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BOOK REVIEW

AFTER PLACEBO: IN MEDICAL RESEARCH AND CLINICAL PRACTICE

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1 | INTRODUCTION

Despite the claim that placebos are powerful[1] and the growing scientific interest—PubMed lists 31 259 scientific articles on this topic—Robin Nunn argues that this large and growing body of research has not succeeded in providing generally accepted answers to the core question: What exactly is a placebo and is there anything that deserves this descriptor?

Building on his earlier work,[2-4] Nunn argues in his book *After placebo: In Medical Research and Clinical Practice* that it is time to abandon the disputed placebo construct. New terms, he argues, are needed to replace it in order to better advance medical research and clinical practice alike. While Nunn admits there are possible negative consequences (since "not knowing and not being able to explain" placebo effects may be uncomfortable [p. 35]), he estimates that science will be expedited as a result of discarding placebo terminology. Nunn presents us with a challenging and interesting perspective that invites consideration by both clinicians and researchers. But is it warranted?

Nunn's criticism of the placebo concept is based on several empirical and theoretical arguments. In the introduction, he states that it is not his intention to solve all definitional problems associated with the term placebo, but rather to promote the rationale for, and confidence in, abandoning it. The term placebo is depicted as a conceptual habit which was useful in the past but which has now lost its purpose and justification. This is exemplified in the second chapter, as a parade of dated and more recent placebo definitions is elegantly summarized, including the usual suspects from Shapiro and Shapiro,[5] Grunbaum,[6] Brody,[7] and Harrington.[8] In the following chapter, the often rather unspectacular reasons underlying often rather spectacular cases are illustrated by the case of Mr Right, who was presumed cured by the intake of a placebo. Nunn's use of the story highlights that the so-called powerful placebo may not be responsible for curing Mr Right. Rather, his experience of clinical change may have been owed to more mundane phenomena such as spontaneous remission or regression to the mean. In subsequent chapters, Nunn aptly deconstructs not only the semantic absurdity of considering the placebo as something *inert*, yet at the same time, *powerful*; he also describes the challenges of proving its effects in meta-analyses (eg, Hróbjartsson and Gøtzsche[9]) and surveys the responses which argue that these analyses are flawed.[10-12] His tour de force analysis underlines the fact that almost any substance can be a placebo, that placebo(-like) effects can even be observed in the absence of the administration of placebos, and that placebos can be part of almost any treatment for any condition.

So how does this concept fare in reality? Not surprisingly, Nunn's verdict is clear: He argues that the logic of placebo definitions is circular and reductive. Current "linear models ignore concepts of sensitivity to initial conditions, non-linear dynamics, self-reference and feedback […]" (p. 65). These problems are seen as the result of the prevailing scientific approach to placebo: he describes it as a "circular logic," since improvements in patients who receive inert treatments are defined as placebo effects, so that observed improvements in patients who received inert treatment are then perceived as placebo effects (p. 89). These logical problems are not eradicated by advocating a linguistic alternative, such as shifting from placebo language to "meaning responses"[13] or "context effects."[14] Nunn argues that these terms are associated with similar conceptual problems and leave us with the same challenges: they are, as he puts it, "black boxes within black boxes" (p. 105). He closes his critique with the statement that medicine is rife with unexplained symptoms and unexplained cures; he concludes that it would be more honest to declare that the reasons, in all these cases, are either unknown or poorly understood. According to Nunn, the attempt to elucidate the reasons for symptom alleviation (or indeed, worsening) is not advanced by the current approach of so-called blinding, as a significant proportion of interventions are too different to be appropriately interchangeable, while others cannot be faked. In conclusion, he argues "instead of saying it's a double-blind experiment with placebo control, say that you are trying to set the same beliefs and expectations in everyone while giving them different treatments" (p. 138).

The book moves on to advocate an alternative "After Placebo" era, replete with placebo-free laws, guidelines, regulations, and medical trainings which, Nunn argues, will offer new implications and opportunities for medicine and health. Placebo-free regulations, for example, will not use the term "placebo-controlled study," yet rather describe the purpose of a clinical investigation which "is to compare the safety and effectiveness of a drug or procedure with reasonable alternatives appropriate in the circumstances" (p.164). The overarching goal is to build a new post-placebo paradigm "so that in future we won't even see the old structure, as today's medicine does not see the structures of ancient medicine" (p. 140). In these sections, Nunn develops his earlier and tantalizingly brief forays in criticizing the placebo concept.[2,3]

All in all, we can agree with Nunn that he is certainly justified in questioning the legitimacy of the current placebo construct and makes a strong case for eliminating and replacing that concept with the notion of, "an intervention intended to influence the patient's beliefs, hopes and expectations" (p. 163). Nunn's point of view is refreshingly original in the long, somewhat protracted debate about terminology in placebo studies.

