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A Taxonomy of Techniques with Potential to Harness Placebo Effects in Non-Malignant Pain

Running head: Taxonomy of techniques to harness placebo effects

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Abstract

Objectives. Placebo effects can be large and clinically meaningful but are seldom fully exploited in clinical practice. This review aimed to facilitate translational research by producing a taxonomy of applicable techniques that could augment placebo analgesia in clinical practice.

Design. Literature review and survey.

Methods. We systematically analysed methods used to elicit placebo effects in 169 clinical and laboratory-based studies involving non-malignant pain, drawn from 7 systematic reviews. In a validation exercise we surveyed 33 leading placebo researchers (M=12 years' research experience, SD=9.8).

Results. The final taxonomy defines 30 procedures that may contribute to placebo effects in clinical and experimental research, proposes 60 possible clinical applications, and classifies procedures into 5 domains: the *Patient's Characteristics and Belief* (5 procedures and 11 clinical applications); the *Practitioner's Characteristics and Beliefs* (2 procedures and 4 clinical applications); the *Healthcare Setting* (8 procedures and 13 clinical applications); *Treatment Characteristics* (8 procedures and 14 clinical applications); and *The Patient-Practitioner Interaction* (7 procedures and 18 clinical applications).

Conclusions. The taxonomy provides a preliminary and novel tool with potential to guide translational research aiming to harness placebo effects for patient benefit in practice.

Keywords: placebos; placebo effect; nocebo effect; translational research; review; classification

Article Summary

Strengths and Limitations of this Study

- This is a novel attempt to use existing studies to conceptualise the factors that might contribute to placebo effects in clinical trials.
- We drew on both clinical trials and laboratory-based studies of placebo effects, in order to generate a more comprehensive list of factors that might contribute to placebo effects than would be possible by relying on just one literature.
- A systematic approach to data synthesis, based on qualitative research methods, was used to identify and classify procedures that might contribute to placebo effects in clinical trials.
- The development of the taxonomy did not incorporate very recent placebo trials or studies.
- The selection of reviews used to determine which original studies to include in the development process was somewhat arbitrary.

Introduction

There is compelling evidence that factors other than the active ingredients of treatment can have substantial effects on symptoms, particularly non-malignant pain^{1,2}. Such 'placebo effects' can be defined as the physiological and/or psychological changes that result from the meaning a person experiences in a health care setting^{3,4}. These effects may be as large as treatment effects⁵ and occur throughout medicine, especially when doctors and patients interact with each other. They are not routinely deliberately harnessed for patient benefit in clinical practice⁶, possibly because doctors often assume they must deceive patients in order to elicit placebo effects^{7,8}. However, this assumption is mistaken because it is not necessary to prescribe placebos in order to elicit placebo effects. For example, the overall analgesic effect of an opioid derives not only from its specific pharmaceutical actions but also from the *meaning* that the patient experiences when consulting the doctor and taking the medicine. The same is true for other types of intervention including physical, surgical, and psychotherapies. One approach that has received initial support is for doctors to use positive suggestion to enhance patients' expectations of benefit⁹. Furthermore, preliminary evidence suggests that openly prescribing placebos might elicit clinically meaningful placebo effects in IBS and depression^{10,11}.

Many techniques and procedures contribute to placebo effects and could potentially be simply and ethically adapted for clinical practice, subject to further testing in practice settings¹². In order to identify and describe such techniques, and thus provide some direction for future research, we reviewed experimental and clinical studies of placebo effects in non-malignant pain. We focused on non-malignant pain because it can be difficult to manage (particularly with current concerns about opioids¹³), the mechanisms underpinning placebo analgesia are reasonably well understood¹⁴, laboratory-based experimental studies often focus on placebo analgesia, and patients with pain have been shown to display substantial and clinically significant placebo effects¹. The aim of this project

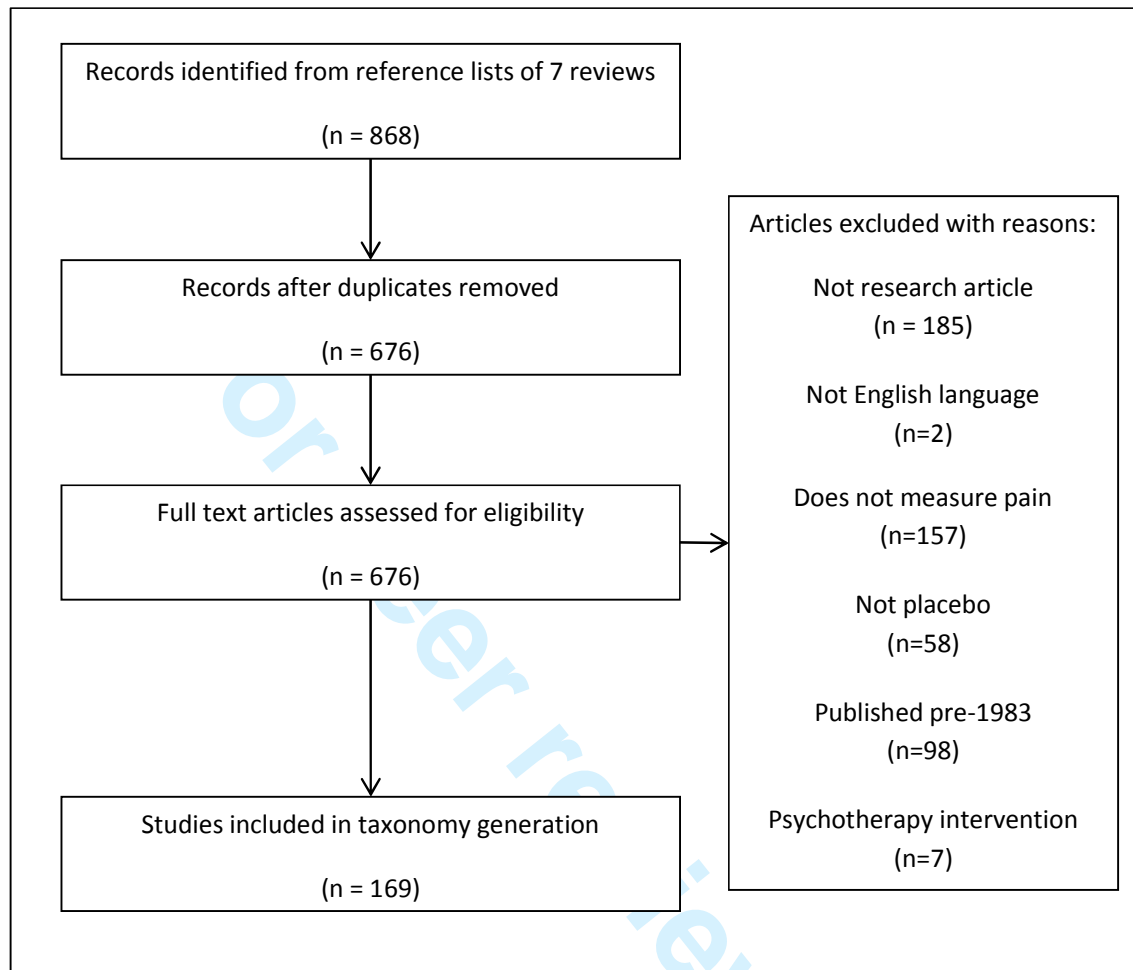
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3 was to facilitate translational research by producing a taxonomy of techniques that may contribute
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5 to observed placebo effects in research settings and could be studied in future as potential
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7 approaches to augmenting placebo enhancement of analgesia in clinical practice.
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11 12 13 **Methods**

14 15 16 17 **Literature Search**

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19 We selected seven systematic reviews of different aspects of the placebo literature, chosen to
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21 enable the extraction of information on placebo procedures from a broad range of settings -
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23 comprehensive reviews¹⁵⁻¹⁷, reviews of placebo effects in clinical populations^{2 18} and reviews of
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25 laboratory-based experimental placebo studies^{19 20}. After removing duplicates and ineligible studies
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27 (see Figure 1), 169 studies were used to develop the taxonomy (for list of included studies see
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29 Supplementary Digital Content).
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Figure 1: Flowchart Showing Identification of Studies



Studies were eligible for inclusion if they: reported original research in which some participants received a placebo intervention, were published since 1983, published in English language, reported a non-malignant pain outcome. Studies were excluded if they: were published before 1983 (because means of generating context-dependent placebo effects may be sensitive to social and cultural changes over time, e.g. patient preferences for particular communication styles and thus their effectiveness in modifying expectations may have changed over time) or examined psychotherapeutic interventions (because it is difficult to disentangle the active ingredients of psychotherapy from the effect of the meaning of the intervention ²¹).

Data Extraction and Synthesis

Descriptions of all events that occurred in the placebo groups during each of the 169 studies (e.g. medical, administrative, and ethical procedures) were extracted into a piloted form by one author and checked by a second. These events were reviewed for duplication and overlap. This resulted in an initial list of 43 procedures that might contribute to placebo effects (e.g. informed consent processes, taking placebo pills, conditioning protocols). Study authors were not contacted for further information about method used.

To synthesise the data and develop our taxonomy items we used systematic and rigorous methods derived from qualitative research. We began with a deductive analysis, which aimed to categorise the procedures in a way that is intuitively appealing, accessible, and clinically relevant by sorting them into five previously-identified contextual domains of healthcare: patients' characteristics/beliefs, practitioners' characteristics/beliefs, doctor-patient relationship, superficial treatment characteristics, and the healthcare environment²². We then engaged in a constant comparative analysis, a technique that originates in grounded theory²³. Procedures and examples of their use were all systematically compared to each other; similar procedures were then merged and all procedures were classified into one of the five domains, the definitions of which were clarified iteratively between all the authors over the course of the classification exercise. This resulted in a more parsimonious list of 29 procedures classified by domain. These 29 procedures were then critically examined to ensure they were theoretically plausible means of producing placebo effects. We focused on three core psychological mechanisms^{16 24-27}: response expectancy²⁸; conditioning and social learning²⁹; and affect, including motivation and anxiety-reduction^{15 30}. However, we acknowledge that these mechanisms are difficult to tease apart³¹ and that alternative mechanisms have been proposed⁴ and so we erred on the side of inclusivity. Neurobiological mechanisms of placebo analgesia have been described^{14 32} but a detailed consideration of how

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3 these might apply to the procedures in the taxonomy would be highly speculative and was beyond
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5 the scope of this project (for discussion of clinical applications of the neuroscience of placebo effects
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7 see³³). Four procedures deemed very unlikely to produce placebo effects (e.g. Conveying a Neutral
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9 Therapeutic Message) were excluded, leaving 25 procedures that might plausibly contribute to
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11 placebo effects. The multidisciplinary team of authors then generated possible clinical applications
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13 of each of these 25 procedures.
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16 17 18 19 **Validating the Taxonomy**

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21 To ensure our taxonomy was comprehensive we surveyed leading placebo researchers (authors of
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23 major publications on placebo effects, attendees at an international symposium on placebo effects,
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25 and GPs with an interest in placebo effects). Ethical approval for the survey was obtained from the
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27 host institution (reference: 4741). Completed electronic surveys including informed consent were
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29 received from 33 researchers (52% response rate) experienced in placebo research (M=12 years'
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31 experience, SD=9.8). Respondents were shown our draft taxonomy and asked whether, for each
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33 domain, they knew of any other procedures that could elicit placebo responses. The proportion
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35 answering yes ranged from 22% (Healthcare Setting domain) to 50% (Superficial Treatment
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37 Characteristics domain). Respondents suggested 85 additions which were screened against existing
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39 items and for theoretical plausibility: 80 of the suggested additions were extra details or suggested
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41 clinical applications of existing items; five were new and distinct plausible procedures that were
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43 added to the taxonomy, giving a final total of 30 items.
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49 **Analysis**

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51 The use of each procedure in the 30-item taxonomy was assessed across all 169 studies in the
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53 review. Two authors independently rated the presence of each procedure in each study (Kappa =
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55 0.93, discrepancies were resolved through discussion).
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Results

The taxonomy defines 30 procedures that may contribute to placebo effects observed in clinical and experimental research, and classifies them into 5 domains. Table 1 presents the main taxonomy, listing and defining all 30 procedures within 5 domains. Table 2 suggests clinical applications of each procedure. Table 3 shows the frequency of use of each procedure in clinical and experimental studies. Below we describe the procedures within each domain in turn.

Table 1. Taxonomy of Procedures to Elicit Placebo Effects in Non-Malignant Pain

Procedure Derived from Literature	Definition
The Patient's Beliefs and Characteristics	
1. Select Participants Based on Treatment History.	Screen and select participants (or subgroups) against inclusion criteria related to issues such as medical/treatment history, e.g. naive to intervention being tested (not just contraindications).
2. Create Positive Expectancy.	Deliberately and explicitly suggest to participants that the intervention will be effective for them (not as part of informed consent process).
3. Reduce Negative Expectancy. ^a	The potentially negative or harmful procedures and characteristics of the treatment are deliberately minimised in information for participants.
4. Convey a Positive Therapeutic Message through Informed Consent Procedures.	Convey (verbally or in writing) a positive therapeutic message through the content of informed consent. The message might be explicit (e.g. "this intervention is usually effective in most people") or implicit (e.g. "this treatment is an antihypertensive").
5. Harness Socio-cultural Context. ^a	Tailor the intervention according to the participant's social and cultural context and history.
The Practitioner's Beliefs and Characteristics	
6. Practitioner Expectancy.	The person delivering the treatment expects it to be effective for the patient.
7. Practitioner's Personal Characteristics.	The practitioner's personal and/or professional characteristics (e.g. status) are modified (through selecting practitioners with different characteristics) and/or emphasised to participants.
The Healthcare Setting	
8. Active Recruitment.	Actively seek out and recruit participants (e.g. advertising for specific types of patients, writing personally to individual eligible patients identified through medical records).
9. Active Retention.	Make participants feel valued by attempting to keep them in a study (e.g. contact participants if they miss an appointment, incentivise attendance through monetary or non-monetary gifts).
10. Follow-up.	Assess participants after the intervention/ experiment to assess long-term maintenance or changes in effects over at least 6 months.
11. Follow a Standardised Protocol.	The intervention is delivered according to a set, scientifically-derived, protocol, lending credibility to the intervention (and is therefore not individualised for each participant).
12. Ethical Oversight.	Study practices and procedures are explicitly regulated and monitored by an institutional ethics committee, lending credibility to the intervention.
13. Participating in Research.	Participants know that they are part of research and contributing to the furthering of human knowledge and/or improvement of healthcare for future patients.
14. Symptom Monitoring.	Monitor participants' symptoms using self-report measures, clinician/experimenter assessment, or objective

15. Enhanced Environment. ^a	measures repeated over time at least twice; patients are aware of the resulting measurements. The physical and interpersonal environment where the intervention is delivered is deliberately enhanced.
Treatment Characteristics	
16. Sham Intervention – Medication.	An inert substance is administered which is manufactured to appear identical to an active medication (e.g. sugar pill, saline IV, topical agent).
17. Sham Interventions – Physical.	A sham physical intervention is administered which is designed to appear identical to the genuine intervention (e.g. de-activated TENS, non-penetrative acupuncture needles at non-acupuncture points).
18. Sham Interventions – Attention Only.	Participants receive study-specific attention in terms of numbers of visits and time spent with study staff but no additional intervention.
19. Ineffective substances. ^a	Products unlikely to be effective or not indicated are administered (e.g. vitamins in the absence of vitamin deficiency).
20. Use Side-Effects.	Potential side-effects are highlighted such that the participant can interpret them as evidence of a potent intervention.
21. Matched treatments.	To secure blinding, placebo/sham treatments are matched to 'real' treatments (e.g. on mode of administration, dosage, frequency of administration, visual appearance, taste, smell, individual titration procedures).
22. Maximised treatment procedures.	The procedures and characteristics of the treatment are exaggerated, e.g. through high dose, use of colour, high frequency, large pill size, lengthy duration of intervention, ritualistic administration.
23. Conditioning.	A desired response (e.g. pain relief) is paired with an intervention stimulus (e.g. placebo cream) so that the participant associates the response with the stimulus.
The Patient-Practitioner Interaction	
24. The Process of Informed Consent.	The participant's formal written and/or verbal informed consent is discussed and obtained.
25. Detailed History.	A detailed personal and/or medical and/or psychosocial history is obtained from the participant.
26. Diagnosis/tests.	Additional tests, examinations, or confirmatory diagnostic procedures are undertaken to establish eligibility for the study.
27. Care.	The practitioner deliberately engages the participant with warmth, compassion and empathy.
28. Patient-Centred Communication. ^a	The practitioner adopts a style of consultation that they consider to be appropriate for a particular patient.
29. Extra Attention.	The participant receives extra attention from being in the study, for example is seen more frequently or for longer than usual.
30. Continuity of Care.	Efforts are made for the same practitioner to see the same participant at each contact.

