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Siemonsma, P.C.

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CHAPTER 3

Benefits of treatment theory in the design of explanatory trials: cognitive treatment of illness perceptions in chronic low back pain rehabilitation as an illustrative example

Petra C. Siemonsma, Carin D. Schroder, Leo D. Roorda, Ant. T. Lettinga

ABSTRACT

Background: Evidence-based treatment is not effective for all patients. Research must therefore be carried out to help clinicians to decide for whom and under what circumstances certain treatment is effective. Treatment theory can assist in designing research that will provide results on which clinical decision-making can be based.

Objective: To illustrate how treatment theory can be helpful in the design of explanatory trials that assist clinical decision-making.

Methods: The benefit of treatment theory was demonstrated by approaching the design of a clinical trial from two perspectives: one without the use of treatment theory and one with the explicit use of treatment theory. Evaluation of the effectiveness of cognitive treatment of illness perceptions for patients with chronic low back pain was used as an illustrative example.

Issues: With treatment theory as the main focus, the intervention became the starting point for the design of an explanatory trial. Potentially relevant patient selection criteria, essential treatment components, the optimal choice of a control group and the selection of outcome measures were specified.

Conclusions: This paper not only describes problems encountered in research on the effectiveness of treatment, but also ways in which to address these problems.
INTRODUCTION

In rehabilitation medicine, considerable efforts have been made to create evidence-based clinical practice, and there is a need for continued efforts (Ebenbichler, Kerschan-Schindl et al., 2008; Frontera, Fuhrer et al., 2005; Stucki & Celio, 2007). Evidence-based medicine (EBM) has been defined as the integration of best research evidence with clinical expertise and patient values (Sackett, Straus et al., 2000). Randomized clinical trials (RCT) have a prominent place in EBM, because they provide a valid answer to the question of whether a certain type of treatment works, or works better than another type of treatment (Fuhrer, 2003). RCTs have been quite successful in proving that rehabilitation treatments are effective on certain parameters and for different medical diagnoses (Guzman, Esmail et al., 2008; Stroke Unit Trailists’ Collaboration, 2001). However, clinical decision-making would benefit more from research that works towards another goal: research that is aimed at improving rehabilitation treatment (Whyte, 2006; Mol, 2006). A logical next step is therefore to design clinical trials that provide answers to questions such as how, why, and for whom certain treatment is effective (Lettinga, Twillert van et al., 2006).

It has been suggested that treatment theory can be helpful in improving rehabilitation practice by providing a basis for clinical decision-making. For example, it can assist in specifying the active components, underlying mechanisms of interventions, and thereby specify the best candidates for a certain treatment (Fuhrer, 2003). Moreover, it can shed crucial light on the choice of appropriate study participants for inclusion, the appropriate outcome measures for assessing treatment response, and the overall study design (Whyte, 2006). Fuhrer has suggested that this is a development from more pragmatic trials towards more explanatory trials¹ (Fuhrer, 2003). Explanatory trials have been defined as studies aimed at theory-testing, elucidating treatment principles, or establishing the mechanisms underlying treatment responses (Fuhrer, 2003). In contrast, trials that make little use of theory, but aim to provide answers to the question of whether or not an intervention works, or works better than another intervention, are referred to as pragmatic trials (Fuhrer, 2003). The prominent position of pragmatic trials in medical research might explain why it appears that researchers

¹ In this debate we adhere to Fuhrer’s distinction, contrasting pragmatic trials with explanatory trials. Discussions in this field are confused by indistinct definitions of terms, and the use overlapping contrasts: besides pragmatic and explanatory trial, also effectiveness versus efficacy studies, and methodological versus theory-driven study design are used.
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In this field are not very explicit about theory when designing trials, something that is criticized by researchers in the fields of psychology and social science (Lambert, Gordon et al., 2006).

In this paper we will demonstrate the added value of treatment theory in the design of explanatory trials, with the help of an example of a certain type of rehabilitation treatment for patients with chronic low back pain: cognitive treatment of illness perceptions (CTIP). The aim of this treatment is to improve physical activity through cognitive restructuring of maladaptive illness perceptions (Siemonsma, Schroder et al., 2008). We will first describe the design of a trial without the explicit use of treatment theory, and then we demonstrate how the design would change if it was based on treatment theory. The assumptions underlying this explanatory design are currently being tested in a theory-driven study. The more general purpose of this paper is to illustrate how treatment theory can be used to refine research designs for the benefit of clinical decision-making.

