From substance to process: a meta-ethnographic review of how healthcare professionals and patients understand placebos and their effects in primary care

Abstract

Research suggests that a ‘placebo’ can improve conditions common in primary care including pain, depression, and irritable bowel syndrome. However, disagreement persists over the definition and clinical relevance of placebo treatments. We conducted a meta-ethnographic, mixed-research systematic review to explore how healthcare professionals and patients understand placebos and their effects in primary care. We conducted systematic literature searches of five databases – augmented by reference chaining, key author searches, and expert opinion – related to views on placebos, placebo effects, and placebo use in primary care. From a total of 34 eligible quantitative, qualitative and mixed-methods articles reporting findings from 28 studies, 21 were related to healthcare professionals’ views, 11 were related to patients’ views, and two were related to both groups. In the studies under review, healthcare professionals reported using placebos at markedly different frequencies. This was highly influenced by how placebos were defined in the studies. Both healthcare professionals and patients predominantly defined placebos as material substances such as ‘inert’ pills, despite this definition being inconsistent with current scientific thinking. However, healthcare professionals also, but less prevalently, defined placebos in a different way: as contextual processes. This better concurs with modern placebo definitions, which focus on context, ritual, meaning, and enactivism. However, given the enduring ubiquity of substance definitions, for both healthcare professionals and patients, we question the practical, clinical validity of stretching the term ‘placebo’ towards its modern iteration. To produce ‘placebo effects’, therefore, primary healthcare professionals may be better off abandoning placebo terminology altogether.

Keywords

Placebos; placebo effects; systematic review; meta-ethnography; primary care.

Introduction

The placebo concept has a long history (Shapiro and Shapiro, 1997), but our modern notion is grounded in how we validate the existence of therapeutic effects through the use of the Randomised Controlled Trial (RCT) (Miller and Brody, 2011). In a RCT a particular mechanism – often a drug mechanism – is isolated by controlling for other factors that might influence the outcome of the trial, including, for example, natural history and regression to the mean. By using a 'placebo' to control for these factors, the RCT has been an effective tool in the advancement of modern medicine (Friedman et al., 2015; Pocock, 1983). However, in order to isolate the particular mechanism under investigation, this process of establishing treatment and control groups in a certain way also controls for contextual or social effects that can occur naturally during treatment; for example, the effects of empathic care, a patient's belief in a treatment, and the method of administration (Walach et al., 2006; Avins et al., 2012; Howick, 2009). It is the natural occurrence of something like these 'placebo' effects, and the idea that they can be deliberately induced in clinical practice, that is the focus of this review.

Research suggests that a 'placebo' can lead to improvements in conditions often treated in primary care environments, including pain (Benedetti, 1996), depression (Kirsch et al., 2002) and irritable bowel syndrome (Kaptchuk et al., 2010). However, disagreement persists over the definition of placebos and their effects (Kirsch, 1997; Moerman and Jonas, 2002; Grünbaum, 1986; Kaptchuk and Miller, 2015; Shapiro and Shapiro, 1997; Colloca and Miller, 2011b), and the efficacy and ethics of using placebos in clinical practice (Colloca and Miller, 2011a; Miller and Colloca, 2009). A previous review suggests that the frequency and circumstances of placebo use in clinical practice vary substantially, that attitudes among

healthcare professionals and patients differ considerably, and that there is no clear definition of placebos in clinical practice (Fässler et al., 2010). In this environment whereby the definition, efficacy and ethics of clinical placebo treatment remain contentious, both the American Medical Association (Bostick et al., 2008) and the British Medical Association (Brannan et al., 2012) currently prohibit the practice of 'placebo prescribing' or 'placebo use' without patient consent.

Given the tantalising yet unproven potential for improving patient outcomes by using placebos in clinical practice, particularly in primary care, we conducted a systematic review of how healthcare professionals and patients understand placebos and their effects in primary care. Our aims are to:

1. Conceptualise how healthcare professionals and patients understand placebos, placebo use, and placebo effects in primary care;
2. Explore the consequences of how healthcare professionals and patients understand placebos, placebo use, and placebo effects in primary care; and
3. Generate new insights into how we conceive of placebos and their effects in primary care.

Methods

Given the conceptual ambiguity in the literature, we conducted an abductive (i.e. orientated towards theory generation), mixed-research synthesis, in which diverse findings from both qualitative and quantitative studies are arranged into a coherent theoretical interpretation (Sandelowski et al., 2012; Pluye and Hong, 2014). This was operationalised using a meta-ethnographic methodology (Noblit and Hare, 1988) situated within a theoretical framework of American pragmatism, whereby a concept is clarified by equating its meaning with the practical implications of its conceived effects (Peirce, 1878/1982).

Methodology

Meta-ethnography is a flexible approach to synthesis, in which both inductive and abductive modes of non-necessary inference (whereby the certainty of formal logic is traded for the possibility of new knowledge) are possible. Although initially used for synthesising a small number of conceptually rich studies, meta-ethnography is now widely used in healthcare to synthesise larger literatures (Atkins et al., 2008; France et al., 2014). And although initially intended to only synthesise qualitative studies, there is no epistemological reason why it cannot be used in a mixed research synthesis, as in this review (Sandelowski et al., 2012; Dixon-Woods et al., 2004).

In meta-ethnography, studies are not just combed for themes that might be similar or different, analysis is instead focussed on actions and processes in their social and historical context (Noblit and Hare, 1988). A meta-ethnographic approach can be directly linked with grounded theory methodology. Indeed, Noblit and Hare (1988: p.63) make this link in the initial monograph, noting that "this is the same as basic theorizing in qualitative research and is conceptualized… as… grounded theory.". Because grounded theory "comprises a systematic… and comparative approach for conducting inquiry for the purposes of constructing theory" (Bryant and Charmaz, 2007: p.1) and focuses on "analysing actions and processes rather than themes and structure" (Charmaz, 2014: p.15), conceiving of meta-ethnography through the prism of grounded theory could make the approach more accessible. We have explored the selection of meta-ethnography in more detail in a recent methods case study (Hardman and Bishop, 2018). Terminology debates notwithstanding, given the complexity and uncertainty surrounding placebos and their effects in primary care, a meta-ethnographic approach is well suited to this review.

Inclusion and exclusion criteria

Table 1 shows inclusion and exclusion criteria. We focussed on the views of healthcare professionals and patients in the context of primary care, in line with our research aims. We excluded clinical trials and laboratory based placebo studies because they do not directly capture the views of healthcare professionals and patients. We excluded qualitative studies nested in clinical trials because such studies focus on views of placebos in trials, not clinical practice (e.g., Bishop et al., 2012). We excluded studies based in hospitals and other secondary or tertiary care settings to restrict findings to primary care.

Table 1: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Healthcare professionals, patients, or potential patients	
Phenomena of interest	Views on placebo effects, placebo response, placebo use	
Context	Primary care	Placebo controls in clinical trials Laboratory based placebo studies
Study design	Empirical studies	Non-published studies RCTs

Search strategy

Systematic literature searches, with no date limits, were conducted in January 2017. The overall strategy reflects guidance on literature searching for meta-ethnographies (Atkins et al., 2008; Malpass et al., 2009; Campbell et al., 2011) and mixed method syntheses (Pope et al., 2007; Dixon-Woods et al., 2006a; Dixon-Woods et al., 2006b). We searched five electronic databases (CINAHL, MEDLINE, Embase, PsychINFO, and Web of Science – see Appendix 1 for specific strategies), conducted reference chaining and key author searches of

first authors, and sought expert opinion by emailing members of the Society for Interdisciplinary Placebo Studies.

Screening and selection

First, studies were screened by title and abstract by the primary author (DH) and a second reviewer (AG). Then, suitable studies were screened by full text. Discrepancies were resolved by discussion among DH, AG, GL and FB. Examples of discrepancies included disagreement on whether studies were in the context of primary care, and whether the phenomenon of interest was placebos or other closely related phenomena such as complementary and alternative medicine.

Quality assessment

Studies were appraised using the Mixed Methods Appraisal Tool (MMAT) (Pluye et al., 2011), designed for appraising and describing the methodological quality of quantitative and qualitative studies for systematic reviews. Early testing suggests it is a reliable tool (Pace et al., 2012). DH appraised all studies, and FB, AG, and GL each appraised a proportion of studies; we reached agreement through discussion. Examples of topics discussed in this process included the categorisation of studies (see Appendix 3 for a list of these categories), and the application of various quality criteria, including consideration given by researchers to context and the appropriate use of measures. Any intractable issues were resolved by majority consensus. However, in line with other meta-ethnographies (Atkins et al., 2008; Malpass et al., 2009) we did not exclude studies based on the appraisal, but instead integrated potential limitations into the synthesis.

Data extraction

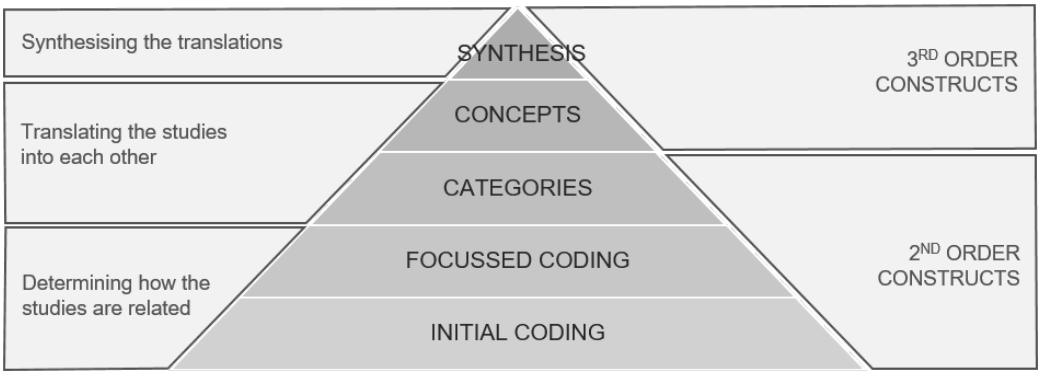
DH formally extracted the following data from all included papers: author, year of publication, country, setting, aims, participants, data collection methods, and main findings. This was checked by FB. We read the studies chronologically as the concept of 'placebo effects' has developed significantly over time (Benedetti, 2014; Shapiro and Shapiro, 1997).

Analysis and synthesis

Analysis and synthesis were orientated in three phases (Noblit and Hare, 1988): determining how the studies are related; translating the studies into each other; and synthesising the translations. On commencing the analysis there was potential for one of the following syntheses, depending on the initial findings (Noblit and Hare, 1988): *reciprocal*, when findings from studies are similar and can be directly translated into one another; *refutational*, when findings from studies are dissimilar or contradictory, and *lines-of-argument*, when findings from studies have similarities and differences and a new context is produced.