^a Items added following survey of researchers.

Table 2. Suggested Potential Clinical Applications of Procedures to Elicit Placebo Effects in Non-Malignant Pain, Subject to Further Research

Procedure	Suggested Clinical Applications
The Patient's Beliefs and Characteristics	
1. Select Participants Based on Treatment History.	Stop prescribing interventions of a type that a patient has previously not responded to (e.g. tablets); instead, prescribe a different, new, type of treatment (e.g. psychological therapy).
2. Create Positive Expectancy.	Tell the patient the intervention is likely to be effective. Elicit patients' treatment and illness beliefs and expectations, and dispel any misconceptions. Empower patients to self-care.
3. Reduce Negative Expectancy.	Limit emphasis on major potential side effects, and describe how uncommon they are. Hide cessation of analgesia administration (e.g. as in Benedetti ³⁴), after obtaining advanced consent and ensuring patients are aware they can request additional analgesia if needed.
4. Convey a Positive Therapeutic Message through Informed Consent Procedures.	Provide written and/or verbal information that conveys a positive therapeutic message about treatment. Provide clear rationale for treatment. Provide patient testimonials and supporting literature / media.
5. Harness Socio-cultural Context.	Elicit patients' culturally embedded treatment and illness beliefs, preferences and expectations, dispelling any misconceptions. Involve significant others in care.
The Practitioner's Beliefs and Characteristics	
6. Practitioner Expectancy.	Only prescribe a treatment to patients when the prescriber expects it will be effective; communicate that expectation to patients.
7. Practitioner's Personal Characteristics.	Honour patient preferences for particular practitioners. Use indicators of expertise/high status in offices, in correspondence, and when referring to other practitioners. Ensure the patient is seen by a practitioner whose views/values are congruent with the patient's.
The Healthcare Setting	
8. Active Recruitment.	Actively seek out patients and invite them to attend clinic regarding a particular intervention (as opposed to waiting for patients to present).
9. Active Retention.	Personally contact patients if they miss an appointment. Use incentives to encourage patients to keep appointments.
10. Follow-up.	Routinely invite patients to book a follow up appointment after an intervention has finished and prior to repeat prescription. Encourage the patient to take responsibility for and self-manage their condition following an intervention.
11. Follow a Standardised Protocol.	Use patient-friendly treatment protocols and share with patients where they fit in that protocol.
12. Ethical Oversight.	Ensure that patients understand that their treatment protocol is

13. Participating in Research.	sanctioned by a higher authority e.g. NICE. Inform patients that all outcomes and GP performance is audited and can contribute to improved knowledge and treatment for future patients.
14. Symptom Monitoring.	Ask patients to monitor their symptoms regularly, for example using email, phone apps, web-based systems, paper forms. Assess treatment outcome. Give patients feedback on symptom improvements following monitoring.
15. Enhanced Environment.	Ensure that the environment is professional, pleasant and peaceful. Employ friendly and helpful support staff.
Treatment Characteristics	
16. Sham Intervention – Medication.	Openly prescribe sham medication. With advanced prior consent, prescribe sham medication.
17. Sham Interventions – Physical.	Openly prescribe sham physical treatments. With advanced prior consent, prescribe sham physical treatments.
18. Sham Interventions – Attention Only.	Increase frequency and duration of consultations.
19. Ineffective substances.	Prescribe substances that are likely not to cause harm but not clearly indicated or substances unlikely to be effective e.g. simple linctus.
20. Use Side-Effects.	Tell patients about side effects associated with positive clinical outcome.
21. Matched treatments.	Design appearance of prescribed substance (e.g. colour, packaging, taste) to match known effective treatments.
22. Maximised treatment procedures.	Within safety limits prescribe higher dose/ higher frequency/ larger pill. Use different colour treatments. Instigate ritualistic procedures patients can perform when taking medicines. Maximise adherence to treatment through education, easy follow up appointments, easy repeat prescription arrangements etc.
23. Conditioning.	Prescribe highest tolerated dose first, then titrate downwards. With consent, begin with active intervention, pair with a seemingly identical placebo then substitute for placebo alone.(e.g. as in Sandler ³⁵)
The Patient-Practitioner Interaction	
24. The Process of Informed Consent.	Actively seek patient consent. Provide treatment options and encourage the patient to choose from these options if they so desire.
25. Detailed History.	Take a detailed medical and psychosocial history/update. Ensure the patient feels listened to, e.g. through non-verbal communication and/or capturing information. Ask questions about the meaning of symptoms.
26. Diagnosis/tests.	Provide a definitive/confident diagnosis. Examine the patient fully.
27. Care.	Allow patient adequate time to tell their story and listen to them. Validate the patient's concerns. Use non-verbal techniques to convey empathy, compassion, warmth. Use touch judiciously.
28. Patient-Centred	Individualise consultation style according to a patient's preference e.g.

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3	Communication.	collaborative vs authoritative.
4		Engage in collaborative decision-making with the patient.
5		Develop shared treatment goals that you and the patient agree on.
6	29. Extra Attention.	Give extra attention to or show more interest in a patient by seeing
7		them more frequently, having longer consultations or visiting at home.
8		Do not rush the patient.
9	30. Continuity of Care.	Ensure patient is cared for by the same doctor.
10		Read records before consultation.
11		

Note. Suggestions for clinical applications pending research into effectiveness and ethical acceptability in clinical settings.

For peer review only

Table 3. Use of Procedures in Placebo Groups of Clinical and Experimental Studies

Procedure	% of studies that used each procedure:	
	Experimental (n=58)	Clinical (n=111)
The Patient's Beliefs and Characteristics		
1. Select Participants Based on Treatment History.	55%	75%
2. Create Positive Expectancy.	76%	5%
3. Reduce Negative Expectancy.	3%	0%
4. Convey a Positive Therapeutic Message through Informed Consent Procedures	43%	1%
5. Harness Socio-cultural Context.	0%	0%
The Practitioner's Beliefs and Characteristics		
6. Practitioner Expectancy.	0%	1%
7. Practitioner's Personal Characteristics.	9%	0%
The Healthcare Setting		
8. Active Recruitment.	14%	16%
9. Active Retention.	3%	2%
10. Follow-up.	2%	16%
11. Follow a Standardised Protocol.	85%	63%
12. Ethical Oversight.	78%	69%
13. Participating in Research.	86%	84%
14. Symptom Monitoring.	95%	89%
15. Enhanced Environment.	5%	0%
Treatment Characteristics		
16. Sham Intervention – Medication.	71%	55%
17. Sham Interventions – Physical.	33%	41%
18. Sham Interventions – Attention Only.	2%	5%
19. Ineffective substances.	0%	1%
20. Use Side-Effects.	0%	1%
21. Matched treatments.	40%	82%
22. Maximised treatment procedures.	22%	3%
23. Conditioning.	41%	0%
The Patient-Practitioner Interaction		
24. The Process of Informed Consent.	88%	77%
25. Detailed History.	19%	33%
26. Diagnosis/tests.	36%	41%
27. Care.	0%	1%
28. Patient-Centred Communication.	0%	0%
29. Extra Attention.	2%	63%
30. Continuity of Care.	7%	14%

The Patient's Characteristics and Beliefs

The taxonomy specifies five procedures that act directly on the patient's characteristics and/or beliefs in ways that might contribute to placebo effects. Procedure 1 involves selecting patients who are most likely to benefit from an intervention based on their history of similar treatments (where similarity is construed broadly at multiple levels, including for example appearance, modality, style, and pharmacology). For example, one might select those patients who have not experienced disappointing results from a similar intervention in the past (as this group might have learned to expect the intervention to fail). This procedure was commonly used by clinical trials and (to a lesser degree) experimental studies.

Procedures 2 (create positive expectancy), 3 (reduce negative expectancy), and 4 (convey a positive therapeutic message), all involve communicating with patients to encourage them to expect beneficial effects of treatment or not to expect side-effects. The majority of experimental studies in our review explicitly encouraged participants to expect treatment benefits, while very few clinical studies explicitly targeted patients' expectations and hardly any studies at all attempted to minimise participants' expectations of side-effects. Procedure 5 involves tailoring the intervention to the patient's socio-cultural context. This approach emerged from the expert feedback and while it seems plausible and ethical to translate into clinical practice, it was not used by any of the reviewed studies.

The procedures in the patients' beliefs and characteristics domain are thought to contribute to placebo effects primarily through altering patients' response expectancy. Selecting patients based on treatment history and tailoring to socio-cultural context are also predicated on learning mechanisms, i.e., learned associations between treatment outcome and treatment properties.

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3 There is some evidence that clinicians can give verbal suggestions to alter patients' expectations in
4 practice and in doing so to reduce patients' pain, particularly acute procedural pain^{9 36}. As part of
5 work to implement these procedures more widely in practice it would be important to investigate
6 how to secure ethically valid consent for treatment. For example, clinicians might want to
7 encourage realistically positive patient expectations while providing information about possible
8 harms without inducing the negative expectations that could trigger nocebo effects^{37 38}.

19 **The Practitioner's Characteristics and Beliefs**

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21 The two procedures in this domain are about using or modifying health care practitioners'
22 characteristics and/or beliefs. Procedure 6 requires a practitioner to expect a treatment to benefit
23 the patient. This might contribute to observed placebo effects in patients by influencing a
24 practitioner's communication about the treatment and hence a patient's response expectations
25 and/or affective response to the consultation. Only 1% of clinical studies and no experimental
26 studies reported modifying practitioners' expectations. This procedure has received little attention
27 in the placebo literature but clinical research in musculoskeletal settings suggests practitioners'
28 outcome expectations can predict patients' pain outcomes³⁹. One way to implement this procedure
29 in practice would be for practitioners to communicate explicitly that they believe a treatment is
30 effective, an approach which clearly overlaps with communication interventions designed to help
31 doctors encourage patients to have positive expectations. Implementing Procedure 6 also depends
32 on practitioners having relevant high quality evidence readily available and accessible and
33 understanding this evidence as it applies to the patient.

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53 A small proportion of studies (9% of experimental studies and no clinical studies) emphasised a
54 practitioner's status or other characteristics (Procedure 7). For some patients a high status
55 practitioner might elicit more confidence in the treatment (and thus higher expectations) and/or a
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3 more positive affective response to the consultation⁴⁰. Some aspects of this procedure are already
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5 part of clinical practice, for example the routine display of medical certificates in doctors' offices;
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7 others are inherent in the tools of the doctor, such as the symbolic properties of the stethoscope⁴¹.
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9 However, there is likely to be scope for testing their effects and augmenting their use if appropriate.
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11 12 13 14 **The Healthcare Setting**

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16 Procedures 8 and 9 relate to the active efforts made in studies to recruit and retain participants
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18 respectively. Clinical and experimental studies both reportedly used these procedures sparingly (<20%
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20 for active recruitment and <5% for active retention). Such efforts may make participants feel valued
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22 and could be implemented in practice through the use of personalised communications from
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24 practitioners to encourage attendance at appointments.
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32 Three of the eight procedures in this domain were used by over half of clinical and experimental
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34 studies and relate to basic structural features of research: following a protocol, ethical oversight, and
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36 participating in research (items 11 to 13). They are thought to impact patients' expectations, by
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38 emphasising the legitimacy of the intervention that is being provided and the importance of the
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40 patient's contribution to a bigger project, i.e. generating knowledge. Translating these procedures
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42 into practice could involve, for example, clinicians explicitly talking with patients about official
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44 guidance and treatment protocols that they are following.
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51 Symptom monitoring (item 14) was commonly used in both clinical and experimental studies. This
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53 could be implemented in practice for example through repeatedly using patient reported outcome
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55 measures (see⁴²) and might contribute to placebo effects through learning mechanisms (e.g. regular
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57 symptom monitoring acts as feedback to motivate health behaviours and/or modify patients' goals).
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3 Alternatively, the mere act of asking a patient to monitor their symptoms could convey an
4 expectation of treatment benefit, altering the meaning of a clinical interaction for the patient.
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6 Traditionally such effects of the act of measurement are dismissed as Hawthorne effects but they
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8 may also be encompassed in broader definitions of placebo effects as meaning effects⁴³ and could
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10 thus enhance effects in clinical practice despite being considered a nuisance in clinical research.
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17 Very few placebo studies (5% of experimental and no clinical studies) reported enhancing the
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19 physical or interpersonal environment (item 15). There is a separate and distinct literature on
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21 environment modifications in health settings that might be usefully integrated with the placebo
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23 literature when developing clinical applications in this area and modelling mechanisms of action^{44 45}.
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28 29 **Treatment Characteristics**

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31 Eight procedures in the taxonomy involve modifying the characteristics of a treatment. Three
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33 involve prescribing sham interventions (sham medication – item 16, sham physical interventions –
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35 item 17, and extra attention – item 18) while a fourth involves prescribing a substance unlikely to be
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37 effective for the symptom in question (item 19). These four procedures represent variations in
38
39 control conditions used in research and were frequently used by both clinical and experimental
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41 studies (with the exception of extra attention which was only used by 2-5% of studies). Such
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43 controls are thought to operate primarily via expectations, while affective pathways may also be
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45 important when extra attention from trial personnel/medical staff is involved. Of all the procedures
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47 in the taxonomy these four that represent control conditions come closest to the traditional notion
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49 of how placebos could be applied in practice. Given ethical concerns around deceptive prescribing
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51 we suggest that translational research might continue to focus on openly prescribing sham
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53 interventions including placebo pills (as in^{10 11}). Other options should not be dismissed entirely
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57 though: advanced consent and even waiving consent are acceptable to some patients and so it is
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3 vital for translational research to continue exploring patients', practitioners', and other stakeholders'
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5 views on the acceptability and ethics of diverse ways of prescribing placebos ⁴⁶⁻⁴⁹.
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11 Three procedures in this domain modify the superficial (non-pharmacological or non-defining)
12 characteristics of treatments. Procedure 20 is to highlight treatment side-effects to patients in order
13 to encourage patients to see the treatment as potent; this item was very rare, used by only 1% of
14 clinical studies. Procedure 21 was much more commonly used and involves matching the
15 appearance of real and control treatments (used by 40% of experimental and 82% of clinical studies),
16 in order to maintain patient blinding. This could be translated into clinical practice by designing the
17 appearance of interventions to match patients' beliefs about what effective interventions look like.
18 Procedure 22 involves maximising or exaggerating the superficial characteristics of treatment in
19 order to generate larger placebo effects for example by using colour, large pill size, or ritualistic
20 administration of medicines, manipulations which could alter the meaning of a treatment for a
21 patient and/or enhance their expectations. 22% of experimental studies reported using this
22 procedure and one way to translate it into practice would be to create (and test) ritualistic
23 procedures for patients to engage in when taking medicines.
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43 The final procedure in this domain – item 23, conditioning to generate placebo effects - was used
44 commonly and exclusively by experimental studies (41%). Conditioning protocols generate placebo
45 effects through learning mechanisms and perhaps could be implemented in practice to reduce
46 pharmaceutical dosages, as was achieved in a pilot study in children with attention deficit disorder ³⁵.
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55 **The Patient-Practitioner Interaction**

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3 The *Patient-Practitioner Interaction* domain incorporates seven procedures related to the
4 interpersonal relationship or interactions between a patient and their health care practitioner.
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6 These procedures are thought to operate primarily through affective mechanisms such as reduced
7 anxiety after telling one's story and being listened to with empathy and acknowledged. Three
8
9 procedures are about specific processes that can occur during consultations – obtaining informed
10 consent (item 24), taking a detailed history (item 25), and performing additional diagnoses or tests
11 (item 26). Arguably these procedures indicate to the patient that the practitioner respects them, is
12 interested in their perspective, and is thorough in their diagnosis. They occur in both clinical and
13 experimental research settings and could be relatively directly translated into practice or optimised
14 if already used.
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28 Two procedures are about the way in which the practitioner engages with the patient:
29 communicating care (item 27), and patient-centred communication (item 28). These procedures
30 were surprisingly very rarely described in the studies included in our review, although recently the
31 nocebo effects of *not* validating a patient's experiences have been shown to be particularly potent⁵⁰.
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33 There is of course a distinct and large literature on doctor-patient communication and fruitful
34 dialogue is beginning to bridge these fields⁵¹.
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45 The final two procedures in this domain refer to more structural aspects of consultations: extra
46 attention (item 29, i.e. longer or more frequent appointments) and continuity of care (item 30). 63%
47 of clinical studies used extra attention while a small proportion of clinical (14%) and experimental
48 (7%) studies reported providing continuity of care. Directly implementing these procedures in
49 practice might be challenging given ever increasing constraints on healthcare resources and drives to
50 reduce cost.
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Discussion

The taxonomy names and describes 30 procedures that may contribute to placebo effects in experimental and clinical studies and classifies them into five domains. It includes 60 theoretically plausible techniques that might be applied clinically, subject to further research on their effectiveness and ethical acceptability in practice. Some of the clinical applications derived from the placebo literature have already been investigated in their own right under other auspices, highlighting the need for the burgeoning translational science of placebo effects to be broad-ranging and interdisciplinary.