DESIGN OF A TRIAL WITHOUT THE EXPLICIT USE OF TREATMENT THEORY

We describe here a trial that was designed to address the question of whether CTIP is effective for patients with chronic low back pain. To answer this question in a methodologically valid way we followed the procedures for the design of a RCT based on the so-called PICO sequence (Sackett et al., 2000) (p15). PICO is an acronym of the step involved in finding the current best evidence: P = patient and/or problem, I = intervention, C = comparison, and O = outcome’ (Sackett et al., 2000) (p.13). We will now specify each of the steps taken.

Patient characteristics (P)
To define P, i.e. the chronic non-specific low back pain patient population, we chose inclusion and exclusion criteria that made the trial comparable with other studies in this field (Tulder van, Koes et al., 1999). A consensus definition of chronic non-specific low back pain was used, including the following 3 inclusion criteria: (i) chronic, defined as pain persisting for more than 12 weeks; (ii) non-specific cause of the low back pain, defined as not attributed to any recognizable pathology, such as tumour, infection, inflammatory process, radicular syndrome, rheumatoid arthritis or fractures; and (iii) low back pain, defined as pain, muscle tension or stiffness, localized below the costal margin and above the inferior gluteal folds, with or without pain in the leg(s) (Tulder van et al., 1999). In addition to meeting the criteria for the medical diagnosis, the patients also had to have some activity limitations in order to qualify for rehabilitation treatment. This was
defined as a score of more than 3 on the Roland Morris Disability Questionnaire (Roland & Fairbank, 2000; Stratford, Binkley et al., 1998), indicating activity limitation in at least 4 physical activities.

**Intervention (I)**
The intervention (I) that we wished to prove effective was CTIP. Illness perceptions are the thoughts that patients themselves have about their illness, that reflect the patient’s personal understanding (or common-sense model) of the illness (Leventhal, Brissette et al., 2003). These include thoughts about the identity, cause, time-line, consequences, personal control, and care and cure of their back pain (Leventhal et al., 2003). The aim of the treatment was to enhance physical activity by cognitive restructuring of the illness perceptions of patients with chronic low back pain. To allow for a change in illness perceptions, and for an increase in physical activity, we developed a treatment protocol that included a maximum treatment intensity of 14 treatment sessions over a period of 10 to 18 weeks. Each treatment session lasted for 1 hour, and included a detailed discussion of the illness perceptions and their influence on physical activity. The one-to-one treatment was provided by a trained physiotherapist, occupational therapist, or psychologist, in an outpatient rehabilitation centre specialized in the multidisciplinary treatment of chronic pain.

**Comparison with control group (C)**
The research design that is considered to be the best design to compensate for threats to internal validity is an RCT (Kazdin AE, 2003) (p.51), and the best comparison (C) in an RCT is usually a control group of patients who receive a placebo treatment and/or no treatment. However, we considered such control treatments to be ethically unacceptable, we decided on a waiting list control group, followed by care as usual. This made it possible to answer the question - “Is CTIP effective for patients with chronic low back pain” - in a justifiable manner.

**Outcome measures (O)**
Outcome measures can be chosen with the aim of objectify the direct target of the treatment (proximal outcomes) or to measure the clinical impact (distal outcomes) (Whyte, 2006). We chose a back-specific generic disability measure, the Quebec Back Pain Disability Scale (QBPDS) (Kopec, 1997) as the distal outcome (O). This measurement instrument is a reliable and valid outcome measure in the field of research on chronic low back pain (Schoppink, Tulder van et al., 1996). Including such an internationally accepted measure in a trial makes comparison with the results of other studies possible, and might facilitate the inclusion of the
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trial in future reviews and meta-analyses (Moher, Schulz et al., 2001). For the assessment of changes in illness perceptions, we chose the Illness Perception Questionnaire (IPQ-R) (Moss-Morris, Weinman et al., 2002) as the proximal outcome, which has been found to be both reliable and valid (Moss-Morris et al., 2002; Weinman, Petrie et al., 1996).