We operationalised this iterative process by adapting Charmaz's (2014) constructionist grounded theory analysis approach (see Figure 1). Coding was conducted not with the aim of being exhaustive, but as a mode by which dominant findings could emerge.

Figure 1: Data analysis and synthesis



Initial coding was conducted by DH. We used the method of constant comparison (Glaser and Strauss, 1967/2009) to create focussed codes, which included the most frequent or significant initial codes. These informed the creation of categories, which are significant focussed codes or patterns interpreted from several codes. We discussed these categories in data meetings, and from these discussions and subsequent analysis we created theoretical concepts (analytic ideas that offer an explanation for the data) which informed the synthesis.

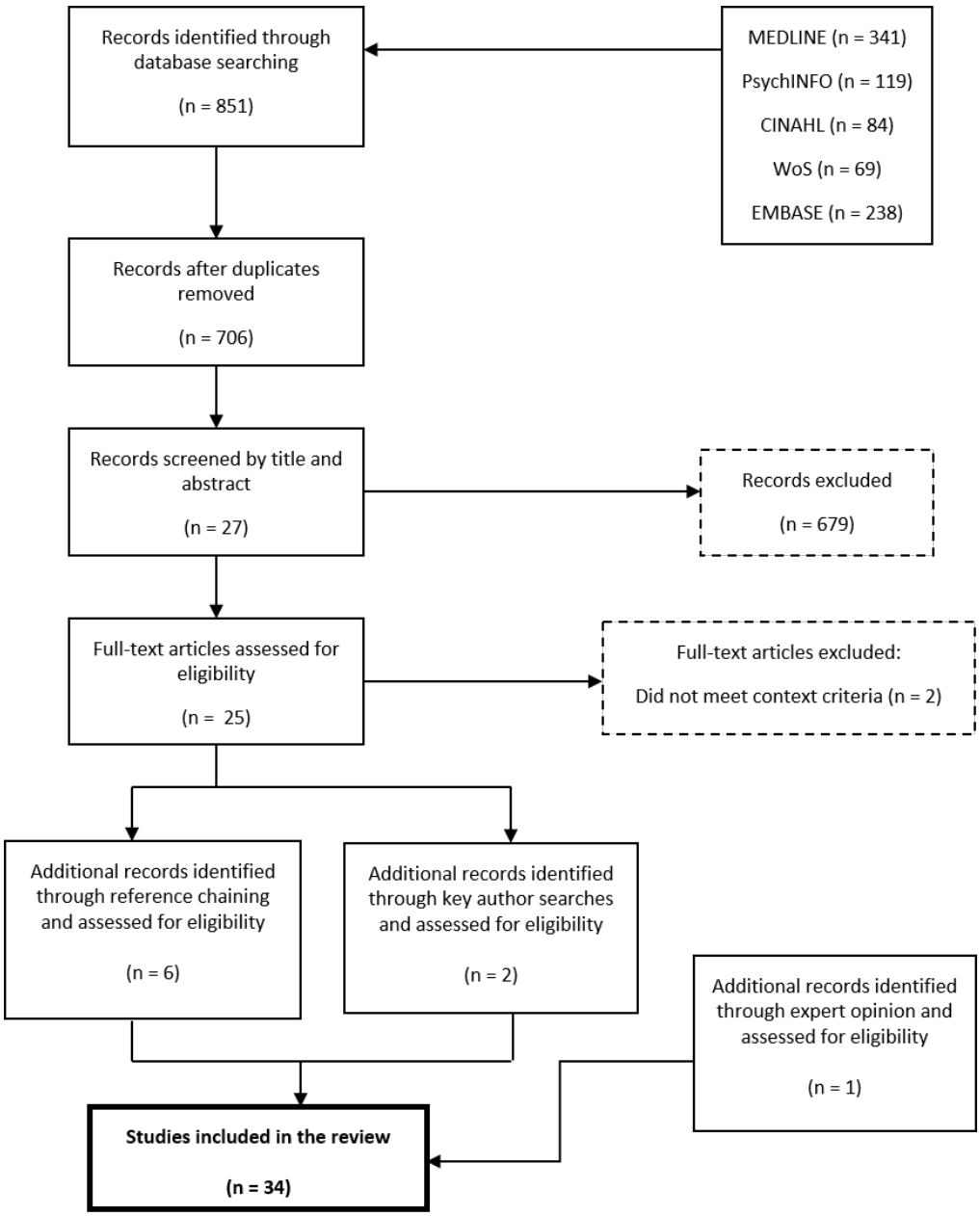
To overcome the incommensurable quantitative and qualitative primary data in a mixed research synthesis, and in line with a meta-ethnographic approach, we focussed analysis at Schutz's (1973) level of second-order constructs, which are the original study authors' interpretations of their data. Interpretations emerging from the review were deemed third order constructs, or "interpretations of interpretations of interpretations" (Noblit and Hare, 1988: p.35). Unlike in some meta-ethnographies, we considered direct participant quotes presented in the studies to be second order constructs; by the time these data are presented in a paper they have already been selected by researchers and removed from their original context, which necessarily involves interpretation.

Results

Searches

Search results are in an adapted PRISMA flow-chart (Moher et al., 2009), in Figure 2.

Figure 2: PRISMA flowchart



Study characteristics

The characteristics of included studies are shown in Table 2 (see Appendix 2 for an expanded table including a summary of study main findings). From 34 eligible articles reporting findings from 28 studies, 21 were related to healthcare professionals' views, 11 were related to patients' views, and two were related to both healthcare professionals' and patients' views. Twenty seven were broadly quantitative, six qualitative, and one mixed methods. Methods of data collection included surveys (n = 30), interviews (n = 4), focus groups (n = 1), and ethnographic observation (n = 1).

Quality assessment

The results of the quality assessment were variable (see Appendix 3). Some studies were well designed and conducted, but we assessed some as being of low quality. Most of the survey-based studies we assessed to be of low quality had a combination of unrepresentative samples and low response rates. And some qualitative studies we assessed to be of low quality generally lacked contextual and reflective considerations. However, some studies that were intuitively interesting, and which contributed rich data to the review, scored badly on the assessment. For example, one ethnographic study (Comaroff, 1976) did not meet the initial screening criteria yet was influential. This highlighted one limitation of the MMAT: the strict requirement for clear research questions and objectives necessarily precludes more exploratory modes of inquiry, such as ethnography. This emphasises the limitations of conducting a quality assessment in a meta-ethnography and supports recent practice not to exclude studies based on formal quality assessment results (Atkins et al., 2008; Malpass et al., 2009).

Table 2: Characteristics of eligible articles (n=34)

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims
1	(Shapiro and Struening, 1973a)	USA	General practice Hospitals Research	Psychiatrists (119) Internists (50) GPs (14) Surgeons (16)	Quantitative survey	To investigate differences in the definition and conception of placebos among physicians.
2	(Shapiro and Struening, 1973b)	USA	General practice Hospitals Research	Psychiatrists (117) Internists (50) GPs (14) Surgeons (14)	Quantitative survey	To assess ethical attitudes towards the use of placebos in treatment and research.
3	(Shapiro and Struening, 1974)	USA	General practice Hospitals Research	Psychiatrists (114) Internists (48) GPs (15) Surgeons (14)	Quantitative survey	To assess the tendency of physicians to attribute the use of placebos or nonspecific treatment to other physicians.
4	(Comaroff, 1976)	UK	General practice	GPs (51)	Qualitative observation Interviews	To investigate how doctors, as placebo prescribers, perceive and employ the placebo concept.
5	(Thomson and Buchanan, 1982)	New Zealand	General practice	GPs (44)	Quantitative survey	To determine GPs' basic understanding of the placebo effect and their views on the use of placebo treatments.
6	(Lynoe et al., 1993)	Sweden	Primary healthcare centre University	Physicians associated with a university (47) GPs (47) Patients (83)	Mainly quantitative survey with some open ended questions	To investigate the attitudes of patients and physicians toward placebo treatment.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims
7	(Hróbjartsson and Norup, 2003)	Denmark	General practice Private practice Hospitals	GPs (182) Hospital physicians (185) Private specialists (136)	Quantitative survey	To investigate the proportion and types of placebo intervention, conditions of use, and attitudes towards use.
8	(Nitzan and Lichtenberg, 2004)	Israel	Hospitals Community clinics	Hospital physicians (31) Head nurses (31) Family physicians (27)	Quantitative survey	To gauge the frequency and circumstances of, and attitude towards, placebo use in clinical practice.
9	(Chen and Johnson, 2009)	New Zealand	Primary Care Clinics	Patients (211)	Quantitative survey	To examine patients beliefs about the placebo effect, views on the use of placebos in clinical practice, and their willingness to participate in a placebo-controlled RCT.
10	(Fässler et al., 2009)	Switzerland	General practice Private practice	Paediatricians (67) Urban GPs (41) Suburban GPs (55) Rural GPs (70)	Quantitative survey	To investigate to what extent and in which way Swiss primary care providers use placebo interventions.
11	(Ferentzi et al., 2010)	Hungary	General practice	GPs (94)	Quantitative survey	To investigate how GPs in Hungary perceived some important aspects of their own placebo use.
12	(Kermen et al., 2010)	USA	Family practice	Family physicians (412)	Mainly quantitative survey with some open ended questions	To gain a better understanding of the role of placebos in clinical practice on a national level.
13	(Fässler et al., 2011)	Switzerland	Primary care	GPs (232) Patients (414)	Quantitative survey with one open-ended question	To compare the proportions of patients and physicians who would accept therapies that work by enhancing self-healing capacities and by exploiting contextual factors.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims
14	(Fent et al., 2011)	Switzerland	Primary care	GPs (8) Internists (2) Paediatrician (1) Psychiatrist (1)	Semi-structured interviews	To explore physicians' views on the use of placebos in daily practice.
15	(Ferentzi et al., 2011)	Hungary	General practice	GPs (169)	Quantitative survey	To provide a detailed description of physicians' attitudes toward, and knowledge of, clinical placebo use.
16	(Kisaalita et al., 2011)	USA	University	Members of the public (103)	Quantitative survey with experimental component	To examine the acceptability and ethics of placebo treatment for pain.
17	(Babel, 2012)	Poland	Primary care	Primary care physicians (190)	Quantitative survey with experimental component	To identify factors that contribute to the high variability of the rates of use of placebo interventions reported in questionnaire surveys.
18	(Kisaalita and Robinson, 2012)	USA	University	Members of the public (100)	Quantitative survey with open-ended question	To examine the acceptability, efficacy and knowledge of analgesic placebo treatments.
19	(Koteles and Ferentzi, 2012)	Hungary	Online news site	Members of the public (6104)	Quantitative survey	To assess the attitudes of laypeople toward deceptive clinical placebo use.
20	(Meissner et al., 2012)	Germany	General practice	GPs (208)	Quantitative survey	To collect data on the use of placebo interventions by GPs in Germany.
21	(Babel, 2013)	Poland	Primary care	Primary care physicians (169)	Quantitative survey	To investigate the behaviour beliefs and attitudes of Polish primary care physicians concerning the use of placebo interventions.
22	(Howick et al., 2013)	UK	Primary care	GPs (783)	Quantitative survey	To investigate the prevalence of placebo use in UK primary care.
23	(Hull et al., 2013)	USA	Primary Care	Patients with chronic illness (853)	Quantitative survey	To examine the attitudes of US patients about the use of placebo treatments in medical care.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims
24	(Linde et al., 2013)	Germany	General practice	GPs (84) Internists (3) Orthopaedists (1)	Quantitative survey (n=80) Cognitive interviews (N=7)	To develop a questionnaire.
25	(Nitzan et al., 2013)	Israel	Academic centres	Students (344)	Quantitative survey	To investigate the opinions of healthy students regarding the acceptability of placebo treatment if they were to experience depression.
26	(Bishop et al., 2014a)	UK	Community	General public (58)	Focus groups	To identify when and why placebo-prescribing in primary care might be acceptable and unacceptable to patients
27	(Bishop et al., 2014b)	UK	General practice	GPs (783)	Qualitative survey	To explore GPs' perspectives on clinical uses of placebos.
28	(Linde et al., 2014)	Germany	Private practice	GPs (319) Internists (311) Orthopaedists (305)	Quantitative survey	To investigate the use of placebos and non-specific treatments among physicians working in private practices in Germany, and how such use is associated with the belief in and the use of complementary and alternative treatments.
29	(Tandjung et al., 2014)	Switzerland	Community	Patients (12)	Semi-structured interviews	To explore patients' conceptualisation, experiences and attitudes regarding the use of placebos in daily clinical practice.
30	(Linde et al., 2015)	Germany	Private practice	Family physicians (319) Internists (311) Orthopaedists (305)	Quantitative survey	To investigate to what extent family physicians, internists and orthopaedists working in private practice in Germany believe in the efficacy of, and use, CAM therapies.
31	(De Gobbi et al., 2016)	Italy	General practice	GPs (62)	Quantitative survey	To investigate placebo use by general practitioners throughout their everyday practice: in particular the frequency of use, placebo features, instructions, and conditions of use.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims
32	(Feffer et al., 2016)	Israel	Outpatient clinic	Patients with depression (96) Healthy members of the public (114)	Quantitative survey	To assess the acceptability of placebo usage among depressed patients
33	(Ortiz et al., 2016)	USA	Primary care	Patients (853)	Qualitative survey	To examine qualitative responses regarding the use of placebo treatments in medical care in a sample of US patients.
34	(Faria et al., 2017)	USA	Community	Parents (1000)	Quantitative survey	To assess parental attitudes regarding placebo use in paediatric randomised controlled trials and clinical care.