We have used rigorous systematic review and qualitative analytic methods complemented by a survey to develop the taxonomy. Investigators often combine multiple techniques in any one 'placebo' (e.g. Create Positive Expectancy + Detailed History + Symptom Monitoring) making it beyond the scope of this project to unpack the effectiveness of individual techniques. Procedures did not always fit neatly into single domains. For example, "Screen for Treatment History" was used to select patients for studies of specific treatments (and was thus placed in the Patient's Beliefs and Characteristics domain), but its clinical application involves selecting a treatment for a specific patient and so could be considered a Treatment Characteristic. Conceptually we would expect interactions between these domains; for example, some procedures categorised in other domains probably operate through causal pathways involving patients' beliefs as proximal determinants of placebo effects⁶³. We feel the benefits of having a hierarchical structure (modifiable as the taxonomy is refined with use) outweigh the difficulties inherent in classification. We could have used many published reviews of placebo studies in non-malignant pain to identify original studies to review. Selecting seven such reviews means not using others, thus we might have missed original studies that would have suggested additional procedures. Surveying leading researchers and

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3 incorporating their suggestions somewhat mitigates this limitation. The reviews that we selected as
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5 the source of our papers and the papers themselves are now somewhat old examples of the
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7 literature. Future work should review very recent papers and iteratively improve the taxonomy
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9 accordingly.
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15 This review extends previous work by Di Blasi et al.²², building on their five domains to
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17 systematically develop a detailed taxonomy. We provide a new overarching framework that avoids
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19 the controversial and limited distinction between pure and impure placebos^{52 53} and integrates ideas
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21 from the rich clinical and experimental literatures on placebo effects in non-malignant pain. Many
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23 of the components we have identified are likely to be important in other placebo-responsive
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25 conditions including depression⁵⁴, irritable bowel syndrome^{55 56}, and insomnia⁵⁷. This taxonomy
26
27 can guide two important and related applied research agendas: 1) to understand the components of
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29 placebo effects in clinical settings^{40 58-61} and 2) to ethically harness evidence-based placebo effects
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31 to benefit patients^{10 11 62}. We hope future studies might draw on the taxonomy to fully describe
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33 their methods and develop new applications, thus facilitating future systematic reviews and the
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35 development of a systematic and theory driven cumulative evidence-base in this complex field.
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43 The taxonomy identifies and classifies procedures that may contribute to placebo effects in clinical
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45 trials and experiments, providing an overarching framework for individual components. However,
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47 we do not suggest that every technique in this taxonomy will produce a placebo effect in every
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49 patient and we do not know from this project which techniques are more effective or how they
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51 might be combined to form ethically acceptable and effective complex interventions. This taxonomy
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53 provides the first attempt at a necessary conceptual tool to facilitate future research on these
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55 questions. For example, systematic reviews could use the taxonomy to code procedures in original
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3 studies, using this information in meta-regression analysis to examine the contribution of different
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5 procedures to placebo effects⁶⁴. New clinical trials and experiments could extend existing work by
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7 systematically examining and comparing the effects and ethical acceptability of different procedures
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9 in the taxonomy, building a cumulative evidence-base that has real pragmatic applicability to clinical
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11 practice. Some of the suggested clinical applications have been investigated more extensively in
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13 other literatures, in particular doctor-patient communication and the healthcare environment. This
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15 emphasises the need for a multi-disciplinary approach to the translation of placebo research into
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17 practice. One fruitful way forward would be to draw on placebo theories to develop and test more
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19 mechanistic models of complex interventions intended to alter the context of healthcare encounters.
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26 Placebo recipients in clinical trials and experiments are exposed to a large number and variety of
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28 procedures, many of which might contribute to measured placebo effects. We have systematically
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30 identified and classified these procedures into five domains, defined them and suggested possible
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32 clinical applications. The resulting taxonomy is presented as a detailed and systematic guide for
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34 future research, which can in turn further refine the taxonomy. Researchers and clinicians can use
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36 the taxonomy to help conceptualise investigations of clinical applications of placebo effects for
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38 patient benefit.
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Competing Interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the

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2
3 submitted work in the previous three years, no other relationships or activities that could appear to
4
5 have influenced the submitted work.
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36 **Contributorship Statement**

37 FB designed and led the study, drafted the manuscript, and is guarantor. FB, GL, AWAG, HE, and PL
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39 secured funding for the project. FB designed the study with input and revisions from GL, BC, AWAG,
40
41 HE, and PL. BC led data collection and analysis with additional data collection and analysis by MH
42
43 and DS. All authors contributed to data interpretation. FB drafted the manuscript and all authors
44
45 revised it for important intellectual content. All authors had full access to all of the data in the study
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47 and can take responsibility for the integrity of the data and the accuracy of the data analysis.
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51 **Data Sharing Statement**

52 No unpublished data available.
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Supplementary Digital Content

List of Included Studies

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	n/a
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	n/a
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	n/a
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, Fig1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22-3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-3
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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BMJ Open

What Techniques Might be Used to Harness Placebo Effects in Non-Malignant Pain? A Literature Review and Survey to Develop a Taxonomy.

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	General practice / Family practice, Research methods, Rheumatology, Rehabilitation medicine
Keywords:	placebos, placebo effect, nocebo effect, translational research, review, classification

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5 **1 What Techniques Might be Used to Harness Placebo Effects in Non-**
6 **2 Malignant Pain? A Literature Review and Survey to Develop a**
7 **3 Taxonomy.**
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13 Running head: Taxonomy of techniques to harness placebo effects
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3 22**Abstract**

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6 23 Objectives. Placebo effects can be clinically meaningful but are seldom fully exploited in clinical
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8 24 practice. This review aimed to facilitate translational research by producing a taxonomy of
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10 25 applicable techniques that could augment placebo analgesia in clinical practice.

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13 26 Design. Literature review and survey.

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16 27 Methods. We systematically analysed methods which could plausibly be used to elicit placebo
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18 28 effects in 169 clinical and laboratory-based studies involving non-malignant pain, drawn from 7
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20 29 systematic reviews. In a validation exercise we surveyed 33 leading placebo researchers (M=12
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22 30 years' research experience, SD=9.8), who were asked to comment on and add to the draft taxonomy
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24 31 derived from the literature.

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27 32 Results. The final taxonomy defines 30 procedures that may contribute to placebo effects in clinical
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29 33 and experimental research, proposes 60 possible clinical applications, and classifies procedures into
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31 34 5 domains: the *Patient's Characteristics and Belief* (5 procedures and 11 clinical applications); the
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33 35 *Practitioner's Characteristics and Beliefs* (2 procedures and 4 clinical applications); the *Healthcare*
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35 36 *Setting* (8 procedures and 13 clinical applications); *Treatment Characteristics* (8 procedures and 14
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37 37 clinical applications); and the *Patient-Practitioner Interaction* (7 procedures and 18 clinical
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39 38 applications).

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41 39 Conclusions. The taxonomy provides a preliminary and novel tool with potential to guide
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43 40 translational research aiming to harness placebo effects for patient benefit in practice.

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45 41 Keywords: placebos; placebo effect; nocebo effect; translational research; review; classification
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Article Summary

Strengths and Limitations of this Study

- This is a novel attempt to use existing studies to conceptualise the factors that might contribute to placebo effects and the associated procedures that could be simply and ethically adapted for clinical practice, subject to further testing .
- We drew on both clinical trials and laboratory-based studies of placebo effects, in order to generate a more comprehensive list of factors that might contribute to placebo effects than would be possible by relying on just one literature.
- A systematic approach to data synthesis, based on qualitative research methods, was used to identify and classify procedures that might contribute to placebo effects in clinical trials.
- The development of the taxonomy did not incorporate very recent placebo trials or studies and the selection of reviews used to determine which original studies to include in the development process was somewhat arbitrary.
- Our taxonomy is presented not as an exhaustive compilation of current methods used in placebo research but as a detailed and systematic guide for future research, which can in turn further refine the taxonomy.

Introduction

There is compelling evidence that factors other than the so-called active components of treatment can have clinically meaningful effects on symptoms, particularly non-malignant pain¹⁻⁴. Such 'placebo effects' can be defined as the physiological and/or psychological changes that result from the meaning derived by a person in a health care setting^{5,6}. From a learning perspective, expectations play a key role in placebo effects.⁷ These effects may be as large as treatment effects⁸ and occur throughout medicine, especially when doctors and patients interact with each other. They are not routinely deliberately harnessed for patient benefit in clinical practice⁹, possibly because doctors often assume they must deceive patients in order to elicit placebo effects^{10,11}. However, this assumption is mistaken because it is not necessary to prescribe placebos in order to elicit placebo effects. For example, the overall analgesic effect of an opioid derives not only from its specific pharmaceutical actions but also from its psychological components, i.e. the *expectations* and *meaning* that the patient derives when consulting the doctor and taking the medicine^{12,13}. The same is true for other types of intervention including physical, surgical, and psychotherapies. One approach that has received initial support is for doctors to use positive suggestion to enhance patients' expectations of benefit⁴. Furthermore, preliminary evidence suggests that openly prescribing placebos might elicit clinically meaningful placebo effects in IBS and depression^{14,15} although this approach entails its own set of ethical challenges^{16,17}.

Placebo researchers have both begun and called for more translational research in this field^{11,18-20}. Such work has thus far typically focused on ethical considerations and narrative approaches to drawing out implications for clinical practice from the placebo literature. We suggest a systematic approach to translational research might be helpful. Many techniques and procedures contribute to placebo effects and could potentially be simply and ethically adapted for clinical practice, subject to further testing in practice settings²¹. In order to identify and describe such techniques, and thus

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3 85 provide some direction for future research, we reviewed experimental and clinical studies of placebo
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5 86 effects in non-malignant pain. We focused on non-malignant pain because it can be difficult to
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7 87 manage (particularly with current concerns about opioids²²), the mechanisms underpinning placebo
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9 88 analgesia are reasonably well understood²³, laboratory-based experimental studies often focus on
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11 89 placebo analgesia, and patients with pain have been shown to display substantial and clinically
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13 90 significant placebo effects¹. The aim of this project was to facilitate translational research by
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15 91 producing a taxonomy of techniques that may contribute to observed placebo effects in research
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17 92 settings and could be studied in future as potential approaches to augmenting placebo
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19 93 enhancement of analgesia in clinical practice.
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26 95 **Methods**

27 28 29 30 97 **Literature Search**

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32 98 We selected seven systematic reviews of different aspects of the placebo literature, chosen from
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34 99 recent reviews available at the time (2012) and based on expert opinion (within the research team)
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36 100 to enable the extraction of information on placebo procedures from a broad range of settings -
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38 101 comprehensive reviews²⁴⁻²⁶, reviews of placebo effects in clinical populations^{2 27} and reviews of
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40 102 laboratory-based experimental placebo studies^{28 29}. The key consideration was that together this
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42 103 collection of reviews should cite a diverse set of studies likely to be using diverse methods to directly
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44 104 (e.g. placebo mechanisms studies) or indirectly (e.g. clinical trials with placebo controls) study
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46 105 placebo effects. After removing duplicates and ineligible studies (see Figure 1), 169 studies were
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48 106 used to develop the taxonomy (for list of included studies see Supplementary Digital Content).
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11 Studies were eligible for inclusion if they: reported original research in which some participants
12 received a placebo intervention, were published since 1983, published in English language, reported
13 a non-malignant pain outcome. Studies were excluded if they: were published before 1983 (because
14 (a) means of generating context-dependent placebo effects may be sensitive to social and cultural
15 changes over time, e.g. patient preferences for particular communication styles and thus their
16 effectiveness in modifying expectations may have changed over time and (b) this yielded a
17 manageable number of papers to analyse which had been published during the 30 years preceding
18 this analysis); or examined any type of psychotherapeutic interventions (because it is difficult to
19 disentangle the active components of psychotherapy from the effect of the meaning of the
20 intervention³⁰).

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36 122 **Data Extraction and Synthesis**

37 123 Descriptions of all events that occurred in the placebo groups during each of the 169 studies (e.g.
38 124 medical, administrative, and ethical procedures) were extracted into a piloted form by one author
39 125 and checked by a second. These events were reviewed for duplication and overlap. This resulted in
40 126 an initial list of 43 procedures that might contribute to placebo effects (e.g. informed consent
41 127 processes, taking placebo pills, conditioning protocols). Study authors were not contacted for
42 128 further information about method used.