Conclusion
By addressing the 4 steps of PICO we thus arrived at a clear description of a trial without the explicit use of treatment theory. We then followed the methodological procedures that have been developed to prove that treatments are effective, in order to answer the question “Is CTIP effective for patients with chronic low back pain”, based on the selected outcome measures. However, to provide clinicians with scientific evidence to improve their clinical practice, we needed to address different types of questions, questions such as how, why, and for whom certain treatment is effective. For this we needed treatment theory, as will be demonstrated below.

DESIGN OF A TRIAL WITH THE EXPLICIT USE OF TREATMENT THEORY
We will now describe how the design of the same trial changes if its effectiveness is evaluated from a theory-driven perspective: a trial with the explicit use of treatment theory. This implied that we had to start with the specification of the content of the treatment and the theories underlying the treatment, with the intervention as the main source of information. This knowledge about the content and assumed working mechanisms of the intervention (I) was then used for the selection of the patient characteristics (P), control group (C) and outcome measures (O). Therefore, we present the results here in a different sequence: IPCO instead of PICO.

Intervention (I)
Leventhal’s Self-Regulation Model (SRM) (Leventhal et al., 2003; Leventhal, Benyamini et al., 1997) was specified as the main theory underlying the intervention (I), e.g. CTIP. Essential to the SRM is the fact that what people themselves think about their illness has a great impact on what they do about it (Leventhal et al., 2003; Petrie, Cameron et al., 2002; Ogden, 2000). As mentioned previously, thoughts about the illness are called illness perceptions, and are grouped in dimensions (Leventhal et al., 2003). An example of illness perceptions and dimensions in the words of a patient: “Suddenly there was this very sharp pain in my back (dimension identity) as I lifted a heavy box off the floor. I think
that by lifting the box something in my back shifted, and that damaged my spine (dimension cause). It’s been 3 years now and the pain has not gone away, I don’t think it will ever go away (dimension time-line). I can’t work (dimension consequences) and the only thing I can do is just take pain-killers if the pain is really bad (dimension personal control). The doctors say that there is nothing they can do about it (dimension care and cure)

A patient’s illness perceptions can be incorrect, incomplete, or include unhelpful thoughts about the back problem and about physical activity, such as: “Taking pain-killers is the best thing to do when my back aches badly”. These thoughts are referred to as maladaptive illness perceptions, and in the SRM it is assumed that maladaptive illness perceptions can lead to maladaptive behaviour. It is further argued that maladaptive illness perceptions must change, so that they become conducive to physical activity, and thus a higher level of activity can be achieved. Changing maladaptive illness perceptions could therefore be specified as the intervening variable in CTIP.

Two active components have been specified in CTIP: mental experimentation and physical experimentation. Mental experimentation was regarded as the main component, because its aim is to change maladaptive perceptions. A Socratic-style dialogue, described by Nelson and others (Nelson, 1994; Vincelli, Choi et al., 2000), has been used as a technique for mental experimentation, especially for disputing maladaptive illness perceptions. In Socratic-style dialogues it is essential that the therapist activates the patient’s thought processes by naïvely questioning the patient’s illness perceptions (for further details see Siemonsma et al. (Siemonsma et al., 2008)). Mental experimentation is also used to strengthen the newly acquired alternative illness perceptions. Physical experimentation has been suggested as an additional treatment component. This type of experimentation is aimed at applying and testing perceptions during daily activities (Siemonsma et al., 2008), by means of home assignments.

The theory of conceptual change, developed by Strike & Posner (Strike & Posner, 1992), has been identified as the theory underlying the process of therapeutic change. The theory explains the causal sequence connecting treatment techniques and outcomes in CTIP, i.e. how the key treatment component of mental experimentation effects maladaptive illness perceptions. In this theory 3 conditions are formulated under which cognitive change (i.e. changes in maladaptive illness perceptions) is likely to occur.