But one is left wondering: is it really necessary to eradicate the term placebo? A number of omissions in Nunn's book lead to an oversimplified depiction of placebo research. For example, Nunn argues that "we should also consider the provider's expectation and conditioning and the collaboration between patient and provider" (p. 80). However, this has been done, for example, in a recent paper investigating neural correlates of physicians during treatment of patients, with the impressive conclusion that physicians activate similar brain regions during the treatment of a patient.[15] Further, Nunn states that placebo theory is dominated by talk of expectation and conditioning while "conditioning is conceived as an unconscious process, in contrast to expectation that is deemed to be conscious" (p. 78). However, other models—such as Bayesian models of perceptual decision—are becoming established as an innovative framework in placebo research,[16] while recent investigations reveal the acquisition of unconscious expectancies.[16] So, in this respect, Nunn has failed to keep abreast of nuanced conceptual change within the field.

Finally, the book highlights some shortcomings of adequate control conditions. His points on these shortcomings are valid though not original, as they have been repeatedly emphasized in placebo research (eg, Blease, Bishop, and Kaptchuk[17]; Howick[18]; and Turner[19]). In addition, some points of criticism on the current control conditions may be questionable. For example, Nunn writes that, "[a] waiting list also implies that they are waiting for something. The presence of interested experts, the hope, the expectation, the possibility of treatment after the waiting period [...]" (p. 74). On the contrary, meta-analyses reveal that waiting lists do not enhance expectations, but rather induce nocebo effects.[20]

On a more general level, one should keep in mind that the placebo concept also has an ethical dimension since in clinical trials, and more troublingly, when administered, in clinical contexts, it typically involves deception. Nunn addresses this issue concluding that, "deception in relation to placebo refers only to some bending of truth. Deciding where the line is, and adjudicating what is outside the line and what gets in, again illustrates the difficulty of dividing the world into placebos and non-placebos" (p. 159). While Nunn relativizes deception on the grounds that "no single rule applies for all people in all situations, such as do not lie or deceive, do tell the truth, the whole truth and nothing but the truth" (p. 155), his analysis here is unconvincing. The overarching duty to inform patients in a transparent manner and to provide truthful disclosure is paramount in clinical practice.[17] This is in line with a deontological normative ethical framework, where it is argued that deception infringes patient autonomy—regardless of potential health gain.[21] Indeed, we must not lose sight of patients' right to autonomous decision making—even in a post-placebo world. It is important to emphasize that this ethical sentiment has been a leitmotif of recent open-label placebo research which advocates the imperative of providing adequate information disclosure for patients.[22] On a related point, Nunn urges, "it is curious that informing patients about the distinction between deemed active ingredients and inactive placebos matters more than information about physicians themselves [...] (p. 159)." Here again, some placebo researchers have bitten the bullet and argued that there ought to be disclosure of information about the influence of physicians (and indeed other healthcare practitioners) in mediating health outcomes (and placebo effects).[21,23]

Nunn's *After Placebo* succeeds by stimulating valuable questions and analysis of the current placebo construct—an important, reasonable, and necessary undertaking. Nunn's writing is engaging and evocative, and *After Placebo* is a worthwhile, accessible read suitable for an interdisciplinary healthcare audience. Large portions of this work function as a critique of the placebo construct not just in medical research, but also in clinical practice. Nevertheless, Nunn's line of argument might not yet be convincing enough to justify the total elimination of placebo terminology. Precisely because the concept of placebo is entrenched in clinical practice, and because it is heterogeneous and broadly diversified, it lends itself to interpretation and discussion—thus fostering progressive, new insights, and findings.

At the beginning of the book, Nunn states, "I will have achieved my purpose if you [...] are at least persuaded that placebo must be considered from more than one viewpoint and that there is no single viewpoint that can ever make sense of placebo" (p. 7). We can surely agree that he accomplishes this aim.

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