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Overcoming disagreement: a roadmap for placebo studies

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Abstract
In the field of placebo studies residual disagreement about the terminology 'placebo' and 'placebo effect' still persists. We differentiate between the conceptualization of placebos in clinical trials; and placebo effects understood as a psychobiological phenomenon. With respect to the latter, we argue that a scientific 'placebo paradigm' has emerged, indicating that—at least among placebo scientists—there exists relatively stable consensus about how to conceive of placebo effects. We claim that existence of a placebo paradigm does not protect concepts from revision; nonetheless, we argue that scientific progress is dependent on, and guided by relative conceptual stability. Therefore, to mount persuasive arguments for conceptual revision in respect of 'placebo effects' we argue, critics either need to defend the claim that a placebo paradigm is not underway, or that there are major scientific failings in respect of it. With these considerations in mind we examine three alternative proposals for conceptual reform: Grünbaum/Howick's relativity models of placebo concepts; Moerman/Brody's meaning response; and Nunn/Turner's proposal for conceptual eliminativism. We derive two conclusions from this evaluation. First, we conclude that no convincing arguments have so far been presented for conceptual overhaul of 'placebo effects.' Notwithstanding this analysis, we conclude that refinement of this concept is likely. Second, we agree with Turner and Nunn that the term 'placebo' in the context of randomized controlled trials remains a source of confusion for many researchers, risking the design and scientific integrity of clinical findings. Therefore, in these contexts, replacing the term 'placebo' with 'control' is justified.

Keywords Placebo · Placebo effect · Meaning response · Conceptual change · Randomized controlled trials · Medical epistemology

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Introduction

Research in placebo studies is burgeoning. One indicator of this surge in scholarship is the volume of scientific papers published: between 2004 and 2016 publications increased over tenfold from around 300 to over 3500 papers (Enck et al. 2017). Yet, despite the intensity of output there is residual debate over key terminology. Discussion focuses on how the terms 'placebo' and 'placebo effect' should be defined.[1] Some scholars support preservation of these terms (e.g. Miller et al. 2009; Kaptchuk and Miller 2015); others propose we retain the terms but redefine them (e.g. Grünbaum 1986; Howick 2017); still others favor eliminating and replacing some of these terms (e.g. Brody 1980, 1999, 2000; Moerman 2002); finally, some argue that we should eliminate this terminology outright (e.g. Nunn 2009a, b; Turner 2012).

In this paper we argue that in order to evaluate definitional disputes it is first important to acknowledge how these terms are used. In what follows we differentiate between two kinds of semantic starting points for definitions of placebo terminology. The first perspective assumes that placebos and/or placebo effects are natural kinds of thing or process that exist in the world, and that our best scientific theories should aim to track the truth about them. For the sake of brevity, we refer to these as 'ontologically-motivated' definitions. A second classification of placebo concepts refers to experimental contexts. The (often) tacit assumption behind this second set of considerations is that placebos primarily have an instrumental function—namely, they help clinical researchers to gauge the size of treatment effects in controlled trials. We refer to these as 'methodologically-motivated' definitions. We observe that proponents of conceptual change sometimes talk at cross-purposes when discussing conceptual revision and that much of the current controversies about the definition of 'placebo effects' stems from a failure to distinguish between these two different epistemological domains of activity: one concerned with investigating the nature of 'placebo effects', the other with epistemological applications of 'treatment controls' for research purposes.

In what follows, we primarily focus on ontological considerations—namely, how to define 'placebo effects' as a phenomenon worthy of scientific investigation. However, in part because of the nature of the justifications offered for how to revise these terms, our analysis will also speak to methodologically-motivated definitions too. In relation to the former—ontological considerations—we argue that the existence of a *progressive scientific paradigm*, which is dependent on certain stable conceptual interpretations of 'placebo' and 'placebo effect', is the most justified starting point to evaluate competing definitional models. Paradigms—a term which we will explicate further—refer to distinctive social and theoretical structures that permit researchers to formulate empirically-informed descriptions about some aspect of the world.

On the face of it, even focusing on a search for a mature paradigm in placebo studies may seem problematic: it might be argued that the current placebo paradigm

[1] While we recognize that the conceptual debate occasionally extends to 'nocebo' and 'nocebo effects' discussion is mostly centered on placebo concepts. Therefore, in this paper we restrict ourselves to placebo concepts.

is the very bone of contention. Drawing on Kuhnian insights from history and philosophy of science we argue that conceptual debates pertaining to science typically involve one of two scenarios: (a) recognition that there is not yet a successful scientific paradigm; or (b) recognition that the existing paradigm is failing in significant ways.

Nonetheless, we also emphasize that the mere existence of a placebo paradigm does not protect its current placebo concepts from revision. Paradigms require some degree of settled consensus about conceptual matters which, in turn, are entwined with theory and methodology; and furthermore, this agreement permits progress in science to occur. Therefore, to mount persuasive arguments for conceptual revision in respect of ontological issues, we argue that critics need to defend the claim that a placebo paradigm is not underway, or that there are major scientific failings in respect of it. From this perspective we make three observations. First, when it comes to the ontologically-motivated project, we argue that refinement of placebo concepts is likely. Second, in respect of that project, we argue that, so far, a convincing case for conceptual overhaul—or something akin to a 'scientific revolution'—has not been made. Third, when it comes to methodologically-motivated conceptual revisions, we argue that there are good grounds for replacing 'placebo' with 'treatment control' to avert terminological proliferation and avoid conceptual confusions.

Disagreement in placebo studies and why it matters

Before delving into three distinctive—and we suggest, the most comprehensively formulated arguments—for conceptual change, it is first valuable to reflect on the range of justifications that have been offered for conceptual revision.

Leading placebo scholar, philosopher and interdisciplinary health researcher, Jeremy Howick identifies a number of negative consequences of conceptual misunderstandings that he contends arise from conceptual confusions; "Mistaken definitions of placebos," he argues, "have led to questionable estimates of placebo effects, unjustified 'placebo' control treatments, and confused debates about the ethics of placebos" (Howick 2017, p. 30). In this way, Howick proposes that greater conceptual clarity will improve methodological precision in clinical trials and lead to greater consistency in debates about the ethical use of placebos.

Taking a different approach, in their highly-cited article entitled 'Deconstructing the Placebo Effect and Finding the Meaning Response' the influential medical anthropologist Daniel Moerman and his colleague Wayne Jonas argue that the placebo effect concept has been expanded, "very broadly to include just about every conceivable sort of beneficial biological, social, or human interaction"; they also argue that the term is used "too narrowly" to include "'natural history' or 'regression to the mean'" (Moerman and Jonas 2002, p. 471): "No wonder," they observe, "things are confusing". On Moerman and Jonas' view, conceptual clarity is conducive to better empirical work and better therapeutic recommendations.

Historian and philosopher of science Robin Nunn also claims that there are serious problems when it comes to the application of placebo terminology in biomedical research. He appears to confine his commentary to the implications of conceptual

revision in placebo studies for its applications in biomedical research: "Professional duties of researchers demand that we purge outdated notions," writes Nunn (Nunn 2009b, p. 51). Specifically, he urges, when it comes to applying this knowledge to clinical trials the implications are "huge": "We need new literature, new textbooks, new training, and new laws that expunge the notion placebo and replace it with something more fundamental…" (Nunn 2009a, p. 1015).