The first condition is that there must be dissatisfaction with current perceptions. For example, during the treatment the therapist may achieve this by
questioning the patient’s illness perception that “lifting a heavy box 3 years ago” is the sole explanation for the current episode of back pain. The aim of such questions is that the patient may then start to doubt his or her current perceptions and become dissatisfied with them. In this case it might be important that the patient realizes that other factors may have contributed to the perseverance of the pain. The second condition is that a new perception must be intelligible to the patient. For example, the therapist might get the patient to think about what other factors could have influenced the back pain: inactivity, stress, tense muscles, etc., thereby stimulating the patient to explore the influence of other factors in their own particular situation. And thirdly, a new perception must appear plausible and beneficial to the patient (Strike et al., 1992). The patient is asked to formulate new ideas about back pain and physical activity that can be helpful in his or her situation. To continue with the example: the patient may conclude that, although lifting the box has initially caused the back pain, the combination of inactivity, stress and tense muscles, may explain why the back continues to be a problem. To arrive at such a conclusion is not a straightforward process; it is a matter of trial and error, rethinking, and renewed trial and error.

Thus, by specifying how the SRM and the theory of conceptual change gave content to the CTIP intervention we could identify the active treatment components (mental experimentation and physical experimentation), which enabled us to describe the assumed process of therapeutic change in more detail. We will now describe how this knowledge about treatment theory was helpful in identifying a sub-group of chronic low back pain patients who were hypothesized to be the most suitable candidates for CTIP.

Patient characteristics (P)
CTIP was developed for patients (P) with chronic low back pain. Therefore the 3 criteria defining chronic non-specific low back pain in the pragmatic trial could also be used as common selection criteria in this explanatory trial. However, CTIP was not intended to solve all problems that patients with chronic low back pain may encounter. The specification of CTIP showed that the intervention was specifically designed for patients who have maladaptive illness perceptions about their chronic low back pain.

In CTIP, any illness perception that appears to be maladaptive can serve as a target for change. A number of illness perceptions in patient with back pain were found to predict poor clinical outcome 6 months after they consulted a general practitioner. These included: (i) expecting the back problem to last for a
long time; (ii) expecting serious consequences later in life; and (iii) little confidence in the controllability of the back problem (Foster, Bishop et al., 2008). As illness perceptions were found to predict the outcome, they must have a central role in the treatment and in the selection of patients, so it was important to measure these perceptions. The IPQ-R (Moss-Morris et al., 2002) was an obvious choice of measurement instrument, because it was specifically designed to measure the dimensions of the SRM. However, other patient characteristics were also considered to be equally important for selecting the best candidates for CTIP.

First of all, the Socratic dialogues used in CTIP rely on a patient’s language skills. For example, to assess illness perceptions about the back problem and to elucidate maladaptive illness perceptions, patients have to be able to formulate their thoughts and reasons. Patients with better language and verbal reasoning skills were therefore assumed to benefit most from CTIP. A language test was therefore selected to objectify these skills, and to avoid undue disadvantage for certain sections of the population, we chose a test that can be used for patients from diverse cultural backgrounds: the Multicultural Capacity Test (MCT) (Bleichrodt & Berg van den, 2004).

Secondly, a patient’s reasoning skills were identified as likely variables for the success of the treatment. In particular, the patient’s ability and inclination to reason rationally about the back problem and physical activity, including solutions, is regarded as prerequisite for participation in a Socratic-style dialogue. We decided to measure this with the Rational Problem Solving scale of the Social Problem Solving Inventory (SPSI) (D’Zurilla & Maydeu-Olivares, 1995; Maydeu-Olivares & D’Zurilla, 1995; Hout van den, 2002), thereby assuming that higher scores are predictive of treatment success.

Thirdly, basic discussion skills are needed to engage in a fruitful discussion about the maladaptive illness perceptions. A patient with good listening skills, who is open-minded and contemplative, is also considered to be a more suitable candidate for CTIP. To objectify this, lower scores on the ‘aggrieved’ scale of the Dutch Personality Questionnaire (NPV) (Luteijn, Starren et al., 2000) were chosen as indicators for suitable candidates for successful treatment.