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55 130 To synthesise the data and develop our taxonomy we used systematic and rigorous methods derived
56 131 from qualitative research. We began with a deductive analysis, which aimed to categorise the

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3 132 procedures in a way that is intuitively appealing, accessible, and clinically relevant by sorting them
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5 133 into five previously-identified contextual domains of healthcare: patients' characteristics/beliefs,
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7 134 practitioners' characteristics/beliefs, practitioner-patient relationship, superficial treatment
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9 135 characteristics, and the healthcare environment³¹. Two authors (BC, FB) performed the initial
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11 136 categorisation which was then reviewed in detail by three other authors (GL, HE, AG). We then
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13 137 engaged in a constant comparative analysis, a technique that originates in grounded theory³². The
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15 138 aim of this part of the analysis was to consolidate the list of procedures and ensure that we only
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17 139 retained those that were distinct from each other. Procedures and examples of their use were all
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19 140 systematically compared to each other; similar procedures were then merged and all procedures
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21 141 were classified into one of the five domains. Two authors (BC, FB) led this work and presented initial
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23 142 findings to the rest of the team for discussion. All authors discussed and agreed on which
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25 143 procedures to merge, which to retain, and how to classify them. During this process, the definitions
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27 144 of the five domains were iteratively modified in order to reduce ambiguity over which procedures
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29 145 should be classified into which domain. . This resulted in a more parsimonious list of 29 procedures
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31 146 classified by domain. All authors discussed and agreed on the final classification of these procedures.
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33 147 These 29 procedures were then critically examined to ensure they were theoretically plausible
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35 148 means of producing placebo effects. We focused on three core psychological mechanisms^{25 33-36}:
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37 149 response expectancy³⁷; conditioning and social learning⁷; and affect, including motivation and
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39 150 anxiety-reduction^{24 38}. However, we acknowledge that these mechanisms are difficult to tease apart
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41 151³⁹ and that alternative mechanisms have been proposed⁶ and so we erred on the side of inclusivity.
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43 152 Neurobiological mechanisms of placebo analgesia have been described^{23 40} but a detailed
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45 153 consideration of how these might apply to the procedures in the taxonomy would be highly
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47 154 speculative and was beyond the scope of this project (for discussion of clinical applications of the
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49 155 neuroscience of placebo effects see⁴¹). Four authors (FB, BC, AG, GL) reviewed all procedures and
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51 156 considered the extent to which each procedure could plausibly produce placebo effects via one or
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53 157 more of the three core psychological mechanisms. Initial findings were shared with the remaining
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3 158 authors and consensus was reached through discussion. Four procedures deemed very unlikely to
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5 159 produce placebo effects (Conveying a Neutral Therapeutic Message; Randomisation; Blinding;
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7 160 Deception) were excluded, leaving 25 procedures that might plausibly contribute to placebo effects.
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9 161 The multidisciplinary team of authors then generated possible clinical applications of each of these
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11 162 25 procedures.
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164 **Validating the Taxonomy**

165 To ensure our taxonomy was comprehensive we surveyed leading placebo researchers (authors of
166 major publications on placebo effects, attendees at an international symposium on placebo effects,
167 and GPs with an interest in placebo effects). These researchers were identified from the systematic
168 reviews and their references used to develop the taxonomy; the list of attendees at Beyond The
169 Placebo: Biomedical Clinical and Philosophical Aspects of the Placebo Effect, held in Ascona
170 Switzerland, August 2012; and GPs within the National Institute for Health Research School for
171 Primary Care Research. Ethical approval for the survey was obtained from the host institution
172 (reference: 4741). Completed electronic surveys including informed consent were received from 33
173 researchers (52% response rate) experienced in placebo research (M=12 years' experience, SD=9.8).
174 Respondents were shown our draft taxonomy and asked whether, for each domain, they knew of
175 any other procedures that could elicit placebo responses. The proportion answering yes ranged
176 from 22% (Healthcare Setting domain) to 50% (Superficial Treatment Characteristics domain).
177 Respondents suggested 85 additions which were screened against existing procedures and for
178 theoretical plausibility: 80 of the suggested additions were extra details or suggested clinical
179 applications of existing procedures; five were new and distinct plausible procedures that were added
180 to the taxonomy, giving a final total of 30 procedures.
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182 Because of our orientation to clinical applications, we have chosen to use clinically-oriented
terminology throughout the taxonomy. However, it is important to note that when used in relation

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3 183 to procedures identified from the literature these terms also relate to the experimental equivalent,
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5 184 such that “patient” also refers to subject/participant, “practitioner” also refers to experimenter, and
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7 185 “intervention” also refers to experimental condition.
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10 186 **Analysis**

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12 187 The use of each of the 30 procedures in the taxonomy was assessed across all 169 studies in the
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14 188 review. Two authors independently rated the presence of each procedure in each study (Kappa =
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16 189 0.93, discrepancies were resolved through discussion).
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191 **Results**

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25 192 The taxonomy defines 30 procedures that may contribute to placebo effects observed in clinical and
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27 193 experimental research, and classifies them into 5 domains. Table 1 presents the main taxonomy,
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29 194 listing and defining all 30 procedures within 5 domains. Table 2 suggests clinical applications of each
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31 195 procedure. Table 3 shows the frequency of use of each procedure in clinical and experimental
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33 196 studies, and is intended as both an approximate guide to whether the procedures derived primarily
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35 197 from one or other literature and as a means to highlight those procedures that are very common
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37 198 and very rare in the literature. Below we describe the procedures within each domain in turn.
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199 Table 1. Taxonomy of Procedures Which Could Plausibly Elicit Placebo Effects in Non-Malignant Pain

Procedure Derived from Literature	Definition and Use in Research Studies
The Patient's Beliefs and Characteristics	
1. Select Patients Based on Treatment History.	Screen and select patients (or subgroups) against inclusion criteria related to issues such as medical/treatment history, e.g. naive to intervention being tested (not just contraindications).
2. Create Positive Expectancy.	Deliberately and explicitly suggest to patients that the intervention will be effective for them (not as part of informed consent process).
3. Reduce Negative Expectancy. ^a	The potentially negative or harmful procedures and characteristics of the treatment are deliberately minimised in information for patients.
4. Convey a Positive Therapeutic Message through Informed Consent Procedures.	Convey (verbally or in writing) a positive therapeutic message through the content of informed consent. The message might be explicit (e.g. "this intervention is usually effective in most people") or implicit (e.g. "this treatment is an antihypertensive").
5. Harness Socio-cultural Context. ^a	Tailor the intervention according to the patient's social and cultural context and history.
The Practitioner's Beliefs and Characteristics	
6. Practitioner Expectancy.	The person delivering the treatment expects it to be effective for the patient.
7. Practitioner's Personal Characteristics.	The practitioner's personal and/or professional characteristics (e.g. status) are modified (through selecting practitioners with different characteristics) and/or emphasised to patients.
The Healthcare Setting	
8. Active Recruitment.	Actively seek out and recruit patients (e.g. advertising for specific types of patients, writing personally to individual eligible patients identified through medical records).
9. Active Retention.	Make patients feel valued by attempting to keep them in a study (e.g. contact patients if they miss an appointment, incentivise attendance through monetary or non-monetary gifts).
10. Follow-up.	Assess patients after the intervention/experiment to assess long-term maintenance or changes in effects over at least 6 months.
11. Follow a Standardised Protocol.	The intervention is delivered according to a set, scientifically-derived, protocol, lending credibility to the intervention (and is therefore not individualised for each patient).
12. Ethical Oversight.	Study practices and procedures are explicitly regulated and monitored by an institutional ethics committee, lending credibility to the intervention.
13. Participating in Research.	Patients know that they are part of research and contributing to the furthering of human knowledge and/or improvement of healthcare for future patients.
14. Symptom Monitoring.	Monitor patients' symptoms using self-report measures, practitioner assessment, or objective measures

15. Enhanced Environment. ^a	repeated over time at least twice; patients are aware of the resulting measurements. The physical and interpersonal environment where the intervention is delivered is deliberately enhanced.
Treatment Characteristics	
16. Sham Intervention – Medication.	An inert substance is administered which is manufactured to appear identical to an active medication (e.g. sugar pill, saline IV, topical agent).
17. Sham Interventions – Physical.	A sham physical intervention is administered which is designed to appear identical to the genuine intervention (e.g. de-activated TENS, non-penetrative acupuncture needles at non-acupuncture points).
18. Sham Interventions – Attention Only.	Patients receive study-specific attention in terms of numbers of visits and time spent with study staff but no additional intervention.
19. Ineffective substances. ^a	Products unlikely to be effective or not indicated are administered (e.g. vitamins in the absence of vitamin deficiency).
20. Use Salient Side-Effects.	Potential side-effects are highlighted such that the patient can interpret them as evidence of a potent intervention.
21. Matched Treatments.	To secure blinding, placebo/sham treatments are matched to 'real' treatments (e.g. on mode of administration, dosage, frequency of administration, visual appearance, taste, smell, individual titration procedures).
22. Maximised Treatment Procedures.	The procedures and characteristics of the treatment are exaggerated, e.g. through high dose, use of colour, high frequency, large pill size, lengthy duration of intervention, ritualistic administration.
23. Conditioning.	A desired response (e.g. pain relief) is paired with an intervention stimulus (e.g. placebo cream) so that the patient associates the response with the stimulus.
The Patient-Practitioner Interaction	
24. The Process of Informed Consent.	The patient's formal written and/or verbal informed consent is discussed and obtained.
25. Detailed History.	A detailed personal and/or medical and/or psychosocial history is obtained from the patient.
26. Diagnosis/tests.	Additional tests, examinations, or confirmatory diagnostic procedures are undertaken to establish eligibility for the study.
27. Care.	The practitioner deliberately engages the patient with warmth, compassion and empathy.
28. Patient-Centred Communication. ^a	The practitioner adopts a style of consultation that they consider to be appropriate for a particular patient.
29. Extra Attention.	The patient receives extra attention from being in the study, for example is seen more frequently or for longer than usual.
30. Continuity of Care.	Efforts are made for the same practitioner to see the same patient at each contact.

200 ^a procedures added following survey of researchers.

201 Table 2. Suggested Potential Clinical Applications of Procedures to Elicit Placebo Effects in Non-
 202 Malignant Pain, Subject to Further Research

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Procedure	Suggested Clinical Applications
The Patient's Beliefs and Characteristics	
1. Select Patients Based on Treatment History.	Stop prescribing interventions of a type that a patient has previously not responded to (e.g. tablets); instead, prescribe a different, new, type of treatment (e.g. psychological therapy).
2. Create Positive Expectancy.	Tell the patient the intervention is likely to be effective. Elicit patients' treatment and illness beliefs and expectations, and dispel any misconceptions. Empower patients to self-care.
3. Reduce Negative Expectancy.	Limit emphasis on major potential side effects, and describe how uncommon they are. Hide cessation of analgesia administration (e.g. as in Benedetti ⁴²), after obtaining advanced consent and ensuring patients are aware they can request additional analgesia if needed.
4. Convey a Positive Therapeutic Message through Informed Consent Procedures.	Provide written and/or verbal information that conveys a positive therapeutic message about treatment. Provide clear rationale for treatment. Provide patient testimonials and supporting literature/media.
5. Harness Socio-cultural Context.	Elicit patients' culturally embedded treatment and illness beliefs, preferences and expectations, dispelling any potentially harmful misconceptions. Involve significant others in care.
The Practitioner's Beliefs and Characteristics	
6. Practitioner Expectancy.	Only prescribe a treatment to patients when the practitioner expects it will be effective; communicate that expectation to patients.
7. Practitioner's Personal Characteristics.	Honour patient preferences for particular practitioners. Use indicators of expertise/high status in offices, in correspondence, and when referring to other practitioners. Ensure the patient is seen by a practitioner whose views/values are congruent with the patient's.
The Healthcare Setting	
8. Active Recruitment.	Actively seek out patients and invite them to attend clinic regarding a particular intervention (as opposed to waiting for patients to present).
9. Active Retention.	Personally contact patients if they miss an appointment. Use incentives to encourage patients to keep appointments.
10. Follow-up.	Routinely invite patients to book a follow up appointment after an intervention has finished and prior to repeat prescription. Encourage the patient to take responsibility for and self-manage their condition following an intervention.
11. Follow a Standardised Protocol.	Use patient-friendly treatment protocols and share with patients where they fit in that protocol.

12. Ethical Oversight.	Ensure that patients understand that their treatment protocol is sanctioned by a higher authority e.g. NICE.
13. Participating in Research.	Inform patients that all outcomes and practitioner performance is audited and can contribute to improved knowledge and treatment for future patients.
14. Symptom Monitoring.	Ask patients to monitor their symptoms regularly, for example using email, phone apps, web-based systems, paper forms. Assess treatment outcome. Give patients feedback on symptom improvements following monitoring.
15. Enhanced Environment.	Ensure that the environment is professional, pleasant and peaceful. Employ friendly and helpful support staff.

Treatment Characteristics

16. Sham Intervention – Medication.	Openly prescribe sham medication. With advanced prior consent, prescribe sham medication.
17. Sham Interventions – Physical.	Openly prescribe sham physical treatments. With advanced prior consent, prescribe sham physical treatments.
18. Sham Interventions – Attention Only.	Increase frequency and duration of consultations.
19. Ineffective substances.	Prescribe substances that are likely not to cause harm but not clearly indicated or substances unlikely to be effective e.g. simple linctus.
20. Use Side-Effects.	Tell patients about side effects associated with positive clinical outcome.
21. Matched treatments.	Design appearance of prescribed substance (e.g. colour, packaging, taste) to match known effective treatments.
22. Maximised treatment procedures.	Within safety limits prescribe higher dose/higher frequency/larger pill. Use different colour treatments. Instigate ritualistic procedures patients can perform when taking medicines. Maximise adherence to treatment through education, easy follow up appointments, easy repeat prescription arrangements etc.
23. Conditioning.	Prescribe highest tolerated dose first, then titrate downwards. With consent, begin with active intervention, pair with a seemingly identical placebo then substitute for placebo alone.(e.g. as in Sandler ⁴³)

The Patient-Practitioner Interaction

24. The Process of Informed Consent.	Actively seek patient consent. Provide treatment options and encourage the patient to choose from these options if they so desire.
25. Detailed History.	Take a detailed medical and psychosocial history/update. Ensure the patient feels listened to, e.g. through non-verbal communication and/or capturing information. Ask questions about the meaning of symptoms.
26. Diagnosis/tests.	Provide a definitive/confident diagnosis. Examine the patient fully.
27. Care.	Allow patient adequate time to tell their story and listen to them. Validate the patient's concerns. Use non-verbal techniques to convey empathy, compassion, warmth. Use touch judiciously.

28. Patient-Centred Communication.	Individualise consultation style according to a patient's preference e.g. collaborative vs authoritative. Engage in collaborative decision-making with the patient. Develop shared treatment goals that you and the patient agree on.
29. Extra Attention.	Give extra attention to or show more interest in a patient by seeing them more frequently, having longer consultations or visiting at home. Do not rush the patient.
30. Continuity of Care.	Ensure patient is cared for by the same practitioner. Read records before consultation.

204 Note. Suggestions for clinical applications pending research into effectiveness and ethical
205 acceptability in clinical settings.