Meanwhile, in this journal, philosopher of science Andrew Turner has meticulously argued that the terms 'placebo' and 'placebo effect' "are fraught with conceptual confusion" (Turner 2012, p. 419). Supporting Nunn's position, Turner recommends we eliminate the terms 'placebo' and 'placebo effect' from scientific and medical discourse altogether; he memorably exhorts, "lumping a disparate range of elements together under these terms is, in essence, like mixing paint colors to get brown" (Turner 2012, p. 1). Agreeing with Nunn, Turner advocates, "abandoning the terms 'placebo' and 'placebo effects' because they serve no analytical purpose" (Turner 2012, p. 430) and claims that conceptual confusions carry clinical implications including the risk of undermining the methodological rigor of randomized controlled trials (RCTs) (Turner 2012, p. 430). However, Turner seems to go even further than Nunn by suggesting that conceptual elimination and replacement of 'placebo' *and* 'placebo effects' is likely to reap benefits for basic scientific research in placebo studies, as well as clinical research involving RCTs.[2]

In summary: there appears to be shared consensus among many placebo researchers, all of whom come at the problem with distinguished yet different kinds of expertise, and who agree that progress in the field of placebo studies is hindered by conceptual murkiness. Reasons for rethinking placebo concepts include: methodological precision in evaluating the effectiveness of treatments in RCTs (Howick 2017; Turner 2012; see also: Blease 2018b; Locher et al. 2018; Gaab et al. 2018; Turner 2018); implications for the accurate measurement of therapeutic placebo effects in clinical encounters (Howick 2017); and implications for clinical ethics, including what might ethically be disclosed to patients to elicit beneficially placebo effects (Howick 2017; also: Blease et al. 2017; Blease et al. 2016; Gaab et al. 2016; Annoni and Miller forthcoming). We agree that these are worthy motivations deserving of scientific and philosophical attention. Our goal is to revisit and critically evaluate the question about conceptual clarity in placebo studies using a Kuhnian framework.

[2] Turner further asserts that it is an empirical question whether purging the old terminology will lead to improved methodological precision in clinical research; noticeably, however, the strength of his argument is premised on the speculation that terminological overhaul will indeed lead to such benefits (Turner 2012, p. 431).

Conceptual consensus in science: a Kuhnian perspective

Notably, debate over the legitimacy of terms 'placebo' and 'placebo effect' is frequently couched in Kuhnian language. For example, Nunn advises that we move towards a "*post*-placebo *paradigm*" (Nunn 2009b, p. 51). Similarly, Miller, Kaptchuk and Colloca contend that, "scientific research on the placebo effect has taken the shape of '*normal science'* without guidance of any systematic theoretical *paradigm*" (Miller et al. 2009, p. 15, italics added). While only some proponents of conceptual change in placebo studies use Kuhn's terminology of 'paradigms' and 'normal science' (e.g. Nunn 2009b; Miller et al. 2009) we suggest that a Kuhnian framework provides a useful model for considering the adequacy of placebo concepts (See also: Blease 2018a, b, p. 414–415).

In particular, we argue that it is possible to endorse prominent aspects of Kuhn's philosophy of science without aligning ourselves to every contentious feature of his body of work (see: Blease 2018a, p. 415). Notwithstanding controversies and criticisms surrounding his seminal work *The Structure of Scientific Revolutions* (1970) it is clear that philosophers of science have paid close attention to Kuhn's recommendation that we observe how scientists *in fact* think, behave and work rather than merely postulate how scientists *ought* to work.[3] Indeed, we venture that key insights from *Structure* are so embedded in contemporary science and technology studies that they have the character of truisms. These insights include Kuhn's claim that for scientific progress to occur, theoretical questions—for example, definitions of fundamental concepts, as well as identification of scientific laws including so-called *ceteris paribus laws* within the special sciences—must be relatively settled to allow empirical research to get underway (Kuhn 1970, p. 13); and finally, that both explicit and tacitly held theoretical, conceptual and methodological commitments guide scientists in conducting their research. We suggest scientific progress and the identification of paradigm-led research affords a useful yardstick for appraising the adequacy of current placebo concepts (Blease 2018a).

Pre-paradigm flux

An important insight of Kuhn is that the route to normal science is arduous: during what he describes as the period of pre-scientific flux, scientists act more like philosophers deliberating on, and disputing, various theoretical and definitional matters. According to Kuhn, then, only when such matters are settled we can speak of the emergence of a scientific paradigm which permits the business of 'normal', cumulative scientific research to get under way. A central premise of this paper is that the field of placebo studies is indeed marked by a 'placebo paradigm' and that 'normal scientific' research is already underway (Blease 2018a, b). If placebo studies can be described as paradigm-driven, on this Kuhnian interpretation, we would expect to find consensus about definitions for 'placebo' and 'placebo effect'.

[3] To this extent Kuhn's proposals embody a version of naturalized epistemology.

Kuhnian paradigms

As noted, Kuhn's philosophy of science has retained a strong legacy, deeply influencing post-positivist philosophy of science. Before defending the idea that there exists a placebo paradigm, it is first necessary to articulate a robust description of how we should interpret 'paradigms' and the nature of scientific change. This is the task of the present section.

Kuhn contended that, "Normal science is predicated on the assumption that the scientific community knows what the world is like" (1970, p. 5). This shared outlook is a result of a common education and training with the upshot that scientists working in a particular field are "relatively unanimous" (1970, p. 177) in their judgments and expectations about the nature of the research. He writes, "In learning a paradigm the scientist acquires theory, methods, and standards together, usually in an inextricable mixture" (1970, p. 177). For Kuhn, a community of scientists working within a particular paradigm shares explicit beliefs such as law-like statements about the domain of research but also tacit knowledge about how to undertake empirical research. Paradigms, on this perspective, determine what counts as an empirical "puzzle" and also sets the standard for how to solve it: i.e., what counts as a "puzzle solution". In this way, the paradigm helps to constrain and structure the nature of research. Normal science is therefore characterized by a degree of complacency among scientists, without which there would be constant instability, confusion, and unrest about how to make progress. In largely assuming the adequacy of the theoretical framework, and of the methodologies that must be applied to address empirical problems, scientists are freed to get on with the business of puzzle-solving that typifies scientific research (1970, pp. 38–39); as Kuhn notes, "The man who premises a paradigm when arguing in its defense can nonetheless provide a clear exhibit of what scientific practice will be like for those who adopt the new view of nature. That exhibit can be immensely persuasive, often compellingly so" (1970, p. 94). Paradigms are conceived as open-ended "objects" for further articulation (1970, p. 23). In this way, normal scientific research allows for the cumulation of knowledge.

To elucidate these terms of art, it is valuable to draw on an historical example; in *Structure* Kuhn leans heavily on Newtonian mechanics to illustrate paradigm-led science. After Newton's *Principia Mathematica* became established as a significant scientific work, Newton's laws formed a theoretical and experimental framework for undertaking problems in physics and mathematical mechanics. The Newtonian paradigm is comprised of "symbolic generalizations"—explicit scientific laws, such as $f=ma$—as well as implicitly held metaphysical assumptions. In respect of the latter, if one accepts Newton's second law of motion, then one must thereby tacitly believe that forces, such as gravity, exist. *Principia* also provides a model for pursing scientific problems and the interpretation of empirical results. Training in Newtonian physics entails propositional knowledge encompassing scientific laws, as well as practical knowledge in applying these laws in, what are judged to be, applicable scenarios. Such 'know-how' includes acceptance that Newton's laws are simple, elegant equations and therefore idealized models—for example, recognition that frictionless planes are not found in nature. Newtonian puzzle-solving involved investigating how

Newton's laws accounted for the movement of the planets, and probing how Newtonian mechanics might apply to liquids.