NB: The following groups of articles each derived from one study: [1 - 3] [11, 15] [22, 27] [23, 33] [28, 30].

Review findings

Early in the analytic process we divided the analysis into two sub-groups: healthcare professionals' views and patients' views. In the healthcare professionals subgroup we identified three categories and 10 sub-categories. In the patients subgroup we identified three categories, seven sub-categories and four secondary sub-categories. These categories, their descriptions, and the studies that contributed data are shown in Table 3 (healthcare professionals' views) and Table 4 (patients' views). Initial findings were diverse, necessitating a lines-of-argument synthesis (Noblit and Hare, 1988).

Table 3: Categories (healthcare professionals' views)

Categories	Sub-categories	Definition	Contributing articles (numbers correspond to those allocated in Table 2)
Metaphysics	Placebos as substances	Healthcare professionals define placebos as material substances	7, 8, 10-12, 14, 21, 24, 27
	Placebos as processes	Healthcare professionals define placebos as processes	4, 7, 8, 10-12, 14, 21, 24, 27, 28
	Placebos as substances and processes	Healthcare professionals define placebos as both material substances and processes	10, 20, 27, 31
Rationale	To induce therapeutic benefit	Placebos used with the intention to induce therapeutic benefit for the patient	4, 10-12, 14, 20, 22
	To manage patients	Placebos used with the intention to manage patients	4, 7, 10, 12, 14, 20-22
	To cope with uncertainty	Placebos used with the intention to cope with situations in which the healthcare professional has no obvious treatment available	4, 12, 20, 28
	To avoid error	Placebos used as a safety net	4, 7
Context	Setting	The situation in which placebos are used, or placebo use is considered	4, 12, 14, 15, 21, 31
	Patient	The type of patient considered in relation to placebos and their effects	7, 12, 14, 15, 21, 31
	Condition	The specific medical condition considered in relation to placebos and their effects	12, 14, 31

Table 4: Categories (patients' views)

Categories	Sub-categories	Secondary sub-categories	Definition	Contributing articles (numbers correspond to those allocated in Table 2)
Metaphysics	Placebos as inert		Defining placebos negatively – as not containing an active agent	13, 18, 23, 29
	Bifurcating nature		The tendency to divide nature into two systems and assign them different degrees of reality	9, 19, 23, 26, 29
Rationale	Acceptable	To induce therapeutic benefit	Believing that for a placebo to be acceptable, the healthcare professional must use it with the intention of inducing therapeutic benefit for the patient	6, 9, 25, 26, 33
		To give hope	Believing that it is acceptable to use a placebo to give a patient hope that they will get better	6, 26
	Unacceptable	To manage patients	Believing that it is unacceptable to use a placebo to manage patients	9, 23
		To save money	Believing that it is unacceptable to use a placebo to save money	26
Efficacy	Patient characteristics		Believing that placebo efficacy is related to patient characteristics	9, 26, 29
	Doubt		Doubting that placebos can be effective in treating patients	26, 29, 33
	Wanting to disprove the power of placebos		Linking placebos with a negative image of self and wanting to show one cannot be fooled by a 'placebo'	26, 29

Heterogeneous findings

In the studies under review, it was especially notable that healthcare professionals reported using placebos at markedly different frequencies. For example, in one study 86% of healthcare professionals reported using placebos in the last year (Hróbjartsson and Norup, 2003); in another 56% reported using them at least once (Kermen et al., 2010); and in another only 17% reported using them at least once (Fässler et al., 2009). This heterogeneity was partly dependent on how placebos were defined in each study; for example, one study recorded differences in use of between 97% and 12% (Howick et al., 2013) depending on the definition. This suggests that understanding how placebos are *defined* in primary care is essential to understand how they are used and what effects they might have. Before investigating the prevalence or effects of placebos, therefore, it is critical to better understand how placebos themselves are defined. This is the focus of our review findings.

Placebo definitions in primary care

Placebos as substances

Healthcare professionals and patients predominantly defined placebos as material substances (Hróbjartsson and Norup, 2003; Ferentzi et al., 2010; Kermen et al., 2010; Fent et al., 2011; Linde et al., 2013; Bishop et al., 2014b; Fässler et al., 2011; Kisaalita and Robinson, 2012; Tandjung et al., 2014; Hull et al., 2013; Nitzan and Lichtenberg, 2004; Fässler et al., 2009; Babel, 2013). Healthcare professionals indicatively defined a placebo as a “pharmacological intervention, for example vitamin tablets, thus reflecting the narrow meaning of the term.” (Hróbjartsson and Norup, 2003: p.162), or as “an inert substance that when taken by a person can have an effect on that person - either good or bad” (Bishop et al., 2014b: p.359). Moreover, although in many surveys the definitions were fixed by the

researchers, when given an opportunity to define placebos themselves, healthcare professionals often focussed explicitly on placebos as inert substances: in one study "the majority of PCPs [primary care providers] stated that a placebo is a dummy drug without substance." (Fent et al., 2011: p.3), and another stated that "physicians intuitively equate placebo or typical placebo with pure placebo [inert substance]… [and] the cognitive interviews clearly confirmed that the concept of impure placebos [substances known to be effective for other conditions] is unfamiliar and confusing to physicians." (Linde et al., 2013: p.364).

Patients also typically defined placebos as inert material substances (Fässler et al., 2011; Kisaalita and Robinson, 2012; Tandjung et al., 2014; Hull et al., 2013). One indicative study stated that, "contrary to how placebo effects are frequently characterized in the scientific community (i.e., psychosocial context and its contribution to treatment efficacy), participants in our sample conceptualized placebo effects as predominately inert." (Kisaalita and Robinson, 2012: p.897). Another found that "the definition of placebo given by the participants mostly matched the common understanding of a pure placebo." (Tandjung et al., 2014: p.1).

The problems with substance definitions

The definition of placebos as material substances dominated the studies. The dominance of a singular definition is beneficial as it may lead to better mutual understanding between healthcare professionals and patients. However, such a substance definition does not dominate modern placebo studies research, because many researchers think it untenable and ultimately nonsensical.

A substance definition is somewhat analogous with the classic definition given by Henry Beecher (1955: p.1602), whereby placebos are "pharmacologically inert substances… having a psychological effect". Our findings suggest that this is still the dominant lay definition. However, even if one disregards the untenable mind/body dualism in the definition, one quickly runs into problems. First, as other researchers have noted, it is conceptually misleading to define any substance as inert, as all substances can be treated in physico-chemical terms if one chooses to do so (Howick, 2017; Grünbaum, 1986); for example, even the classic sugar pill is not inert to a diabetic. In this sense, the distinction between 'pure' and 'impure' placebos is not just, as our findings suggest, confusing (e.g. Linde et al., 2013), but untenable.

If one accepts, therefore, that nothing is inert, the only credible substance definition one is left with is that of 'impure' placebos: substances which are known to be effective for treating other conditions. However, if we interrogate this version of the substance definition, it too breaks down. A classic, and contentious, example of an 'impure' placebo is an antibiotic given for a viral, rather than a bacterial infection. In the first instance the substance (the antibiotic pill) is a placebo, in the latter instance it is not. Yet in both cases it is the same substance. In another example, a sugar pill given for a headache is a placebo, but is not when put in one's tea. In both cases it cannot be that the substance *itself* is the placebo, that is paradoxical, as the same substance is placebo and non-placebo in different situations. 'Impure' placebos, therefore, are as untenable as 'pure' ones. However, in the studies under review, healthcare professionals also conceived of placebos in a less paradoxical way.

