Cognitive Bias and Heuristics in Patients with Knee Osteoarthritis Being Treated with Open Label Placebo. Protocol For an Explorative Study Using Questionnaire and Group Concept Mapping Designs in Participants from a Randomised Clinical Trial Evaluating Two Different Conversations Designed to Reinforce Open Label Placebo Response in Knee Osteoarthritis.

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FULL TITLE

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SHORT TITLE

Cognitive biases and Heuristics In patients with knee osteoarthritiS (CHIPS).

INTERNAL PROTOCOL ID

P:\BFH\PARKER\APPI2\MSK\Placebo and Context\Tommy Annfeldt (PhD)\CHIPS_Cognitive bias and Heuristics In Patients with osteoarthritiS

DATA APPROVAL NUMBER

P-2021-451

PATIENT RESEARCH PARTNERS

This protocol has been reviewed by two patient research partners with knee osteoarthritis (male and female, neither of which who participated in the parent RCT study).

BACKGROUND

Placebo has previously been suggested to have clinical effect on patient-related subjective outcomes such as pain, stiffness, and self-reported function, in patients with knee osteoarthritis (OA) (1). It has also been suggested that open label placebo result in a higher effect than blinded placebo (1). And while the clinical use of placebo is still under debate and ethical examination, a recent review suggested that 63%-77% of surveyed physicians use placebo weekly, and it is estimated that 40% of all prescriptions functions as placebo (2). Thus, the use of placebo in a real-world clinic setting is widespread and, it is increasingly recognised that placebo should be considered either as a treatment option or as an add on to the treatment (2).

Placebos, although pharmacologic inert substances, triggers an effect and a subsequent response through a complex series of neurochemical, -hormonal, and -biological mechanisms that are still not fully understood (2). Although the exact interplay between contextual factors and the brain has not yet been fully alluded to in connection to the placebo response, it is recognised as a mind-body phenomenon and thus a result of the psychosocial context around the patient and the therapy including the patient's own characteristics (3).

Other contextual factors that can influence the placebo effect include the placebo itself, where taste(4) colour, and route of administration (1) have all shown to influence the outcome, but also personality (5) and the healthcare provider and patient relationship (2).

Behavioural Economics

Behavioural economics (BE) study the effects of psychological, cognitive, emotional, cultural, and social factors on the decisions of individuals. Conventional economics (CE) assumes that all people are both rational and selfish however, in practice this is often not the case, which leads to the failure of traditional models. Central to BE are cognitive biases (CB), and heuristics (H) which are used to explain the decisions and choices that people make. Cognitive biases are systematic patterns of deviation from norm or rationality in judgment, while heuristics are tactics, or mental shortcuts to aid in the decision-making process. Cognitive biases and heuristics are often used to explain certain patterns of seemingly irrational behaviour and decisions.

Although originated in economics academia, theories such as CB/H developed in BE are increasingly being used in healthcare to facilitate good health decisions, improved care, and in designing new interventions (6).

Cognitive biases have also been shown to influence how patients and non-patients rate their own health or that of others (7). Most studies are concerned with how CB/H influence physician´s and nurse´s decisions however, a more advanced understanding of what influences patients' decisions could open the door for specialised design of treatment contexts, and ad-on programs to treatments. This could increase the adherence to treatment regimens as well as the overall efficacy experienced by the patient leading to better outcomes as well as a better usage of healthcare resources.

Problem statement:

Cognitive bias and heuristics have shown to influence how we make decisions about health and medicine, and they have also been shown to influence how we rate our own health. Less is known about which specific cognitive biases and/or heuristics that are in play when patients form their treatment expectations and evaluate their health following an intervention.

STUDY AIM

This study aims to understand if certain cognitive biases and heuristics are present in patients with knee (OA) being treated with open label placebo.

STUDY PURPOSE

Understanding which cognitive biases and/or heuristics that are in play when patients evaluate their health following open label placebo, allows future treatment context to be designed in a way that actively utilises these to obtain a greater magnitude of response.