According to Kuhn paradigm change only occurs when increasing number of anomalies arise with the existing paradigm. He urges that, anomalies become serious when they strike at the fundamental generalizations of the paradigm and persistently resist attempts at resolution; and when there is some pressing social need to resolve the anomalies in question (1970, p. 82). Nonetheless, Kuhn notes that, "if an anomaly is to evoke crisis, it must usually be more than an anomaly" (1970, p. 82). In other words, the stubbornness of such anomalies to resist resolution over time, as well as the accumulation of numerous different, less significant anomalies, also serve to threaten the integrity of the paradigm and tip the scientific community into a 'crisis'. He observes, however, that in most cases even the most intractable of problems usually yields to normal science (1970, p. 81); modifications of the paradigm can also occur. Kuhn recognized that there can be continual improvement of the paradigm through experimentation: as such, paradigms are not intractably fixed; he wrote: "More than any other sort of normal research, the problems of paradigm articulation are simultaneously theoretical and experimental" (1970, p. 33). For example, he observes,

> Before he could construct his equipment and make measurements with it, Coulomb had to employ electrical theory to determine how his equipment should be built. The consequence of his measurements was a refinement of that theory. (1970, pp. 33–34).

Nonetheless, as Alexander Bird notes, Kuhn's historical account is enriched when we acknowledge "the typology of change" need not involve the choice between the rigid preservation of a paradigm versus its dramatic overthrow, during what Kuhn referred to as "scientific revolutions" (Bird 2014, p. 53). Instead, a continuum of less remarkable changes can arise (ibid): indeed, as Bird notes, incommensurable paradigm change, or so-called scientific revolutions, are relatively rare (p. 57). Instead, peripheral changes to a paradigm or even modifications of law-like statements may also gradually occur during the course of normal research (Bird 2014, pp. 50–51; see also: Laudan 1986, pp. 67ff).

Summary

In short, drawing on a Kuhnian framework, we propose that proponents of placebo revision need to argue for one of two things. The first option is to provide evidence that a placebo paradigm has not yet emerged. Here proponents of conceptual change might propose that there is a need to revise key terms in order for scientific research to get off the ground. A second option is to claim that a placebo paradigm is underway but that sufficiently serious anomalies have arisen to warrant major conceptual revisions or scientific 'revolution'.

We argue that, so far, leading proponents of conceptual revision sometimes deploy the language of Kuhn in their argumentation but, so far, do not provide

grounds for substantial overhaul in respect of 'placebo effects' (Blease 2018a, b). We conclude that conceptual refinement, and revision in placebo studies is certainly a possibility. Methodological considerations, as we later argue, are a separate issue: here, we express support for terminological revision on practical grounds.

The placebo paradigm

Both from a genealogical and Kuhnian point of view, the current field of placebo studies may be understood to have emerged as a response to a particular epistemic anomaly and puzzle. This anomaly, which was observed for the first time during the first placebo-controlled experiments by Beecher (Beecher 1955) is that people assigned to the control group in a clinical trial often report significant improvements even though they have received no medication. How is this possible? Answering this question has been the main focus of a growing strands of different theoretical and empirical inquiries which, over the last 40 years, has consolidated into a distintive, burgeoning and interdisciplinary field of research ('placebo studies'). Thus, from the context of discovery, the term "placebo" is historcally linked with "placebo effects". Today, however, this shared terminology masks two distinctive domains of scientific activity and application, as we discuss below.

Metaphysical beliefs and tacit assumptions

What constellation of fundamental or tacit assumptions, if any, might appear to be held among researchers working in the field of placebo studies? In what follows, by applying a Kuhnian framework to placebo studies, we draw on high impact original scientific articles, review papers, and a recent consensus report by a group of placebo experts (Evers et al. 2018) to explore evidence for the existence of a placebo paradigm aimed at investigating placebo effects (Blease 2018a, p. 420).

Placebo researchers appear to subtly distinguish between two senses of the word 'placebo': (1) *placebos* as methodological controls in RCTs; and (2) *placebos* as interventions that, owing to their intrinsic properties, are believed to be ineffective for a particular condition but which may be intentionally or unintentionally administered in clinical settings, or experimental placebo research, with the aim of placating patients and/or with the goal of eliciting *placebo effects* (for summary, see Table 1). While we distinguish these different uses of the word 'placebo' we suggest that they are often confused by health researchers. In basic research placebos may be administered deceptively or 'open-label' whereupon patients are informed that the pill or treatment is a 'placebo', which is typically defined as a treatment that may work due to 'mind–body effects'. In basic research, the aim of using deceptive or indeed open-label placebos is to investigate if, and how, *placebo effects* are elicited.

When it comes to their use as *methodological instruments* in RCTs, placebos, it is argued, should be designed to mimic the so-called 'verum' treatment under

Table 1 Placebo concepts: variety of usage among placebo researchers

Placebos

1. **Methodological controls in RCTs**

   Placebos in clinical trials should ideally be indistinguishable from so-called verum treatments under investigation, except for the latter's particular hypothesized remedial factor(s). Placebos in RCTs are epistemological tools to screen out the 'noise' of clinical research (see Placebo Responses, below)

   or

2. **Interventions used in patient care**

   Interventions that, owing to their intrinsic properties, are ineffective for a particular condition or symptom(s), but which may be intentionally or unintentionally administered in clinical settings or experimental placebo research, to placate patients and/or with the aim of eliciting *placebo effects*

Placebo effects

Placebo effects engage perceptual and cognitive processes to produce salubrious, psychobiological events. Placebo effects are considered amenable to scientific investigation using the methods and techniques of the behavioral and psychological sciences. A growing body of research shows that placebo effects have considerable potential to alleviate many commonly-experienced symptoms and conditions (e.g., pain, depression, anxiety, irritable bowel syndrome)

Placebo responses

Placebo responses encompass the range of outcomes that arise after the administration of placebos in RCTs. These responses may include such factors as spontaneous remission, regression to the mean, Hawthorne Effects, etc. Placebo responses may (under the right conditions) also include *placebo effects*

investigation (Blease 2018b; Gaab et al. 2018; Howick 2017). The underlying claim is that placebos should be indistinguishable from the verum treatment except for the particular aspect of the treatment that is hypothesized to be remedial. Placebos in RCTs are therefore used to screen out the noise of clinical research which can encompass: spontaneous remission among patients, regression to the mean, Hawthorne effects and reporting bias among patients, as well as placebo effects proper (Kaptchuk and Miller 2015). Placebos in this clinical research context are tacitly understood as epistemological tools ('controls') for measuring treatment effects. Furthermore, it should be noted that not all researchers who employ placebos in RCTs seem to grasp the nuances described here (this, of course, has been a bone of contention among those urging for conceptual revision) (see also: Blease 2018b; Gaab et al. 2018; Howick 2017; Locher et al. 2018).

The second interpretation of placebos as treatment tools, or as devices for further exploration in basic research, embeds a very different set of fundamental assumptions. Here, as previously noted, scientific researchers adhere to the notion that placebos may be employed to elicit *placebo effects.* 'Placebo effects' are believed to comprise a range of genuine, psychobiological events that engage "specific, quantifiable, and relevant areas of the brain" (Kaptchuk and Miller 2015). Today, placebo effects are considered amenable to scientific investigation using the methods and techniques of the behavioral and psychological sciences. An added social impetus for this research is that placebo effects are understood to invoke salubrious, symptom-alleviating psychobiological pathways in patients suffering from some commonly-presented symptom. Other tacitly held assumptions which are often sometimes articulated by placebo researchers include the claim that 'placebos'

understood as 'dummy treatments' (when used either in clinical or experimental contexts) are not necessary (nor may they be causally sufficient) to elicit the *placebo effect* proper (Evers et al. 2018; Kaptchuk et al. 2010).