Placebos as processes

Although healthcare professionals commonly defined placebos as material substances, they also, although much less commonly, defined placebos in a different way: as processes (Comaroff, 1976; Hróbjartsson and Norup, 2003; Nitzan and Lichtenberg, 2004; Fässler et al., 2009; Ferentzi et al., 2010; Kermen et al., 2010; Fent et al., 2011; Babel, 2013; Linde et al., 2013; Bishop et al., 2014b; Linde et al., 2014). For example, in one study "some [healthcare professionals] commented that a placebo does not necessarily need to be a pill, but can also be a… treatment." (Fent et al., 2011: p.3). This process definition can also include the belief, promoted by some researchers, that "certain physician rituals and behaviors… promote the placebo effect. This effect, which we refer to as the process-of-treatment effect, has also been referred to as the context effect." (Kermen et al., 2010: p.639). Other process definitions of placebos included interventions (Hróbjartsson and Norup, 2003; Fässler et al., 2009; Bishop et al., 2014b), healing procedures (Ferentzi et al., 2010), the consultation itself (Fent et al., 2011), and empathic treatment (De Gobbi et al., 2016).

By conceiving of placebos as processes, a minority of healthcare professionals are more in agreement with modern scientific placebo theoretical paradigms, including the context of treatment (Di Blasi et al., 2001), meaning responses (Brody, 1997; Moerman, 2002), healing rituals and symbols (Brown, 2013; Kaptchuk and Miller, 2015; Miller and Colloca, 2010), and enactivism (Ongaro and Ward, 2017). By avoiding reference to material substances and untenable distinctions between specific and non-specific treatment, these theories focus on the interaction between healthcare professionals, patients, and their environment – on processes – and how harnessing these elements might improve symptoms.

Placebos as substances and processes

Despite examples in the studies under review of process definitions that better accord with modern conceptions of placebos, some healthcare professionals defined placebos as both substances *and* processes (Meissner et al., 2012; Bishop et al., 2014b; De Gobbi et al., 2016; Fässler et al., 2009). For example, one healthcare professional defined a placebo as "a treatment or medication" (Bishop et al., 2014b: p. 359), and another noted that "everything I do or prescribe has some placebo quality" (Bishop et al., 2014b: p. 361). This highlights that even when healthcare professionals advocate a more viable process orientated definition, they may still also conceive of placebos as substances that can be prescribed to a patient.

Rationales

Although substance and process definitions emerged in the studies under review, as previously outlined healthcare professionals and patients both broadly favoured a substance placebo definition. However, there was less agreement over another review finding: the acceptable rationales for using placebos.

Only two rationales of placebo treatment were acceptable to patients: inducing therapeutic benefit (Lynoe et al., 1993; Chen and Johnson, 2009; Nitzan et al., 2013; Ortiz et al., 2016; Bishop et al., 2014a) and giving hope (Lynoe et al., 1993; Bishop et al., 2014a). Although inducing therapeutic benefit was also a common rationale given by healthcare professionals (Comaroff, 1976; Fässler et al., 2009; Ferentzi et al., 2010; Kermen et al., 2010; Fent et al., 2011; Meissner et al., 2012; Howick et al., 2013), they also gave other rationales including managing patients (Comaroff, 1976; Hróbjartsson and Norup, 2003; Fässler et al., 2009; Kermen et al., 2010; Fent et al., 2011; Meissner et al., 2012; Babel, 2013; Howick et al., 2013), coping with uncertainty (Comaroff, 1976; Kermen et al., 2010; Meissner et al.,

2012; Linde et al., 2014), and avoiding error (Comaroff, 1976; Hróbjartsson and Norup, 2003). This suggests that some healthcare professionals, but not patients, view placebos as viable clinical management tools as well as potential therapeutic treatments.

Context

The last major category we identified was context. In many studies, healthcare professionals and patients defined placebos contextually, related to the setting (Comaroff, 1976; Kermen et al., 2010; Fent et al., 2011; Bishop et al., 2014a; Linde et al., 2014), patient characteristics (Hróbjartsson and Norup, 2003; Kermen et al., 2010; Fent et al., 2011; Ferentzi et al., 2011; De Gobbi et al., 2016; Babel, 2013; Chen and Johnson, 2009; Bishop et al., 2014b; Tandjung et al., 2014), and condition (Kermen et al., 2010; Fent et al., 2011; De Gobbi et al., 2016). The author of one study noted that "what is considered to be 'placebo therapy' in one situation may not be described as such in another." (Comaroff, 1976: p.83). This explicitly relative notion of placebos was prevalent in a number of studies including one where "more than 90% of physicians expressed a strong belief that the potential benefit of placebos depends on the type of disease and the personality characteristics of the patient treated." (Kermen et al., 2010: p.639), and another where ten of the 12 patient participants thought that patient characteristics influenced the placebo effect (Tandjung et al., 2014).

A contextual understanding of placebos has implications for placebo definitions and rationales for placebo use. It supports process orientated definitions by identifying placebos as a relative concept, suggesting healthcare professionals should tailor placebo treatment to the specific patient, setting and condition in front of them.

Discussion

Findings from our review suggest that placebo definitions used by healthcare professionals and patients in primary care settings can be split broadly into two categories: material substances, and processes. Older, untenable placebo definitions are generally substance orientated, whereas more modern definitions are broadly process orientated. However, despite advances in conceptual placebo studies research, healthcare professionals and patients in primary care still primarily define placebos as 'inert' substances. We now explore the implications of these findings.

Modern placebo definitions are process orientated

As we have previously noted, there is common consensus in the scientific literature that definitions characterising placebos as substances are incoherent. We posit that the move towards more coherent, modern definitions is characterised by an, often unsaid, metaphysical move from understanding placebos as material substances, to understanding them as processes.

This move occurs when understanding placebos through a meaning paradigm (Brody, 1997; Moerman, 2002), whereby placebo effects are replaced with "the psychological and physiological effects of *meaning* in the treatment of illness" (Moerman, 2002: p, 14). Through a ritual paradigm, whereby "in a broad sense, placebo effects are improvements in patients' symptoms that are attributable to their participation in the therapeutic encounter, with its rituals, symbols, and interactions." (Kaptchuk and Miller, 2015: p, 8). Or through an embodied (Thompson et al., 2009) or enactive paradigm, whereby placebo effects are situated within a system where "the parts of our bodies, our overall bodily relationship to the environment, and the practically and culturally meaningful structures within that

environment, are all co-emergent and co-dependent aspects of a single web of dynamic relations." (Ongaro and Ward, 2017: p, 528). However, although meaning, ritual, or enactive accounts of healing processes seem useful, they struggle to effectively delineate placebo from non-placebo, as any kind of treatment can be conceived of in these terms. There is, however, one process-orientated placebo theory in which the distinction is better addressed.

Delineating placebo from non-placebo

Noting that the technical vocabulary used to define placebos was confusing and obscure, Adolf Grünbaum (1986) defined placebos as treatment processes that are remedial for a target disorder. He then delineated non-placebo from placebo therapy by aligning non-placebo therapy with *characteristic* treatment factors, and placebo therapy with *incidental* treatment factors. The treatment factors are relative to the condition in question, and the therapeutic theory which states how a given therapy for a target disorder will provide clinical benefit. For example, the characteristic factor of a therapy involving giving amoxicillin for an infection would be the bacteriolytic properties of penicillin, whereas an incidental factor might be a patient's expectations about the potential effect of the drug.

Howick (2017) modified Grünbaum's definition, presenting placebos as relative to the patient as well as the condition and therapeutic theory as in Grünbaum's original version. This is reflected in our finding that healthcare professionals and patients conceive of placebos in the context of patient characteristics, as well as the setting and condition. We posit that the minority view of placebos as contextual treatment processes, emerging from this review, could be aligned with Howick's (2017) version of Grünbaum's definition. However, there are practical issues around such a definition.

The problems of persistent placebo substances

Howick's (2017) definition is credible, and aligns with some of our findings, but we must note that considerable theoretical manoeuvring is required to achieve this. We are left with placebos as contextual treatment processes, relative to a therapeutic theory, the condition in question, and the patient. This is in stark contrast to our finding that most healthcare professionals and patients conceive of placebos as inert material substances.

In the face of critique that we should drop the placebo concept completely (e.g., Moerman, 2013; Nunn, 2009b; Nunn, 2009a; Turner, 2012), Howick (2017: p, 1369) noted that "it seems that the correct strategy for the philosopher is… to try again: to try to produce an acceptable account of placebos that does not fall prey to linguistic confusions.". He may have achieved this, but in the face of our findings it is questionable how much clinical utility such a definition has in practice. As Howard Brody (1997: p, 79) noted, "it is hard to define 'placebo effect' without engaging in a small-scale project to reform modern medical thinking, making the definition useless for the unconverted". Our review findings suggest that such reform has not yet occurred.

Implications for research

Our findings suggest that much research into placebos and their effects in primary care is undermined by incoherent definitions. There is a disconnect between modern placebo theories and lay definitions, but there are also differences in how researchers frame placebos for participants in their studies; this undermines the results of some of the studies under review as it is questionable what exactly they are investigating. We suggest that further theoretical research is required to complement empirical placebo studies. Moreover, given the contextual nature of the placebo phenomenon, supported by our review findings, we promote

more naturalistic and contextual research approaches, such as ethnography, which are currently underrepresented in placebo studies research.

Implications for clinical practise

Our review suggests there is a considerable disconnect between modern scientific definitions of placebos, and how healthcare professionals and patients define them. This has consequences. If to achieve a credible definition one has to stretch 'placebo' so far that only placebo studies researchers understand the term, it has questionable clinical utility. To produce 'placebo effects', therefore, primary healthcare professionals may be better off abandoning placebo terminology altogether.

Strengths and limitations of the review

A strength of this review is that both qualitative and quantitative studies were included, ensuring a broad range of findings was synthesised. However, post-hoc analysis showed that, although both quantitative and qualitative studies contributed to the findings, qualitative articles dominated. In the healthcare professionals subgroup there were four key articles (Comaroff, 1976; Kermen et al., 2010; Fent et al., 2011; Bishop et al., 2014b), and in the patients subgroup there were three (Bishop et al., 2014a; Tandjung et al., 2014; Ortiz et al., 2016). It has to be considered that findings from this review may be shaped by the findings from these seven key articles, although findings from other studies were, nevertheless, broadly consistent with the main line-of-argument.

And although the abductive logic of a meta-ethnographic lines-of-argument synthesis allows one to create new theory from complex data by inferring the best conceived explanation for observed phenomena, this necessarily means that the findings are tentative; further inquiry is required to test the recommendations from this review.

Conclusion

Based on a systematic meta-ethnographic review of 34 articles, we suggest that the central problem for placebos and their effects in primary care is the disconnect between viable modern placebo definitions and how healthcare professionals and patients define them. This has led to confusion and uncertainty in placebo research and clinical practice, which has undermined prevalence of use data and misinformed debate on clinical placebo use. Moreover, we suggest that once the term 'placebo' is stretched to its modern iteration, it may have limited clinical value.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This paper presents independent research funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR). The views expressed are those of the authors and not necessarily those of the NIHR, the NHS or the Department of Health.

References

Atkins S, Lewin S, Smith H, et al. (2008) Conducting a meta-ethnography of qualitative literature: Lessons learnt. *BMC medical research methodology* 8: 21.

