Tidsskrift for Forskning i Sygdom og Samfund.

The discussion on placebo is at times rather heated with very different understandings of the phenomenon being presented. Some scholars argue that treatments have no or only negligible placebo effects and that the apparent occurrence of a placebo effect in various clinical trials is due to methodological weaknesses of the trials (Hróbjartsson & Gøtzsche 2001). Others, including some medical doctors, psychologists, and anthropologists, argue that there is a real effect, which cannot be attributed to a substance or a specific technique used and suggest, »placebo is a bad word for a good effect« (Olesen, 2006). The placebo effect has attracted negative connotations and in RCTs (randomized clinical trials), in the effort to identify the "real" effect of a substance, placebos are marginalised. As a result, the placebo effect has obtained the connotation of a non-real, as opposed to a real effect.

Currently however, the placebo effect and the working mechanisms behind it are in some research communities being transformed into a therapeutic ally. There is growing awareness that these, as yet unknown, mechanisms may be important working agents, which one could explore and utilize. For example, there is growing interest in the symbolic, meaningful, and ritual aspects of a treatment (e.g. Kaptchuk 2002 ; Moerman & Jonas 2002; Brody 2010; Ostenfeld-Rosenthal 2012), and psychological theories of expectation and conditioning play a significant role in placebo research (e.g. Benedetti 2006; Vase, L. et al. 2002). The placebo effect and working mechanisms are also explored from a psycho-neuro-immunological perspective (e.g. Fields et al 1997; Fenwick 2001), and the doctor-patient relationship and the practitioner's attitude, body language and verbal and non-verbal communication strategies in the understanding of placebo mechanisms are considered from the perspective of the "doctor-as-drug" (Brody 2001; Helman 2001).

A question, which arises in relation to an open and active use of placebo mechanisms is whether it is possible to use these mechanisms in an ethically sound way. In a recent survey of 987 British doctors 97% admitted that they had prescribed sugar pills, saline injections, or treatment without evidence-based effect at some point in their careers. Half said that they had told the patient that the treatment had helped other patients, but without saying explicitly that it neither contained known active substances nor had proven efficacy (Howick et al. 2013). Is it possible to deal with this challenge in an ethical sound way? Is it possible to inform patients that they are given placebo in a way, which maintains the belief that the treatment might help them? These and other questions are discussed in this issue.

In this issue, we are fortunate to be able to provide a Danish translation of the article by the anthropologist Daniel Moerman and the medical doctor Wayne Jonas on the concept of *meaning response*. It is an article we may designate as "classical" although it was published only 14 years ago as it has been cited numerous times by all kinds of researchers dealing with the placebo. As a medical anthropologist Moerman looks at the cultural dimensions of the placebo. The main argument of the article is thus to stop using what they call a meaningless concept as *placebo* and replace it with the concept of *meaning response*.

A quotation by Socrates sets the agenda:

> "(The cure for the headache) was a kind of leaf, which required to be accompanied by a charm, and if a person would repeat the charm at the same time that he used the cure, he would be made whole; but that without the charm the leaf would be of no avail." (quoted in Moerman & Jonas 2002)

Especially two studies form the basis of the argument made by Moerman and Jonas. One is of a group of medical students who were asked to participate in a study of two new drugs, one a tranquilizer and the other a stimulant. Each student was given a packet containing either one or two blue or red inert tablets. The students' responses to a questionnaire indicated that 1) the red tablets acted as stimulants while the blue ones acted as depressants and 2) two tablets had more effect than one. These results, the authors say, can only be explained by *meaning* (and thus culture): 1) Red means "up," "hot," "danger," while blue means "down," "cool," "quiet" and 2) two means more than one (Moerman and Jonas 2002:472).

In a British study, paraphrased by Moerman and Jonas, 835 women who regularly used analgesics for headache were randomly assigned to one of four groups. One group received aspirin labelled with a well-known brand name. The other groups received either the same aspirin in a plain package, placebo marked with the same brand name or unmarked placebo. In this study, branded aspirin worked better than unbranded aspirin, which worked better than branded placebo, which worked better than unbranded placebo. Moerman's and Jonas's conclusion is that aspirin relieves headaches, but so does the knowledge that the pills you are taking are "good" ones. This leads to the following definition of the placebo:

> "…the physiologic or psychological effects of meaning in the…treatment of illness" (Moerman and Jonas, 2002: 472).