For peer review only

206 Table 3. Use of Procedures in Placebo Groups of Clinical and Experimental Studies

Procedure	% of studies that used each procedure:	
	Experimental (n=58)	Clinical (n=111)
The Patient's Beliefs and Characteristics		
1. Select Intervention Based on Patient's Treatment History.	55%	75%
2. Create Positive Expectancy.	76%	5%
3. Reduce Negative Expectancy.	3%	0%
4. Convey a Positive Therapeutic Message through Informed Consent Procedures	43%	1%
5. Harness Socio-cultural Context.	0%	0%
The Practitioner's Beliefs and Characteristics		
6. Practitioner Expectancy.	0%	1%
7. Practitioner's Personal Characteristics.	9%	0%
The Healthcare Setting		
8. Active Recruitment.	14%	16%
9. Active Retention.	3%	2%
10. Follow-up.	2%	16%
11. Follow a Standardised Protocol.	85%	63%
12. Ethical Oversight.	78%	69%
13. Participating in Research.	86%	84%
14. Symptom Monitoring.	95%	89%
15. Enhanced Environment.	5%	0%
Treatment Characteristics		
16. Sham Intervention – Medication.	71%	55%
17. Sham Interventions – Physical.	33%	41%
18. Sham Interventions – Attention Only.	2%	5%
19. Ineffective substances.	0%	1%
20. Use Side-Effects.	0%	1%
21. Matched treatments.	40%	82%
22. Maximised treatment procedures.	22%	3%
23. Conditioning.	41%	0%
The Patient-Practitioner Interaction		
24. The Process of Informed Consent.	88%	77%
25. Detailed History.	19%	33%
26. Diagnosis/tests.	36%	41%
27. Care.	0%	1%
28. Patient-Centred Communication.	0%	0%
29. Extra Attention.	2%	63%
30. Continuity of Care.	7%	14%

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3 208 **The Patient's Characteristics and Beliefs**
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6 209 The taxonomy specifies five procedures that act directly on the patient's characteristics and/or
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8 210 beliefs in ways that might contribute to placebo effects. Procedure 1 involves selecting patients who
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10 211 are most likely to benefit from an intervention based on their history of similar treatments (where
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12 212 similarity is construed broadly at multiple levels, including appearance, modality, style, and
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14 213 pharmacology). For example, one might select those patients who have not experienced
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16 214 disappointing results from a similar intervention in the past (as the latter group might have learned
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18 215 to expect the intervention to fail). This procedure was commonly used by clinical trials and (to a
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20 216 lesser degree) experimental studies.
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27 218 Procedures 2 (create positive expectancy), 3 (reduce negative expectancy), and 4 (convey a positive
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29 219 therapeutic message), all involve communicating with patients to encourage them to expect
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31 220 beneficial effects of treatment or not to expect side-effects. The majority of experimental studies in
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33 221 our review explicitly encouraged patients to expect treatment benefits, while very few clinical
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35 222 studies explicitly targeted patients' expectations and hardly any studies at all attempted to minimise
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37 223 patients' expectations of side-effects. Procedure 5 involves tailoring the intervention to the
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39 224 patient's socio-cultural context. This approach emerged from the expert feedback and while it
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41 225 seems plausible and ethical to translate into clinical practice, it was not used by any of the reviewed
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43 226 studies.
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50 228 The procedures in the patients' beliefs and characteristics domain are thought to contribute to
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52 229 placebo effects primarily through altering patients' response expectancy. Selecting patients based
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54 230 on treatment history and tailoring to socio-cultural context are also predicated on learning
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56 231 mechanisms, i.e., learned associations between treatment outcome and treatment properties.
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3 232 There is some evidence that clinicians can give verbal suggestions to alter patients' expectations in
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5 233 practice and in doing so to reduce patients' pain, particularly acute procedural pain⁴⁴. As part of
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7 234 work to implement these procedures more widely in practice it would be important to investigate
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9 235 how to secure ethically valid consent for treatment. For example, clinicians might want to
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11 236 encourage realistically positive patient expectations while providing information about possible
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13 237 harms without inducing the negative expectations that could trigger nocebo effects^{45 46}.

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18 19 239 **The Practitioner's Characteristics and Beliefs**

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21 240 The two procedures in this domain are about using or modifying health care practitioners'
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23 241 characteristics and/or beliefs. Procedure 6 requires a practitioner to expect a treatment to benefit
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25 242 the patient. This might contribute to observed placebo effects in patients by influencing a
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27 243 practitioner's communication about the treatment and hence a patient's response expectations
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29 244 and/or affective response to the consultation. Only 1% of clinical studies and no experimental
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31 245 studies reported modifying practitioners' expectations. This procedure has received little attention
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33 246 in the placebo literature but clinical research in musculoskeletal settings suggests practitioners'
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35 247 outcome expectations can predict patients' pain outcomes⁴⁷. One way to implement this procedure
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37 248 in practice would be for practitioners to communicate explicitly that they believe a treatment is
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39 249 effective, an approach which clearly overlaps with communication interventions designed to help
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41 250 doctors encourage patients to have positive expectations. Implementing Procedure 6 also depends
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43 251 on practitioners having relevant high quality evidence readily available and accessible and
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45 252 understanding this evidence as it applies to the patient.

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53 254 A small proportion of studies (9% of experimental studies and no clinical studies) emphasised a
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55 255 practitioner's status or other characteristics (Procedure 7). For some patients a high status
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57 256 practitioner might elicit more confidence in the treatment (and thus higher expectations) and/or a
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3 257 more positive affective response to the consultation⁴⁸. Some aspects of this procedure are already
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5 258 part of clinical practice, for example the routine display of medical certificates in doctors' offices;
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7 259 others are inherent in the tools of the doctor, such as the symbolic properties of the stethoscope⁴⁹.
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9 260 However, there is likely to be scope for testing their effects and augmenting their use if appropriate.
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14 262 **The Healthcare Setting**

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16 263 Procedures 8 and 9 relate to the active efforts made in studies to recruit and retain patients
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18 264 respectively. Clinical and experimental studies both reportedly used these procedures sparingly (<20%
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20 265 for active recruitment and <5% for active retention). Such efforts may make patients feel valued and
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22 266 could be implemented in practice through the use of personalised communications from
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24 267 practitioners to encourage attendance at appointments.
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31 269 Three of the eight procedures in this domain were used by over half of clinical and experimental
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33 270 studies and relate to basic structural features of research: following a protocol, ethical oversight, and
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35 271 participating in research (procedures 11 to 13). They are thought to impact patients' expectations,
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37 272 by emphasising the legitimacy of the intervention that is being provided and the importance of the
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39 273 patient's contribution to a bigger project, i.e. generating knowledge. Translating these procedures
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41 274 into practice could involve, for example, clinicians explicitly talking with patients about official
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43 275 guidance and treatment protocols that they are following.
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50 277 Symptom monitoring (procedure 14) was commonly used in both clinical and experimental studies.
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52 278 This could be implemented in practice for example through repeatedly using patient reported
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54 279 outcome measures (see⁵⁰) and might contribute to placebo effects through learning mechanisms
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56 280 (e.g. regular symptom monitoring acts as feedback to motivate health behaviours and/or modify
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3 281 patients' goals). Alternatively, the mere act of asking a patient to monitor their symptoms could
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5 282 convey an expectation of treatment benefit, altering the meaning of a clinical interaction for the
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7 283 patient. Traditionally such effects of the act of measurement are dismissed as Hawthorne effects
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9 284 but they may also be encompassed in broader definitions of placebo effects as meaning effects⁵¹
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11 285 and could thus enhance effects in clinical practice despite being considered a nuisance in clinical
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13 286 research.

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20 288 Very few placebo studies (5% of experimental and no clinical studies) reported enhancing the
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22 289 physical or interpersonal environment (procedure 15). There is a separate and distinct literature on
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24 290 environment modifications in health settings that might be usefully integrated with the placebo
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26 291 literature when developing clinical applications in this area and modelling mechanisms of action^{52,53}.

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30 293 **Treatment Characteristics**

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33 294 Eight procedures in the taxonomy involve modifying the characteristics of a treatment. Three
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35 295 involve prescribing sham interventions (sham medication – procedure 16, sham physical
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37 296 interventions – procedure 17, and extra attention – procedure 18) while a fourth involves
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39 297 prescribing a substance unlikely to be effective for the symptom in question (procedure 19). These
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41 298 four procedures represent variations in control conditions used in research and were frequently
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43 299 used by both clinical and experimental studies (with the exception of extra attention which was only
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45 300 used by 2-5% of studies). Such controls are thought to operate primarily via expectations, while
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47 301 affective pathways may also be important when extra attention from trial personnel/medical staff is
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49 302 involved. Of all the procedures in the taxonomy these four that represent control conditions come
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51 303 closest to the traditional notion of how placebos could be applied in practice. Given ethical concerns
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53 304 around deceptive prescribing we suggest that translational research might continue to focus on
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55 305 openly prescribing sham interventions including placebo pills (as in^{14,15}). Other options should not
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3 306 be dismissed entirely though: advanced consent and even waiving consent are acceptable to some
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5 307 patients and so it is vital for translational research to continue exploring patients', practitioners', and
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7 308 other stakeholders' views on the acceptability and ethics of diverse ways of prescribing placebos⁵⁴⁻⁵⁷.
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13 310 Three procedures in this domain modify the superficial (non-pharmacological or non-defining)
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15 311 characteristics of treatments. Procedure 20 is to highlight treatment side-effects to patients in order
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17 312 to encourage patients to see the treatment as potent; this procedure was very rare, used by only 1%
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19 313 of clinical studies. Procedure 21 was much more commonly used and involves matching the
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21 314 appearance of real and control treatments (used by 40% of experimental and 82% of clinical studies),
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23 315 in order to maintain patient blinding. This could be translated into clinical practice by designing the
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25 316 appearance of interventions to match patients' beliefs about what effective interventions look like.
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28 317 Procedure 22 involves maximising or exaggerating the superficial characteristics of treatment in
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30 318 order to generate larger placebo effects for example by using colour, large pill size, or ritualistic
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32 319 administration of medicines, manipulations which could alter the meaning of a treatment for a
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34 320 patient and/or enhance their expectations. 22% of experimental studies reported using this
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36 321 procedure and one way to translate it into practice would be to create (and test) ritualistic
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38 322 procedures for patients to engage in when taking medicines.
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45 324 The final procedure in this domain – procedure 23, conditioning to generate placebo effects - was
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47 325 used commonly and exclusively by experimental studies (41%). Conditioning protocols generate
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49 326 placebo effects through learning mechanisms and perhaps could be implemented in practice to
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51 327 reduce pharmaceutical dosages, as was achieved in a pilot study in children with attention deficit
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53 328 disorder⁴³.
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330 **The Patient-Practitioner Interaction**

331 The *Patient-Practitioner Interaction* domain incorporates seven procedures related to the
332 interpersonal relationship or interactions between a patient and their health care practitioner.
333 These procedures are thought to operate primarily through affective mechanisms such as reduced
334 anxiety after telling one's story and being listened to with empathy and acknowledged, although
335 more cognitive pathways via expectations are also plausible⁵⁸. Three procedures are about specific
336 processes that can occur during consultations – obtaining informed consent (procedure 24), taking a
337 detailed history (procedure 25), and performing additional diagnoses or tests (procedure 26).
338 Arguably these procedures indicate to the patient that the practitioner respects them, is interested
339 in their perspective, and is thorough in their diagnosis. They occur in both clinical and experimental
340 research settings and could be relatively directly translated into practice or optimised if already used.

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342 Two procedures are about the way in which the practitioner engages with the patient:
343 communicating care (procedure 27), and patient-centred communication (procedure 28). These
344 procedures were surprisingly very rarely described in the studies included in our review, although
345 recently the nocebo effects of *not* validating a patient's experiences have been shown to be
346 particularly potent⁵⁹. There is of course a distinct and large literature on doctor-patient
347 communication and fruitful dialogue is beginning to bridge these fields⁶⁰.

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349 The final two procedures in this domain refer to more structural aspects of consultations: extra
350 attention (procedure 29, i.e. longer or more frequent appointments) and continuity of care
351 (procedure 30). 63% of clinical studies used extra attention while a small proportion of clinical (14%)
352 and experimental (7%) studies reported providing continuity of care. Directly implementing these
353 procedures in practice might be challenging given ever increasing constraints on healthcare
354 resources and drives to reduce cost.

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Discussion

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8 357 The taxonomy names and describes 30 procedures that may contribute to placebo effects in
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10 358 experimental and clinical studies and classifies them into five domains. It includes 60 theoretically
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12 359 plausible clinical applications, subject to further research on their effectiveness and ethical
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14 360 acceptability in practice. Some of the clinical applications derived from the placebo literature have
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16 361 already been investigated in their own right under other auspices, highlighting the need for the
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18 362 burgeoning translational science of placebo effects to be broad-ranging and interdisciplinary.

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25 364 We have used rigorous systematic review and qualitative analytic methods complemented by a
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27 365 survey to develop the taxonomy. Investigators often combine multiple techniques in any one
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29 366 'placebo' (e.g. Create Positive Expectancy + Detailed History + Symptom Monitoring) making it
30
31 367 beyond the scope of this project to unpack the effectiveness of individual techniques. Procedures
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33 368 did not always fit neatly into single domains. For example, "Screen for Treatment History" was used
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35 369 to select patients for studies of specific treatments (and was thus placed in the Patient's Beliefs and
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37 370 Characteristics domain), but its clinical application involves selecting a treatment for a specific
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39 371 patient and so could be considered a Treatment Characteristic. Conceptually we would expect
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41 372 interactions between these domains; for example, some procedures categorised in other domains
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43 373 probably operate through causal pathways involving patients' beliefs as proximal determinants of
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45 374 placebo effects⁶¹. We feel the benefits of having a hierarchical structure (modifiable as the
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47 375 taxonomy is refined with use) outweigh the difficulties inherent in classification. We could have
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49 376 used many published reviews of placebo studies in non-malignant pain to identify original studies to
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51 377 review. Selecting seven such reviews means not using others, thus we might have missed original
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53 378 studies that would have suggested additional procedures. Surveying leading researchers and
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55 379 incorporating their suggestions somewhat mitigates this limitation. Our sample of researchers was

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3 380 intended to be purposive, in that we wanted to obtain the views of leading researchers in the field.
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5 381 By using multiple means of identifying such individuals internationally we feel we have achieved this.
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7 382 The reviews that we selected as the source of our papers and the papers themselves are now
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9 383 somewhat old examples of the literature; and our choice to exclude papers published before 1983
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11 384 was arguably somewhat arbitrary. Future work should review very recent papers and iteratively
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13 385 improve the taxonomy accordingly.
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20 387 This review extends previous work by Di Blasi et al.³¹, building on their five domains to
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22 388 systematically develop a detailed taxonomy. We provide a new overarching framework that avoids
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24 389 the controversial and limited distinction between pure and impure placebos^{62 63} and integrates ideas
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26 390 from the rich clinical and experimental literatures on placebo effects in non-malignant pain. Many
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28 391 of the components we have identified are likely to be important in other placebo-responsive
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30 392 conditions including depression⁶⁴, irritable bowel syndrome^{65 66}, and insomnia⁶⁷. This taxonomy
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32 393 can guide two important and related applied research agendas: 1) to understand the components of
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34 394 placebo effects in clinical settings^{48 68-71} and 2) to ethically harness evidence-based placebo effects
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36 395 to benefit patients^{14 15 72}. We hope future studies might draw on the taxonomy to fully describe
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38 396 their methods and develop new applications, thus facilitating future systematic reviews and the
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40 397 development of a systematic and theory driven cumulative evidence-base in this complex field.
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47 399 The taxonomy identifies and classifies procedures that may contribute to placebo effects in clinical
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49 400 trials and experiments, providing an overarching framework for individual components. However,
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51 401 we do not suggest that every technique in this taxonomy will produce a placebo effect in every
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53 402 patient and we do not know from this project which techniques are more effective or how they
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55 403 might be combined to form ethically acceptable and effective complex interventions. This taxonomy
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3 404 provides the first attempt at a necessary conceptual tool to facilitate future research on these
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5 405 questions. For example, systematic reviews could use the taxonomy to code procedures in original
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7 406 studies, using this information in meta-regression analysis to examine the contribution of different
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9 407 procedures to placebo effects⁷³. New clinical trials and experiments could extend existing work by
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11 408 systematically examining and comparing the effects and ethical acceptability of different procedures
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13 409 in the taxonomy, building a cumulative evidence-base that has real pragmatic applicability to clinical
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15 410 practice. Some of the suggested clinical applications have been investigated more extensively in
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17 411 other literatures, in particular doctor-patient communication and the healthcare environment. This
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19 412 emphasises the need for a multi-disciplinary approach to the translation of placebo research into
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21 413 practice. One fruitful way forward would be to draw on placebo theories to develop and test more
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23 414 mechanistic models of complex interventions intended to alter the context of healthcare encounters.
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30 416 Placebo recipients in clinical trials and experiments are exposed to a large number and variety of
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32 417 procedures, many of which might contribute to placebo effects. Researchers seeking to develop a
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34 418 translational science of placebo effects are thus faced with myriad possibilities. We have
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36 419 systematically identified and defined these procedures, classified them into five domains, and
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38 420 suggested possible clinical applications. The resulting taxonomy is presented as a preliminary but
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40 421 detailed and systematic guide for future research, which should in turn further refine the taxonomy.
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42 422 Ultimately we hope to better conceptualise investigations of clinical applications of placebo effects
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44 423 in order to maximise opportunities for patient benefit.
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Competing Interests