A further nuanced belief—one that is not always expressed with clarity or consistency across placebo research—is the distinction between *placebo responses* and *placebo effects* (these terms are occasionally defined in opposing ways, if at all). Nonetheless, increasingly *placebo responses* are tacitly understood to encompass the range of outcomes that arise after the administration of placebos in RCTs (Evers et al. 2018). As noted above, this may include such factors as spontaneous remission among patients, regression to the mean, and so on. Notably, there appears to be general consensus among researchers that placebo responses may (under the right conditions) include the *placebo effect*—which, as mentioned—is unquestionably the locus of scientific placebo research (Miller et al. 2009; Evers et al. 2018).

Symbolic generalizations and puzzle-solving

A wealth of evidence indicates that symbolic generalizations underpin the vast majority of studies in placebo research. The special sciences often refer to laws that vary under different antecedent conditions as *ceteris parabis laws*; these laws are clearly in operation in ongoing placebo research. Psychological mechanisms which are considered to be responsible for placebo effects include (but are not limited to) "response expectancies", and "classical (Pavlovian) conditioning" (Colloca and Miller 2011, p. 1923; Benedetti 2014, pp. 39–46; Evers et al. 2018). For example, within empirical investigations in placebo studies, "response expectancy" is variously understood as the patient's expectation that a treatment or intervention will be effective for their symptoms (e.g., Kirsch 1997; Berna et al. 2017; Vase et al. 2005). Classical conditioning, on the other hand, refers to repeated associations between a neutral stimulus and an active medication (an 'unconditioned stimulus'); as a result of these repeated associations in certain circumstances, placebos (or indeed, even verum medications) can be interpreted as the neutral stimulus which leads to the elicitation beneficial effects that are characteristic of active medications (Finniss et al. 2010, p. 687; Colloca and Miller 2011, p. 1923). On a Kuhnian framework, symbolic or law-like generalizations, combined with metaphysical beliefs provide a substructure for 'puzzle-solving'. We suggest that the puzzle-solving that is emblematic of normal scientific research is underway in placebo studies. We focus on three such foci.

First, is the puzzle about whether placebo effects are significant and remedial, and if so, for which conditions or symptoms? Extensive current research has—and continues to investigate—the therapeutic significance of the placebo effect for a wide range of illnesses. To date, researchers conclude that placebo effects are potentially beneficial for subjectively self-reported symptoms, rather than as cures for diseases [e.g., "there is no evidence that placebos can shrink tumors… [P]lacebo effects do not alter the pathophysiology of diseases" (Kaptchuk and Miller 2015, p. 8)]. Researchers have found sizeable placebo effects in relieving pain, depression, anxiety, and fatigue (Finniss et al. 2010; Kaptchuk and Miller 2015). Current and ongoing research is aimed at exploring placebo effects in these and other conditions

including cancer-related fatigue, migraines, irritable bowel syndrome, and nausea (e.g., Vase et al. 2003; Zhou et al. 2018). Further puzzles include comparing the size of placebo effects with common medications for these conditions (Chvetzoff and Tannock 2003; Kirsch et al. 2008; Temple and Ellenberg 2000).

Another puzzle-solving activity is aimed at investigating factors that influence the magnitude of placebo effects. Among the guiding theoretical assumptions are ideas that placebo effects are mediated by patient expectations and/or by classical conditioning, and that these psychological mechanisms can be triggered by a range of proximal factors in clinical and in healthcare research environments. Proximal cues believed to be relevant in the elicitation of placebo effects include socio-emotional communication style such as patients' perceptions about warmth and competence of practitioners (Howe et al. 2017; Kaptchuk et al. 2008) and the perceived 'status' of treatment paraphernalia including perceptions about the level of invasiveness of treatments; the experience of treatment side effects; and branding. (e.g., Berna et al. 2017; Kam-Hansen et al. 2014). Guided by implicit and explicit theoretical commitments about the nature of placebos and placebo effects, these studies aim to reveal in greater detail the factors that are responsible for influencing expectations and conditioning effects. The long-term, and frequently expressed goal of much of this research is to harness and augment placebo effects to improve patient well-being (Kaptchuk and Miller 2015, p. 6; see also: Price et al. 2008; Finniss et al. 2010, p. 689).

Additional studies pertaining to this empirical agenda include, but are by no means limited to, investigating whether verbal suggestions can manipulate patients' expectations thereby influencing the size of placebo effects (Benedetti and Amanzio 1997; Price et al. 1999; Vase et al. 2003); and research aimed at understanding whether deception is necessary to elicit placebo effects. With regard to the latter, so-called "open-label placebo" studies variously examine whether 'placebo pills'—described as "inactive substances" (normally understood to be treatments that are compositionally ineffective for a particular condition)—can elicit placebo effects. Experimental research includes the honest administration of placebos combined with other behavioral cues (e.g. optimism, confidence, and a comforting and reassuring demeanor) (Kaptchuk et al. 2010; Carvalho et al. 2016; Charlesworth et al. 2017; Zhou et al. 2018). Further studies are directed at the role of nonconscious cues in activating placebo effects (Jensen et al. 2012).

A third set of puzzle-solving activities are investigations into neural and cognitive pathways that give rise to placebo effects. So far, this research focuses primarily on a neuroscientific level by examining the neuroanatomy of placebo analgesia using PET and functional fMRI (Wager et al. 2004; Benedetti et al. 2005). Other studies focus on investigating the role of neurotransmitters such as endorphins, dopamine, cholecystokinin in placebo effect analgesia (Benedetti and Amanzio 1997; Benedetti et al. 2007; Finniss and Benedetti 2005).

Beyond this, other strands of empirical enquiry include: exploring patient-factors including the possibility that some individuals may be more liable to experience placebo effects than others. This multi-level research agendum investigates genetic signatures that may undergird the elicitation of placebo pathways—the so-called "placebome" (Hall et al. 2015) as well as the significance of dispositional (or personality) traits in placebo-effect responders (Geers et al. 2005).

Summary of the placebo paradigm

These puzzle-solving activities, we suggest, indicate that a placebo paradigm is underway; to reiterate, in proposing the existence of a placebo paradigm, we do not mean to suggest that conceptual matters are fixed for all time. We suggest that relative stability in respect of key concepts and 'laws' have given risen to extensive empirical growth. These experimental activities are the means by which placebo concepts are likely to be refined and sharpened (see: Kuhn 1970, p. 33; Bird 2014, p. 50). Therefore, when it comes to ontologically-motivated definitions of placebo concepts, we argue the burden is on proponents of conceptual overhaul to make the case that there is not yet a mature science of placebo studies, *or* to provide evidence that the placebo paradigm is now riddled with insurmountable anomalies. In Sect. 5, we suggest that, in respect of both options, no convincing arguments have so far been presented. Before turning our attention to this objective, we first address the question about whether there can be more than one placebo paradigm.

A Placebo paradigm in respect of RCTs?

So far, we have argued that a placebo paradigm has emerged with respect to placebo effects as a psychobiological phenomenon. It might be contended that it is also possible to speak of a distinctive paradigm that pertains to methodological placebos. Since the issue of multiple placebo paradigms can easily lead to befuddlement, it is important to emphasize the scope of the term 'paradigm' and why it clearly applies to psychobiological phenomena but, at best, only indirectly to methodological usage of placebo concepts. In short, we argue there is only one contender for a 'placebo paradigm'.