Avins AL, Cherkin DC, Sherman KJ, et al. (2012) Should we reconsider the routine use of placebo controls in clinical research? *Trials* 13: 44-44.

Babel P. (2012) The Effect of Question Wording in Questionnaire Surveys on Placebo Use in Clinical Practice. *Evaluation and the Health Professions* 35: 447-461.

Babel P. (2013) Use of Placebo Interventions in Primary Care in Poland. *Medical Principles and Practice* 22: 484-488.

Beecher HK. (1955) The powerful placebo. *Journal of the American Medical Association* 159: 1602-1606.

Benedetti F. (1996) The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain* 64: 535-543.

Benedetti F. (2014) *Placebo effects*, Oxford: Oxford University Press.

Bishop FL, Aizlewood L and Adams AEM. (2014a) When and why placebo-prescribing is acceptable and unacceptable: a focus group study of patients' views. *PLoS ONE* 9: e101822.

Bishop FL, Howick J, Heneghan C, et al. (2014b) Placebo use in the UK: A qualitative study exploring GPs' views on placebo effects in clinical practice. *Family Practice* 31: 357-363.

Bishop FL, Jacobson EE, Shaw JR, et al. (2012) Scientific tools, fake treatments, or triggers for psychological healing: How clinical trial participants conceptualise placebos. *Social Science & Medicine* 74: 767-774.

Bostick NA, Sade R, Levine MA, et al. (2008) Placebo use in clinical practice: report of the American Medical Association Council on Ethical and Judicial Affairs. *Journal of Clinical Ethics* 19: 58.

Brannan S, Chrispin E, Davies M, et al. (2012) *Medical Ethics Today The BMA's Handbook of Ethics and Law: Third Edition*: John Wiley and Sons.

Brody H. (1997) The doctor as therapeutic agent: a placebo effect research agenda. In: Harrington A (ed) *The placebo effect: an interdisciplinary exploration.* USA: Harvard University Press, 77-92.

Brown WA. (2013) *The placebo effect in clinical practice*, New York: Oxford University Press.

Bryant A and Charmaz K. (2007) Introduction, grounded theory research: methods and practices. In: Bryant A and Charmaz K (eds) *The SAGE handbook of grounded theory*. London: Sage Publications Ltd, 1-28.

Campbell R, Pound P, Morgan M, et al. (2011) Evaluating meta-ethnography systematic analysis and synthesis of qualitative research. *Health Technology Assessment* 15.

Charmaz K. (2014) *Constructing Grounded Theory*, London: Sage Publications.

Chen GF and Johnson MH. (2009) Patients' attitudes to the use of placebos: results from a New Zealand survey. *N Z Med J* 122: 35-46.

Colloca L and Miller FG. (2011a) Harnessing the placebo effect: The need for translational research. *Philosophical Transactions of the Royal Society B: Biological Sciences* 366: 1922-1930.

Colloca L and Miller FG. (2011b) How placebo responses are formed: a learning perspective. *Philosophical Transactions of the Royal Society B: Biological Sciences* 366: 1859-1869.

Comaroff J. (1976) A bitter pill to swallow: placebo therapy in general practice. *The Sociological Review* 24: 79-96.

De Gobbi R, Brocadello B, Bonato CA, et al. (2016) Placebo in general practice. [Italian]. *Ricerca e Pratica* 32: 4-11.

Di Blasi Z, Harkness E, Ernst E, et al. (2001) Influence of context effects on health outcomes: a systematic review. *The Lancet* 357: 757-762.

Dixon-Woods M, Agarwal S, Young B, et al. (2004) Integrative approaches to qualitative and quantitative evidence. *London: Health Development Agency* 181.

Dixon-Woods M, Bonas S, Booth A, et al. (2006a) How can systematic reviews incorporate qualitative research? A critical perspective. *Qualitative Research* 6: 27-44.

Dixon-Woods M, Cavers D, Agarwal S, et al. (2006b) Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. *BMC Med Res Methodol* 6: 35.

Faria V, Kossowsky J, Petkov MP, et al. (2017) Original Articles: Parental Attitudes About Placebo Use in Children. *The Journal of Pediatrics* 181: 272-278.e210.

Fässler M, Gnadinger M, Rosemann T, et al. (2011) Placebo interventions in practice: A questionnaire survey on the attitudes of patients and physicians. *British Journal of General Practice* 61: 101-107.

Fässler M, Gnädinger M, Rosemann T, et al. (2009) Use of placebo interventions among Swiss primary care providers. *BMC Health Services Research* 9.

Fässler M, Meissner K, Schneider A, et al. (2010) Frequency and circumstances of placebo use in clinical practice - a systematic review of empirical studies. *BMC Medicine* 8.

Feffer K, Lichtenberg P, Becker G, et al. (2016) A comparative study with depressed patients on the acceptability of placebo use. *General Hospital Psychiatry* 41: 53-56.

Fent R, Rosemann T, Fässler M, et al. (2011) The use of pure and impure placebo interventions in primary care - A qualitative approach. *BMC Family Practice* 12.

Ferentzi E, Köteles F and Bárdos G. (2010) The Therapeutic use of placebos among Hungarian GPs: A preliminary research report. *Clinical and Experimental Medical Journal* 5: 21-25.

Ferentzi E, Köteles F and Bárdos G. (2011) The use of placebos in medical practice. A questionnaire survey among GPs of Hungary. *Clinical and Experimental Medical Journal* 5: 73-84.

France EF, Ring N, Thomas R, et al. (2014) A methodological systematic review of what's wrong with meta-ethnography reporting. *BMC Medical Research Methodology* 14: 119-119.

Friedman LM, Furberg C, DeMets DL, et al. (2015) *Fundamentals of clinical trials*, New York: Springer.

Glaser BG and Strauss AL. (1967/2009) *The discovery of grounded theory: Strategies for qualitative research*: Transaction publishers.

Grünbaum A. (1986) The placebo concept in medicine and psychiatry. *Psychological Medicine* 16: 19-38.

Hardman D and Bishop FL. (2018) *The importance of logic when choosing how to approach a systematic review: lessons from a meta-ethnography of how healthcare professionals and patients understand placebos and their effects in primary care*. Available at: http://methods.sagepub.com/case/systematic-review-healthcare-professionals-and-patients-placebos-effects.

Howick J. (2009) Escaping from placebo prison. *BMJ* 338.

Howick J. (2017) The relativity of ‘placebos’: defending a modified version of Grünbaum’s definition. *Synthese* 194: 1363-1396.

Howick J, Bishop FL, Heneghan C, et al. (2013) Placebo Use in the United Kingdom: Results from a National Survey of Primary Care Practitioners. *PLoS ONE* 8.

Hróbjartsson A and Norup M. (2003) The use of placebo interventions in medical practice - A national questionnaire survey of Danish clinicians. *Evaluation & The Health Professions* 26: 153-165.

Hull SC, Colloca L, Avins A, et al. (2013) Patients’ attitudes about the use of placebo treatments: telephone survey. *BMJ : British Medical Journal* 347.

Kaptchuk TJ, Friedlander E, Kelley JM, et al. (2010) Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One* 5: e15591.

Kaptchuk TJ and Miller FG. (2015) Placebo Effects in Medicine. *New England Journal of Medicine* 373: 8-9.

Kermen R, Hickner J, Brody H, et al. (2010) Family Physicians Believe the Placebo Effect Is Therapeutic But Often Use Real Drugs as Placebos. *Family Medicine* 42: 636-642.

Kirsch I. (1997) Specifying Nonspecifics: Psychological Mechanisms of Placebo Effects. In: Harrington A (ed) *The Placebo Effect, an Interdisciplinary Exploration.* United States of America: First Harvard University Press.

Kirsch I, Moore TJ, Scoboria A, et al. (2002) The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention & Treatment* 5.

Kisaalita NR and Robinson ME. (2012) Analgesic Placebo Treatment Perceptions: Acceptability, Efficacy, and Knowledge. *Journal of Pain* 13: 891-900.

Kisaalita NR, Roditi D and Robinson ME. (2011) Factors affecting placebo acceptability: deception, outcome, and disease severity. *J Pain* 12: 920-928.

Koteles F and Ferentzi E. (2012) Ethical aspects of clinical placebo use: what do laypeople think? *Eval Health Prof* 35: 462-476.

Linde K, Alscher A, Friedrichs C, et al. (2015) Belief in and use of complementary therapies among family physicians, internists and orthopaedists in Germany -cross-sectional survey. *Family Practice* 32: 62-68.

Linde K, Friedrichs C, Alscher A, et al. (2013) Use of Placebos and Nonspecific and Complementary Treatments by German Physicians - Rationale and Development of a Questionnaire for a Nationwide Survey. *Forschende Komplementarmedizin* 20: 361-367.

Linde K, Friedrichs C, Alscher A, et al. (2014) The use of placebo and non-specific therapies and their relation to basic professional attitudes and the use of complementary therapies among German physicians--a cross-sectional survey. *Plos One* 9: e92938-e92938.

Lynoe N, Mattsson B and Sandlund M. (1993) The attitudes of patients and physicians toward placebo treatment - A comparative study. *Social Science and Medicine* 36: 767-774.

Malpass A, Shaw A, Sharp D, et al. (2009) “Medication career” or “moral career”? The two sides of managing anti-depressants: a meta-ethnography of patients experience of antidepressants. *Social Science & Medicine* 68.

Meissner K, Höfner L, Fässler M, et al. (2012) Widespread use of pure and impure placebo interventions by GPs in Germany. *Family Practice* 29: 79-85.

Miller FG and Brody H. (2011) Understanding and harnessing placebo effects: Clearing away the underbrush. *Journal of Medicine and Philosophy* 36: 69-78.

Miller FG and Colloca L. (2009) The legitimacy of placebo treatments in clinical practice: Evidence and ethics. *American Journal of Bioethics* 9: 39-47.

Miller FG and Colloca L. (2010) Semiotics and the placebo effect. *Perspectives in Biology and Medicine* 53: 509-516.

Moerman DE. (2002) *Meaning, medicine and the 'placebo effect',* USA: Cambridge University Press.

Moerman DE. (2013) Against the " placebo effect" : A personal point of view. *Complementary Therapies in Medicine* 21: 125-130.

Moerman DE and Jonas WB. (2002) Deconstructing the placebo effect and finding the meaning response. *Annals Of Internal Medicine* 136: 471-476.

Moher D, Liberati A, Tetzlaff J, et al. (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine* 6: e1000097.

Nitzan U, Feffer K, Bloch Y, et al. (2013) Consenting not to be informed: a survey on the acceptability of placebo use in the treatment of depression. *Journal of Nervous & Mental Disease* 201: 345-347.

Nitzan U and Lichtenberg P. (2004) Questionnaire survey on use of placebo. *British Medical Journal* 329: 944-946.