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5 447 have influenced the submitted work.
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36 **Contributorship Statement**

37 461 FB designed and led the study, drafted the manuscript, and is guarantor. FB, GL, AWAG, HE, and PL
38
39 462 secured funding for the project. FB designed the study with input and revisions from GL, BC, AWAG,
40
41 463 HE, and PL. BC led data collection and analysis with additional data collection and analysis by MH
42
43 464 and DS. All authors contributed to data interpretation. FB drafted the manuscript and all authors
44
45 465 revised it for important intellectual content. All authors had full access to all of the data in the study
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47 466 and can take responsibility for the integrity of the data and the accuracy of the data analysis.
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51 **Data Sharing Statement**

52 468 No unpublished data available.
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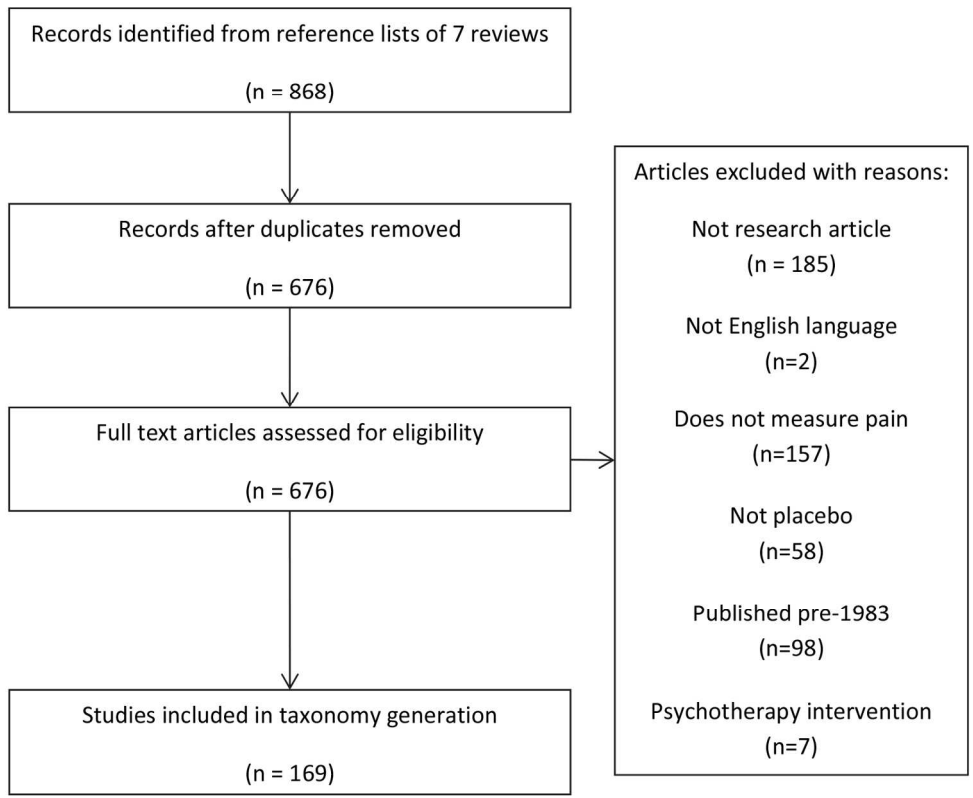
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Flowchart Showing Identification of Studies

155x127mm (300 x 300 DPI)

Supplementary Digital Content

List of Included Studies

[1-169]

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	n/a
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	n/a
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	n/a
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, Fig1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22-3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-3
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

What Techniques Might be Used to Harness Placebo Effects in Non-Malignant Pain? A Literature Review and Survey to Develop a Taxonomy.

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Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	General practice / Family practice, Research methods, Rheumatology, Rehabilitation medicine
Keywords:	placebos, placebo effect, nocebo effect, translational research, review, classification

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5 **1 What Techniques Might be Used to Harness Placebo Effects in Non-**
6 **2 Malignant Pain? A Literature Review and Survey to Develop a**
7 **3 Taxonomy.**
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13 Running head: Taxonomy of techniques to harness placebo effects
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3 22**Abstract**

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6 23 Objectives. Placebo effects can be clinically meaningful but are seldom fully exploited in clinical
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8 24 practice. This review aimed to facilitate translational research by producing a taxonomy of
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10 25 techniques that could augment placebo analgesia in clinical practice.

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13 26 Design. Literature review and survey.

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16 27 Methods. We systematically analysed methods which could plausibly be used to elicit placebo
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18 28 effects in 169 clinical and laboratory-based studies involving non-malignant pain, drawn from 7
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20 29 systematic reviews. In a validation exercise we surveyed 33 leading placebo researchers (M=12
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22 30 years' research experience, SD=9.8), who were asked to comment on and add to the draft taxonomy
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24 31 derived from the literature.

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27 32 Results. The final taxonomy defines 30 procedures that may contribute to placebo effects in clinical
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29 33 and experimental research, proposes 60 possible clinical applications, and classifies procedures into
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31 34 5 domains: the *Patient's Characteristics and Belief* (5 procedures and 11 clinical applications); the
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33 35 *Practitioner's Characteristics and Beliefs* (2 procedures and 4 clinical applications); the *Healthcare*
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35 36 *Setting* (8 procedures and 13 clinical applications); *Treatment Characteristics* (8 procedures and 14
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37 37 clinical applications); and the *Patient-Practitioner Interaction* (7 procedures and 18 clinical
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39 38 applications).

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41 39 Conclusions. The taxonomy provides a preliminary and novel tool with potential to guide
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43 40 translational research aiming to harness placebo effects for patient benefit in practice.

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45 41 Keywords: placebos; placebo effect; nocebo effect; translational research; review; classification
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Article Summary

Strengths and Limitations of this Study

- This is a novel attempt to use existing studies to identify the factors that might contribute to placebo effects and the associated procedures that could be simply and ethically adapted for clinical practice, subject to further testing .
- We drew on both clinical trials and laboratory-based studies of placebo effects, in order to generate a more comprehensive list of factors that might contribute to placebo effects than would be possible by relying on just one literature.
- A systematic approach to data synthesis, based on qualitative research methods, was used to identify and classify procedures that might contribute to placebo effects in clinical trials.
- The development of the taxonomy did not incorporate very recent placebo trials or studies and the selection of reviews used to determine which original studies to include in the development process was somewhat arbitrary.
- Our taxonomy is presented not as an exhaustive compilation of current methods used in placebo research but as a detailed and systematic guide for future research, which can in turn further refine the taxonomy.

Introduction

There is compelling evidence that factors other than the so-called active components of treatment can have clinically meaningful effects on symptoms, particularly non-malignant pain¹⁻⁴. Such 'placebo effects' can be defined as the physiological and/or psychological changes that result from the meaning derived by a person in a health care setting^{5,6}. Expectations – which can be generated, for example, by verbal suggestion or previous experience - play a key role in placebo effects.⁷ These effects may be as large as treatment effects⁸ and occur throughout medicine, especially when doctors and patients interact with each other. They are not routinely deliberately harnessed for patient benefit in clinical practice⁹, possibly because doctors often assume they must deceive patients in order to elicit placebo effects^{10,11}. However, this assumption is mistaken because it is not necessary to prescribe placebos in order to elicit placebo effects. For example, the overall analgesic effect of an opioid derives not only from its specific pharmaceutical actions but also from its psychological components, i.e. the *expectations* and *meaning* that the patient derives when consulting the doctor and taking the medicine^{12,13}. The same is true for other types of intervention including physical, surgical, and psychotherapies. One approach that has received initial support is for doctors to use positive suggestion to enhance patients' expectations of benefit⁴. Furthermore, preliminary evidence suggests that openly prescribing placebos might elicit clinically meaningful placebo effects in IBS and depression^{14,15} although this approach entails its own set of ethical challenges^{16,17}.

Placebo researchers have called for more translational research in this field^{11,18-20}. Such work has thus far typically focused on ethical considerations and narrative approaches to drawing out implications for clinical practice from the placebo literature. We suggest a systematic approach to translational research might be helpful. Many techniques or procedures contribute to placebo effects and could potentially be simply and ethically adapted for clinical practice, subject to further

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3 85 testing in practice settings²¹. In order to identify and describe such techniques, and thus provide
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5 86 some direction for future research, we reviewed experimental and clinical studies of placebo effects
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7 87 in non-malignant pain. We focused on non-malignant pain because it can be difficult to manage
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9 88 (particularly with current concerns about opioids²²), the mechanisms underpinning placebo
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11 89 analgesia are reasonably well understood²³, laboratory-based experimental studies often focus on
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13 90 placebo analgesia, and patients with pain have been shown to display substantial and clinically
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15 91 significant placebo effects¹. The aim of this project was to facilitate translational research by
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17 92 producing a taxonomy of techniques that may contribute to placebo effects observed in research
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19 93 settings and could be studied as options for augmenting placebo enhancement of analgesia in
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21 94 clinical practice.
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28 96 **Methods**

29 97 30 98 **Literature Search**

31 99 We selected seven systematic reviews of different aspects of the placebo literature, chosen from
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33 100 recent reviews available at the time (2012) and based on expert opinion (within the research team)
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35 101 to enable the extraction of information on placebo procedures from a broad range of settings -
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37 102 comprehensive reviews²⁴⁻²⁶, reviews of placebo effects in clinical populations^{2 27} and reviews of
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39 103 laboratory-based experimental placebo studies^{28 29}. The key consideration was that this collection
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41 104 of reviews should cite a diverse set of studies likely to be using diverse methods to directly (e.g.
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43 105 placebo mechanisms studies) or indirectly (e.g. clinical trials with placebo controls) study placebo
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45 106 effects. After removing duplicates and ineligible studies (see Figure 1), 169 studies were used to
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47 107 develop the taxonomy (for a list of included studies see Supplementary Digital Content).
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11 112 Studies were eligible for inclusion if they: reported original research in which some participants
12 received a placebo intervention; reported a non-malignant pain outcome; were published since 1983;
13 113 and were published in English language. Studies were excluded if they: were published before 1983
14 114 (because (a) means of generating context-dependent placebo effects may be sensitive to social and
15 115 cultural changes over time, e.g. patient preferences for particular communication styles and thus
16 116 their effectiveness in modifying expectations may have changed over time and (b) this yielded a
17 117 manageable number of papers to analyse which had been published during the 30 years preceding
18 118 this analysis); or examined any type of psychotherapeutic interventions (because it is difficult to
19 119 disentangle the active components of psychotherapy from the effect of the meaning of the
20 120 intervention³⁰).

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36 123 **Data Extraction and Synthesis**

37 124 Descriptions of all events that occurred in the placebo groups during each of the 169 studies (e.g.
38 125 medical, administrative, and ethical procedures) were extracted into a piloted form by one author
39 126 and checked by a second. These events were reviewed for duplication and overlap. This resulted in
40 127 an initial list of 43 procedures that might contribute to placebo effects (e.g. informed consent
41 128 processes, taking placebo pills, conditioning protocols). Study authors were not contacted for
42 129 further information about method used.

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55 131 To synthesise the data and develop our taxonomy we used systematic and rigorous methods derived
56 132 from qualitative research. We began with a deductive analysis, which aimed to categorise the

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3 133 procedures in a way that is intuitively appealing, accessible, and clinically relevant by sorting them
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5 134 into five previously-identified contextual domains of healthcare: patients' characteristics/beliefs,
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7 135 practitioners' characteristics/beliefs, practitioner-patient relationship, superficial treatment
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9 136 characteristics, and the healthcare environment³¹. Two authors (BC, FB) performed the initial
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11 137 categorisation which was then reviewed in detail by three other authors (GL, HE, AG). We then
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13 138 engaged in a constant comparative analysis, a technique that originates in grounded theory³². The
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15 139 aim of this part of the analysis was to consolidate the list of procedures and ensure that we only
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17 140 retained those that were distinct from each other. Procedures and examples of their use were all
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19 141 systematically compared to each other; similar procedures were then merged and all procedures
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21 142 were classified into one of the five domains. Two authors (BC, FB) led this work and presented initial
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23 143 findings to the rest of the team for discussion. All authors discussed and agreed on which
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25 144 procedures to merge, which to retain, and how to classify them. During this process, the definitions
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27 145 of the five domains were iteratively modified in order to reduce ambiguity over which procedures
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29 146 should be classified into which domain. This resulted in a more parsimonious list of 29 procedures
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31 147 classified by domain. All authors discussed and agreed on the final classification of these procedures.
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33 148 These 29 procedures were then critically examined to ensure they were theoretically plausible
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35 149 means of producing placebo effects. We focused on three core psychological mechanisms^{25 33-36}:
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37 150 response expectancy³⁷; conditioning and social learning⁷; and affect, including motivation and
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39 151 anxiety-reduction^{24 38}. However, we acknowledge that these mechanisms are difficult to tease apart
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41 152³⁹ and that alternative mechanisms have been proposed⁶ and so we erred on the side of inclusivity.
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43 153 Neurobiological mechanisms of placebo analgesia have been described^{23 40} but a detailed
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45 154 consideration of how these might apply to the procedures in the taxonomy would be highly
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47 155 speculative and was beyond the scope of this project (for discussion of clinical applications of the
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49 156 neuroscience of placebo effects see⁴¹). Four authors (FB, BC, AG, GL) reviewed all procedures and
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51 157 considered the extent to which each procedure could plausibly produce placebo effects via one or
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53 158 more of the three core psychological mechanisms. Initial findings were shared with the remaining
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3 159 authors and consensus was reached through discussion. Four procedures deemed very unlikely to
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5 160 produce placebo effects (Conveying a Neutral Therapeutic Message; Randomisation; Blinding;
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7 161 Deception) were excluded, leaving 25 procedures that might plausibly contribute to placebo effects.
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9 162 The multidisciplinary team of authors (including for example GPs, clinical and health psychologists,
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11 163 and complementary medicine specialists) then generated possible clinical applications of each of
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13 164 these 25 procedures.
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166 **Validating the Taxonomy**

167 To ensure our taxonomy was comprehensive we surveyed leading placebo researchers (authors of
168 major publications on placebo effects, attendees at an international symposium on placebo effects,
169 and GPs with an interest in placebo effects). These researchers were identified from the systematic
170 reviews and their references used to develop the taxonomy; the list of attendees at Beyond The
171 Placebo: Biomedical Clinical and Philosophical Aspects of the Placebo Effect, held in Ascona
172 Switzerland, August 2012; and GPs within the National Institute for Health Research School for
173 Primary Care Research. Ethical approval for the survey was obtained from the host institution
174 (reference: 4741). Completed electronic surveys including informed consent were received from 33
175 researchers (52% response rate) experienced in placebo research (M=12 years' experience, SD=9.8).
176 Respondents were shown our draft taxonomy and asked whether, for each domain, they knew of
177 any other procedures that could elicit placebo responses. The proportion answering yes ranged
178 from 22% (Healthcare Setting domain) to 50% (Superficial Treatment Characteristics domain).
179 Respondents suggested 85 additions which were screened against existing procedures and for
180 theoretical plausibility: 80 of the suggested additions were extra details or suggested clinical
181 applications of existing procedures; five were new and distinct plausible procedures that were added
182 to the taxonomy, giving a final total of 30 procedures.