This is a definition, which is very much at a distance from the placebo of RCT's and in our view more useful in many contexts.

The final paragraph of the article explicitly draws on the concept of culture in relation to medicine. Anthropologists, the authors say, understand culture as complex webs of meaning, metaphors, and signs. Insofar as 1) meaning has biological consequence and 2) meanings vary across cultures, biology also differs in different places, not because of genetics but because of culture. As an example, Moerman and Jonas, point to the concept of *local biology* developed by anthropologist Margaret Lock who argues that menopause as seemingly identical physiological processes can be perceived and thus biologically and culturally expressed very differently in different cultures. Consequently, meaning responses and the mechanisms behind vary across cultures. On par with the article in this issue by Skyt & Vase the article by Moerman and Jonas concludes with reference to the Socrates quotation by suggesting to take Socrates's "charms" seriously in order to enrich the meaning of medicine and make it work better, i.e. an invitation to use placebo mechanisms actively.

Folklorist Lars Ole Andersen agrees in his article with many of the other authors contributing to this issue on the need to dismantle the placebo concept. He focuses on the potential of therapeutic power of *imagination*. Speaking from the position of folklore his contribution differs from the other ones, not the least because he looks into the historical period between late 18th century and late 19th century in an exploration of how imagination was employed, discussed, and investigated as a therapeutic vehicle among medical doctors and other health care providers. Andersen argues that the discussions on the healing potentials of imagination in the 19th century have much in common with the present "modern" discussions on placebo as they mostly concern the same kind of problems: What kind of effects can the mind initiate? How can we differentiate between a natural development of the disease and a placebo effect and the power of imagination? How can the power of the imagination or the placebo effect be controlled?

In a dashing overview Andersen introduces to the history of placebo discussions with particular attention to discussions on imagination. He has been able to find literary discussions of a phenomenon named *placebo* in a text by the British medical doctor William Cullen published as early as 1772 and demonstrates how the discussion continues over the next century mixing up with discussions of the potential healing power of the imagination. He lays out how discussions of imagination also covers birthmarks on foetuses (caused by the mother's imagination during pregnancy), and how it was revealed to be the main driving force behind the workings of mesmerism (that by its proponents were explained to work by animal magnetism). In addition, Andersen demonstrates how the founder of homeopathy, Samuel Hahnemann, himself admitted that he in several cases used medications without any form of medicine as he found that the intake of medications, made of e.g. milk powder, by the power of imagination would be able to make patients improve.

The historical overview is instructive in so far that it reminds us that neither the placebo discussion nor the discussion of the healing power of imagination are new and that many medical doctors and lay healers over the last centuries have used medications and therapies that worked primarily by the power of imagination. What we would, however, like to remind the readers is that even though the historical perspective is instructing, it does not solve the question of what is actually referred to by the concept of placebo. Andersen's work points to one aspect of the placebo, the imagination of the patient, while other authors contributing to this issue point to many other factors "hidden" in the placebo concept. Andersen does, however, agree with several other contributors in that we should stop discussing placebo as a black box and start to discuss more accurately the different working mechanisms covered by the concept. Andersen suggests, that it could be valuable to consider the patient as actively producing meaning based on complex and culturally distinct symbolic systems as an important perspective on the placebo effect. That which is called "placebo" may be conceived as techniques to raise patients' resources and abilities to gain self-efficacy and acquire different strategies to handle a life with disease.