METHOD

STUDY DESIGN

This study combines a global questionnaire sent to *all* participants from the study "*Reinforcement of Treatment Response in Knee Osteoarthritis: A Randomised Trial*" (Clinical trial.gov registration: NCT05225480) with structured conceptualization based on group interviews with responders and non-responders respectively from the same study; the group content mapping (GCM) method.

This design will allow us to get in-depth knowledge on *one particular* heuristic based on the questionnaire, while the GCM methods will provide a broader view of other potential concepts and CB/H that might be present in this patient group.

QUESTIONNAIRE

A review (8) examining the most studied CB/H in medical decision making for both healthcare personnel and patients, was used to short list 5 CB/H (table 1). The reason for shortlisting them can be found in table 1. After having reviewed the references from the review (8) connected with the 5 selected CB/H, we chose to investigate the effect of the *affect heuristic* (AH) using the questionnaire developed by (Skagerlund K. et al., 2020) (11) to quantify the presence and impact of the AH on all participants. Reasons for choosing to investigate the AH and excluding the other 4 CB/H can be found in table 1.

The questionnaire will have two sections and will be used to determine if, and to what degree, participants are influenced by the AH. Later the strength of the AH will be correlated to the change in the individual's ΔVAS pain score (baseline VAS – follow up VAS) via regression.

Section 1: are there an affective tag associated with OLP and the conversation?

This section is intended to investigate whether participants have attached a positive or negative affect tag to OLP and/or the conversation.

- Question #1 asks the participant to rate their experience of the OLP procedure on a 7-point Likert scale
- Question #2 asks the participant to rate their experience of the conversation on a 7-point Likert scale

Section 2: impact of the affect heuristic.

Based on the correlation between perceived risk and benefit, it can be determined how strong the AH is influencing the individual participant (11). If participants are strictly rational and not susceptible to the AH there would be no correlation. If they are influenced by the AH, we would see a positive correlation between benefit and risk i.e., the more perceived benefit the less risky the activity would seem. Questions will be translated from Swedish to Danish by two investigators (EEW, TKA) and compared for consistency. Disagreements will be solved by consensus by the two investigators.

- Question 3 – 67: questions related to the "perceived benefit" of a range of activities translated from (11)
- Questions 68 – 113: questions related to the "perceived risk" of the same range of activities translated from (11).

COGNITIVE BIAS OR HEURISTIC	**DESCRIPTION** (8)	**REASON FOR SHORTLISTING**	**REFS FROM** (8) **THAT ASSESSED THE CB/H**	**REASONS FOR INCLUDING OR EXCLUDING FROM THE QUESTIONNAIRE**
AFFECT HEURISTIC	*Representations of objects and events in people's minds are tagged to varying degrees with affect. People consult or refer to an 'affective pool' (containing all the positive and negative tags associated with the representations consciously or unconsciously) in the process of making judgments.*	If participants experienced the conversations as pleasant, they are likely to "tag" the treatment with a positive tag. Thus, when asked about their knee OA symptoms they recall the positive-, or negative tag	(25) (26a) (27) (28) (29)	Include. AH can impact how the participant judges the effect of the intervention based on a positive or negative tag.
AVAILABILITY BIAS	*People assess the probability of an event by the ease with which the instance or occurrences can be recalled.*	They only remember the most recent feelings and not the entire duration since last visit. Or, if either being in pain or free of pain is more memorable to them, then this is more likely to stick out.	(46a) (47a) (48) (49a) (50a) (51) (52) (53a) (54) (55a) (56) (57a) (58) (59a) (60) (61a) (62) (63a)	Exclude. This CB is more relevant in the moment of deciding to participate or not. Or when judging a situation involving others. E.g., when someone makes a decision based on anecdotal evidence.