Being problem-focused, rather than emotion-focused, was assumed to be a fourth predictor of treatment success. In the SRM, 2 parallel processes are described in response to illness. One involves the regulation of emotions in reaction to fear, and the other involves the regulation of behaviour based on illness perceptions (Leventhal et al., 2003; Leventhal et al., 1997). As the aim of CTIP is to change the patient’s behaviour, i.e. to increase physical activity by
adjusting maladaptive illness perception, this involves being problem-focussed rather than emotion-focused. We decided to use the scales of the Utrecht Coping List (UCL) (Schreurs, Willige van de et al., 1993) to measure problem-focused coping (Kloens, Barelds et al., 2002). These scales focus on a systematic and goal-orientated approach to problems, and assess rational reactions to problems (Kloens, Barelds et al., 2004).

Using treatment theory in the design of the explanatory trial thus draws attention to important variables that can be studied in the trial. Potentially relevant patient characteristics with respect to CTIP that became apparent were: (i) maladaptive illness cognitions; (ii) language skills; (iii) reasoning skills; (iv) discussion skills; and (v) focus on rational problem-solving. Evidence for the hypothesized working mechanism of CTIP will most likely be found in patients with those 5 characteristics. This will therefore assist doctors and therapists in identifying patients who are suitable candidates for this specific intervention.

Comparison with control group (C)

Knowledge about the content and assumed working mechanisms of the intervention can also be of help in choosing the optimal comparison or control group (C). The research question “Which patients, with what characteristics, benefit most from CTIP” can not be answered by comparison of a CTIP group with a waiting list (no treatment) group, as proposed in the pragmatic trial. The best comparison for this purpose can be found within the treatment group by comparing suitable patients (i.e. those who have positive predictors) with patients who are hypothesized to be less suitable (i.e. those who have negative predictors). Instead of solely searching for the overall effects of CTIP for all patients with chronic low back problems, this explanatory design focused on matching patient characteristics and treatment content.

In order to make the trial even more explanatory, we adapted the design to enable us to study the impact of patient suitability on treatment outcome. Therefore, the number of patients randomized to the treatment group was doubled, making it possible to analyse the effects of the potentially relevant patient characteristics on treatment response within the treatment group. In doing so, the crucial research question became: “Which patients, with what characteristics, benefit most from CTIP?” Finally, we will now describe how treatment theory provided information about the treatment aims, which we then used to select appropriate outcome measures.
Outcome measures (O)
The aim or distal outcome (O) of CTIP was to increase physical activity in daily life. We selected a patient-specific activity measure allowing for personal relevance and circumstances because, according to the SRM, what people themselves think about their illness has a great impact on what they do about it (Leventhal et al., 1997; Ogden, 2000; Leventhal et al., 2003). Such a measure was considered to be more fitting for CTIP than a generic low back measure (such as the QBPDS) that was suggested for the pragmatic trial. Generic measures aim to objectify changes in general disability, and present the patient with a fixed list of activities, some of which may not be relevant. The Patient-Specific Functioning List (Beurskens, Vet de et al., 1999) was expected to be sensitive to changes in those activities that are important to the individual patient, and was therefore chosen as the distal outcome measure. Several acronyms are used for this measure (PSFL, PSK, PSFS, PSC and MC (main complaint)).

The IPQ-R was selected as a proximal outcome measure in the pragmatic trial, in order to objectify the process of therapeutic change. However, specification of the content of CTIP indicated that this instrument was not appropriate to measure the changes in illness perceptions that are intended to be achieved with CTIP. It does, indeed, measure changes in the number of illness perceptions, but fails to detect in-depth changes in the content of the perceptions (French & Weinman, 2008). In line with suggestions that have been made about how to compensate for these weaknesses in the IPQ-R (French et al., 2008), we added a purpose-made questionnaire, including open-ended questions about back pain illness perceptions, despite the fact that such a qualitative measure has methodological limitations with regard to validity and reliability.