The next article in this issue is by Toke Barfod, an unusual medical doctor in so far that he has explored placebo since the mid 1990s when he was still a medical student. At that time he explored how doctors, patients, and researchers used the term ″placebo" and what understandings they each had of this concept (Barfod 1996). Since then he has been a recurrent medical expert on placebo in Danish media while he has followed an ordinary medical path leading him to his present position as a consultant at a department of infectious diseases at a regional hospital in Denmark. In this issue, his paper has the appealing title: ″Could we call it something else", and he argues for the need not to talk about "placebo" but to explicate the various elements of treatment that traditionally has been covered by this term. Among the elements traditionally associated with the placebo concept, he points to patients' *expectations* of efficacy and *perceived* care. Doctors do not want to support unrealistic expectations of a treatment, he claims, and they are reluctant to be experienced as somebody who "plays the nice guy", and as such they instantly evade when confronted with the placebo. We should stop talking about placebo with all the negative symbolic implications of that concept, and instead focus attention on issues that truly belong to the "soft" end of medical practice, but nevertheless are decisive for the course of a treatment, he suggests. He points to the patient's attitude and interpretation of pain, disease, and prognosis; the empathy and care provided by the practitioner; and the need for trust in the patient-practitioner relationship. In contrast to medical doctors, the alternative practitioners (or CAM practitioners as they are mostly called in the international literature) are likely to employ these elements more deliberately, Barfod claims. They often work actively with hope for a good prognosis. The patient needs to have confidence that the best possible treatment has been selected under the current circumstances and needs to feel comfortable with the treatment. As many practitioners consider these the very elements, which are active in the treatment, it seems absurd to Barfod to call them "placebo"; they are to be considered as therapeutic techniques.

The recommendation from Barfod is that future clinical trials distinguish between four possible causes of healing: (1) the improvement of health happening by itself without any contact with a health care practitioner; (2) the improvement, which is initiated by what could be called the preliminary factors (contact with a professional, care, getting a diagnosis, etc.); (3) improvements caused by factors accompanying treatment (trust in the treatment, the act of being in treatment, etc.); and (4) the improvements caused by the specific factors of the treatment. What is needed in order to create an environment in which all of these factors are acknowledged as important for treatment is that not only the practitioners and researchers need to change their attitudes, but also politicians, heads of health care institutions, and the health care administration, need to change their mind-sets. In order for that to happen, it seems necessary to stop using the placebo concept and instead start to call a spade a spade; to talk about all the "soft" and low prioritized elements of treatments.

It is refreshing to have a medical doctor well suited within the public health care system and working with hard core disease like e.g. AIDS try to break down the invisible walls constructed by what we might call an "abuse" of the placebo concept. We can only welcome an increasing awareness of the soft side of medicine in health care of the future.

Ina Skyt and Lene Vase are psychologists and their contribution is a literature review on placebo mechanisms in relation to chronic pain. The review outlines current knowledge of placebo effects in chronic pain treatment and discusses the very important question of how placebo components of treatments can be optimized in clinical practice as well as the ethical dilemmas related to this usage. The review goes systematically through a range of placebo enhancing factors: treatment history, patient-practitioner relationship, verbal suggestions, expectations and emotions, and the neurobiological basis for placebo analgesia. Drawing on the definition of the placebo effect as "the reduction in a symptom as a result of factors related to the patient's *perception* of the therapeutic intervention", Skyt and Vase highlight patients' *perception* as the most important factor in the placebo effect.

Following from that the patient-practitioner relationship takes central stage. The authors find that studies in which positive and specific verbal suggestions for pain relief is given have larger placebo effect compared to studies with uncertain or negative verbal suggestions, proposing that the placebo effect can profitably be optimized in clinical practice by shaping verbal suggestions in specific ways. Practitioners should be careful when informing patients about treatment effect and try to point out positive and realistic expectations, yet without deceiving or misleading patients. Closely related is the fact that treatment of chronic pain is affected by prior treatment history. As an implication for clinical practice clinicians may actively try to enhance patients' treatment experiences by creating positive associations between treatment effects and pain medication.

As part of patients' perceptions expectations of the outcome of a certain treatment also play a central role and it is important to notice that expectations co-exist with emotions. Consequently, practitioners who try to optimize treatment expectations may also benefit from paying attention to patients' emotions with the aim of preventing negative emotions and promoting positive ones.

Until recently it has been taken for granted that in order to obtain a placebo effect it must be administered deceptively. However, Skyt and Vase point to more recent studies, which indicate that openly administered placebo treatments without deception can contribute to treatment outcomes, thereby furthering that the bare presence of psychosocial factors like a supportive patient-practitioner relationship and a specific treatment ritual can lead to clinically meaningful symptom improvements probably because patients expect an effect.