			(64a) (65) (66) (67)	
DEFAULT BIAS	*Individuals have a strong tendency to remain at status quo, because the disadvantage of leaving it seems larger than the advantages.*	Having knee pain due to OA might have been their "default" state for many years, and leaving that state introduces uncertainty.	(90) (91) (92) (93)	Exclude. More likely to influence the decision to do something else than what they usually do. And thus not likey
IMPACT BIAS	*People tend to overestimate the long-term impact of positive and negative events.*	If they had a good experience in the conversation this bias could lead to an improved response	(97) (98) (99) (100) (101) (102a) (103) (104) (105) (106)	Excluded. The impact bias has more to do with how we might assess what might happen in the future, or what the effect on others might be. E.g., we are more likely the negative effect a disease has on others quality of life. Or to overestimate the positive effect an action will have in the future.
OUTCOME BIAS	*Allowing a prior event or decision outcome to influence subsequent independent decisions.*	The participants have made an explicit decision to participate in the study, and thus unconsciously are more prone to wanting a good effect.	(210) (211) (212a)	Excluded. Outcome bias would be relevant if we asked participants if participating would be a good decision. In that case, the outcome bias would dictate, that those with a positive outcome would view the decision to decide as a good decision.

Table 1: CB and HE shortlisted and the reasons for including/ excluding in the questionnaire (8).

Questionnaire Data Collection

All participants from the study "*Reinforcement of Treatment Response in Knee Osteoarthritis: A Randomised Trial*" will receive an invitation to populate the questionnaire in their electronic mailbox (Mit.dk) via the software Research Electronic Data Capture (REDCap) with an introduction and explanation on the objective of the questionnaire.

For each populated questionnaire 10 DKK will be donated to the Parker Institute´s patient organisation. Each week following the first email, the survey will be resent to those who did not

respond to the first survey round, until the survey has been sent a total of three times (or 100% response rate has been achieved whichever comes first).

Data will be collected and managed using REDCap electronic data capture tools hosted at The Parker Institute, Frederiksberg and Bispebjerg Hospital, Denmark. REDCap is a secure, web-based software platform supporting data capture for research studies, providing validated data capture, audit trails for tracking data manipulation automated export functions to statistical programs (9,10).

GROUP CONCEPT MAPPING (GCM)

Using the group concept mapping data, we will explore what concepts and CB/H that are present in the responders- and non-responders respectively and compare the similarities and differences between the two groups.

GCM is a formal group process using a structured approach to identify ideas on a topic of interest and organize them into domains based on a mixed-method participatory design that incorporates group processes and multivariate statistical analyses (multidimensional scaling and hierarchical cluster analysis) (12,13).

The structured conceptualization will be captured, and conceptualised using the software *Concept System GroupWisdom software,* (14) which supports the steps in the GCM process.

Group Content Mapping Data Generation

The concept mapping method used in this study is based on William Trochim's framework for concept mapping that follows six predefined steps to yield the conceptual presentation. (15,16,17,18). All GCM sessions will be carried out via in-person attendance of all group members in the respective groups.

Step 1. Preparation

This step contains two aspects, selecting participants and developing the focus. Selecting participants should aim at using a broad heterogeneous group to ensure a wide variety of viewpoints. Responders and non-responders respectively (as defined below), from the RCT study

"*Reinforcement of Treatment Response in Knee Osteoarthritis: A Randomised Trial*", will be invited to take part in the concept mapping session in random order until the desired number of groups have been reached.

When developing the focus, a seeding question based on the aim of this study will be asked to the participants.

Seeding question: *Tænk så bredt som muligt - hvad var din begrundelse for at sige ja til en saltvandsindsprøjtning, og hvilke forventninger havde du (både til indsprøjtningen og samtalen)?*

Thinking as broad as you can – what was your reason for accepting a saline injection, and what expectations did you have (both for the injection as well as the conversation)?

The seeding question will be tested with the patient research partners beforehand, to make sure it resonates with patients, and invites participants to share emotions and statements. The concept mapping software will be used to sort the statements into meaningful categories/themes and guide the brainstorming in the desired direction. In addition, a rating focus will be used to identify which statements are of most importance.