Properly understood, paradigms are structures that enable discoveries about some aspect of the world: "Normal science is predicated on the assumption that the scientific community knows what the world is like" (Kuhn 1970, p. 5)". In the case of ontologically-motivated definitions of placebo this targeted inquiry is clear: namely, scientific efforts aim to improve understanding of the nature of placebo concepts as 'natural' phenomena. However, within methodological contexts such as RCTs scientists do not strive for any such directed understanding of placebo phenomena per se. Rather, within clinical trials placebos are understood to be valuable devices which form part of an epistemological toolkit for investigating treatments. In this way, methodological placebos are construed as instruments. Of course, improvements in best practice with respect to RCTs can certainly be influenced by the accumulated findings of scientific paradigms e.g., by insights from patient-doctor social psychology, and our best understanding of the placebo effect, which can (and indeed *have*) led to the requisite of double-blinding as a standard in clinical trials. However, these considerations do not translate to methodological placebos comprising a distinctive paradigm of their own[4]—a notion which we argue constitutes a category mistake.

[4] Even to adopt the broader notion that clinical trials/RCTs (somehow) comprise a paradigm arguably stretches conceptualization of the term beyond a Kuhnian interpretation. To put things another way: while we can acknowledge that the medical sciences are paradigm-led, the question about whether aspects of medical epistemology constitute a paradigm per se—similar to whether scientific epistemol-

Notwithstanding, none of the foregoing reflections preclude revision to the term placebo as it arises in methodological contexts. Definitional amendments or indeed elimination of concepts is certainly possible outside of paradigm-driven science. Such revisions may be justified, for example, on philosophical or pragmatic grounds, including e.g., the need for terminological consistency or avoidance of confusions in usage.

In summary: placebos in RCTs are conceived as instruments—not objects, in the Kuhnian sense, for further directed scrutiny. However, this status does not grant methodologically-motivated revisions of the term placebo immunity from justifications for conceptual change, as we discuss below.

Three proposals for conceptual change

Using the standpoint of the placebo paradigm, in this section we evaluate three prominent but different proposals for conceptual change.

Grünbaum and Howick: the relativity of placebos

Grünbaum (1986) and Howick (2017) define 'placebo' and 'placebo effect' from methodologically-motivated starting points. Notably, however, their approaches attempt to bridge definitions of placebo concepts in use in both methodological (i.e. RCT) and ontological (i.e. scientific explorations of placebo effect) domains. This, we suggest, creates some complications. Since Grünbaum's account predates and acts as a template for Howick's model we begin by considering Grünbaum's conceptual framework.

Grünbaum proposes that we can typically differentiate between 'characteristic' and 'incidental' features of treatments which, in turn, are *relative to,* or dependent on, our theories about how a particular treatment works for a particular condition (Grünbaum 1986, p. 33). For example, the characteristic features of amoxicillin are its antibiotic constituent; the incidental features include its coloration, taste, bulking agent, branding, and price (see also: Blease 2018b). In contrast, Grünbaum says that placebos lack characteristic factors for the treatment of a given condition. Placebo effects, on the other hand, are defined as any beneficial health effects that are owed to the incidental features of a placebo. Furthermore, when used in a clinical contexts Grünbaum claims that placebos may be intentionally or unintentionally prescribed: in the former case, the clinician is aware that the treatment he or she prescribes is a placebo; in the latter case, the clinician mistakenly believes that the prescription has characteristic factors that are remedial for a target disorder.

Footnote 4 (continued)
ogy (such as Kuhn's insights) itself comprise a paradigm—is a meta-philosophical issue which takes us far beyond the remit of this paper (see Haack 2009 on characterizations of naturalized epistemology which speak to this debate).

While Grünbaum's account has been challenged on a number of grounds [see Howick 2017 for an excellent overview] the most common criticism is the failure of his framework to accommodate a special role for "patient expectations" in mediating placebo effects (Greenwood 1997; Waring 2003; Howick 2017). For example, Waring argues, "psychological factors such as a patient's expectations of benefit seem closer to what we intend by the placebo concept" (Waring 2003, p. 14 cited in Howick 2017). Notice then, that in taking this criticism seriously, Waring (and other scholars since, including Howick) thereby embrace an enthusiasm to embed our best scientific understanding of placebo effects (i.e. ontological considerations about *what* placebo effects are) in addressing and succeeding Grünbaum's overarching scheme. And indeed, in a recent publication, Howick has produced an ambitious and elaborate revision of Grünbaum's model.

Howick proposes that, "a treatment process is a [generic] placebo when none of the characteristic treatment factors C are effective… in patients X for D"; he defines "characteristic features" as a feature of treatments that "(1) *is not expectancy that a treatment is effective*; and (2) that has an incremental benefit on the target disorder over a legitimate placebo control" (Howick 2017, italics added). Finally, according to Howick, a placebo effect is, "either (a) a remedial effect produced by the incidental features of some treatment… or (b) any effect of a generic placebo" (Howick 2017). Howick defines "intentional placebos" as a treatment process that satisfies the following four conditions, of which he stipulates the fourth is not strictly necessary though it normally holds:

(1) the treatment is a generic placebo [as defined above]
(2) the practitioner believes that the characteristic factors all fail to be remedial for a given disease;
(3) the practitioner believes that some patients will benefit from the treatment due to one or more of its incidental features;
(4) (optional) the practitioner "abets, or at least acquiesces in" the patient's belief that, by virtue of some set of characteristic factors belonging to the treatment, it will be remedial for the given disease.

[Adapted from Howick (2017)]

Evaluation of relativity models from the placebo paradigm

Observe that according to both Howick and Grünbaum's respective models 'placebos' *and* 'placebo effects' are terms with shifting referents (Blease 2018b). From this perspective, the placeholders of the terms 'placebo' and 'placebo effects' are determined by theories about how particular treatments work—that is, in each case, by reference to their hypothesized characteristic and incidental features. Notably, then, in answer to Grünbaum's critics, Howick is also keen to give a nod to ontological concerns—hence his move to integrate "response expectancies" into his model. In so doing, Howick implicitly appears to acknowledge advances in scientific research into the placebo effect: he does not challenge the adequacy of "response expectancies" as an organizing tenet within empirical research. Nonetheless, even while attempting to embed current scientific thinking on the nature of placebo effects

(vis-à-vis "response expectancies") his account is expansive. In upholding point (a) [a placebo effect may be "a remedial effect produced by the incidental features of some treatment…"], the effects produced by the incidental features of a treatment or a 'generic placebo' (on Howick's construal) *may* be owed to placebo effects (as these are conceived in the placebo paradigm), but equally they may be owed to *any other incidental, salubrious psychobiological processes* (e.g. Pygmalion Effects, or other processes that might arise). In light of his aim to accommodate ongoing scientific conceptualizations of placebo effects, the upshot is an account that is too permissive since, he ultimately fails to properly distinguish placebo effects from other possible effects.

To recap: unlike the placebo paradigm definition of 'placebo effects', Howick's model is not strictly committed to *identifying* placebo effects with distinctive psychobiological mechanisms (response expectancies, and classical conditioning). In addition, the very reason for accommodating 'response expectancies' in his model was, in part, to answer Grünbaum's critics, and to acknowledge the widespread, scientific usage of the term but this incurs some consequences for his model. Should any other beneficial, (*non-response expectancy*) psychobiological mechanisms be discovered Howick's definition of placebo effects will be rendered outdated. Indeed, instead of overthrowing scientific current understanding of placebo effects, Howick's account ossifies it by embedding it within his schema. In depending on a key symbolic generalization of the placebo paradigm (namely, expectation theory) this account seems to unquestionably support current scientific endeavors; moreover, if he wishes to deviate from this analysis, we are owed an account of the ways in which he takes issue with the quality of this ongoing scientific research program. To do so would be to engage in discussion from *within* the placebo paradigm.