The finding that patients' perception of a treatment contributes to the efficacy of both active and inactive treatments has led to new ways of integrating knowledge of placebo factors in clinical practice. The discussion, Skyt and Vase say, is no longer whether inactive agents should be administered in ethically questionable ways, but rather how active agents can be administered in a context that favours the patient's perception of the treatment so the overall treatment efficacy can be enhanced. To shape patients' expectations in a positive way thus becomes important for healthcare practitioners. This is, however, often complicated as written information primarily provides negative information (on e.g. risk) and fails to emphasize positive treatment outcomes. In the first place, the authors argue, this reduces the possible placebo effect, but of equal importance we think is the fact that the focus on negative information is counteractive to patients' hope, which may very well be another fundamental factor of a healing process.

Overall the review suggests that psychosocial placebo components can interact with neurobiological factors and thereby contribute to the efficacy of pharmaceutical pain treatments, and following that practitioners should be aware of how placebo components may either enhance or reduce the outcome of active treatment effects in chronic pain patients. By establishing a warm and empathic patient-practitioner relationship and by directly asking patients about expectations and emotions in an attempt to optimize expectations in a realistic manner, practitioners may have the opportunity to influence and optimize treatment outcome.

The article points to very important issues related to the placebo, but one very important placebo component, which has not been addressed by the authors, is *culture*. The patients' *perceptions* most likely are linked to the *meaning* ascribed to a phenomenon and to the *belief* in this phenomenon and thus to *culture*. This connection points to the influence on treatment outcomes of the culture in which the treatment takes place both at a macro- (the culture) and a micro-level (the clinical setting).

Anthropologist Sylvie Fainzang takes an unconventional but very relevant perspective on the placebo in her contribution. She explores two issues, which until now have passed unnoticed: the perceptions laypersons hold of placebos and their reasons for resorting to placebos and/or the placebo effect within the framework of family medication, on one hand, and the perceptions and uses by pharmacists in response to the demands of clients, on the other. This focus on patients' and pharmacists' discourses and practices with regard to placebos is seen in the context of their perception of pharmaceutical risks.

The article is based on three fieldworks not primarily dealing with placebo. However, Fainzang's data showed that there exists a social configuration never explored, in so far that individuals choose to resort to placebo for family members within the framework of family medication. As such, she takes Arthur Kleinman's sector model of the healthcare system seriously in relation to the placebo and suggests that a major part of not only diagnosing and treatment but apparently also placebo practices takes place in the popular sector. This has the important implication, that not only the general conception of placebo as something which occurs in the interaction between doctor and patient (the "doctor effect") must be reconsidered. The use of placebo practices in the domestic sphere is also important and points to what Fainzang calls a "trusted person effect". This effect can result from trust put in a family member or close friend or from the patients' conviction in the competence of the person advising them. According to Fainzang, the family use of a placebo aims to mitigate the risks associated with consuming certain pharmaceuticals. Fainzang also investigates pharmacists' discourses and practices with regard to placebos. As regards the placebo effect within this context she finds in addition to the "doctor effect" and "trusted person effect", what she calls the "pharmacist effect" since it is the pharmacist who dispenses the product beyond even the medical prescription. Fainzang sees these three working mechanisms of the placebo as of the same nature belonging to the same category of healing resting in interpersonal relations.

This leads to the issue of ethics coming to the fore of the discussion Fainzang had with her informants. The social actors, Fainzang writes, never mention the subject of placebos without linking the words and observations concerning their uses to ethical considerations. Their arguments to justify the use, or refusal, of placebos mobilize ethical and therapeutic reasons in unequal proportions that vary depending on the individuals. Thus, the contrasting positions which form the basis of the choice to use a placebo or not result from the alchemy of the concerns of the management of therapeutic risks and the management of ethical concerns. Being a "true" anthropologist Fainzang contemplates "the social life" of the placebo.