Step 2. Generation of Statements

During this step the statements will be generated using the brainstorming format; that is, people are encouraged to generate a lot of statements without criticism or discussion regarding legitimacy. As the statements are generated, they will be entered into the software, with the screen projected so that all participants can see the statements. After the generation of statements, these will be read and re-written, if necessary, by the participants to ensure clarity and avoid duplicates. If over 100 statements are generated, participant will be asked to examine of there are redundancies or if one statement can represent a subset of others.

Step 3. Structuring of Statements

The final statements are sorted into meaningful piles by each participant. When each participant has finished sorting the statements, they will be put into a matrix allowing for quantification of

how the individual participant conceptualize the statements and which statements are conceptually agreeable between participants.

Step 4. Representation of Statements

The representation of statements is presented using multidimensional scaling analysis on a map with statements that have been sorted frequently together placed close to each other. The results will be represented in a two-dimensional graph (19).

Secondly a hierarchical cluster analysis (20,21) is performed to identify which statements presumably represent the same concepts. The number of clusters needed, for the best representation of the sorted statements, is decided by looking at different cluster map representation of the data. The decision of number of clusters needed rely on the number of concepts developed by the participants (e.g., the highest number one participant use, is the maximum number of clusters and the lowest number of clusters one participant use will be the lower limit of clusters looked at). The typical solution will be a cluster map between 3 to 12 clusters. A cluster map has a good representation of the results when statements in the different clusters make sense as concepts.

Finally, a point map and a cluster map are generated. These maps are based on the average rating across participants for each statement and each cluster. All participants will be asked to rate the relevance of each statement and each cluster on a five-point scale; 1: ‘Not relevant for people in my situation’, 2: ‘Rarely relevant for people in my situation, 3: ‘Sometimes relevant for people in my situation, 4: ‘Very relevant for people in my situation, and 5: ‘Of essential relevance for people in my situation.

Step 5. Interpretation of Maps

The participants will be asked to interpret the results that have emerged in the different maps, there should be 6 maps available:

1. The statement list.

2. The cluster list.
3. The point map.
4. The cluster map.
5. The point rating map.
6. The cluster rating map.

Each of these maps/list represents the results from the different steps in the concept mapping session. The participants will be asked to look at the statements in the different clusters, on the cluster map, and decide whether statements are presented in the right group or needs to be removed and name each cluster. Agreement is reached by discussion.

Secondly the point rating map and cluster rating map is presented to the participants, and they are asked to examine if the rating of the statements makes sense. Secondly, they are sked to assess if the names given based on the cluster map, still fits when looking at the cluster rating map. Lastly, it is checked whether the concept (name of the cluster) is closely related to the highest rated statement within that cluster.

Step 6. Utilization of Maps

Using the concept maps and statements, we will assess if they belong to specific CB/H or, if they fit into one of the proposed taxonomies of CB/H. This can be used to design contextual factors to target these specific cognitive biases and heuristics to further improve the response to open label placebo.

Group Concept Mapping Participants

A list of randomly selected responders, and non-responders respectively from the study "*Reinforcement of Treatment Response in Knee Osteoarthritis: A Randomised Trial*", will be generated and participants will be contacted by TSJ or TKA and asked if they wish to participate in a group concept mapping interview.

Definition of responders and non-responders

Participants from the trial "*Reinforcement of Treatment Response in Knee Osteoarthritis: A Randomised Trial*" will be defined as responders if they belong to the upper quartile of the ΔVAS (those who had the greatest positive changes) and non-responders will be defined as those belonging to the lower quartile of the delta VAS (those who had the smallest change).

Number of participants

Usually, it takes two to three concept mapping sessions with groups of 4-6 persons to reach saturation of the concepts/statements given by the participants. Therefore, a total of 18 participants will be sought recruited from each group (responder/non-responder) to participate in the GCM sessions after which the concept mapping expert (TSJ) will assess if saturation has been reached, if not, additional sessions will be held.