Another problem arises. When it comes to the second clause (b) [a placebo effect may be "any effect of a generic placebo"] we see that placebo effects need not be remedial effects at all: as Howick states, they can be "*any effects*" of a generic placebo. This means that (for example) Hawthorne Effects and subjective reporting biases might also be classified as placebo effects (since these are legitimate "effects" of generic placebos on Howick's model). Again, manifestly this is not what scientific researchers working within the placebo paradigm interpret placebo effects to encompass; instead, the term 'placebo responses' is used to differentiate this panoply of possible responses to receiving a control treatment in a clinical trial.

We suggest that in conflating two domains—(1) the methodological use of placebos in RCTs, and (2) placebo effects as an object of scientific scrutiny—Howick's model, perhaps inevitably, disappoints. Certainly, he does not offer strong scientific reasons for revising how 'placebo effects' are understood from the perspective of scientific research—to do so, he needs to show that anomalies or a breakdown in research has arisen.

It is also important to evaluate how Howick's conceptualization of placebos in clinical contexts compares with usage in the placebo paradigm. Reflect again on this model: "a treatment process is a [generic] placebo when none of the characteristic treatment factors C are effective… in patients X for D" (Howick 2017). Notice that within the placebo paradigm, so-called 'open-label placebos' involve

practitioners disclosing how placebo effects are believed to arise.[5] Therefore, an interesting incongruity between Howick's scheme and this particular clinical usage of 'placebos' is that open-label placebos *cannot* accurately be defined *as* 'placebos' on his model. On this point, a possible reply could be that of deciding that 'open-label placebos' are, according to Howick's definition, not 'placebos.' Nonetheless, we emphasize that this leads to some knotty practical issues with his account.

Other concerns arise in relation to Howick's definition of 'placebos' as they pertain to methodological concerns (i.e. conceptualizations in RCTs); we revisit this in Sect. 5.3.1 when we address problems anticipated by Nunn (2009a, b) and Turner (2012) that we suggest are not fully addressed by Howick in his 2017 paper. For now, we conclude that, while Howick's model is ambitious, ultimately, this may also be its downfall: in its attempt to provide a grand theory of placebo that bridges two disparate spheres of activity—the use of placebos in RCTs, on the one hand, and the science of placebo effects, on the other—it fails to adequately mount the case for conceptual revision in either domain.

Brody and Moerman: meaning models

A very different approach to conceptual revision is located in the writings of Howard Brody and Dan Moerman's meaning-based models (Brody 1980, 1999, 2000; Moerman 2002; Moerman and Jonas 2002). These independently proposed accounts pursue ontologically-motivated conceptualizations of 'placebo effects'; they do so, by re-conceiving placebo effects as therapeutic "meaning"-responses. Brody argues that 'placebo responses' are defined by "A change in the body…that occurs as the result of the symbolic significance which one attributes to an event or object in the healing environment" (Brody and Brody 2000, p. 9). On Brody's account "symbolic significance" is in turn described as "the meaning of the illness experience for the patient in a positive direction" (Brody and Brody 2000, p. 84). Moerman also follows this line of thought, and argues that the meaning response is "the psychological and physiological effects of *meaning* in the treatment of illness" (Moerman 2002, p. 14).

Both Brody and Moerman propose that the "meaningfulness" of some aspect of care, including an intervention, elicits a causal chain of neurobiological events that generate therapeutic effects. Meaning models also emphasize that such therapeutic effects can arise *without* the administration of placebos. Indeed, both scholars focus their attention on re-conceiving placebo effects as meaning responses, and have much less to say about 'placebos' whether in clinical trials, or clinical contexts. Unlike Grünbaum and Howick's conceptual approaches, these scholars argue that the terms 'placebo' and 'placebo effect' are *not*

[5] For descriptions of conditions under which open-label placebos are prescribed, including disclosure statements, see (for example): Kaptchuk et al. (2010), Carvalho et al. (2016) and Charlesworth et al. (2017).

conceptually entwined. For example, Moerman states that, "The one thing we can be absolutely sure of here is that placebos do not cause the placebo effect. Placebos are inert. To be inert is to not do anything" (Moerman 2002, p. 14; see also: Moerman and Jonas 2002, p. 471). Moerman also appears to defend the notion that 'placebos' are inert substances used to measure the effectiveness of 'verum' treatments in RCTs (Moerman 2002, p. 22ff).

Evaluation of meaning models from the placebo paradigm

The attempt to re-conceive placebo effects as "meaning responses" has been criticized widely (see: Annoni and Blease 2018; Miller et al. 2009). For example, Miller et al. (2009) argue that meaning response models present too broad a definition of the range of therapeutic effects that can occur in the clinical encounter. Indeed, despite Moerman and Jonas' criticism that the concept placebo effect has been expanded "very broadly to include just about every conceivable sort of beneficial biological, social, or human interaction" (2002, p. 471) they maintain that their own definition of meaningfulness can be ascribed to "*Most elements of medicine*" (2002, p. 473, italics added)—a definition that arguably renders the concept ambiguous. It should also be acknowledged that the vagueness of the term 'meaning' is a problem that Brody and Moerman independently concede but admit that they are unable to illuminate further (see, for example, Moerman 2002, pp. 148–149; Annoni and Blease 2018).

We therefore point to two problems. First, on this line of reasoning, replacing one allegedly vague term ('placebo effects') with another ('meaning responses') provides unpersuasive grounds for the necessity of conceptual revision. In light of the imprecision associated with the term 'meaning' it seems clear that a 'meaning response paradigm'—as a successor scientific paradigm to the current 'placebo paradigm'—is unlikely to emerge (at least, not without further refinement to the concept 'meaning' offered in these accounts). This may help to explain why meaning response models have received less attention in placebo studies in recent years. To date, neither Brody nor Moerman attacks the empirical success (or otherwise) of what we have identified as the placebo paradigm: to do so would provide a valuable starting point to mount claims for conceptual revision.

Second, Brody and Moerman's references to symbolism and semiotics, render meaning models (as currently construed) outside the remit of normal scientific research even while their purported cascade of neurobiological effects does not (see also: Miller and Colloca 2010, who also advocate semiotics as a means to explicate placebo effects). While others have criticized the meaning hypothesis as not yet scientifically tested (Howick 2017), the stronger argument being mounted here is that, in its current state, the meaning hypothesis and other proposed articulations of placebo effects with symbolism and semiotics are not scientifically test*able* and therefore unsuitable for scientific paradigm-driven research.