The most far-reaching article in this issue is no doubt the one provided by Harald Walach, a German psychologist who for many years has been engaged with researching healing processes in clinical trials and in the literature across the disciplines of psychology, medicine and sociology. In the article provided for this issue, Walach sets out to provide information, which can bring us one step further than the article by Moerman and Jonas (2004), also provided in this issue.

Walach demonstrates how the placebo has been treated like "noise and a nuisance" in the medical discourse on trials of efficacy of pharmaceuticals, and acknowledging the importance of separating the effect of the pharmaceutical product from the effect of any other element of a treatment he points to the need for acknowledging the therapeutic effectiveness in any kind of health care. That is, we need to not only focus on biochemical elements of a treatment but also to consider and acknowledge all the other things happening in a medical or health care encounter and the influence this may have on the outcome of the treatment. He claims that behind what has been called "the placebo effect" we see self-healing at work.

Drawing on research from primarily medicine and psychology, Walach sketches out a picture of discussions and research on placebo since the time of Beecher's influential paper from 1955 in which he introduced the possible potentials of effects induced not by the pharmaceuticals but by other elements of a treatment.

Walach counter fights the likewise influential article by Hróbjartsson & Gøtzsche (2001) in which they conclude that a meta-analysis of clinical trials with placebo groups demonstrates that the placebo effect is insignificant. In relation to this, Walach points to a more recent analysis of basically the same trials in which it is demonstrated that when accounting for the difference between groups of no-treatment and placebo and between groups of placebo and treatment, it becomes clear that placebo is significantly more effective than no-treatment; and perhaps more importantly it is demonstrated that the treatment effect is correlated with the placebo effect (Howick et al 2013). That is, "real" treatments work better if there is a high placebo effect. If this holds true, then it provides the reason for developing the elements, which are not part of the "real" treatment in order to support the healing of the patient. We thus need to train doctors to support the effectiveness of the pharmaceutical and surgical treatments they provide through their clinical manners and the way they support the patients.

For Walach it is important to realize that the placebo is not just something working on the minds of patients, and he points to research on biological transmitter systems of the body, which has demonstrated that these systems are influenced by non-pharmaceutical elements of a treatment. But most importantly, Walach points to research that demonstrates which elements of the treatment have been proven to be effective and enhance the healing process. These elements include the conceptualization of health and disease, the ascribed power of the healer, the rituals related to the treatment, the trust and hope patients may experience, and the positive expectations patients may have. In conclusion Walach states that self-healing is not something happening in a void. Rather we should conceptualize self-healing as processes inherent in the biology of humans that can be triggered by the elements a therapeutic situation not related to the treatment itself. In this he points to a very important area that needs further attention.

With this special issue, »Placebo«, we have brought a broad range of researchers together to contribute to a clarification of the use and meaning of the placebo concept as well as the use of placebo treatments and possible working mechanisms. It is our hope that the contributions will stimulate a qualified research based discussion of the elements of treatment often considered as "soft" and not specifically treatment related. The articles demonstrate very well that such issues are indeed important, not only as general means to establish working relationships between health care practitioners, but more importantly as therapeutic allies that actually support healing processes.

In relation to this, the majority of the contributors have addressed the issue of ethics. If the problem is not to provide "fake" medications but rather to improve the elements of a therapeutic encounter that supports the efficacy of the treatment offered, the ethical issue does however seem to disappear. The concept of *culture* (perceptions, conceptualisations, belief, meaning) has run as a red thread through many of the articles and likewise the concept of *ritual* has been mentioned as an important working mechanism by several authors. This points to the significance of these concepts if we are going to obtain a deeper understanding of the non-pharmaceutical elements of treatment.

In conclusion it is important to stress the need to research in more detail the ways in which the non-pharmaceutical elements of a therapeutic encounter works. Just as importantly we need to start teaching medical students, nurses, and other health care practitioners, that they themselves are part of the intervention and teach them how they can influence the healing processes of patients by the way they behave in the medical encounter. In a time when the majority of patients suffer from chronic conditions that cannot be healed by pharmaceuticals and more persons than ever have to live for prolonged time with disabilities and impediments caused by disease and biomedical treatments, this seems more important than ever.

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