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3 183 Because of our orientation to clinical applications, we have chosen to use clinically-oriented
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5 184 terminology throughout the taxonomy. However, it is important to note that when used in relation
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7 185 to procedures identified from the literature these terms also relate to the experimental equivalent,
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9 186 such that “patient” also refers to subject/participant, “practitioner” also refers to experimenter, and
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11 187 “intervention” also refers to experimental condition.
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14 188 **Analysis**

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17 189 The use of each of the 30 procedures in the taxonomy was assessed across all 169 studies in the
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19 190 review. Two authors independently rated the presence of each procedure in each study (Kappa =
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21 191 0.93, discrepancies were resolved through discussion).
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25 26 27 193 **Results**

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29 194 The taxonomy defines 30 procedures that may contribute to placebo effects observed in clinical and
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31 195 experimental research, and classifies them into 5 domains. Table 1 presents the main taxonomy,
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33 196 listing and defining all 30 procedures within 5 domains. Table 2 suggests clinical applications of each
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35 197 procedure. Table 3 shows the frequency of use of each procedure in clinical and experimental
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37 198 studies, and is intended as both an approximate guide to whether the procedures derived primarily
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39 199 from one or other literature and as a means to highlight those procedures that are very common
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42 200 and very rare in the literature. Below we describe the procedures within each domain in turn.
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201 Table 1. Taxonomy of Procedures Which Could Plausibly Elicit Placebo Effects in Non-Malignant Pain

Procedure Derived from Literature	Definition and Use in Research Studies
The Patient's Beliefs and Characteristics	
1. Select Patients Based on Treatment History.	Screen and select patients (or subgroups) against inclusion criteria related to issues such as medical/treatment history, e.g. naive to intervention being tested (not just contraindications).
2. Create Positive Expectancy.	Deliberately and explicitly suggest to patients that the intervention will be effective for them (not as part of informed consent process).
3. Reduce Negative Expectancy. ^a	The potentially negative or harmful procedures and characteristics of the treatment are deliberately minimised in information for patients.
4. Convey a Positive Therapeutic Message through Informed Consent Procedures.	Convey (verbally or in writing) a positive therapeutic message through the content of informed consent. The message might be explicit (e.g. "this intervention is usually effective in most people") or implicit (e.g. "this treatment is an antihypertensive").
5. Harness Socio-cultural Context. ^a	Tailor the intervention according to the patient's social and cultural context and history.
The Practitioner's Beliefs and Characteristics	
6. Practitioner Expectancy.	The person delivering the treatment expects it to be effective for the patient.
7. Practitioner's Personal Characteristics.	The practitioner's personal and/or professional characteristics (e.g. status) are modified (through selecting practitioners with different characteristics) and/or emphasised to patients.
The Healthcare Setting	
8. Active Recruitment.	Actively seek out and recruit patients (e.g. advertising for specific types of patients, writing personally to individual eligible patients identified through medical records).
9. Active Retention.	Make patients feel valued by attempting to keep them in a study (e.g. contact patients if they miss an appointment, incentivise attendance through monetary or non-monetary gifts).
10. Follow-up.	Assess patients after the intervention/experiment to assess long-term maintenance or changes in effects over at least 6 months.
11. Follow a Standardised Protocol.	The intervention is delivered according to a set, scientifically-derived, protocol, lending credibility to the intervention (and is therefore not individualised for each patient).
12. Ethical Oversight.	Study practices and procedures are explicitly regulated and monitored by an institutional ethics committee, lending credibility to the intervention.
13. Participating in Research.	Patients know that they are part of research and contributing to the furthering of human knowledge and/or improvement of healthcare for future patients.
14. Symptom Monitoring.	Monitor patients' symptoms using self-report measures, practitioner assessment, or objective measures

15. Enhanced Environment. ^a	repeated over time at least twice; patients are aware of the resulting measurements. The physical and interpersonal environment where the intervention is delivered is deliberately enhanced.
Treatment Characteristics	
16. Sham Intervention – Medication.	An inert substance is administered which is manufactured to appear identical to an active medication (e.g. sugar pill, saline IV, topical agent).
17. Sham Interventions – Physical.	A sham physical intervention is administered which is designed to appear identical to the genuine intervention (e.g. de-activated TENS, non-penetrative acupuncture needles at non-acupuncture points).
18. Sham Interventions – Attention Only.	Patients receive study-specific attention in terms of numbers of visits and time spent with study staff but no additional intervention.
19. Ineffective substances. ^a	Products unlikely to be effective or not indicated are administered (e.g. vitamins in the absence of vitamin deficiency).
20. Use Salient Side-Effects.	Potential side-effects are highlighted such that the patient can interpret them as evidence of a potent intervention.
21. Matched Treatments.	To secure blinding, placebo/sham treatments are matched to 'real' treatments (e.g. on mode of administration, dosage, frequency of administration, visual appearance, taste, smell, individual titration procedures).
22. Maximised Treatment Procedures.	The procedures and characteristics of the treatment are exaggerated, e.g. through high dose, use of colour, high frequency, large pill size, lengthy duration of intervention, ritualistic administration.
23. Conditioning.	A desired response (e.g. pain relief) is paired with an intervention stimulus (e.g. placebo cream) so that the patient associates the response with the stimulus.
The Patient-Practitioner Interaction	
24. The Process of Informed Consent.	The patient's formal written and/or verbal informed consent is discussed and obtained.
25. Detailed History.	A detailed personal and/or medical and/or psychosocial history is obtained from the patient.
26. Diagnosis/tests.	Additional tests, examinations, or confirmatory diagnostic procedures are undertaken to establish eligibility for the study.
27. Care.	The practitioner deliberately engages the patient with warmth, compassion and empathy.
28. Patient-Centred Communication. ^a	The practitioner adopts a style of consultation that they consider to be appropriate for a particular patient.
29. Extra Attention.	The patient receives extra attention from being in the study, for example is seen more frequently or for longer than usual.
30. Continuity of Care.	Efforts are made for the same practitioner to see the same patient at each contact.

202 ^a procedures added following survey of researchers.

203 Table 2. Suggested Potential Clinical Applications of Procedures to Elicit Placebo Effects in Non-
 204 Malignant Pain, Subject to Further Research

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Procedure	Suggested Clinical Applications
The Patient's Beliefs and Characteristics	
1. Select Patients Based on Treatment History.	Stop prescribing interventions of a type that a patient has previously not responded to (e.g. tablets); instead, prescribe a different, new, type of treatment (e.g. psychological therapy).
2. Create Positive Expectancy.	Tell the patient the intervention is likely to be effective. Elicit patients' treatment and illness beliefs and expectations, and dispel any misconceptions. Empower patients to self-care.
3. Reduce Negative Expectancy.	Limit emphasis on major potential side effects, and describe how uncommon they are. Hide cessation of analgesia administration (e.g. as in Benedetti ⁴²), after obtaining advanced consent and ensuring patients are aware they can request additional analgesia if needed.
4. Convey a Positive Therapeutic Message through Informed Consent Procedures.	Provide written and/or verbal information that conveys a positive therapeutic message about treatment. Provide clear rationale for treatment. Provide patient testimonials and supporting literature/media.
5. Harness Socio-cultural Context.	Elicit patients' culturally embedded treatment and illness beliefs, preferences and expectations, dispelling any potentially harmful misconceptions. Involve significant others in care.
The Practitioner's Beliefs and Characteristics	
6. Practitioner Expectancy.	Only prescribe a treatment to patients when the practitioner expects it will be effective; communicate that expectation to patients.
7. Practitioner's Personal Characteristics.	Honour patient preferences for particular practitioners. Use indicators of expertise/high status in offices, in correspondence, and when referring to other practitioners. Ensure the patient is seen by a practitioner whose views/values are congruent with the patient's.
The Healthcare Setting	
8. Active Recruitment.	Actively seek out patients and invite them to attend clinic regarding a particular intervention (as opposed to waiting for patients to present).
9. Active Retention.	Personally contact patients if they miss an appointment. Use incentives to encourage patients to keep appointments.
10. Follow-up.	Routinely invite patients to book a follow up appointment after an intervention has finished and prior to repeat prescription. Encourage the patient to take responsibility for and self-manage their condition following an intervention.
11. Follow a Standardised Protocol.	Use patient-friendly treatment protocols and share with patients where they fit in that protocol.

12. Ethical Oversight.	Ensure that patients understand that their treatment protocol is sanctioned by a higher authority e.g. NICE.
13. Participating in Research.	Inform patients that all outcomes and practitioner performance is audited and can contribute to improved knowledge and treatment for future patients.
14. Symptom Monitoring.	Ask patients to monitor their symptoms regularly, for example using email, phone apps, web-based systems, paper forms. Assess treatment outcome. Give patients feedback on symptom improvements following monitoring.
15. Enhanced Environment.	Ensure that the environment is professional, pleasant and peaceful. Employ friendly and helpful support staff.

Treatment Characteristics

16. Sham Intervention – Medication.	Openly prescribe sham medication. With advanced prior consent, prescribe sham medication.
17. Sham Interventions – Physical.	Openly prescribe sham physical treatments. With advanced prior consent, prescribe sham physical treatments.
18. Sham Interventions – Attention Only.	Increase frequency and duration of consultations.
19. Ineffective substances.	Prescribe substances that are likely not to cause harm but not clearly indicated or substances unlikely to be effective e.g. simple linctus.
20. Use Side-Effects.	Tell patients about side effects associated with positive clinical outcome.
21. Matched treatments.	Design appearance of prescribed substance (e.g. colour, packaging, taste) to match known effective treatments.
22. Maximised treatment procedures.	Within safety limits prescribe higher dose/higher frequency/larger pill. Use different colour treatments. Instigate ritualistic procedures patients can perform when taking medicines. Maximise adherence to treatment through education, easy follow up appointments, easy repeat prescription arrangements etc.
23. Conditioning.	Prescribe highest tolerated dose first, then titrate downwards. With consent, begin with active intervention, pair with a seemingly identical placebo then substitute for placebo alone.(e.g. as in Sandler ⁴³)

The Patient-Practitioner Interaction

24. The Process of Informed Consent.	Actively seek patient consent. Provide treatment options and encourage the patient to choose from these options if they so desire.
25. Detailed History.	Take a detailed medical and psychosocial history/update. Ensure the patient feels listened to, e.g. through non-verbal communication and/or capturing information. Ask questions about the meaning of symptoms.
26. Diagnosis/tests.	Provide a definitive/confident diagnosis. Examine the patient fully.
27. Care.	Allow patient adequate time to tell their story and listen to them. Validate the patient's concerns. Use non-verbal techniques to convey empathy, compassion, warmth. Use touch judiciously.

28. Patient-Centred Communication.	Individualise consultation style according to a patient's preference e.g. collaborative vs authoritative. Engage in collaborative decision-making with the patient. Develop shared treatment goals that you and the patient agree on.
29. Extra Attention.	Give extra attention to or show more interest in a patient by seeing them more frequently, having longer consultations or visiting at home. Do not rush the patient.
30. Continuity of Care.	Ensure patient is cared for by the same practitioner. Read records before consultation.

206 Note. Suggestions for clinical applications pending research into effectiveness and ethical
207 acceptability in clinical settings.

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208 Table 3. Use of Procedures in Placebo Groups of Clinical and Experimental Studies

Procedure	% of studies that used each procedure:	
	Experimental (n=58)	Clinical (n=111)
The Patient's Beliefs and Characteristics		
1. Select Intervention Based on Patient's Treatment History.	55%	75%
2. Create Positive Expectancy.	76%	5%
3. Reduce Negative Expectancy.	3%	0%
4. Convey a Positive Therapeutic Message through Informed Consent Procedures	43%	1%
5. Harness Socio-cultural Context.	0%	0%
The Practitioner's Beliefs and Characteristics		
6. Practitioner Expectancy.	0%	1%
7. Practitioner's Personal Characteristics.	9%	0%
The Healthcare Setting		
8. Active Recruitment.	14%	16%
9. Active Retention.	3%	2%
10. Follow-up.	2%	16%
11. Follow a Standardised Protocol.	85%	63%
12. Ethical Oversight.	78%	69%
13. Participating in Research.	86%	84%
14. Symptom Monitoring.	95%	89%
15. Enhanced Environment.	5%	0%
Treatment Characteristics		
16. Sham Intervention – Medication.	71%	55%
17. Sham Interventions – Physical.	33%	41%
18. Sham Interventions – Attention Only.	2%	5%
19. Ineffective substances.	0%	1%
20. Use Side-Effects.	0%	1%
21. Matched treatments.	40%	82%
22. Maximised treatment procedures.	22%	3%
23. Conditioning.	41%	0%
The Patient-Practitioner Interaction		
24. The Process of Informed Consent.	88%	77%
25. Detailed History.	19%	33%
26. Diagnosis/tests.	36%	41%
27. Care.	0%	1%
28. Patient-Centred Communication.	0%	0%
29. Extra Attention.	2%	63%
30. Continuity of Care.	7%	14%

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3 **210 The Patient's Characteristics and Beliefs**
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6 211 The taxonomy specifies five procedures that act directly on the patient's characteristics and/or
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8 212 beliefs in ways that might contribute to placebo effects. Procedure 1 involves selecting patients who
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10 213 are most likely to benefit from an intervention based on their history of similar treatments (where
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12 214 similarity is construed broadly at multiple levels, including appearance, modality, style, and
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14 215 pharmacology). For example, one might select those patients who have not experienced
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16 216 disappointing results from a similar intervention in the past (as the latter group might have learned
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18 217 to expect the intervention to fail). This procedure was commonly used by clinical trials and (to a
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20 218 lesser degree) experimental studies.
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27 220 Procedures 2 (create positive expectancy), 3 (reduce negative expectancy), and 4 (convey a positive
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29 221 therapeutic message), all involve communicating with patients to encourage them to expect
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31 222 beneficial effects of treatment or not to expect side-effects. The majority of experimental studies in
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33 223 our review explicitly encouraged patients to expect treatment benefits, while very few clinical
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35 224 studies explicitly targeted patients' expectations and hardly any studies attempted to minimise
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37 225 patients' expectations of side-effects. Procedure 5 involves tailoring the intervention to the
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39 226 patient's socio-cultural context. This approach emerged from the expert feedback and while it
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41 227 seems plausible and ethical to translate into clinical practice, it was not used by any of the reviewed
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43 228 studies.
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50 230 The procedures in the patients' beliefs and characteristics domain are thought to contribute to
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52 231 placebo effects primarily through altering patients' response expectancy. Selecting patients based
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54 232 on treatment history and tailoring to socio-cultural context are also predicated on learning
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56 233 mechanisms, i.e., learned associations between treatment outcome and treatment properties.
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3 234 There is some evidence that clinicians can give verbal suggestions to alter patients' expectations in
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5 235 practice and that this reduces patients' pain, particularly acute procedural pain⁴⁴. As part of work
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7 236 to implement these procedures more widely in practice it would be important to investigate how to
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9 237 secure ethically valid consent for treatment. For example, clinicians might want to encourage
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11 238 realistically positive patient expectations while providing information about possible harms without
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13 239 inducing the negative expectations that could trigger nocebo effects^{45,46}.

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18 19 241 **The Practitioner's Characteristics and Beliefs**

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21 242 The two procedures in this domain are about using or modifying health care practitioners'
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23 243 characteristics and/or beliefs. Procedure 6 requires a practitioner to expect a treatment to benefit
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25 244 the patient. This might contribute to observed placebo effects in patients by influencing a
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27 245 practitioner's communication about the treatment and hence a patient's response expectations
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29 246 and/or affective response to the consultation. Only 1% of clinical studies and no experimental
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31 247 studies reported modifying practitioners' expectations. This procedure has received little attention
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33 248 in the placebo literature but clinical research in musculoskeletal settings suggests practitioners'
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35 249 outcome expectations can predict patients' pain outcomes⁴⁷. One way to implement this procedure
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37 250 in practice would be for practitioners to communicate explicitly that they believe a treatment is
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39 251 effective, an approach which clearly overlaps with communication interventions designed to help
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41 252 doctors encourage patients to have positive expectations. Implementing Procedure 6 also depends
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43 253 on practitioners having relevant high quality evidence readily available and accessible and
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45 254 understanding this evidence as it applies to the patient.