It might be countered that any such "meaning response" models are not intended to be amenable to scientific investigation. This approach would involve a radical departure from the current placebo paradigm. In response, Brody clearly intends for the meaning model to embrace (or eventually to lead to) a scientific program

of research (2000)—though, as argued above his proposals are not (yet) sufficiently developed to supplant (or refine) the current placebo paradigm. On the other hand, Moerman's stance is more ambivalent. He objects to a decompositional or mechanistic analysis of meaning responses (2002, p. 138), and argues, "[M]eaning is a relationship, a correspondence between one thing and another… knowing how these kinds of relationships work…is a hallmark of humanity" (Moerman 2002, p. 149) and proposes that meaningful experiences *activate* neurobiological processes (Moerman 2002, p. 141). The question that Moerman's model leaves unanswered is: What is the relationship between "meaningfulness" and these cognitive and neurobiological processes? Does he consider "meaning responses" to be scientifically explicable? Disappointingly, in his monograph, he sidesteps the problem, pegging it as a "more research needed" issue (Moerman 2002, p. 147). In a recent joint paper, he maintains this ambiguous outlook. On the one hand, he argues:

> We currently have many neuroscientific studies of placebo controls, based on producing and analyzing fMRI scans. What we propose to *add* is ethnomethodological fieldwork studies, so that we might start to build a picture of the logic of meaning responses. (Hutchinson and Moerman 2018, p. 376, italics added)

This suggests some measure of preservation with respect to current placebo research; yet, more strongly the authors concomitantly propose abandonment of the scientific project. Ironically, in making their case they also employ Lakatos' language of natural scientific theory change; by urging that current placebo research programs are, "degenerative and terminally so. Another research program is required" (Hutchinson and Moerman 2018, p. 377), such a program, they propose, should employ the techniques of ethnomethodology. Further elaboration is required to understand what ethnomethodology might offer: what its techniques and methods involve; how they can help to determine 'meaningfulness'; and how we might better understand the putative therapeutic effects of meaning responses in medicine.

As noted, when it comes to conceiving 'placebos' in methodological contexts Moerman and Brody provide less by way of critique or commentary. Moerman assumes that 'placebos' are a category of 'things" in the world which are defined a priori as inactive or "inert" substances. This stands in opposition to the interpretation of placebos in RCTs as a moving target that is dependent on the treatment under investigation (see also: Blease 2018b; Gaab et al. 2018). Notwithstanding, similar to Moerman, scientists working within the placebo paradigm often refer to 'placebos' in clinical contexts (including in placebo experimental contexts) as 'pills' or 'sham medication'. Within the placebo paradigm, 'inertness' or rather 'ineffectiveness' is shorthand for the negligible compositional effects of the placebo 'pill' in treating a condition or set of symptoms (Kaptchuk and Miller 2015; Blease et al. 2017). It is not clear whether Moerman wishes to suggest something stronger, namely that pills are genuinely inert. ["The one thing of which we can be absolutely certain," he argues, "is that placebos *do not* cause placebo effects. Placebos are inert and don't cause anything" (Moerman and Jonas 2002, p. 471)]. Moerman's argumentation can be challenged on two grounds, since there are two possible, distinctive kinds of response to the administration of placebos. First, are those cases where the

pills generate effects outside of placebo effects (i.e. unmediated by perception); as Golomb et al. have argued, placebos—even when interpreted as being sugar pills, i.e. microcrystalline cellulose or lactose pills—always have *some* kind of effects in virtue of their molecular composition, and sometimes these effects even influence the outcome of clinical trials (Golomb et al. 2010). Second, from the perspective of the placebo paradigm, placebos *are* understood to potentially elicit placebo effects: on this conceptual framework, it is the *perception* of the placebo pill (in conjunction with other cues) that may elicit these effects. Therefore, Moerman's claim that "Placebos are inert and don't cause anything" is unreasonably strong, requiring a more nuanced elucidation.

In summary: in light of the vagueness associated with 'meaning response' models and the omission of detailed clarification about methodologies and techniques for investigating meaning in medicine, we argue there are currently insufficient reasons to give up on the placebo paradigm, and to adopt Moerman or Brody's conceptual scheme.

Nunn and Turner: conceptual eliminativism

Other philosophers and historians take a very different tack in proposing conceptual revision. Nunn and Turner argue that placebo concepts should be eliminated from use altogether (Nunn 2009a; Turner 2012). For example, Turner argues that any ontologically-motivated attempt to define *placebo effects* is misguided. He argues that 'placebo effects' refers to a loose collection of disparate psychological effects/responses and there is no scientific gain to be obtained from classifying these under the same explanatory label (Turner 2012, p. 428). Instead, he proposes that the concept would be more usefully and more accurately fragmented into distinct scientific descriptions of specific purported psychobiological pathways (i.e. responses, classical conditioning, etc.) according to our best scientific evidence (Turner 2012, pp. 428–429).

Again, wielding Okham's razor, and appealing to the need for pragmatic clarity, Turner insists that we should drop reference to placebos in clinical trials and should simply speak of certain "control roles" or "comparisons" (Turner 2012, p. 427). For Nunn and Turner, the logic behind comparing a treatment with a control group is simply to evaluate whether some aspect of that treatment is efficacious. Therefore, in light of this epistemic aim, Turner argues, a 'placebo' should mimic *every* aspect of the treatment under scrutiny except for the particular feature that is hypothesized to be remedial. This interpretation of how placebos should be understood in RCTs appears to be shared by many placebo scientists (see also: Gaab et al. 2018; Howick and Hoffmann 2018).

Turner considers the term 'placebo' to be a source of methodological error: he argues that we commit an intuitive category mistake when we suppose that placebos are 'particular things'. The error, he claims, is located in the assumption that, "'placebos' are conceptually prior to placebo comparisons: as if it were possible to take a jar of 'placebos' off the shelf, ready to use in some forthcoming RCT" (Turner 2012,

p. 423). When this happens, he asserts, "Talk of 'placebos' can tempt us to neglect questions about the adequacy of the placebo group" with the result that "the credibility of trial results are often diminished" (Turner 2012, p. 430). *Methodologically-speaking*—like Nunn—Turner considers the term 'placebo' to be redundant at best, epistemologically harmful at worst (Turner 2012, p. 430). In summary: Turner and Nunn propose elimination and replacement of the term 'placebo' in RCTs with the terms 'control' or 'comparison', not least to improve understanding about the role of placebos among clinical researchers (see: Turner 2018).[6]

Evaluation of eliminative models from the placebo paradigm

While Nunn remains silent on the issue, Turner argues that the term 'placebo effects' would be more usefully replaced by descriptions of psychobiological pathways—for example, 'response expectancies', 'conditioning', and so on. Is he correct in thinking that scientific research would be expedited if 'placebo effects' was eliminated from usage? To examine his point, consider first, the terms 'placebo effects' and 'response expectancy'. If we assume that these concepts are semantically isomorphic it is unclear what we would gain from replacing the former with the latter term. If, on the other hand, 'placebo effects' is better understood as an umbrella term for a diverse range of psychobiological processes, then conceptual revision, as Turner, argues might be conceivable.

Scientists working in placebo studies *do* appear to differentiate between these mechanisms, apparently with explanatory gain. For example, there is ongoing theoretical discussion about whether response expectancies and classical conditioning amount to distinctive processes (Stewart-Williams and Podd 2004). We argue that replacement by further definitional fragmentation is unwarranted—at least for now: placebo scientists appear to be fully cognizant of multiple psychobiological pathways that, they argue, give rise to 'placebo effects.' In summary: Turner's point is not as persuasive as it needs to be for elimination and replacement to go through. Scientists appear to benefit from explanatory consilience as well as an empirically productive conceptual framework when they subsume these psychobiological processes under a single 'placebo effect' model. Conceptual refinement, when it arises, we suggest is likely to be driven from within, via anomalies arising from scientific articulation of the placebo paradigm (i.e. through puzzle-solving).