Noblit GW and Hare RD. (1988) *Meta-ethnography: synthesizing qualitative studies,* California: Sage.

Nunn R. (2009a) It's time to put the placebo out of our misery. *BMJ: British Medical Journal (Online)* 338.

Nunn R. (2009b) Placebo effects without placebos? More reason to abandon the paradoxical placebo. *The American Journal Of Bioethics: AJOB* 9: 50-52.

Ongaro G and Ward D. (2017) An enactive account of placebo effects. *Biology & Philosophy*: 1-27.

Ortiz R, Hull SC and Colloca L. (2016) Patient attitudes about the clinical use of placebo: qualitative perspectives from a telephone survey. *Bmj Open* 6.

Pace R, Pluye P, Bartlett G, et al. (2012) Testing the reliability and efficiency of the pilot Mixed Methods Appraisal Tool (MMAT) for systematic mixed studies review. *International Journal of Nursing Studies* 49: 47-53.

Peirce CS. (1878/1982) How to make our ideas clear. In: Thayer HS (ed) *Pragmatism the classic writings.* Cambridge: Hackett Publishing Company, 79-100.

Pluye P and Hong QN. (2014) Combining the power of stories and the power of numbers: mixed methods research and mixed studies reviews. *Annu Rev Public Health* 35: 29-45.

Pluye P, Robert E, Cargo M, et al. (2011) *Proposal: A mixed methods appraisal tool for systematic mixed studies reviews*. Available at: http://mixedmethodsappraisaltoolpublic.pbworks.com.

Pocock SJ. (1983) *Clinical trials: a practical approach,* Chichester: John Wiley & Sons.

Pope C, Popay J and Mays N. (2007) *Synthesising Qualitative And Quantitative Health Research : A Guide To Methods*, Buckingham, US: Open University Press.

Sandelowski M, Voils CI, Leeman J, et al. (2012) Mapping the mixed methods–mixed research synthesis terrain. *Journal of mixed methods research* 6: 317-331.

Schutz A. (1973) *Collected papers I: the problem of social reality,* The Hague: Martinus Nijhoff.

Shapiro AK and Shapiro E. (1997) *The powerful placebo: from ancient priest to modern physician,* United States of America: John Hopkins University Press.

Shapiro AK and Struening EL. (1973a) Defensiveness in the definition of placebo. *Comprehensive Psychiatry* 14: 107-120.

Shapiro AK and Struening EL. (1973b) The use of placebos: A study of ethics and physicians' attitudes. *Psychiatry in Medicine* 4: 17-29.

Shapiro AK and Struening EL. (1974) A comparison of the attitudes of a sample of physicians about the effectiveness of their treatment and the treatment of other physicians. *Journal of Psychiatric Research* 10: 217-229.

Tandjung R, Tang H, Fässler M, et al. (2014) The patient's perspective of placebo use in daily practice: a qualitative study. *Swiss medical weekly* 144.

Thompson JJ, Ritenbaugh C and Nichter M. (2009) Reconsidering the Placebo Response from a Broad Anthropological Perspective. *Culture, Medicine, and Psychiatry* 33: 112-152.

Thomson RJ and Buchanan WJ. (1982) Placebos and general practice: attitudes to, and the use of, the placebo effect. *The New Zealand Medical Journal* 95: 492-494.

Turner A. (2012) 'Placebos' and the logic of placebo comparison. *Biology & Philosophy* 27: 419-432.

Walach H, Falkenberg T, Fønnebø V, et al. (2006) Circular Instead of Hierarchical: Methodological Principles for the Evaluation of Complex Interventions. *BMC Medical Research Methodology* 6: 29.

Supplementary material

Appendix 1: database search strategies

MEDLINE

1	(MH "Placebo Effect+")
2	(MH "Placebos")
3	1 OR 2
4	(MH "Health Personnel+")
5	doctor* OR clinician* OR nurse* OR GP* OR physician* OR "medical practitioner*"
6	(MH "Patients+")
7	patient*
8	4 OR 5 OR 6 OR 7
9	3 AND 8
10	(MH "Health Facilities+")
11	(MH "General Practice+")
12	primary care OR primary health care OR primary healthcare OR family practice OR general practice OR clinical practice OR clinical setting
13	10 OR 11 OR 12
14	9 AND 13
15	(MH "Randomized Controlled Trials as Topic+")
16	"randomi?ed controlled trial*" OR RCT OR trial OR double-blind
17	15 OR 16
18	14 NOT 17

PsychINFO

1	DE "Placebo"
2	DE "Health Personnel" OR DE "Allied Health Personnel" OR DE "Medical Personnel" OR DE "Mental Health Personnel"
3	doctor* OR clinician* OR nurse* OR GP* OR physician* OR "medical practitioner*"
4	patient*
5	2 OR 3 OR 4
6	1 AND 5
7	DE "Treatment Facilities" OR DE "Clinics" OR DE "Community Mental Health Centers" OR DE "Halfway Houses" OR DE "Hospitals" OR DE "Nursing Homes" OR DE "Therapeutic Camps"
8	DE "Clinical Practice"
9	DE "Primary Health Care"
10	primary care OR primary health care OR primary healthcare OR family practice OR general practice OR clinical practice OR clinical setting
11	7 OR 8 OR 9 OR 10
12	6 AND 11
13	"randomi?ed controlled trial*" OR RCT OR trial OR double-blind
14	12 NOT 13

Embase Classic + Embase

1	placebo effect/
2	exp health care personnel/
3	(doctor* or clinician* or nurse* OR GP* or physician* or "medical practitioner*").mp.
4	patient*.mp.
5	2 OR 3 OR 4
6	1 AND 5
7	exp health care facility/
8	general practice/
9	(primary care or primary health care or primary healthcare or family practice or general practice or clinical practice or clinical setting).mp.
10	7 OR 8 OR 9
11	6 AND 10
12	randomized controlled trial/
13	("randomi?ed controlled trial" or RCT or trial OR double-blind).mp.
14	12 OR 13
15	11 NOT 14

CINAHL Plus with full text

1	(MH "Placebo Effect")
2	(MH "Placebos")
3	1 OR 2
4	(MH "Health Personnel+")
5	doctor* OR clinician* OR nurse* OR GP* OR physician* OR "medical practitioner*"
6	(MH "Patients+")
7	patient*
8	4 OR 5 OR 6 OR 7
9	3 AND 8
10	(MH "Health Facilities+")
11	(MH "Primary Health Care")
12	(MH "Family Practice")
13	primary care OR primary health care OR primary healthcare OR family practice OR general practice OR clinical practice OR clinical setting
14	10 OR 11 OR 12 OR 13
15	9 AND 14
16	(MH "Randomized Controlled Trials")
17	"randomi?ed controlled trial*" OR RCT OR trial OR double-blind
18	16 OR 17
19	15 NOT 18

Web of Science

1	TS="placebo effect*"
2	TS=(doctor* OR clinician* OR nurse* OR GP OR physician* OR "medical practitioner*")
3	TS=patient*
4	2 OR 3
5	1 AND 4
6	TS=(primary care OR primary health care OR primary healthcare OR family practice OR general practice OR clinical practice OR clinical setting)
7	5 AND 6
8	TS=(“randomi?ed controlled trial*” OR RCT OR trial OR double-blind)
9	7 NOT 8