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53 256 A small proportion of studies (9% of experimental studies and no clinical studies) emphasised a
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55 257 practitioner's status or other characteristics (Procedure 7). For some patients a high status
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57 258 practitioner might elicit more confidence in the treatment (and thus higher expectations) and/or a
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3 259 more positive affective response to the consultation⁴⁸. Some aspects of this procedure are already
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5 260 part of clinical practice, for example the routine display of medical certificates in doctors' offices;
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7 261 others are inherent in the tools of the doctor, such as the symbolic properties of the stethoscope⁴⁹.
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9 262 However, there is likely to be scope for testing their effects and augmenting their use if appropriate.
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14 264 **The Healthcare Setting**

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16 265 Procedures 8 and 9 relate to the efforts made in studies to actively recruit and retain patients
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18 266 respectively. Clinical and experimental studies both reportedly used these procedures sparingly (<20%
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20 267 for active recruitment and <5% for active retention). Such efforts may make patients feel valued and
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22 268 could be implemented in practice through the use of personalised communications from
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24 269 practitioners to encourage attendance at appointments.
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31 271 Three of the eight procedures in this domain were used by over half of clinical and experimental
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33 272 studies and relate to basic structural features of research: following a protocol, ethical oversight, and
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35 273 participating in research (procedures 11 to 13). They are thought to impact patients' expectations,
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37 274 by emphasising the legitimacy of the intervention that is being provided and the importance of the
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39 275 patient's contribution to a bigger project, i.e. generating knowledge. Translating these procedures
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41 276 into practice could involve, for example, clinicians explicitly talking with patients about official
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43 277 guidance and treatment protocols that they are following.
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50 279 Symptom monitoring (procedure 14) was commonly used in both clinical and experimental studies.
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52 280 This could be implemented in practice for example through repeatedly using patient reported
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54 281 outcome measures (see⁵⁰) and might contribute to placebo effects through learning mechanisms
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56 282 (e.g. regular symptom monitoring acts as feedback to motivate health behaviours and/or modify
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3 283 patients' goals). Alternatively, the mere act of asking a patient to monitor their symptoms could
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5 284 convey an expectation of treatment benefit, altering the meaning of a clinical interaction for the
6
7 285 patient. Traditionally such effects of the act of measurement are dismissed as Hawthorne effects
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9 286 but they may also be encompassed in broader definitions of placebo effects as meaning effects⁵¹
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11 287 and could thus enhance effects in clinical practice despite being considered a nuisance in clinical
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13 288 research.

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20 290 Very few placebo studies (5% of experimental and no clinical studies) reported enhancing the
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22 291 physical or interpersonal environment (procedure 15). There is a separate and distinct literature on
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24 292 environment modifications in health settings that might be usefully integrated with the placebo
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26 293 literature when developing clinical applications in this area and modelling mechanisms of action^{52,53}.

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30 295 **Treatment Characteristics**

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32 296 Eight procedures in the taxonomy involve modifying the characteristics of a treatment. Three
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34 297 involve prescribing sham interventions (sham medication – procedure 16, sham physical
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36 298 interventions – procedure 17, and extra attention – procedure 18) while a fourth involves
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38 299 prescribing a substance unlikely to be effective for the symptom in question (procedure 19). These
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40 300 four procedures represent variations in control conditions used in research and were frequently
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42 301 used by both clinical and experimental studies (with the exception of extra attention which was only
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44 302 used by 2-5% of studies). Such controls are thought to operate primarily via expectations, while
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46 303 affective pathways may also be important when extra attention from trial personnel/medical staff is
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48 304 involved. Of all the procedures in the taxonomy these four that represent control conditions come
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50 305 closest to the traditional notion of how placebos could be applied in practice. Given ethical concerns
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52 306 around deceptive prescribing we suggest that translational research might continue to focus on
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54 307 openly prescribing sham interventions including placebo pills (as in^{14,15}). Other options should not

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3 308 be dismissed entirely though: advanced consent and even waiving consent are acceptable to some
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5 309 patients and so it is vital for translational research to continue exploring patients', practitioners', and
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7 310 other stakeholders' views on the acceptability and ethics of diverse ways of prescribing placebos⁵⁴⁻⁵⁷.
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13 312 Three procedures in this domain modify the superficial (non-pharmacological or non-defining)
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15 313 characteristics of treatments. Procedure 20 is to highlight treatment side-effects to patients in order
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17 314 to encourage patients to see the treatment as potent; this procedure was very rare, used by only 1%
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19 315 of clinical studies. Procedure 21 was much more commonly used and involves matching the
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21 316 appearance of real and control treatments (used by 40% of experimental and 82% of clinical studies),
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23 317 in order to maintain patient blinding. This could be translated into clinical practice by designing the
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25 318 appearance of interventions to match patients' beliefs about what effective interventions look like.
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28 319 Procedure 22 involves maximising or exaggerating the superficial characteristics of treatment in
29
30 320 order to generate larger placebo effects for example by using colour, large pill size, or ritualistic
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32 321 administration of medicines, manipulations which could alter the meaning of a treatment for a
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34 322 patient and/or enhance their expectations. 22% of experimental studies reported using this
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36 323 procedure and one way to translate it into practice would be to create (and test) ritualistic
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38 324 procedures for patients to engage in when taking medicines.
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45 326 The final procedure in this domain – procedure 23, conditioning to generate placebo effects - was
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47 327 used commonly and exclusively by experimental studies (41%). Conditioning protocols generate
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49 328 placebo effects through learning mechanisms and perhaps could be implemented in practice to
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51 329 reduce pharmaceutical dosages, as was achieved in a pilot study in children with attention deficit
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53 330 disorder⁴³.
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3 332 **The Patient-Practitioner Interaction**

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5 333 The *Patient-Practitioner Interaction* domain incorporates seven procedures related to the
6
7 334 interpersonal relationship or interactions between a patient and their health care practitioner.
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9 335 These procedures are thought to operate primarily through affective mechanisms such as reduced
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11 336 anxiety after telling one's story and being listened to with empathy and acknowledged, although
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13 337 more cognitive pathways via expectations are also plausible⁵⁸. Three procedures are about specific
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15 338 processes that can occur during consultations – obtaining informed consent (procedure 24), taking a
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17 339 detailed history (procedure 25), and performing additional diagnoses or tests (procedure 26).
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19 340 Arguably these procedures indicate to the patient that the practitioner respects them, is interested
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21 341 in their perspective, and is thorough in their diagnosis. They occur in both clinical and experimental
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23 342 research settings and could be relatively directly translated into practice or optimised if already used.
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344 Two procedures are about the way in which the practitioner engages with the patient:
345 communicating care (procedure 27), and patient-centred communication (procedure 28). These
346 procedures were surprisingly very rarely described in the studies included in our review, although
347 recently the nocebo effects of *not* validating a patient's experiences have been shown to be
348 particularly potent⁵⁹. There is of course a distinct and large literature on doctor-patient
349 communication and fruitful dialogue is beginning to bridge these fields⁶⁰.

350

351 The final two procedures in this domain refer to more structural aspects of consultations: extra
352 attention (procedure 29, i.e. longer or more frequent appointments) and continuity of care
353 (procedure 30). 63% of clinical studies used extra attention while a small proportion of clinical (14%)
354 and experimental (7%) studies reported providing continuity of care. Directly implementing these
355 procedures in practice might be challenging given ever increasing constraints on healthcare
356 resources and drives to reduce cost.

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Discussion

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8 359 The taxonomy names and describes 30 procedures that may contribute to placebo effects in
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10 360 experimental and clinical studies and classifies them into five domains. It includes 60 theoretically
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12 361 plausible clinical applications, subject to further research on their effectiveness and ethical
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14 362 acceptability in practice. Some of the clinical applications derived from the placebo literature have
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16 363 already been investigated in their own right under other auspices, highlighting the need for the
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18 364 burgeoning translational science of placebo effects to be broad-ranging and interdisciplinary.

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25 366 We have used rigorous systematic review and qualitative analytic methods complemented by a
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27 367 survey to develop the taxonomy. Investigators often combine multiple techniques in any one
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29 368 'placebo' (e.g. Create Positive Expectancy + Detailed History + Symptom Monitoring) making it
30
31 369 beyond the scope of this project to unpack the effectiveness of individual techniques. Procedures
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33 370 did not always fit neatly into single domains. For example, "Screen for Treatment History" was used
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35 371 to select patients for studies of specific treatments (and was thus placed in the Patient's Beliefs and
36
37 372 Characteristics domain), but its clinical application involves selecting a treatment for a specific
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39 373 patient and so could be considered a Treatment Characteristic. Conceptually we would expect
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41 374 interactions between these domains; for example, some procedures categorised in other domains
42
43 375 probably operate through causal pathways involving patients' beliefs as proximal determinants of
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45 376 placebo effects⁶¹. We feel the benefits of having a hierarchical structure (modifiable as the
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47 377 taxonomy is refined with use) outweigh the difficulties inherent in classification. We could have
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49 378 used many published reviews of placebo studies in non-malignant pain to identify original studies to
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51 379 review. Selecting seven such reviews means not using others, thus we might have missed original
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53 380 studies that would have suggested additional procedures. Surveying leading researchers and
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55 381 incorporating their suggestions somewhat mitigates this limitation. Our sample of researchers was

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3 382 intended to be purposive, in that we wanted to obtain the views of leading researchers in the field.
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5 383 By using multiple means of identifying such individuals internationally we feel we have achieved this.
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7 384 The reviews that we selected as the source of our papers and the papers themselves are now
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9 385 somewhat old examples of the literature; and our choice to exclude papers published before 1983
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11 386 was arguably somewhat arbitrary. Future work should review very recent papers and iteratively
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13 387 improve the taxonomy accordingly.
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20 389 This review extends previous work by Di Blasi et al.³¹, building on their five domains to
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22 390 systematically develop a detailed taxonomy. We provide a new overarching framework that avoids
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24 391 the controversial and limited distinction between pure and impure placebos^{62 63} and integrates ideas
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26 392 from the rich clinical and experimental literatures on placebo effects in non-malignant pain. Many
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28 393 of the components we have identified are likely to be important in other placebo-responsive
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30 394 conditions including depression⁶⁴, irritable bowel syndrome^{65 66}, and insomnia⁶⁷. This taxonomy
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32 395 can guide two important and related applied research agendas: 1) to understand the components of
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34 396 placebo effects in clinical settings^{48 68-71} and 2) to ethically harness evidence-based placebo effects
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36 397 to benefit patients^{14 15 72}. We hope future studies might draw on the taxonomy to fully describe
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38 398 their methods and develop new applications, thus facilitating future systematic reviews and the
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40 399 development of a systematic and theory driven cumulative evidence-base in this complex field.
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47 401 The taxonomy identifies and classifies procedures that may contribute to placebo effects in clinical
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49 402 trials and experiments, providing an overarching framework for individual components. However,
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51 403 we do not suggest that every technique in this taxonomy will produce a placebo effect in every
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53 404 patient and we do not know from this project which techniques are more effective or how they
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55 405 might be combined to form ethically acceptable and effective complex interventions. This taxonomy
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3 406 provides the first attempt at a necessary conceptual tool to facilitate future research on these
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5 407 questions. For example, systematic reviews could use the taxonomy to code procedures in original
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7 408 studies, using this information in meta-regression analysis to examine the contribution of different
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9 409 procedures to placebo effects⁷³. New clinical trials and experiments could extend existing work by
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11 410 systematically examining and comparing the effects and ethical acceptability of different procedures
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13 411 in the taxonomy, building a cumulative evidence-base that has real pragmatic applicability to clinical
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15 412 practice. Some of the suggested clinical applications have been investigated more extensively in
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17 413 other literatures, in particular doctor-patient communication and the healthcare environment. This
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19 414 emphasises the need for a multi-disciplinary approach to the translation of placebo research into
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21 415 practice. One fruitful way forward would be to draw on placebo theories to develop and test more
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23 416 mechanistic models of complex interventions intended to alter the context of healthcare encounters.
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30 418 Placebo recipients in clinical trials and experiments are exposed to a large number and variety of
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32 419 procedures, many of which might contribute to placebo effects. Researchers seeking to develop a
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34 420 translational science of placebo effects are thus faced with myriad possibilities. We have
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36 421 systematically identified and defined these procedures, classified them into five domains, and
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38 422 suggested possible clinical applications. The resulting taxonomy is presented as a preliminary but
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40 423 detailed and systematic guide for future research, which should in turn further refine the taxonomy.
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42 424 Ultimately we hope to better conceptualise investigations of clinical applications of placebo effects
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44 425 in order to maximise opportunities for patient benefit.
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3 448 submitted work in the previous three years, no other relationships or activities that could appear to
4
5 449 have influenced the submitted work.
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36 **Contributorship Statement**

37 463 FB designed and led the study, drafted the manuscript, and is guarantor. FB, GL, AWAG, HE, and PL
38
39 464 secured funding for the project. FB designed the study with input and revisions from GL, BC, AWAG,
40
41 465 HE, and PL. BC led data collection and analysis with additional data collection and analysis by MH
42
43 466 and DS. All authors contributed to data interpretation. FB drafted the manuscript and all authors
44
45 467 revised it for important intellectual content. All authors had full access to all of the data in the study
46
47 468 and can take responsibility for the integrity of the data and the accuracy of the data analysis.
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51 **Data Sharing Statement**

52 470 No unpublished data available.
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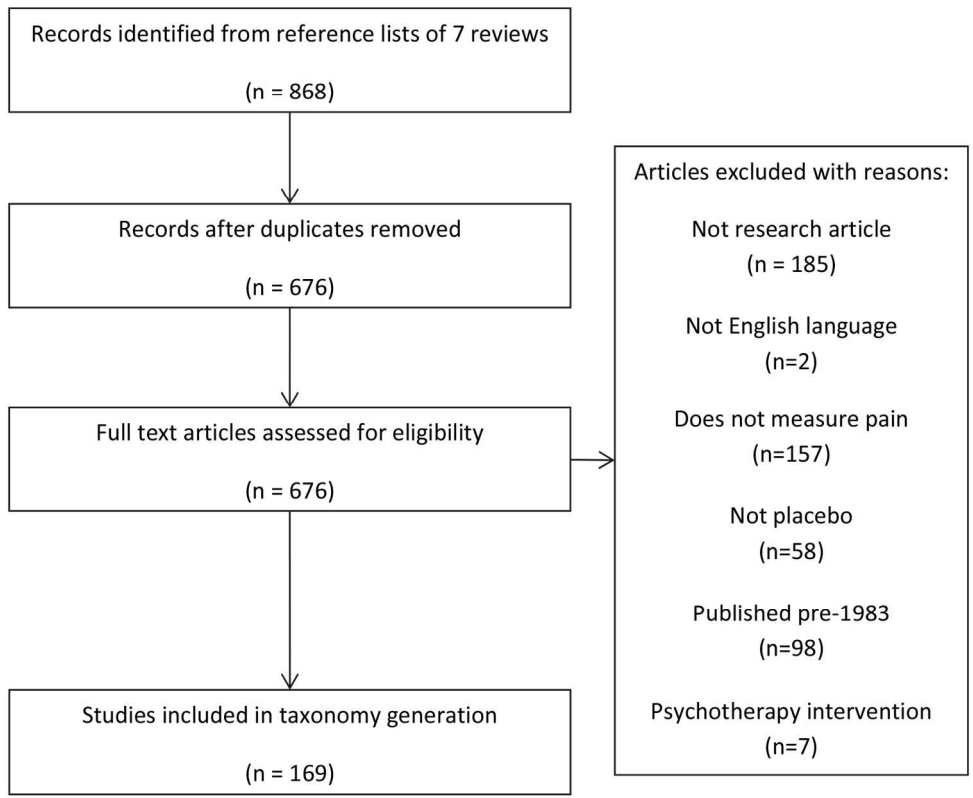
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Flowchart Showing Identification of Studies

155x127mm (300 x 300 DPI)

Supplementary Digital Content

List of Included Studies

[1-169]

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	n/a
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	n/a
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	n/a
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, Fig1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22-3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22-3
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

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