When it comes to use of the placebo concept in RCTs, Nunn and Turner assert that placebos should *not* be conceived as 'things' but rather as epistemological tools deployed for the logic of treatment comparison. Turner emphasizes that the term 'placebo' in RCTs is a continued sourced of unwitting confusion among clinical researchers, and as a consequence the scientific integrity of clinical trials is often jeopardized (see also: Blease 2018b; Kirsch 2009). He observes that this happens when clinical researchers reify the term placebo, and assume that it is a 'thing' (e.g.

[6] It should be pointed out, however, that in an unexpected and perhaps unnecessarily concessionary conclusion, Turner closes his 2012 paper by declaring that he would be "happy to use the term 'placebo comparison'" (2012, p. 431).

a sugar pill) rather than a tool for gauging the efficacy of a treatment. The failure to mimic the incidental features of the verum in the placebo intervention can result in patients (and practitioners) "breaking blind"—that is, accurately guessing that they have been allocated to the 'placebo' (or indeed, the verum) arm of the trial. For example, failure to operationalize placebos properly can lead to over-estimates about efficacy of the verum treatment (see: Gaab et al. 2018; Howick and Hoffmann 2018).

This brings us to a question that Howick reflects on in his revision of Grünbaum's model—why not simply adopt the terminology "control"? In responding to this criticism, Howick says:

> Once we have described the features of the treatment, [sic] to drop the term 'placebo' altogether, Turner argues. Yet [it] does not follow from the fact that adequate descriptions of terms are useful, and that they can, in principle, be replaced by the descriptions, that we should give up on trying to provide an adequate characterization of a term… [M]oreover, as my initial remarks about the connection with randomized trial methodology indicate, important epistemic and ethical issues are involved along with the conceptual ones. Simply dropping the term will not make these issues go away. (Howick 2017, p. 1369)

Again, the blending of ontological issues (with regard to definitions of the *placebo effect*) and methodological concerns (*placebos in RCTs*) in this response stands in need of justification. As previously noted, we argue that these two applications of the term 'placebo' are distinctive and must remain so. The discovery of placebo effects with the launch of controlled trials (Kaptchuk et al. 2009) is not a strong justification for this phenomenon to be conceptually or terminologically wedded to concepts of placebos in clinical trials, in perpetuity. The point is also raised by Blease who argues that, "Diachronically (or historically speaking) the terms *placebo* and "placebo effect" have undergone semantic evolution…These semantic changes have been masked by nominal (if not conceptual) continuity." (Blease 2018a, p. 424).

Therefore, we respectfully disagree with Howick, and submit a partial defense of Turner's central contention. Even beyond these problems with Howick's conceptual model, we suggest that his schema is unlikely to enhance health researchers' (probably limited) understanding of placebos, and may add layers of confusion to conceptual matters among clinical researchers and scientists alike. We certainly do agree with Turner (and Howick) that clinical researchers often misconceive placebos thereby undermining the methodological integrity of RCTs. But to address this problem, we cautiously advocate Turner's (and Nunn's) view that continued use of the term 'placebo' in RCTs risks undermining the very logic behind controlled trials. Whether terminological overhaul is likely to happen, is another matter (Turner 2018). Regardless, improved epistemological education in respect of placebos in RCT is necessary (see: Blease et al. 2017; Gaab et al. 2018; Howick and Hoffmann 2018).

In summary: we suggest that while Turner does not provide strong justifications for terminological revision of 'placebo effect' in scientific research, both Nunn and Turner make persuasive contributions to the debate about terminological revision and replacement of the term 'placebo' in the context of RCTs. Their pragmatic justifications, we suggest, simplify and clarify the role of placebos in clinical trials.

Conclusions and recommendations

Placebo studies needs a roadmap for thinking about disagreement. We proposed that major disputes about placebo concepts and their resolution are best understood by striving to identify paradigm-driven placebo research. Therefore, in this paper, we explored conceptual debates using a Kuhnian framework. We noted that relative stability about conceptual matters is imperative for scientific placebo research to get off the ground; we argued that the scientific strides that have emerged in the basic research in placebo studies are nontrivial. Against these considerations, we proposed that proponents of revision to placebo concepts have two choices. Either they can argue that basic scientific research in placebo studies is lacking; or that serious empirical problems arise with current conceptualizations of placebo effects, and that a scientific revolution is warranted. The former, we suggest, is a tall order, and in any case not one that has successfully been proposed by advocates of conceptual overhaul. Indeed, the latter option requires critics to give due acknowledgement to the placebo paradigm.

Using this Kuhnian framework, we examined three different kinds of proposal for conceptual change in respect of the term 'placebo effect'. In our analysis we argued Grünbaum and Howick's models; Brody and Moerman's meaning response models; and Turner's eliminative strategy presented no strong justifications to reconceive or discard the term 'placebo effects'.

On the other hand, when it comes to the term 'placebo', context matters. The case for conceptual revision can also be made in clinical research usage. 'Placebos' as methodological tools in clinical trials should ideally mimic every aspect of a verum treatment except for the hypothesized remedial component. Nunn and Turner argued that the term 'placebo' is not analytically useful, and may even risk methodological error. We agree. Notice that this use of 'placebo' contrasts with a second, distinctive interpretation of placebos as they are used in patient contexts. This latter usage of the term by placebo scientists refers to treatments that are not known to be effective for a particular condition and may elicit *placebo effects* (as defined above) under particular proximal conditions.

Two courses of action may prevent methodological error arising from misunderstandings about placebo concepts among clinical researchers and medics. First—as Nunn and Turner recommend—we might eliminate the term outright, and undertake the mammoth task of re-educating clinical researchers to use the term 'control' or 'comparison' group in clinical trials, instead. While this is clearly a radical proposal we do not believe it is impracticable although it presents onerous challenges. The second option is to embark on the same immense task of promoting, and re-educating clinical researchers, and medical educators about placebo concepts whilst also conserving the term 'placebo' for research purposes. It should be noted that Turner suggests that this may be a satisfactory compromise (Turner 2012, p. 431). A compromising, middle-ground may be to adopt the term 'placebo-control' rather than simply 'placebo' in clinical contexts. In the long-run it may ultimately be more fruitful for medical research to gradually adopt the more radical eliminative strategy, and to get rid of the term 'placebo'. However, we underline that epistemological

and scientific literacy about placebos and placebo effects must underpin any reform strategy.

When it comes to the term 'placebo effects', what are the prospects for conceptual revision? The fact that normal scientific research is underway does not safeguard placebo concepts from further refinement or even wholesale revision: as Kuhn emphasized, paradigm articulation is "simultaneously theoretical and experimental" (1970, p. 33). Nonetheless, conceptual revision will almost certainly be precipitated by anomalies arising from within the paradigm.

Although not yet widespread, very recently the call for conceptual adjustments in respect of 'placebo effects' has been made, notably by pioneering scientists who work in the field. For example, in a recent paper Kaptchuk articulates various anomalies in respect of expectancy and conditioning theories (Kaptchuk 2018). From the vantage point of the placebo paradigm, these criticisms identify specific problems that have arisen as a result of ongoing 'puzzle-solving' (Kaptchuk 2018, pp. 319–322). Among Kaptchuk's observations is his claim that, "*new data* has yet to be *incorporated* into expectancy theories"; and he concludes that "expectation theories need *refinement*" (Kaptchuk 2018, p. 321, italics added; see also: Ongaro and Kaptchuk 2018).[7] From a paradigm-led perspective, the tightening of concepts is to be expected as science bootstraps its way to the truth: we forecast continued honing of what is meant by the term 'placebo effect'.

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[7] We note that, while conceptual refinement of 'placebo effects' is in the offing, fully developed testable hypotheses have not yet accompanied these developments.

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