Appendix 2: Expanded study characteristics table with summary of main findings

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
1	(Shapiro and Struening, 1973a)	USA	General practice Hospitals Research	Psychiatrists (119) Internists (50) GPs (14) Surgeons (16)	Quantitative survey	To investigate differences in the definition and conception of placebos among physicians.	Physicians tended to align placebo use with other physicians and with specialties other than their own. Physicians tended to define placebos so their speciality would be excluded from the definition. GPs included active drugs in the definition of placebos more frequently than other specialties.
2	(Shapiro and Struening, 1973b)	USA	General practice Hospitals Research	Psychiatrists (117) Internists (50) GPs (14) Surgeons (14)	Quantitative survey	To assess ethical attitudes towards the use of placebos in treatment and research.	Older physicians and those who spent more time in private practice were more critical of placebo use. Physicians who were more research active were less critical of placebo use. GPs were generally critical towards placebo use.
3	(Shapiro and Struening, 1974)	USA	General practice Hospitals Research	Psychiatrists (114) Internists (48) GPs (15) Surgeons (14)	Quantitative survey	To assess the tendency of physicians to attribute the use of placebos or nonspecific treatment to other physicians.	Physicians generally attributed the use of placebos or nonspecific treatment to other physicians and specialties more than themselves. However, GPs were less likely to do this. Physicians tended to exclude their own specialty from their definition of placebos.
4	(Comaroff, 1976)	UK	General practice	GPs (51)	Qualitative observation Interviews	To investigate how doctors, as placebo prescribers, perceive and employ the placebo concept.	Placebo use was primarily identified as a process by which physicians managed patients, maintained their social role or coped with medical uncertainty.
5	(Thomson and Buchanan, 1982)	New Zealand	General practice	GPs (44)	Quantitative survey	To determine GPs' basic understanding of the placebo effect and their views on the use of placebo treatments.	Most GPs would deliberately use a placebo treatment in some circumstances. However, GPs tended to downplay their use of placebos compared with that of colleagues.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
6	(Lynoe et al., 1993)	Sweden	Primary healthcare centre University	Physicians associated with a university (47) GPs (47) Patients (83)	Mainly quantitative survey with some open ended questions	To investigate the attitudes of patients and physicians toward placebo treatment.	Regarding placebo treatment, patients were generally more paternalistic than physicians. For GPs, the use of 'impure placebos' was more acceptable than 'pure placebos'.
7	(Hróbjartsson and Norup, 2003)	Denmark	General practice Private practice Hospitals	GPs (182) Hospital physicians (185) Private specialists (136)	Quantitative survey	To investigate the proportion and types of placebo intervention, conditions of use, and attitudes towards use.	86% of GPs used placebo interventions at least once, and 48% used placebo interventions more than ten times in the last year. 46% of GPs found placebos ethically acceptable. 30% of GPs believe placebos affect 'objective outcomes'. The main reason for using placebos was to avoid a confrontation with a patient.
8	(Nitzan and Lichtenberg, 2004)	Israel	Hospitals Community clinics	Hospital physicians (31) Head nurses (31) Family physicians (27)	Quantitative survey	To gauge the frequency and circumstances of, and attitude towards, placebo use in clinical practice.	60% of participants used placebos. 94% found placebos 'generally or occasionally effective'. Family physicians' most common reason for use was to manage patients.
9	(Chen and Johnson, 2009)	New Zealand	Primary Care Clinics	Patients (211)	Quantitative survey	To examine patients beliefs about the placebo effect, views on the use of placebos in clinical practice, and their willingness to participate in a placebo-controlled RCT.	Patients thought placebo use appropriate when it is for therapeutic benefit, requested by the patient, or when no other treatments are available. Patients thought placebo use inappropriate when it is for the benefit of the physician or when it 'seemed dangerous'.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
10	(Fässler et al., 2009)	Switzerland	General practice Private practice	Paediatricians (67) Urban GPs (41) Suburban GPs (55) Rural GPs (70)	Quantitative survey	To investigate to what extent and in which way Swiss primary care providers use placebo interventions.	More participants used impure placebos (57%) than pure placebos (17%). Paediatricians used pure placebos and deception more than GPs. The most common premise for placebo use was that they can be used in partnership with patients. Impure placebos were deemed more ethically acceptable than pure placebos, although participants were uncertain about the ethical legitimacy of placebo use.
11	(Ferentzi et al., 2010)	Hungary	General practice	GPs (94)	Quantitative survey	To investigate how GPs in Hungary perceived some important aspects of their own placebo use.	(Preliminary report) Over 80% of GPs used placebos, most commonly for symptoms such as 'anxiety, fatigue, sleep disorders and functional problems'. Most GPs (84%) considered placebo use ethical when conducted for therapeutic benefit. Physicians called for official guidance on placebo use.
12	(Kermen et al., 2010)	USA	Family practice	Family physicians (412)	Mainly quantitative survey with some open ended questions	To gain a better understanding of the role of placebos in clinical practice on a national level.	56% had used a placebo in clinical practice. 40% had used an antibiotic as a placebo and 11% had used 'inert substances'. 85% believed placebos have both 'psychological and physical benefits'. 61% recommended a placebo rather than no treatment. 97% believed that doctors' rituals and/or behaviours contribute to placebo effects. The most common reason for placebo use was 'after unjustified demand for medication'.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
13	(Fässler et al., 2011)	Switzerland	Primary care	GPs (232) Patients (414)	Quantitative survey with one open-ended question	To compare the proportions of patients and physicians who would accept therapies that work by enhancing self-healing capacities and by exploiting contextual factors.	87% of patients and 97% of GPs thought that belief in a therapy can improve 'physical complaints'. Patients supported placebo treatment more than GPs. 90% of GPs admitted to using treatments that take advantage of 'non-specific effects'. 70% of patients wanted to be informed about non-specific treatments, yet GPs thought this figure would only be 33%.
14	(Fent et al., 2011)	Switzerland	Primary care	GPs (8) Internists (2) Paediatrician (1) Psychiatrist (1)	Semi-structured interviews	To explore physicians' views on the use of placebos in daily practice.	Most participants described placebos as 'pure placebos'; most 'impure placebos' were not regarded as placebos. Participants used placebos mostly when there was 'no satisfactory somatic explanation'. Participants generally were unclear on the ethical status of placebo treatment, were uncertain how to communicate such treatment to patients, and would welcome more guidance.
15	(Ferentzi et al., 2011)	Hungary	General practice	GPs (169)	Quantitative survey	To provide a detailed description of physicians' attitudes toward, and knowledge of, clinical placebo use.	(Full report of no.11) 83% of participants had used placebos. Most participants regarded placebos as both ethical and effective.
16	(Kisaalita et al., 2011)	USA	University	Members of the public (103)	Quantitative survey with experimental component	To examine the acceptability and ethics of placebo treatment for pain.	Placebos described as 'medication shown to be a powerful analgesic in some people' were perceived to be as deceptive as those described as 'standard drug treatment'. Participants 'tolerated moderate effectiveness and considerable negative consequences in an acceptable placebo'.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
17	(Babel, 2012)	Poland	Primary care	Primary care physicians (190)	Quantitative survey with experimental component	To identify factors that contribute to the high variability of the rates of use of placebo interventions reported in questionnaire surveys.	Participants asked about 'placebo interventions' said the never used them significantly more than participants asked about 'nonspecific treatment methods'.
18	(Kisaalita and Robinson, 2012)	USA	University	Members of the public (100)	Quantitative survey with open-ended question	To examine the acceptability, efficacy and knowledge of analgesic placebo treatments.	Participants mostly thought of placebos as inert and had differing views regarding the effectiveness of placebo treatment.
19	(Koteles and Ferentzi, 2012)	Hungary	Online news site	Members of the public (6104)	Quantitative survey	To assess the attitudes of laypeople toward deceptive clinical placebo use.	Participants thought 'helping patients is more important than avoiding deception' illustrating a pragmatic view towards placebo treatment.
20	(Meissner et al., 2012)	Germany	General practice	GPs (208)	Quantitative survey	To collect data on the use of placebo interventions by GPs in Germany.	88% of GPs had used a placebo at least once. The use of 'impure placebo's was more common than 'pure placebos'. The main reason for placebo treatment was 'a possible psychological effect', although patient expectation was also a common reason. Most GPs thought placebo treatment ethical if used to elicit a psychological effect.
21	(Babel, 2013)	Poland	Primary care	Primary care physicians (169)	Quantitative survey	To investigate the behaviour beliefs and attitudes of Polish primary care physicians concerning the use of placebo interventions.	80% of participants used placebo interventions. The most common placebos were vitamins and homeopathy. 84% thought placebos effective, but 54% thought them only effective for patients with 'subjective symptoms'. 73% thought individual traits were important for effectiveness. 65% thought patients' expectations important.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
22	(Howick et al., 2013)	UK	Primary care	GPs (783)	Quantitative survey	To investigate the prevalence of placebo use in UK primary care.	12% of GPs had used pure placebos and 97% had used impure placebos, at least once. 1% used pure placebos and 77% used impure placebos at least once a week. Most (66% for pure, 84% for impure) GPs thought placebos ethical in 'some circumstances'.
23	(Hull et al., 2013)	USA	Primary Care	Patients with chronic illness (853)	Quantitative survey	To examine the attitudes of US patients about the use of placebo treatments in medical care.	50-84% of participants thought placebo treatment acceptable depending on 'doctors' level of certainty about the benefits and safety of the treatment, the purpose of the treatment, and the transparency with which the treatment was described to patients'. 22% of participants thought placebo treatment unacceptable.
24	(Linde et al., 2013)	Germany	General practice	GPs (84) Internists (3) Orthopaedists (1)	Quantitative survey (n=80) Cognitive interviews (N=7)	To develop a questionnaire.	The questions on 'typical placebos and complementary treatments' were understandable and 'easy to answer'. However, interviews suggest that these issues are 'difficult to grasp in a quantitative survey'. The concept 'non-specific treatment' was thought vague. Study authors suggest direct observation would be a useful data collection method.
25	(Nitzan et al., 2013)	Israel	Academic centres	Students (344)	Quantitative survey	To investigate the opinions of healthy students regarding the acceptability of placebo treatment if they were to experience depression.	70% of participants would agree to placebo treatment as 'a first-line treatment'. 88% of participants did not think placebo treatment deceitful.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
26	(Bishop et al., 2014a)	UK	Community	General public (58)	Focus groups	To identify when and why placebo-prescribing in primary care might be acceptable and unacceptable to patients	Participants had two broad perspectives: 'consequentialist', whereby they focussed on the potential benefits of placebo treatment; and 'respecting autonomy', whereby they focussed on the negative effects of deception in treatment. 'Placebo' was generally thought to mean 'ineffective'. Some participants thought the careful use of language may enable ethical placebo treatment.
27	(Bishop et al., 2014b)	UK	General practice	GPs (783)	Qualitative survey	To explore GPs' perspectives on clinical uses of placebos.	GPs generally defined placebos negatively, as in 'lacking something'. GPs described myriad possible' harms and benefits of placebo prescribing'. Some GPs thought placebos beneficial, although some thought they should not be used for ethical reasons.
28	(Linde et al., 2014)	Germany	Private practice	GPs (319) Internists (311) Orthopaedists (305)	Quantitative survey	To investigate the use of placebos and non-specific treatments among physicians working in private practices in Germany, and how such use is associated with the belief in and the use of complementary and alternative treatments.	30% of GPs had used non-specific therapies; 35%, had used placebos or 'non-specific therapies'. Use of pure and/or impure placebos was associated with 'being a GP, being an internist, and having unorthodox professional views'.
29	(Tandjung et al., 2014)	Switzerland	Community	Patients (12)	Semi-structured interviews	To explore patients' conceptualisation, experiences and attitudes regarding the use of placebos in daily clinical practice.	Participants mostly defined placebos as something matching the definition of 'pure placebos'. Most participants believed placebos' mainly worked via psychological effects'. The acceptability of placebo use was generally related to treatment success.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
30	(Linde et al., 2015)	Germany	Private practice	Family physicians (319) Internists (311) Orthopaedists (305)	Quantitative survey	To investigate to what extent family physicians, internists and orthopaedists working in private practice in Germany believe in the efficacy of, and use, CAM therapies.	Family physicians' agreed more with statements on the need of more time and the patient–doctor relationship'. Family physicians were more positive about utilising placebos than internists or orthopaedists.
31	(De Gobbi et al., 2016)	Italy	General practice	GPs (62)	Quantitative survey	To investigate placebo use by general practitioners throughout their everyday practice: in particular the frequency of use, placebo features, instructions, and conditions of use.	84% of GPs had used a placebo in the last 6 months. Placebo were mainly used for 'problems of low clinical significance' (85%). 13% of GPs had given 'pure placebos'. Reasons for giving placebos included for 'frequent attenders' and for patients with 'unexplained symptoms'. None of the GPs used placebo treatment openly.
32	(Feffer et al., 2016)	Israel	Outpatient clinic	Patients with depression (96) Healthy members of the public (114)	Quantitative survey	To assess the acceptability of placebo usage among depressed patients	57% of patients with depression and 71% of healthy members of the public would give consent for placebo treatment for future depression 72% of patients with depression and 78% of healthy members of the public would give consent for placebo treatment for general medical conditions.
33	(Ortiz et al., 2016)	USA	Primary care	Patients (853)	Qualitative survey	To examine qualitative responses regarding the use of placebo treatments in medical care in a sample of US patients.	'Lack of harm' and 'potential benefit' were the most common acceptable justifications for placebo use. Participants who did not think placebo use acceptable most commonly thought that doctors are obliged to 'do more'. The following other themes emerged: 'the issue of whether a doctor was transparent about placebo use, including honesty'; patients' 'right to know'; and the 'power of the mind'.

	Source article	Country	Setting	Participants (n)	Methods of data collection	Aims	Main findings related to primary care
34	(Faria et al., 2017)	USA	Community	Parents (1000)	Quantitative survey	To assess parental attitudes regarding placebo use in paediatric randomized controlled trials and clinical care.	86% of parents considered placebo use acceptable in some paediatric care situations. 6% of parents found the use of placebos in children 'always unacceptable'. The acceptability of placebo treatment was influenced by factors including: doctors' opinions on the therapeutic benefit of the treatment; the conditions of use; transparency; safety; and the 'purity of placebos'.