Conclusion
By designing this explanatory trial in an IPCO rather than PICO sequence, we could make explicit use of treatment theory in the overall design. By specifying the content and working mechanism of the intervention (I) in a theory-driven way, we obtained the necessary knowledge for the choice of appropriate participants (P), control group (C) and outcome measures (O). This made it possible to address the clinically relevant research question “Which patients, with what characteristics, benefit most from CTIP?”. This might provide clinicians with evidence-based knowledge with which to improve their clinical practice.
DISCUSSION AND CONCLUSIONS
Pragmatic trials have provided proof for the overall effectiveness of multidisciplinary treatment for patients with chronic low back pain (Ostelo, Tulder van et al., 2004; Guzman et al., 2008). This has been a very important first step for rehabilitation medicine, because it has also provided care financers with the evidence to legitimize clinical practice (Lambert et al., 2006; Goldenberg, 2006; Mol, 2006). However, a serious limitation of pragmatic trials is their inability to explain how the results came about (Fuhrer, 2003), in other than methodological terms. Indeed, pragmatic trials are more methodology-driven than theory-driven. The specification of treatment theory has been suggested as a means to contribute in a crucial way to a better understanding of research results, and therewith to improve clinical decision-making (Whyte, 2006). We hope that we have illustrated this clearly with the help of the example of CTIP.

To begin with, we have demonstrated how treatment theory can be helpful in identifying the best candidates for a specific intervention (in this case CTIP). Identifying treatment-relevant patient characteristics is an important issue in research on the effectiveness of treatment. This implies that the characteristics on which the potential effects of the treatment depend should be studied, and not be randomized and diluted over the treatments that are the object of study (Goldenberg, 2006). The patient characteristics that evolved from the specification of treatment theory in the CTIP example are not commonly identified as predictors of outcome in the literature, unlike demographic factors and illness severity. Such variables, which are predictive irrespective of the type of treatment, are called prognostic variables (Whyte, 2006). It is important to distinguish prognostic variables from treatment response variables (Whyte, 2006). Characteristics such as language, reasoning, and discussion skills relate to the patient’s ability to engage in, understand, and co-operate with CTIP, and are therefore treatment response variables, i.e. variables that are predictive of the magnitude of treatment impact on the outcome (Whyte, 2006). The hypothesized predictors are so specific for CTIP, that when they are confirmed in an explanatory clinical trial, they can be very relevant for clinical decision-making. This will address an important limitation in the current paper: how much truth is hidden in the assumptions drawn from treatment theory and as applied in the research design?

We also demonstrated with the example of CTIP that the specification of treatment theory can assist in the choice of outcome measures, and especially those measures instruments that can assess the extent to which interventions
achieve own aims, and not only meet the conventional standards of reliability and validity. It is especially important that the chosen outcome measures match the short- and longer-term aims of the intervention. For example, the IPQ-R is not suitable for the measurement of in-dept changes in maladaptive illness perceptions, as hypothesized in CTIP, and may therefore present misleading results. This may also apply to generic measures such as the QBPDS, because the items that are included may have no personal relevance. Thus, in the explanatory trial the focus is on the selection of measurement instruments that match the treatment-specific aims, whereas in the pragmatic trial the focus was on methodological criteria and international consensus about the outcome measure.

In conclusion, EBM is criticized for being methodology-based, favouring pragmatic trials and meta-analysis (Sackett, Rosenberg et al., 1996; Fuhrer, 2003; Goldenberg, 2006), and for focusing on patient populations with a specific medical diagnosis, rather than on sub-groups of patients who are suitable candidates for rehabilitation treatment (Lambert et al., 2006; Biswas, Umakanth et al., 2007). In rehabilitation, EBM was therefore considered to be insufficiently specific to support clinical decision-making (Goldenberg, 2006; Mol, 2006; Struhkamp, Mol et al., 2008). The illustrative example of CTIP in this paper showed that even one single method of rehabilitation treatment is based on a complex set of theories, components and practices, and such complexities are often overlooked in pragmatic trials (Lettinga et al., 2006; Campbell, Fitzpatrick et al., 2000; Mol, 2006; Whyte, 2003). Integrating both PICO process and treatment theory, we have demonstrated that EBM can be used to facilitate clinical decision-making. With treatment theory as the main focus, the intervention became the starting point for the design of a trial. We therefore suggest that in these cases IPCO should be used instead of PICO. Our critical reflections on EBM should not be taken as criticism of EBM itself, but of the strict procedures involved. We have not only pointed out problems that can be encountered in research on the effectiveness of treatment, but have also demonstrated ways in which to address these problems.

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