Concept mapping personnel

The sessions will be led by TSJ, who is an expert in concept mapping, and EG-N. The project manager TKA will be present during the sessions to observe.

DURATION OF THE STUDY

Two to three concept mapping sessions will be performed during May depending on number of sessions needed to reach saturation in the statement.

The Questionnaire will also be sent out during May.

Data will be analysed after summer after which a manuscript will be prepared and sent to selected publishers ultimo 2023.

RESEARCH ETHICS

According to the Danish regulations, questionnaires and interviews does not require submission to, or approval from, the Health Research Ethics Committee.

Questionnaire

Participants will be invited via an introductory email with information regarding the project in an easy-to-understand plain Danish. Herein they will be informed that participation is completely voluntarily, and that they can choose to opt-out at any time without having to explain why.

An informed consent form (ICF) will be prepared and included in the introductory email. When a participant chooses to answer the questionnaire, they will check a box stating that they acknowledge that they have read and understood the ICF. This will be captured along with the responses to the questionnaire.

Group Content Mapping

When a potential participant is contacted via phone regarding the GCM sessions, they will receive oral information regarding the project. The information will be given in easy-to-understand plain Danish. If a participant wishes to participate, they will receive a written description of the project and the role of the participant. If a participant still wishes to participate, they will be invited to a concept mapping session.

All participants will be informed, that participation in the GCM sessions is completely voluntarily, and that they can choose to opt-out at any time without having to explain why.

An informed consent form (ICF) will be prepared and must be signed and dated by the participants prior to participation in the GCM sessions. A copy of the from is provided to the participants. Prior to consent, it must be ensured that a potential participant has been given enough time to consider his or her participation. The signed ICF must remain in each participant's study file and must be available for verification by inspection at any time.

After a participant has signed the ICF, the following information will be collected from the participant's medical records:

- Contact information
- Response status on all endpoints from the study "Reinforcement of Treatment Response in Knee Osteoarthritis: A Randomised Trial".

SOURCE DOCUMENTS

Source documents are defined as populated questionnaires, data from the concept mapping sessions and the participants medical records.

REGULATORY STANDARDS

Information on this study will be published on the ClinicalTrials.gov website prior to data collection.

PARTICIPANT CONFIDENTIALITY

When data from this study is published, the presentation format will not include names, recognisable photos, personal information, or other data which compromises the anonymity of participating participants. If statements from the concept mapping sessions are used to emphasize the findings, no personal information will be present in the statement.

DATA PROTECTION ACT AND GENERAL DATA PROTECTION REGULATION

The study will be conducted in accordance with the Data Protection Act and follow the General Data Protection Regulation. The study´s data management and data security procedures are approved by the Regional Knowledge Centre on Data Protection Compliance (videnscenter for dataanmeldelser i Region Hovedstaden) on behalf of the Danish Data Protection agency as a sub study under the study "*Reinforcement of Treatment Response in Knee Osteoarthritis: A Randomised Trial*" (P-2021-451).

All demographic and personal identifier data will be stored electronically for analysis and reporting. Upon completion of data entry, the information will be checked to ensure acceptable accuracy and completeness. All data will be anonymized when the study has been completed.

FINANCING INFORMATION

This study is initiated by PhD student Tommy K Annfeldt. No specific funding has been received, however salary of TSJ, EGN, EEW, and LEK is covered by the Parker Institute. TKA is employed by Biogen International GmbH and the Parker Institute however, his salary is paid solely by Biogen International GmbH. LV is employed by the University of Aarhus. If future financial support is obtained, it will be disclosed to the participants and reported in the final article.

PUBLICATION

The development of the research article will be coordinated by Tommy K Annfeldt, and all individuals who have provided significant input to study design, implementation, conduct and interpretation, and fulfil the requirements for authorship as recommended by the international committee of medical journal editors (ICMJE) will be eligible to be mentioned as authors.

In accordance with the principles of the Helsinki declaration, all results of the study, positive as well as negative and inconclusive will be published.

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