Appendix 3: Quality assessment

MMAT Methodological Criteria Assessment

http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/84371689/MMAT%202011%20criteria%20and%20tutorial%202011-06-29updated2014.08.21.pdf

Initial screening questions for inclusion in MMAT assessment

Are there clear qualitative and quantitative research questions (or objectives*), or a clear mixed methods question (or objective*)?	**Yes**	**No**	**Can't tell**
Do the collected data address the research question (objective)? E.g., consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components).	Yes	No	Can't tell

Overall score

No of studies	Percent	Rating
33	97	Yes
0	0	No
1	3	Can't tell

Total number of included studies

Number	**33**
Percent	**97**

MMAT criteria

Types of mixed methods study components or primary studies	Methodological quality criteria (Yes/No/Can't tell)
1. Qualitative	1.1. Are the sources of qualitative data (archives, documents, informants, observations) relevant to address the research question (objective)?
	1.2. Is the process for analyzing qualitative data relevant to address the research question (objective)?
	1.3. Is appropriate consideration given to how findings relate to the context, e.g., the setting, in which the data were collected?
	1.4. Is appropriate consideration given to how findings relate to researchers' influence, e.g., through their interactions with participants?
2. Quantitative randomized controlled (trials)	2.1. Is there a clear description of the randomization (or an appropriate sequence generation)?
	2.2. Is there a clear description of the allocation concealment (or blinding when applicable)?
	2.3. Are there complete outcome data (80% or above)?
	2.4. Is there low withdrawal/drop-out (below 20%)?
3. Quantitative nonrandomized	3.1. Are participants (organizations) recruited in a way that minimizes selection bias?
	3.2. Are measurements appropriate (clear origin, or validity known, or standard instrument; and absence of contamination between groups when appropriate) regarding the exposure/intervention and outcomes?
	3.3. In the groups being compared (exposed vs. non-exposed; with intervention vs. without; cases vs. controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups?
	3.4. Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)?
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the quantitative research question (quantitative aspect of the mixed methods question)?
	4.2. Is the sample representative of the population understudy?
	4.3. Are measurements appropriate (clear origin, or validity known, or standard instrument)?

	4.4. Is there an acceptable response rate (60% or above)?
5. Mixed methods	5.1. Is the mixed methods research design relevant to address the qualitative and quantitative research questions (or objectives), or the qualitative and quantitative aspects of the mixed methods question (or objective)?
	5.2. Is the integration of qualitative and quantitative data (or results*) relevant to address the research question (objective)?
	5.3. Is appropriate consideration given to the limitations associated with this integration, e.g., the divergence of qualitative and quantitative data (or results*) in a triangulation design?
	Criteria for the qualitative component (1.1 to 1.4), and appropriate criteria for the quantitative component (2.1 to 2.4, or 3.1 to 3.4, or 4.1 to 4.4), must be also applied

Key

Criteria met (%)	Rating
100	****
75	***
50	**
25	*
0	

Overall Score

No of studies	Percent	Rating
6	18	****
15	46	***
12	36	**
0	0	*
0	0	

NB: ‘Can’t tell’ (C) is scored as ‘No’ (N).

Assessment

No	Study title	Lead author	Year	Comments	Criteria score (Y/N/C)				Overall score
1	Defensiveness in the definition of placebo	Shapiro	1973	Risk of selection bias.	3.1	3.2	3.3	3.4	***
					N	Y	Y	Y	
2	The use of placebos: A study of ethics and physicians' attitudes	Shapiro	1973	Risk of selection bias.	3.1	3.2	3.3	3.4	***
					N	Y	Y	Y	
3	A comparison of the attitudes of a sample of physicians about the effectiveness of their treatment and the treatment of other physicians	Shapiro	1974	Risk of selection bias.	3.1	3.2	3.3	3.4	***
					N	Y	Y	Y	
4	A bitter pill to swallow: placebo therapy in general practice	Comaroff	1976	Study is appropriate for the research question. The researcher reflects on how the findings relate to the context and her disciplinary assumptions. The analytic process is not clear.					Did not meet screening criteria
5	Placebos and general practice: attitudes to, and the use of, the placebo effect	Thomson	1982	Participant recruitment methods do not minimise bias. Small sample size.	4.1	4.2	4.3	4.4	**
					N	Y	N	Y	
6	The attitudes of patients and physicians toward placebo treatment - A comparative study	Lynoe	1993	The patient group is more heterogeneous than the groups of physicians. Patients sampled consecutively.	3.1	3.2	3.3	3.4	***
					N	Y	Y	Y	
7	The use of placebo interventions in medical practice - A national questionnaire survey of Danish clinicians	Hrobjartsson	2003	Study is appropriate, well designed and well conducted.	3.1	3.2	3.3	3.4	****
					Y	Y	Y	Y	
8	Questionnaire survey on use of placebo	Nitzan	2004	Sample not representative.	3.1	3.2	3.3	3.4	**

No	Study title	Lead author	Year	Comments	Criteria score (Y/N/C)				Overall score
					N	Y	N	Y	
9	Patients' attitudes to the use of placebos: results from a New Zealand survey	Chen	2009	Low response rate.	4.1	4.2	4.3	4.4	***
					Y	Y	Y	N	
10	Use of placebo interventions among Swiss primary care providers	Fassler	2009	Low response rate. Demographic information is only available for the whole sample, not each group.	3.1	3.2	3.3	3.4	**
					Y	Y	C	N	
11	The Therapeutic use of placebos among Hungarian GPs: A preliminary research report	Ferentzi	2010	Very low response rate. Not enough information to determine if the sample is representative	4.1	4.2	4.3	4.4	**
					Y	C	Y	N	
12	Family physicians believe the placebo effect is therapeutic but often use real drugs as placebos	Kermen	2010	Low response rate.	4.1	4.2	4.3	4.4	***
					Y	Y	Y	N	
13	Placebo interventions in practice: A questionnaire survey on the attitudes of patients and physicians	Fassler	2011	Well conducted study. High response rate.	3.1	3.2	3.3	3.4	****
					Y	Y	Y	Y	
14	The use of pure and impure placebo interventions in primary care - a qualitative approach	Fent	2011	Researchers do not reflect in any detail on how their influence may have affected results. Little contextual exploration.	1.1	1.2	1.3	1.4	**
					Y	Y	N	N	
15	The use of placebos in medical practice. A questionnaire survey among GPs of Hungary	Ferentzi	2011	Very low response rate.	4.1	4.2	4.3	4.4	**
					Y	C	Y	N	
16	Factors affecting placebo acceptability: deception, outcome, and disease severity	Kisaalita	2011	Sample likely not representative of the population. No response rate recorded.	3.1	3.2	3.3	3.4	**
					N	Y	Y	C	
17		Babel	2012	No record of response rate.	3.1	3.2	3.3	3.4	***

No	Study title	Lead author	Year	Comments	Criteria score (Y/N/C)				Overall score
	The Effect of Question Wording in Questionnaire Surveys on Placebo Use in Clinical Practice				Y	Y	Y	C	
18	Analgesic Placebo Treatment Perceptions: Acceptability, Efficacy, and Knowledge	Kisaalita	2012	Sample likely not representative of the population. No response rate recorded.	3.1 N	3.2 Y	3.3 Y	3.4 C	**
19	Ethical aspects of clinical placebo use: what do laypeople think?	Koteles	2012	Sample not representative.	3.1 N	3.2 Y	3.3 Y	3.4 Y	***
20	Widespread use of pure and impure placebo interventions by GPs in Germany	Meissner	2012	Low response rate	4.1 Y	4.2 Y	4.3 Y	4.4 N	***
21	Use of Placebo Interventions in Primary Care in Poland	Babel	2013	Results might not be representative of the population.	4.1 Y	4.2 N	4.3 Y	4.4 Y	***
22	Placebo use in the United kingdom: results from a national survey of primary care practitioners	Howick	2013	Low response rate.	4.1 Y	4.2 Y	4.3 Y	4.4 N	***
23	Patients' attitudes about the use of placebo treatments: telephone survey	Hull	2013	Low response rate. Demographic data only available for whole sample. Inferential statistical results not recorded.	4.1 Y	4.2 Y	4.3 N	4.4 N	**
24	Use of Placebos and Nonspecific and Complementary Treatments by German Physicians - Rationale and Development of a Questionnaire for a Nationwide Survey	Linde	2013	Method of analysis is quite vague. Very little primary data reported.	1.1 Y	1.2 N	1.3 Y	1.4 N	**
25		Nitzan	2013	Sample not representative.	4.1	4.2	4.3	4.4	***

No	Study title	Lead author	Year	Comments	Criteria score (Y/N/C)				Overall score
	Consenting not to be informed: a survey on the acceptability of placebo use in the treatment of depression				N	Y	Y	Y	
26	When and why placebo-prescribing is acceptable and unacceptable: a focus group study of patients' views	Bishop	2014	Well designed and conducted.	1.1 Y	1.2 Y	1.3 Y	1.4 Y	****
27	Placebo use in the UK: a qualitative study exploring GPs' views on placebo effects in clinical practice	Bishop	2014	Well designed and conducted.	1.1 Y	1.2 Y	1.3 Y	1.4 Y	****
28	The use of placebo and non-specific therapies and their relation to basic professional attitudes and the use of complementary therapies among German physicians--a cross-sectional survey	Linde	2014	Low response rate.	3.1 Y	3.2 Y	3.3 Y	3.4 N	***
29	The patient's perspective of placebo use in daily practice: a qualitative study	Tandjung	2014	Appropriate consideration to reflexivity not given.	1.1 Y	1.2 Y	1.3 Y	1.4 N	***
30	Belief in and use of complementary therapies among family physicians, internists and orthopaedists in Germany - cross-sectional survey	Linde	2015	Low response rate.	3.1 Y	3.2 Y	3.3 Y	3.4 N	***
31	Placebo in general practice	De Gobbi	2016	Sample not representative.	4.1 Y	4.2 N	4.3 C	4.4 Y	**
32	A comparative study with depressed patients on the acceptability of placebo use	Feffer	2016	Well designed and conducted.	3.1 Y	3.2 Y	3.3 Y	3.4 Y	****

No	Study title	Lead author	Year	Comments	Criteria score (Y/N/C)				Overall score
					5.1	5.2		5.3	
					Y	Y		N	
33	Patient attitudes about the clinical use of placebo: qualitative perspectives from a telephone survey	Ortiz	2016	Low response rate. No contextual or reflexive consideration for qualitative component.	1.1	1.2	1.3	1.4	**
					Y	Y	N	N	
					4.1	4.2	4.3	4.4	
					Y	C	Y	N	
34	Parental Attitudes About Placebo Use in Children	Faria	2017	Well designed and conducted.	4.1	4.2	4.3	4.4	****
					Y	Y	Y	Y	